제26회
기초의학 학술대회

The 26th Federation Meeting of Korean Basic Medical Scientists 2018

2018.6.29(금)
서울대학교 의과대학

4차 산업혁명과
미래의학의 플랫폼

참여학회

대한기생충학 · 열대의학회
대한미생물학회, 대한바이러스학회
대한법의학회, 대한병리학회
대한생리학회, 대한약리학회
대한예방의학회, 대한의사학회
대한해부학회, 생화학분자생물학회

주관 : 서울대학교 의과대학 주최 : 대한기초의학협의회

후원 : KMA 대한의사협회 Korean Medical Association 대한의학회 Korean Academy of Medical Sciences 서울특별시의사회 SEOUL MEDICAL ASSOCIATION

참여하여 주신 모든 업체에 감사드립니다.

제26회
기초의학 학술대회 협찬

고려제강(주)
라이카코리아 바이오시스템즈
로킷
이매진사이언스
질병관리본부 국립보건연구원 국가병원체자원은행
홍덕산업(주)
(주) AT Pharma

(가나다순)

회원 여러분의 많은 관심을 부탁드립니다.

목 차

모시는 글

존경하는 대한기초의학회 회원님들께 !

21세기가 열린 지도 벌써 스무 해 가까운 세월이 흐르고 있습니다.

생명공학의 시대라는 기치 하에 화려하게 시작한 새 세기와 새 천년은 단순히 한 해가 새롭게 열리는 물리적 시간의 변화일 뿐이었다는 일각의 지적은 여지없이 멋지게 빗나가고 말았습니다. 채 20년도 지나지 않은 현재를 돌아보니 그 변화는 가히 혁명적이라 할 수 있습니다. 금세기 초에는 human genome project를 중심으로 한 그저 인간유전자 분석이 화두려니 했는데 유전학 분야의 발전은 말할 것도 없고 big data, 인공지능(AI), 사물인터넷(IoT), 3세대 유전자 가위의 등장 등 그 발전이 가히 혁명적이어서 이들에 의한 변화를 총체적으로 소위 4차 산업혁명이라 칭하지 않을 수 없는 시대를 맞고 있습니다.

이러한 급변하는 학문적 상황 가운데 이제 오는 6월 29일 제26회 기초의학 학술대회를 연건동에 위치하는 서울대학교 의과대학 캠퍼스 내에서 독립적으로 개최하고자 합니다. 위에서 설명 드린 학문 조류의 흐름에 맞추어 '4차 산업혁명과 미래의학의 플랫폼' 이라는 주제를 설정하여 보았습니다. 이미 참석 대상이신 12개 학회 중 1-2 학회를 제외한 모든 학회들이 이 학문적 추세에 맞는 주제를 결정하시어 학술대회를 준비하고 계신 것으로 알고 있어 그 노고에 머리 숙여 깊은 감사의 인사를 드립니다. 학문의 성격 상 산업현장에서 4차 산업혁명을 직접적으로 주도하지는 못하지만 조용히 그리고 쉬지 않고 그 학문적 근거들을 창출하고자 최선을 다하여 기초의학에 전념해 온 우리 회원들의 노고와 학문적 관심, 열정, 성취에 박수를 보내며 이번 학술대회의 현장에서 그 발전의 내용과 정도를 서로 확인하시며 더 큰 발전의 발판을 이루시게 되기를 기원합니다.

모쪼록 많은 분들이 참석하시어 4차 산업혁명 추진의 현 주소와 지향점을 확인하시고 그를 바탕으로 구현될 미래의학의 구심점을 우리 대한민국 기초의학자들이 담당해야 한다는 사명감이 확인되는 공고한 자리가 되게 해주시기를 당부드립니다.

마지막으로 기초의학 학술대회를 지원해주시는 대한의사협회와 대한의학회에 심심한 감사의 인사를 드리고 주관대학으로 협조를 아끼지 않으신 서울대학교 의과대학 학장님과 모든 직원들께도 아울러 심심한 감사의 인사를 드립니다. 아울러 현장에서 성심껏 이 학술대회를 준비하고 진행시켜 온 조직위원회 멤버들에게도 가슴어린 감사의 인사를 드립니다.

추운 겨울이 끝나고 희망의 봄이 열리는 이때에 우리 회원 모두에게도 특별한 감사의 인사를 드리며 본인과 가족 모두의 건강을 기원하고 특히 커다란 학문적 성취가 있으시기를 소망하며 초청인사에 대신합니다. 감사합니다.

2018년 6월

제26회 기초의학 학술대회 대 회 장 **최 명 식**
조직위원장 **이 왕 재**

제26회 기초의학 학술대회 조직위원회

대 회 장	최명식	서울대학교 의과대학	간행위원장	조남혁	서울대학교 의과대학
조직위원장	이왕재	서울대학교 의과대학	홍보위원장	예상규	서울대학교 의과대학
총무위원장	강재승	서울대학교 의과대학	섭외위원장	최민호	서울대학교 의과대학
학술위원장	김성준	서울대학교 의과대학	재무위원장	석승혁	서울대학교 의과대학

각 학회 회장단

회 장	박 현	원광대학교 의과대학	대한기생충학·열대의학회
회 장	박인달	고신대학교 의과대학	대한미생물학회
회 장	안진현	성균관대학교 의과대학	대한바이러스학회
회 장	이숭덕	서울대학교 의과대학	대한법의학회
회 장	박재복	대구가톨릭대학교 의과대학	대한병리학회
회 장	박경표	서울대학교 치의학전문대학원	대한생리학회
회 장	김경근	전남대학교 의과대학	대한약리학회
회 장	박병주	서울대학교 의과대학	대한예방의학회
회 장	신동원	전북대학교 자연과학대학	대한의사학회
회 장	유영현	동아대학교 의과대학	대한해부학회
회 장	오우택	KIST	생화학분자생물학회
이사장	이건국	국립암센터	대한병리학회
이사장	서인석	서울대학교 의과대학	대한생리학회
이사장	최보율	한양대학교 의과대학	대한예방의학회
이사장	안규윤	전남대학교 의과대학	대한해부학회

총무분과

기모란	국립암센터 국제암대학원
김영수	연세대학교 의과대학
김지연	고신대학교 의과대학
김형표	연세대학교 의과대학
박만성	고려대학교 의과대학
박성환	고려대학교 의과대학
신은희	서울대학교 의과대학
윤 식	부산대학교 의과대학
이연수	가톨릭대학교 의과대학
장성호	서울대학교 의과대학
허강민	충남대학교 의과대학

학술분과

강재승	서울대학교 의과대학
고상백	연세대학교 원주의과대학
김소희	아주대학교 약학대학
김재우	연세대학교 의과대학
문경철	서울대학교 의과대학
박규상	연세대학교 원주의과대학
박종완	서울대학교 의과대학
신의철	카이스트 의과학대학원
이근화	제주대학교 의과대학
최은경	서울대학교 의과대학
하홍일	국립과학수사연구원
한은택	강원대학교 의학전문대학원

간행분과

강동묵	성균관대학교 의과대학
김범준	서울대학교 의과대학
김희진	연세대학교 치과대학
신규환	연세대학교 의과대학
우소연	이화여자대학교 의과대학
이민구	연세대학교 의과대학
정지영	고신대학교 의과대학
조성일	서울대학교 의과대학
한은택	강원대학교 의학전문대학원
홍순원	연세대학교 의과대학

섭외분과

강건욱	서울대학교 약학대학
배영안	가천대학교 의학전문대학원
신의철	카이스트 의과학대학원
오재근	대전대학교 한의과대학
우선희	충남대학교 약학대학
이근화	제주대학교 의과대학
장기택	성균관대학교 의과대학
정채용	전남대학교 의과대학
최재욱	고려대학교 의과대학
한 진	인제대학교 의과대학

홍보분과

김병주	부산대학교 한의학전문대학원
김인범	가톨릭대학교 의과대학
김택중	인제대학교 의과대학
김형건	단국대학교 의과대학
박현우	연세대학교 생명시스템대학
박혜진	국립과학수사연구원
배영안	가천대학교 의학전문대학원
송문정	고려대학교 생명과학대학
이근화	제주대학교 의과대학
이중정	계명대학교 의과대학
이호창	충북대학교 의과대학

재무분과

강윤경	인제대학교 의과대학
국 현	전남대학교 의과대학
기모란	국립암센터 국제암대학원
김성수	서울대학교 인문학연구원
김지연	고신대학교 의과대학
노상재	전북대학교 의과대학
박만성	고려대학교 의과대학
신은희	서울대학교 의과대학
염재범	인제대학교 의과대학
유임주	고려대학교 의과대학

(분과위원은 가나다순)

전체 일정

학 회 명	주 제
8:30~	등록
9:00~12:00	오전 세션
12:00~13:30	점심 시간 의과대학 · 의학전문대학원생 구연발표 / 포스터 자유발표
13:30~13:40	개회식
13:40~14:30	특강 "4차 산업혁명시대와 정밀의료" 박웅양 (성균관대학교 삼성서울병원 삼성유전체연구소장)
14:30~14:45	휴식 / 이동
14:45~17:45	오후 세션

포스터발표 장소

발표장소	발표번호	소속학회
융합관 1층 GDR2 (107-2호)	M-001~M-006	의과대학 · 의학전문대학원 학생발표
융합관 1층 GDR3 (107-3호)	P-001~P-030 P-166~P-179 P-229~P-230	대한기생충학 · 열대의학회 대한약리학회 생화학분자생물학회
융합관 1층 GDR4 (107-4호)	P-031~P-076	대한미생물학회 대한바이러스학회 대한법의학회
융합관 1층 로비	P-077~P-081 P-202~P-228 P-231~P-244	대한법의학회 대한해부학회 생화학분자생물학회
융합관 지하 1층 로비	P-082~P-165 P-180~P-201	대한병리학회 대한생리학회 대한예방의학회 대한의사학회

각 학회 및 심포지엄 안내

학 회 명	주 제	시 간	장 소
대한기생충학 · 열대의학회	기생충-숙주간 상호작용 및 면역 Parasite-host Mutual Interaction and Immunity	08:50-12:15	학생관 제1강의실 (101호)
대한미생물학회 대한바이러스학회 공동개최	항생제 내성과 차세대 치료기법 / 숙주와 병원체 상호작용의 임상적 중요성 신종 및 변종 바이러스 / 바이러스 감염과 숙주 반응 Anti-microbial Resistance and Next-generation Therapeutics Clinical Significance of Host-pathogen Interactions Newly Emerging and Re-emerging Viruses Viral Infection and Host Responses	09:00-17:55	학생관 제2강의실 (106호)
대한법의학회	법의학과 의료사고 Forensic Medicine and Medical Misadventure	09:00-17:45	교육관 강당 (401호)
대한병리학회	의료 빅데이터: 병리연구에서의 활용 가능성 Medical Big Data: Application in Pathology Research	14:45-17:30	행정관 대강당 (301호)
대한생리학회	정밀의료시대의 베타세포 병태생리 Pathophysiology of Pancreatic β-cells in the Era of Precision Medicine	14:45-17:45	융합관 박희택홀 (101호)
대한약리학회	섬유화 질환의 발병기전 및 치료 Pathogenesis and Treatment of Fibrosis-associated Diseases	09:00-12:00	행정관 대강당 (301호)
대한예방의학회	4차 산업혁명, 헬스케어 3.0시대의 질병예방 전략 Disease Prevention Strategy of 4th Industrial Revolution and Heath Care 3.0	14:30-18:30	융합관 양윤선홀 (102호)
대한의사학회	1987 민주화와 한국 의료계의 역할 1987 Democratic Transition and the Role of Health Professions in Korea	14:10-18:10	융합관 GDR1 (107-1호)
대한해부학회	해부학에서의 차세대 융합연구 (나노, 센서, 플랫폼) Next Generation Convergence Research in Anatomy (Nano, Sensor, Flatform)	14:30-18:00	종합실습동 함춘강의실
생화학분자생물학회	대사 경로의 연구 – 최신 동향과 리뷰 Metabolic Pathways – Latest Research and Review	14:45-17:45	학생관 제1강의실 (101호)

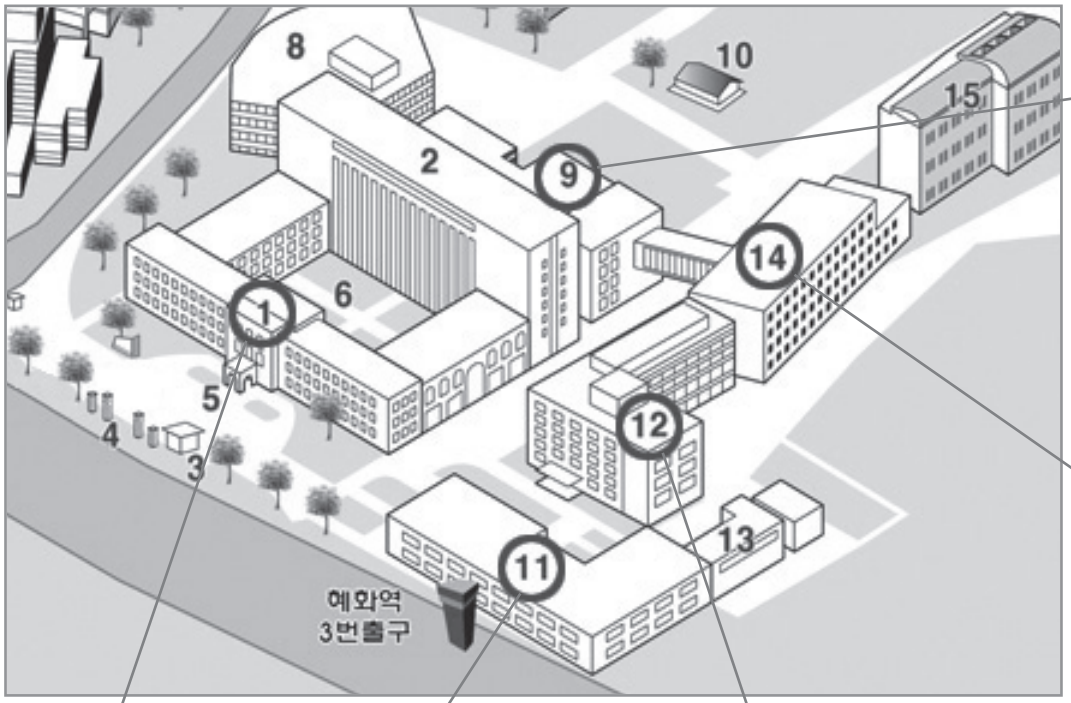
전체 일정

장소 / 시간	학생관		교육관	행정관	융합관				종합실습동
	제1강의실 (101호)	제2강의실 (106호)	강당 (401호)	대강당 (301호)	박희택홀 (101호)	양윤선홀 (102호)	GDR1 (107-1호)	GDR2 (107-2호)	함춘강의실
08:30-	등록								
09:00-12:00	대한 기생충학 · 열대의학회	대한미생물학회 대한바이러스학회	대한법의학회	대한약리학회					
12:00-13:30					점심시간, 포스터 자유발표			의과대학 의학전문대학원 학생발표	
13:30-14:30				개회식					
				특강					
14:30-18:00	생화학분자 생물학회	대한미생물학회 대한바이러스학회	대한법의학회	대한병리학회	대한생리학회	대한예방의학회	대한의사학회		대한해부학회

• **특강 :** 박웅양 (성균관대학교 삼성서울병원 삼성유전체연구소장) "4차 산업혁명시대와 정밀의료"

*포스터발표는 융합관 1층과 지하 1층에서 진행됩니다.

장소 안내



9 종합실습실

함춘강의실
대한해부학회

14 융합관

1층: 등록데스크, 전시회, 포스터발표
지하 1층: 포스터발표
박희택홀(101호): 대한생리학회
양윤선홀(102호): 대한예방의학회
GDR1(107-1호): 대한의사학회
GDR2(107-2호): 의과대학 · 의학전문대학원 학생발표
GDR3(107-3호): 포스터발표
GDR4(107-4호): 포스터발표

1 행정관

대강당(301호)
대한약리학회
개회식, 특강
대한병리학회

11 학생관

제1강의실(101호)
대한기생충학 · 열대의학회
생화학분자생물학회

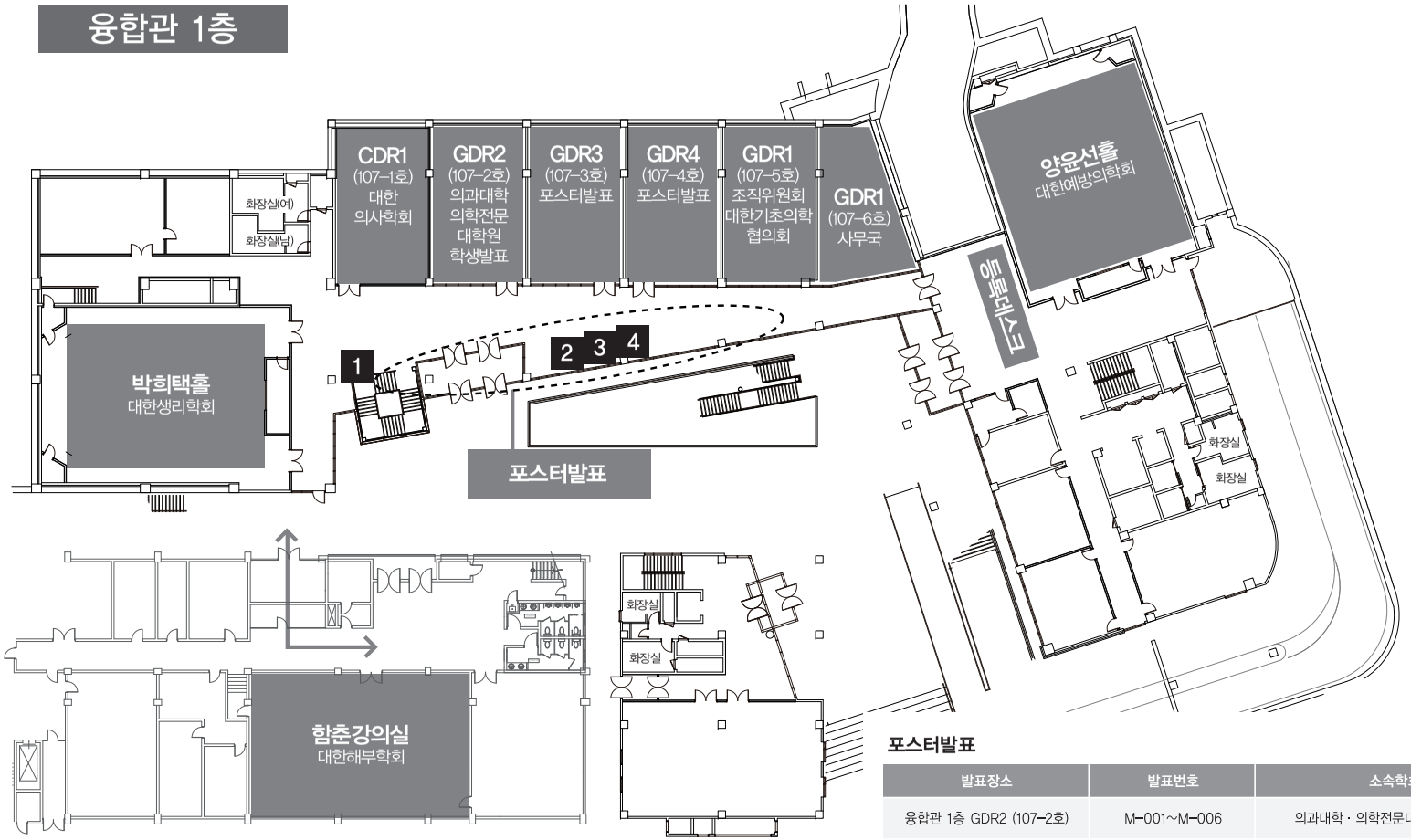
제2강의실(106호)
대한미생물학회
대한바이러스학회

12 교육관

강당(401호)
대한법의학회

장소 안내

융합관 1층



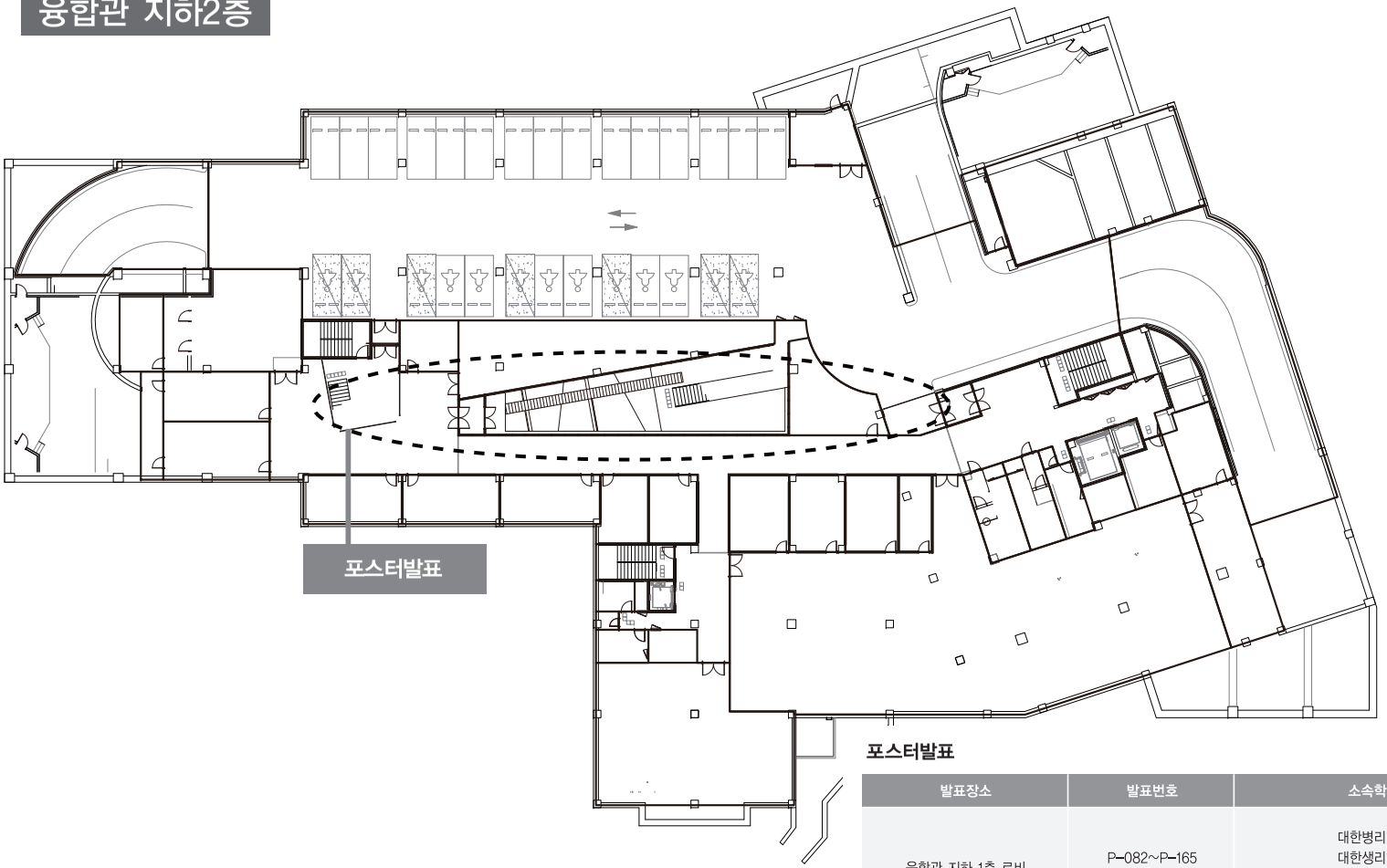
전시회

1	질병관리본부 국립보건연구원 국가병원체자원은행
2	이매진사이언스
3	로킷
4	라이카코리아 바이오시스템즈

포스터발표

발표장소	발표번호	소속학회
융합관 1층 GDR2 (107-2호)	M-001~M-006	의과대학 · 의학전문대학원 학생발표
융합관 1층 GDR3 (107-3호)	P-001~P-030 P-166~P-179 P-229~P-230	대한기생충학 · 열대의학회 대한약리학회 생화학분자생물학회
융합관 1층 GDR4 (107-4호)	P-031~P-076	대한미생물학회 대한바이러스학회 대한법의학회
융합관 1층 로비	P-077~P-081 P-202~P-228 P-231~P-244	대한법의학회 대한해부학회 생화학분자생물학회

융합관 지하2층



포스터발표

발표장소	발표번호	소속학회
융합관 지하 1층 로비	P-082~P-165 P-180~P-201	대한병리학회 대한생리학회 대한예방의학회 대한의사학회

개회식 및 특강

6월 29일(금) 13:30–14:30 장소 : 행정관 대강당 (301호)

개회식	사회 : 강재승 (총무위원장, 서울대학교 의과대학)
개회선언 및 개회사	최명식 (대회장, 서울대학교 의과대학) 이왕재 (조직위원장, 서울대학교 의과대학)
축사	최대집 (대한의사협회 회장) 장성구 (대한의학회 회장) 신찬수 (서울대학교 의과대학 학장)
후원금 및 감사패 전달	박홍준 (서울특별시의사회 회장) 조양혁 (전임 조직위원장, 가톨릭대학교 의과대학) 신찬수 (서울대학교 의과대학 학장)
특강	좌장 : 김성준 (학술위원장, 서울대학교 의과대학)
4차산업혁명시대와 정밀의료	박웅양 (성균관대학교 삼성서울병원 삼성유전체연구소장)

대한기생충학 · 열대의학회

6월 29일(금) 08:50–12:15 장소 : 학생관 제1강의실 (101호)

기생충–숙주간 상호작용 및 면역

Parasite-host Mutual Interaction and Immunity

08:50-09:00	인사말	박현 (회장, 원광대학교 의과대학)
Session I.		좌장 : 최민호 (서울대학교 의과대학)
09:00-09:30	질편모충에 감염된 전립선세포의 염증반응에 의한 전립선증식	류재숙 (한양대학교 의과대학)
09:30-10:00	Three Dimensional Cell Environment Model for Assessment of Malignant Transformation Associated with *Clonorchis sinensis* Infestation	박장호 (서울아산병원 의생명연구소)
10:00-10:30	Development of a Novel Peptide Aptamer to Detect Zika Virus and Application	여선주 (원광대학교 의과대학)
10:30-10:45	휴식	
Session II.		좌장 : 이영하 (충남대학교 의과대학)
10:45-11:15	Immune Regulation of *Toxoplasma gondii* Used to Overcome Intractable Disease	신은희 (서울대학교 의과대학)
11:15-11:45	Advanced Host-directed Therapy for New Therapeutic Insights from the T*oxoplasma gondii*	양철수 (한양대학교 과학기술대학)
11:45-12:15	Neuroinflammation as a Potential Therapeutic Target	송견지 (가톨릭관동대학교 의과대학)
12:15-	포스터 시상 및 폐회사	

대한미생물학회 & 대한바이러스학회 공동개최

6월 29일(금) 09:00-17:55 장소 : 학생관 제2강의실 (106호)

항생제 내성과 차세대 치료기법 / 숙주와 병원체 상호작용의 임상적 중요성
신종 및 변종 바이러스 / 바이러스 감염과 숙주 반응
Anti-microbial Resistance and Next-generation Therapeutics
Clinical Significance of Host-pathogen Interactions
Newly Emerging and Re-emerging Viruses
Viral Infection and Host Responses

S1. Anti-microbial Resistance and Next-generation Therapeutics: 항생제 내성과 차세대 치료기법

좌장 : 조남혁 (서울대학교 의과대학)

9:00-9:25	Redirecting an Anticancer Compound to Antibiotics against Drug-resistant Bacterial Pathogens	조유희 (차의과학대학교 약학대학)
9:25-9:50	Enhancement of Intracellular Survival of *Brucella abortus* in Professional Phagocytes, RAW 264.7 Cells, by Mutagenesis of BruA2_1031 Gene	정명환 (경상대학교 의과대학)
9:50-10:15	The Hepcidin-ferroportin Axis Controls the Iron Content of Salmonella-containing Vacuoles in Macrophages	임대진 (전남대학교 의과대학)
10:15-10:30	휴식	

S2. Newly Emerging and Re-emerging Viruses: 신종 및 변종 바이러스

좌장 : 황응수 (서울대학교 의과대학)

10:30-11:10	Stem Cells and Dengue Virus Infections	Oscar Guey Chuen Perng (National Cheng Kung University, Taiwan Stem Cells and Dengue Virus Infections, Taiwan)
11:10-11:35	Development of DNA Vaccine Candidates against Severe Fever with Thrombocytopenia Syndrome (SFTS)	박수형 (카이스트 의과학대학원)
11:35-12:00	Neuraminidase Inhibitor Resistance Markers among Avian Influenza Viruses N3~N9 Subtypes	송민석 (충북대학교 의과대학)
12:00-14:45	점심식사 및 휴식, 이동	

S3. Clinical Significance of Host-pathogen Interactions: 숙주와 병원체 상호작용의 임상적 중요성

좌장 : 김화중 (충남대학교 의과대학)

14:45-15:10	Vector-borne Infectious Diseases	김동민 (조선대학교 의과대학)
15:10-15:35	Cytosolic Receptor Nod2 in Infectious Diseases	박종환 (전남대학교 수의과대학)
15:35-16:00	Role of the Microbiota and Its Potential in Mucosal Vaccination	김동현 (서울대학교 의과대학)
16:00-16:15	휴식	

S4. Viral Infection and Host Responses: 바이러스 감염과 숙주 반응

좌장 : 이재면 (연세대학교 의과대학)

16:15-16:40	A Hepatitis B Virus-interacting Protein Selectively Regulates IRE1α and Protects Tumor Cells from ER Stress-induced Cell Death	김균환 (건국대학교 의과대학)
16:40-17:05	Role of Nucleoprotein in the Pathogenesis of Influenza Virus	김두진 (한국생명공학연구원)
17:05-17:30	Insights into Varicella Zoster Virus (VZV)-mediated Innate Immune Evasion Mechanisms	신옥 (고려대학교 의과대학)
17:30-17:55	CMV and Immunosenescence: Relevance to Cardiovascular Diseases	윤종찬 (한림대학교 의과대학)

대한법의학회

6월 29일(금) 09:00-17:45 장소 : 교육관 강당 (401호)

법의학과 의료사고

Forensic Medicine and Medical Misadventure

Part I 의료사고의 현재

좌장 : 이숭덕 (서울대학교 의과대학)

09:00-09:40	의료사고의 판례 경향	노태헌 (인천지방법원 부천지원)
09:40-10:20	의료사고 감정	박형천 (한국의료분쟁조정중재원)
10:20-10:40	휴식	

좌장 : 양경무 (국립과학수사연구원)

10:40-11:20	의료사고의 민사적 해결	유현정 (나음법률사무소)
11:20-12:00	의료사고에 대한 새로운 접근	이호 (전북대학교 의과대학)
12:00-14:45	점심식사 및 휴식, 이동	

Part II 의료사고에서 법의학의 역할

좌장 : 이상한 (경북대학교 의과대학)

14:45-15:25	의료사고 관련 부검 현황	박재홍 (국립과학수사연구원 중앙법의학센터)
15:25-16:05	의료사고에서 법의학의 역할	이숭덕 (서울대학교 의과대학)
16:05-16:25	휴식	

좌장 : 허기영 (부산대학교 의과대학)

16:25-17:45	자유연제(구연)	
	우리나라 사망진단서 서식의 변천 과정과 개선의 필요성	이상한 (경북대학교 의과대학)
	사망진단서 개선을 위한 제언	이숭덕 (서울대학교 의과대학)
	탄소 동위원소 분석을 통한 백골화 골격의 연대추정 사례 보고	박종필 (국립과학수사연구원)
	Study on Necrophagous Entomofauna Collected from Autopsies in Seoul, Incheon and the Part of Geonggi Area	신상언 (고려대학교 의과대학)
	Impact of Pesticide Restriction on Pesticide Poisoning Death in South Korea: a 10-year Autopsy Study (2008-2017)	이낙원 (국립과학수사연구원)
	The Application of the Kvaal Method to Estimate the Age of Live Korean Subjects Using Digital Panoramic Radiographs	노병윤 (국립과학수사연구원)

대한병리학회

6월 29일(금) 14:45–17:30 장소 : 행정관 대강당 (301호)

의료 빅데이터: 병리연구에서의 활용 가능성

Medical Big Data: Application in Pathology Research

좌장 : 강경훈 (서울대학교 의과대학)
문경철 (서울대학교 의과대학)

14:45-15:15	미토콘드리아 유전자에 대한 NGS의 적용 및 종양에서의 활용 가능성 탐색	김문영 (서울대학교 의과대학)
15:15-15:45	NGS를 이용한 법유전학 마커의 분석과 활용	신경진 (연세대학교 의과대학)
15:45-16:05	휴식	
16:05-16:35	의료 빅데이터와 기계학습을 이용한 정밀의료 응용	강재우 (고려대학교 정보대학)
16:35-17:05	분산형 생명의료 빅데이터 연구를 위한 서울대학교병원 CDM 구축 현황 및 향후 계획	김광수 (서울대학교병원 임상의과학정보실)
17:05-17:30	건강보험심사평가원 청구자료의 이용	변선주 (한림대학교 동탄성심병원)

대한생리학회

6월 29일(금) 14:45–17:45 장소 : 융합관 박희택홀 (101호)

정밀의료시대의 베타세포 병태생리

Pathophysiology of Pancreatic β-cells in the Era of Precision Medicine

공동주최 : 계명대학교 의과대학 비만매개질환 MRC 연구센터
연세대학교 원주의과대학 미토콘드리아 스트레스 자기방어 연구센터

좌장 : 송대규 (계명대학교 의과대학)
서인석 (서울대학교 의과대학)

14:45-14:50	개회	
14:50-15:20	Trafficking vs. Gating Regulation for KATP Channels in Pancreatic Beta Cells	호원경 (서울대학교 의과대학)
15:20-15:45	Glucotoxicty and CD36 Signaling in Pancreatic Beta Cell	원규장 (영남대학교 의과대학)
15:45-16:10	Pancreatic Beta-cell Neogenesis from Alpha-cells by Glucagon-like Peptide-1	전희숙 (가천대학교 의과대학)
16:10-16:25	휴식	
16:25-16:50	Essential Role of PRMT1 in Pancreatic Beta-cells	김하일 (KAIST)
16:50-17:15	Incretin Biology in Koreans	조영민 (서울대학교 의과대학)
17:15-17:40	Targeting PGC-1a to Protect Glucose-toxicity in Beta-cells	윤건호 (가톨릭대학교 의과대학)
17:40-17:45	폐회	

대한약리학회

6월 29일(금) 09:00–12:00 장소 : 행정관 대강당 (301호)

섬유화 질환의 발병기전 및 치료

Pathogenesis and Treatment of Fibrosis-associated Diseases

09:00-09:10	개회사	김경근 (회장, 전남대학교 의과대학)

Session 1. 폐 섬유화 질환

좌장 : 김소희 (아주대학교 약학대학)

09:10-09:40	Role of Transglutaminase 2 in the Pathogenesis of Idiopathic Pulmonary Fibrosis	김인규 (서울대학교 의과대학)
09:40-10:10	CST3 and GDF15 are Potential Therapeutics for Pulmonary Fibrosis	박종완 (서울대학교 의과대학)
10:10-10:30	휴식	

Session 2. 간 및 신장 섬유화 질환

좌장 : 박종완 (서울대학교 의과대학)

10:30-11:00	Oxidative Stress and Kidney Fibrosis: Recent Insights into Established Therapeutic Targets	하헌주 (이화여자대학교 약학대학)
11:00-11:30	Stem Cells as a Tool for the Treatment of Fibrotic Diseases and Screening of New Anti-fibrotic Drugs	김종훈 (고려대학교 생명과학대학)
11:30-12:00	Hepcidin as a Novel Anti-fibrotic Hepatokine to Inhibit HSC Activation	한창엽 (원광대학교 의과대학)

대한예방의학회

6월 29일(금) 14:30–18:30 장소 : 융합관 양윤선홀 (102호)

4차 산업혁명, 헬스케어 3.0시대의 질병예방 전략

Disease Prevention Strategy of 4th Industrial Revolution and Heath Care 3.0

제1부 대한예방의학회 총회

사회 : 기모란 (총무이사, 국립암센터 국제암대학원대학교)

14:30-14:35	개회사	최보율 (이사장, 한양대학교 의과대학)
14:35-14:45	안건처리: 대한예방의학회 정관개정	최보율 (이사장, 한양대학교 의과대학)
14:45-15:00	대한예방의학회 후속세대 양성 TFT 보고	감신 (TFT 위원장, 경북대학교 의과대학)

제2부 심포지엄

사회 : 고상백 (학술위원장, 연세대학교 원주의과대학)

좌장 : 이경수 (영남대학교 의과대학)

15:10-17:30	주제발표	
	4차 산업혁명과 예방의학의 역할	이영성 (충북대학교, 한국보건의료연구원장)
	공통데이터모델 기반 분산형 바이오헬스 통합 데이터망 구축 기술	박래웅 (아주대학교, 대한의료정보학회 이사장)
	왜 '4차 산업혁명론' 이 문제인가?	홍성욱 (서울대학교 자연과학대학)
	소비자 중심 건강정보와 맞춤예방	강건욱 (서울대학교 의과대학)
	빅데이터의 공익적 활용	김재용 (한양대학교 의과대학)
17:40-18:30	토론	김소윤 (연세대학교 의과대학) 김현창 (연세대학교 의과대학) 변혜진 (연구공동체 건강과 대안) 황승식 (연세대학교 보건대학원)

대한의사학회

6월 29일(금) 14:10–18:10 장소 : 융합관 GDR1 (107–1호)

1987 민주화와 한국 의료계의 역할

1987 Democratic Transition and the Role of Health Professions in Korea

1부 기획발표

좌장 : 신영전 (한양대학교)

세션 1. 구술사로 본 민주화 운동속의 의료인

14:20-14:35	의료인 민주화 운동에 대한 구술사 작업 시론-의사 양길승 사례를 중심으로	이현숙 (연세대학교)
14:35-15:00	회고담: 한 의료인이 겪은 70-80년대 한국의 민주화 과정	양길승 (녹색병원 이사장)
15:00-15:10	토론 및 질의응답	

세션 2. 1987 민주화와 의료계의 역할

15:10-15:30	한국 민주화운동 속 부검논쟁	최규진 (인하대학교)
15:30-15:50	한국과 일본에서 노동안전보건운동의 전개와 안전보건 시민권	김직수 (사회공공연구원)
15:50-16:00	토론	
16:00-16:10	휴식	

2부 자유주제 발표

자유주제 발표 1 사회 : 이경록 (연세대학교)

16:10-16:25	조선의 유행성 열병 대응- 16, 17세기 온역 전문의서	김상현 (한국한의학연구원)
16:25-16:40	조선시대 전염병 대책과 활인서 운영 혜민서	김성수 (서울대학교)
16:40-16:55	미국 보건권력의 상호작용: 20세기 초 결핵 요양소를 중심으로	김서형 (인하대학교)
16:55-17:05	전체토론	

자유주제 발표 2 사회 : 김옥주 (서울대학교)

17:05-17:20	1894년 홍콩 페스트의 유행과 동화의원의 공간변화	신규환 (연세대학교)
17:20-17:35	한국전쟁 이후 한센병 정책의 전환 -코크레인 보고서를 중심으로	김원중 (연세대학교)
17:35-17:50	1987년 에이즈예방법 제정과 반미주의	김택중 (인제대학교)
17:50-18:00	전체토론	
18:00-18:10	폐회	

대한해부학회

6월 29일(금) 14:30-18:00 장소 : 종합실습동 함춘강의실

해부학에서의 차세대 융합연구 (나노, 센서, 플랫폼)

Next Generation Convergence Research in Anatomy (Nano, Sensor, Platform)

좌장: 이동섭 (서울대학교 의과대학)

14:30-15:10	Bio-inspired Nanomedicine	주진명 (울산대학교 의과대학)
15:10-15:50	Micro/Nanotechnology-based Biosensor Platforms for Biomedical Applications	황교선 (경희대학교 의과대학)
15:50-16:00	휴식	
16:00-16:40	RNAi-based Nanoparticle for Neuropathic Pain	김동운 (충남대학교 의과대학)
16:40-17:20	A Calcium- and Light-gated Switch to Induce Gene Expression in Activated Neurons	이동민 (고려대학교 의과대학)
17:20-18:00	What Drive Us to Eat- The Neuroscience of Appetite	최형진 (서울대학교 의과대학)

생화학분자생물학회

6월 29일(금) 14:45–17:45 장소 : 학생관 제1강의실 (101호)

대사 경로의 연구 – 최신 동향과 리뷰

Metabolic Pathways - Latest Research and Review

좌장 : 박병현 (전북대학교 의과대학)

14:45-15:15	The Nuclear Receptor SHP Is a Critical Regulator of Nutrient Sensing, Basal Autophagy, and Energy Homeostasis	이재만 (경북대학교 의과대학)
15:15-15:45	How Metabolic Stress Leads to Chronic Diseases - Role of TonEBP	권혁무 (UNIST)
15:45-16:15	Hepatic Steatosis and Insulin Resistance via Endocytosis of TLR4/NOX2 in Macrophage	정원일 (KAIST)
16:15-16:35	휴식	
16:35-17:05	Lessons from Hepatocyte-specific Sirtuin 6 Knockout Mice: Activation of All Three Canonical Pathways of the UPR Is Not a Prerequisite for the Development of NAFLD	박병현 (전북대학교 의과대학)
17:05-17:45	Journey to Explore Glucose Homeostasis	안용호 (연세대학교 의과대학)

제26회 기초의학 학술대회 초록집

심포지엄 목록 및 초록

2018 The 26th Federation Meeting of Korean Basic Medical Scientists

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[1]Department of Microbiology, Chonnam National University Medical School, Gwangju, 61468, Republic of Korea, [2]Department of Molecular Medicine (BK21plus), Chonnam National University Graduate School, Gwangju, 61468, Republic of Korea

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[1]Department of Microbiology and Immunology, Seoul National University College of Medicine, Seoul, Korea; [2]Department of Pathology and [3]Comprehensive Cancer Center, University of Michigan Medical School, Ann Arbor, Michigan, USA

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[1]Infectious Disease Research Center, Korea Research Institute of Bioscience and Biotechnology (KRIBB), Daejeon, South Korea; [2]Department of Biochemistry, Chungnam National University, Daejeon, South Korea; [3]University of Science and Technology (UST), Daejeon, South Korea

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[1]Department of Biomedical Sciences, College of Medicine, Korea University Guro Hospital, Seoul, Republic of Korea; [2]Department of Biosystems and Biotechnology, Division of Biotechnology, College of Life Sciences and Biotechnology, Korea University, Seoul, Republic of Korea; [3]Department of Molecular Cell Biology, Sungkyunkwan University School of Medicine, Suwon, Republic of Korea; [4]Department of Microbiology, Chungbuk National University, Cheongju, Republic of Korea

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[1]국립과학수사연구원 서울과학수사연구소 법의조사과, [2]국립과학수사연구원 중앙법의학센터, [3]가톨릭대학교 의과대학 해부학교실

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[1]Department of Legal Medicine, Korea University College of Medicine, Seoul, South Korea; [2]Medical Examiner's Office, National Forensic Service, Wonju, Korea

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[1]Section of Human Identification, Medical Examiner's Office, National Forensic Service, 10, Ipchun-ro, Wonju-si, Gangwon-do, Republic of Korea; [2]Section of Human Identification, Department of Forensic Medicine Investigation, National Forensic Service Seoul Institute, 139, Jiyang-ro, Yangcheon-gu, Seoul, Republic of Korea; [3]Department of Oral Medicine, School of Dentistry, Chosun University, 309, Pilmun-daero, Dong-gu, Gwangju, Republic of Korea

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[1]Lee Gil Ya Cancer and Diabetes Institute, Gachon University, [2]College of Pharmacy and Gachon Institute of Pharmaceutical Science, Gachon University, [3]Gachon Medical Research Institute, Gil Hospital

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[1]Department of Pharmacology, School of Medicine, Wonkwang University, [2]College of Pharmacy, Seoul National University, Seoul, Korea

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김재용
한양대학교 의과대학

대한의사학회

S54 **구술사로 본 의료인의 민주화운동: 의사 양길승 사례를 중심으로**
이현숙
연세대학교 의학사연구소

S55 **한 의료인이 겪은 한국의 민주화과정**
양길승
녹색병원 이사장

S56 **한국 민주화운동 속 부검논쟁**
최규진
인하대학교 의과대학 의학교육학교실

S57 **한국과 일본에서 노동안전보건운동의 전개와 안전보건 시민권**
김직수
사회공공연구원

S58 **조선의 유행성 열병 대응 - 16, 17세기 온역 전문의서**
김상현
한국한의학연구원 미래의학부

S59 **조선시대 전염병 대책과 활인서 운영**
김성수
서울대학교 인문학연구원

S60 **미국 보건권력의 상호작용: 20세기초 결핵 요양소를 중심으로**
김서형
인하대학교 인경교양교육연구소

S61 **1894년 홍콩 페스트의 유행과 동화의원의 공간변화**
신규환
연세대학교 의과대학 인문사회의학교실 의사학과

S62 **한국전쟁 이후 한센병 정책의 전환-코크레인 보고서를 중심으로**
김원중
연세대학교 의과대학 인문사회의학교실 의사학과

S63 **1987년 에이즈예방법 제정과 반미주의**
김택중
인제대학교 의과대학 인문사회의학교실

대한해부학회

S64 **Bio-inspired Nanomedicine**
Jinmyoung Joo[1,2]*
[1]Department of Convergence Medicine, [2]Biomedical Engineering Research Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul 05505 Korea

S65 **Micro/Nanotechnology-based Biosensor Platforms for Biomedical Applications**
Hye Jin Kim[1], Yong Kyoung Yoo[1], Myung-Sic Chae[1], Dong Sung Park[1], Jae Hyun Kim[1], Jinsik Kim[2], Kyo Seon Hwang[1]
[1]Department of Clinical Pharmacology and Therapeutics, College of Medicine, Kyung Hee University, Seoul 02447, Republic of Korea; [2]Department of Medical Biotechnology, College of Life Science and Biotechnology, Dongguk University, Seoul 04620, Republic of Korea

S66 **RNAi-based Nanoparticle for Neuropathic Pain**
Dong Woon Kim
Department of Anatomy and Cell Biology, Brain Research Institute, Chungnam National University School of Medicine, Daejeon, 35015, Republic of Korea

S67 **A Calcium- and Light-gated Switch to Induce Gene Expression in Activated Neurons**
Dongmin Lee[1,2]
[1]Department of Biomedical Science, Brain Korea 21 PLUS, College of Medicine, Korea University, Seoul, Republic of Korea; [2]Department of Anatomy, College of Medicine, Korea University, Seoul, Republic of Korea

S68 **What Drive us to Eat- The Neuroscience of Appetite**
Hyung Jin Choi
Department of Anatomy, College of Medicine, Seoul National University, Seoul, Korea

생화학분자생물학회

S69 **The Nuclear Receptor SHP is a Critical Regulator of Nutrient Sensing, Basal Autophagy, and Energy Homeostasis**
Jae Man Lee
Department of Biochemistry and Cell Biology, Cell and Matrix Research Institute, School of Medicine, Kyungpook National University, Daegu, Republic of Korea

S70 **How Metabolic Stress Leads to Chronic Diseases - Role of TonEBP**
Hyug Moo Kwon
UNIST

S71 **Hepatic Steatosis and Insulin Resistance via Endocytosis of TLR4/NOX2 in Macrophage**
Won-Il Jeong
Laboratory of Liver Research, Graduate School of Medical Science and Engineering, KAIST, Daejeon 34141, Korea

S72 **Lessons from Hepatocyte-specific Sirtuin 6 Knockout Mice: Activation of All Three Canonical Pathways of the UPR is Not a Prerequisite for the Development of NAFLD**
In-Hyuk Bang and Byung-Hyun Park
Department of Biochemistry, Chonbuk National University Medical School, Jeonju, Jeonbuk 54896, Korea

S73 **A Journey to Explore Glucose Homeostasis**
Yong Ho Ahn
연세대학교 의과대학

4차산업혁명시대와 정밀의료

특강

일시 : 6월 29일(금) 13:40-14:30
장소 : 행정관 대강당 (301호)

2018 The 26th Federation Meeting of Korean Basic Medical Scientists

S1

Utility of Integrated Clinical and Genomic Data in the Era of Industry 4.0

Woong-Yang Park

Samsung Genome Institute, Samsung Medical Center and Sungkyunkwan University School of Medicine

We live in the fourth industrial age, which is explained by the keywords of super-intelligence and super-connectivity. In the healthcare field, there is an opportunity to create new healthcare services based on big data and artificial intelligence technologies. Based on the patient's clinical and genomic information, new diagnostic techniques and therapies can be developed, and technology for predicting diseases can be developed by applying artificial intelligence technology to people's health information in public database. We have an opportunity to utilize large-scale healthcare big data including clinical tests and health checkups and to implement new services using excellent information communication networks. In particular, it can secure competitive research and technology in the future health care field by utilizing unique contents such as genetic characteristics, food and environment, and disease characteristics of Koreans as well as East Asians. Genomic information produced through the national public health genome database and NGS clinical tests conducted in hospitals is an invaluable resource for future medical care. The time when the new paradigm of the Fourth Industrial Revolution arrives will be a chance to challenge new challenges in healthcare research and development with limited resources and markets.

기생충-숙주간 상호작용 및 면역

Parasite-host Mutual Interaction and Immunity

대한기생충학 · 열대의학회

일시 : 6월 29일(금) 08:50-12:15

장소 : 학생관 제1강의실 (101호)

2018 The 26th Federation Meeting of Korean Basic Medical Scientists

S2

질편모충에 감염된 전립선세포의 염증반응에 의한 전립선증식

류재숙, 한익환, 김정현, 김상수

한양대학교 의과대학 환경의생물학교실

WHO(2012)보고에 의하면 질편모충에 의한 감염은 매년 2억 7천만이 감염된다고 추정하고 있다. 질편모충은 전립선염을 일으키며, 양성전립선비대(BPH)와 전립선암 조직에서 관찰되었다.

이번 연구에서는 질편모충이 전립선에 감염되었을 때 일어나는 염증반응이 전립선세포(전립선암세포, 양성전립선비대세포)의 증식을 일으키는지 알아보고 그 기전을 알아보고자하였다.

질편모충은 전립선상피세포에 부착 및 세포독성작용을 하고, EMT(Epithelial-Mesenchymal transition)를 유도하였다. 전립선세포는 염증매개물질(cytokine, ROS)을 생산하고, 염증세포(중성구, 단핵구)의 이동을 일으켰다. 염증매개물질 중 IL-6는 대식세포를 M2로 분화시켜서 전립선암의 악화(증식, 이동, 침습)를 유도하였다. 한편 양성전립선비대 상피세포에 질편모충을 감염시키면 비만세포 이동을 촉진하였는데, 활성화된 비만세포에서 나오는 chemokine은 기질세포의 증식을 일으켰다. 또한 증식이 일어난 기질세포에서 나온 염증매개물질은 양성전립선비대 상피세포의 증식을 일으켰다. 따라서 질편모충은 전립선염을 유도하고 전립선 증식 및 전립선암의 악화에 기여함을 알수 있었다.

이상의 결과를 종합할 때 전립선상피세포에 질편모충의 감염은 cytokine을 포함한 염증매개물질의 생산을 증가시키고, 염증세포(중성구, 대식세포와 비만세포)의 이동 및 활성화를 유도하여 염증반응을 증폭시켰다. 이런 염증반응은 전립선의 증식과 전립선암의 악화에도 기여하였는데, 특히 IL-6가 중요한 역할을 함을 알 수 있었다.

Keywords: 질편모충, 염증반응, 전립선기질세포증식, 전립선암악화, IL-6

S3

Three Dimensional Cell Environment Model for Assessment of Malignant Transformation Associated with *Clonorchis sinensis* Infestation

Jhang Ho Pak

Department of Convergence Medicine University of Ulsan College of Medicine & Asan Institute for life Sciences, Asan Medical Center

Clonorchis sinensis is a carcinogenic human liver fluke. Its infection promotes persistent oxidative stress and chronic inflammation environments in the bile ducts and surrounding liver tissues, which provokes epithelial hyperplasia, periductal fibrosis, and even cholangiocarcinoma (CCA). The proposed pathogenic mechanisms of chronic liver fluke-associated CCA include physical damage to the biliary epithelia caused by the feeding and migration of the worms, immunopathology owing to infection-related inflammation, and direct effect of the excretory-secretory products (ESPs). A microfluidic three-dimensional (3D) cell culture assay system was applied to mimic in vivo host-parasite interactions under cholangiocyte microenviroment. Also, 3D culture spheroids were employed to examine the reiterative and continuous effects of the fluke infection on host cells.

S4

Development of a Novel Peptide Aptamer to Detect Zika Virus and Application

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Backgrounds: Most people infected with the Zika virus don' t show any symptoms, blood donors may not know they have been infected. Thus, there is an urgent need for a specific high throughput diagnostic assay to discriminate ZIKV infection from other flaviviruses. However, the development of a monoclonal antibody to discriminate DENV and ZIKV infection has been limited due to due to high level of cross-reactivity among flaviviruses. Therefore, there has been growing interest in the development of alternative antibody (aptamer)-based biosensors because their simplicity and low cost are attractive for point-of-care diagnosis, especially in low-resource areas. In contrast to nucleic acid aptamer, peptide aptamer has not been challenged in diagnostic system in spite of great potential of in silico designed peptide as diagnostic aptamer.

Methods and Results: In this study, a novel protocol to develop novel peptide aptamer derived from potential epitopes of ZIKV envelope protein was newly established and the experimental validation method to evaluate function of a peptide aptamer was presented by immunoassay to detect virus in patient sera and urine. Through experimental results, four criteria were suggested for development of in silico-modeled peptide aptamer: lower binding energy than -6.5 kcal/mol, lower root-mean-square deviation than 4Å, outward position of N-terminus, and interactive site to avoid transmembrane domain. The Z_10.8 peptide (KRAVVSCAEA) corresponding to these criteria recognized ZIKV envelope protein ($P < 0.01$) and virus ($P < 0.001$). A pair of peptides-linked sandwich fluorescence-linked immunosorbent assay showed the specificity of ZIKV ($P < 0.001$). Furthermore, it maintained the same limit of detection (1×10^4 $TCID_{50}$/mL) in the presence of human sera and urine.

Conclusion: Therefore, in silico computerized peptide aptamer can detect ZIKV in immunoassay specifically.

Keywords: Zika Virus, Peptide Aptamer, Immunoassay, Serum, Urine

S5

Immune Regulation of *Toxoplasma gondii* Used to Overcome Intractable Disease

Ji-Hun Shin[1], Sang-Gyun Kim[1], Seung-Hwan Seo[1], Jung-Pyo Yang[1], and Eun-Hee Shin[1,2]

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[2]*Seoul National University Bundang Hospital, Seongnam 13620, Korea*

Diseases that are hardly curable with the modern medical science are named by intractable disease. Among the intractable disease, Alzheimer' s disease (AD) and cancer are important disease affecting human happiness and life extension, and simultaneously it is hard to treat. These diseases are often caused by abnormal immunity and, accordingly, treated and controlled by immune regulation targeted by pathological abnormal immune response. The important immune regulation for curing AD may be an increase of the activation of microglial cells and a decrease of the inflammatory reaction in the brain. In cancer therapy, the increases in cytotoxic T cells and NK cells as well as cytotoxic reactions such as TNF-α, IFN-γ, and NO are helpful for cancer therapy. In a recent, the therapeutic approach for the intractable disease has been developed by various ways. Among them, *Toxoplasma gondii* (*T. gondii*) has been studied as an effective parasite as therapeutic agents for cancer and AD in our lab. The cause is that parasite lives in the host for a long time, interacts with host mutually, and regulate host immunity. *T. gondii* has a capacity to regulate host immunity depending on the strains of *T. gondii*. On this point, we studied on immune characterization of *T. gondii* infection in the brain using ME49 strain, and used RH strain for cancer therapy. If ME49 *T. gondii* infected to the brain, microglial cell activated to M1 phenotypes. However, NO production that are related with immunopathology and tissue damage are inhibited. These immune-regulations are very important to AD inhibition without neurodegeneration. In cancer therapy, we have been focused on *T. gondii*-derived profilin-like protein (TgPLP) inducing TLR-based IL-12 production and dense granule protein 16 (GRA16) inducing p53-dependent apoptosis. Our results demonstrated that TgPLP shows an important anti-cancer adjuvant effect and GRA16 increases the apoptosis of cancer cells by the restoration of p53 mutation. In this presentation, we are going to explain on the immune regulation of *T. gondii* for therapeutic mechanisms of intractable diseases.

Keywords: Host-parasite relationship, *Toxoplasma gondii*, Alzheimer' s Disease, Cancer, Immune Response

S6

Advanced Host-Directed Therapy for New Therapeutic Insights from the *Toxoplasma gondii*

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Host-directed therapies (HDTs) focus on ameliorating the severity of disease and improving treatment outcomes. HDTs constitute a range of therapeutic agents such as repurposed drugs, small molecules, synthetic nucleic acids, biologics (such as monoclonal antibodies), cytokines, cellular therapy, recombinant proteins, and micronutrients. The intracellular parasite *Toxoplasma gondii* has unique dense granule antigens (GRAs) that are crucial for host infection. Emerging evidence suggests that GRAs of *T. gondii* is a promising serodiagnostic marker in toxoplasmosis; however, little is known about the intracellular regulatory mechanisms involved in the GRAs-induced host responses. Herein, we found that GRAs interacts with host proteins involved in antimicrobial host defense mechanisms and mitochondria activation as a therapeutic strategy for tuberculosis, and sepsis and tumor, respectively. Taken together, by directly targeting host factors, HDTs enhance immune responses and fine-tune inflammation, and can thus be used to treat infectious and inflammatory diseases.

Keywords: *Toxoplasma gondii* GRA, *Mycobacterium tuberculosis*, Sepsis, Tumor, PKCα

S7

Neuroinflammation as a Potential Therapeutic Target: Transformation of Microglia to the Neuroprotective Phenotype

Gyun Jee Song[1,2]

[1]*Institute for Transnational Neuroscience, Incheon ST. Mary's Hospital, Incheon, 21431, South Korea;* [2]*Department of Medical Science, International ST Mary's hospital, Catholic Kwandong University, Incheon, South Korea*

Microglia are the resident innate immune cells of the central nervous system that mediate brain homeostasis maintenance. Microglia-mediated neuroinflammation is a hallmark shared by various neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and multiple sclerosis. Numerous studies have shown microglial activation phenotypes to be heterogeneous; however, these microglial phenotypes can largely be categorized as being either M1 or M2 type. Although the specific classification of M1 and M2 functionally polarized microglia remains a topic for debate, the use of functional modulators of microglial phenotypes as potential therapeutic approaches for the treatment of neurodegenerative diseases has garnered considerable attention. This presentation will review M1 and M2 microglial phenotypes and their relevance in neurodegenerative disease models, as described in recent literature. The modulation of microglial polarization toward the M2 phenotype may lead to development of future therapeutic and preventive strategies for neuroinflammatory and neurodegenerative diseases. Therefore, modulating glia-polarization using small-molecules is a potential therapeutic strategy. In our recent study, microglia-based phenotypic screening had identified several hit compounds, which inhibits LPS-induced NO production in microglia. For example, a small molecule, SNU-BP inhibited pro-inflammatory cytokines and inducible nitric oxide synthase in LPS-stimulated microglia (M1 phenotype), and potentiated interleukin-4-induced arginase-1 expression (M2 phenotype). PPAR-γ was identified as a molecular target of SNU-BP. The anti-inflammatory effect of SNU-BP was attenuated by genetic and pharmacological inhibition of PPAR-γ. In addition, SNU-BP induced an anti-inflammatory phenotype in astrocytes as well, by inhibiting pro-inflammatory NO and TNF-α, while increasing anti-inflammatory genes, such as arginase-1 and Ym-1. Finally, SNU-BP, a functional modulator of microglial phenotypes, exhibited an anti-inflammatory effect in the LPS-injected mouse brain, demonstrating a protective potential for neuroinflammatory diseases. Currently, our lab has focused on the autophagy modulators which have neuroprotective effects as well as anti-neuroinflammatory effects.

Keywords: Neuroinflammation, Microglia, Neuroprotective phenotype, Neurodegenerative Disease, M1/M2 Phenotype

항생제 내성과 차세대 치료기법 /
숙주와 병원체 상호작용의 임상적 중요성
신종 및 변종 바이러스 / 바이러스 감염과 숙주 반응

Anti-microbial Resistance and Next-generation Therapeutics
Clinical Significance of Host-pathogen Interactions
Newly Emerging and Re-emerging Viruses
Viral Infection and Host Responses

대한미생물학회 & 대한바이러스학회

일시 : 6월 29일(금) 09:00–17:55
장소 : 학생관 제2강의실 (106호)

2018 The 26th Federation Meeting of Korean Basic Medical Scientists

S8

Redirecting an Anticancer Compound to Antibiotics against Drug-resistant Bacterial Pathogens

Hye-Jeong Jang, In-Young Chung, Bi-o Kim, Eun Sook Kim, Seok-Ho Kim, You-Hee Cho*

Department of Pharmacy, College of Pharmacy and Institute of Pharmaceutical Sciences, CHA University, Seongnam, 13488, Korea

Drug repositioning is to apply known drugs and compounds to treat new indications, based on their advantage in regards to success rate and safety issues during the clinical trials. In this study, we identified a known anticancer compound (X) that exhibited weak antibacterial activity with MIC of 50 μg/ml against a hospital-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) strain. Among the congeneric compounds with different substituents at the N3 position of the X scaffold, those with short alkyl chains (e.g. c5 with a hexyl chain) displayed better solubility and more potent antibacterial activity with MIC of 3.13 μg/ml against MRSA, which is in a clinically achievable range. Their antibacterial activity against Gram-negative bacteria was evident only in the presence of the outer membrane-permeabilizing agent, polymyxin B. The antibacterial efficacy of c5 was confirmed using the *Drosophila* systemic infection model. We characterized five c5-resistant MRSA mutants to better understand the mode of action. All of these c5-resistant MRSA mutants carry mutations in the *ubiE* gene for quinone metabolism and respiratory electron transfer and subsequently exhibit reduced respiration activity. Furthermore, the antibacterial activity of c5 was abolished either by an antioxidant, *N*-acetylcysteine, or in anaerobic condition. This suggests that the antibacterial mechanism involves reactive oxygen species (ROS) presumably generated during respiratory electron transport. The present study provides an insight into "drug redirecting" based on an ROS-generating pharmacophore, which can be accomplished by chemical modifications for selective entry into the target cells.

Keywords: MRSA, Gram-positive, Antibacterial, Drug-repurposing, Drug-redirecting

S9

Enhancement of Intracellular Survival of *Brucella abortus* in Professional Phagocytes, RAW264.7cells, by Mutagenesis of BruA2_1031 gene

Myunghwan Jung[1], Soo Jin Shim[2],Young Bin Im[2], Woo Bin Park[2], and Han Sang Yoo[2]*

[1]*Department of Microbiology, Research Institute of Life Sciences, Gyeongsang National University School of Medicine;*
[2]*Department of Infectious Diseases, College of Veterinary Medicine, Seoul National University*

Since recognizing the interaction between *Brucella* and host cells is crucial to the elucidation of the infectious process, priority tasks in *Brucella* researches is investigation of genes related to pathogenicity. To demonstrate the roles of *Brucella* genes, RAW 264.7 cells were infected with the *Brucella abortus* wild-type and mutant strains (generated using transposon mutagenesis), after which the different transcriptional responses of the infected cells were determined using microarray.Following infection, enhanced strategies for intracellular survival, such as down-regulation of genes associated with cytokine responses and apoptosis, were observed in RAW 264.7 cells infected with C3 mutant strain, when compared to the transcriptional responses of wild-type infected cells. The mutation site of C3 mutant strain was determined as the ATP-binding cassette transporter permease (BruAb2_1031) using sequence analysis. These results were evidenced by an increased level of intracellular survival of the C3 mutant strain. Our results indicate that the BruAb2_1031 gene might be closely related with intracellular survival of *B. abortus* in RAW 264.7 cells.

Keywords: BruAb2_1031 gene, Intracellular survival, *Brucella* mutant, *Brucella abortus*

S 10

The Hepcidin-Ferroportin Axis Controls the Iron Content of Salmonella-Containing Vacuoles in Macrophages

Daejin Lim[1,2], Kwang Soo Kim[1,2], Jae-Ho Jeong[1,2], Hyun-Ju kim[1,2], Miryoung Song[1,2], Hyon E. Choy[1,2]

[1]Department of Microbiology, Chonnam National University Medical School, Gwangju, 61468, Republic of Korea, [2]Department of Molecular Medicine (BK21plus), Chonnam National University Graduate School, Gwangju, 61468, Republic of Korea

Macrophages release iron into bloodstream via the membrane-bound iron export protein, ferroportin (FPN). The hepatic iron-regulatory hormone hepcidin controls FPN internalization and degradation in response to bacterial infection. *Salmonella typhimurium* is capable of invading macrophages and proliferating in the *Salmonella*-containing vacuole (SCV). Hepcidin is reported to increase the mortality of *Salmonella*-infected animals by increasing the bacterial load in macrophages. Here, we assess the iron levels and find that hepcidin increases iron content in the cytosol but decreases it in the SCV through FPN on the SCV membrane. Loss of FPN from the SCV via the action of hepcidin impairs the generation of bactericidal reactive oxygen species (ROS) as the iron content decreases. We conclude that FPN is required to provide sufficient iron to the SCV, where it serves as a cofactor for the generation of antimicrobial ROS rather than a nutrient for *Salmonella*.

Keywords: Salmonella typhimurium, Hepcidin, Ferroportin, Iron, Reactive Oxygen Species

S11

Stem Cells and Dengue Virus Infections

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Dengue is one of the most troublesome mosquito-borne human viral diseases in the world. The disease mainly affects tropical and subtropical temperate zone, where dengue is year round and high percentage of populations are infected by the dengue virus (DENV) based upon the serological studies. Although preventive dengue vaccine has been licensed, the limited efficacy and possible dire consequences in vaccinated subjects resulting in the world-wide vaccination has been put on hold. Mosquitoes play important role in the spread of DENV, however, escalating reports on other routes of transmission, such as mother-to-baby vertical transmission (so called congenital dengue), blood transfusion, stem cells and organ transplantations, have been documentedin recent years, suggesting that DENV may have a capacity of staying in human body for a period without induction of clinical symptoms. Our recent report suggests that the frequency of asymptomatic DENV infection is estimated at 1 per 1000 people in a community and local community survey has identified a few asymptomatic subjects with high viral titers circulating in peripheral blood. Furthermore, recent report through model analysis indicates that asymptomatic or inapparent DENV infection accounting for 80% of transmission. With the intensified frequency of human migrations and the convenience of air travel nowadays, DENV can be disseminated into a country without border in no time, enhancing the dilemma of and threaten in public health control globally. This presentation summarizes and highlights some important issues regarding the role of stem and/or progenitor cells in dengue pathogenies during acute phase and its significance in asymptomatic infected individuals, whether persistent or latent infections, who may pave a new avenue in dissemination of the DENV globally without borders, and to whom the challenging tasks of public health regarding disease control. Theoutcomes of the current presentation suggest that DENV can evade human immune system and cohabitate with its host peacefully,and that a new challenge path in prevention and control measure to mitigate the cycling pattern of DENV outbreak is warranted.

Keywords: Stem cells, dengue virus, Flaviviruses, asymptomatic infections, persistent and/or latent infections

S 12

Development of DNA Vaccine Candidates against Severe Fever with Thrombocytopenia Syndrome (SFTS)

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Severe Fever with Thrombocytopenia Syndrome (SFTS) is a new emerging tick-borne disease caused by the phlebovirus, SFTS virus (SFTSV). SFTSV is a member of the order Bunyavirales, family Phenuiviridae, Phlebovirus genus that was discovered in central China in 2009 and has since been identified in both South Korea and Japan. SFTS has a fatality rate of 12% and as high as 30% in some areas, and the major clinical symptoms of SFTS are fever, vomiting, diarrhea, multiple organ failure, thrombocytopenia, leukopenia and elevated liver enzyme levels. However, there are no licensed vaccines approved for human use. Here, we developed vaccine candidates for SFTS using DNA vaccine-based platform, and we examined the immunogenicity and the protective efficacy. SFTS DNA vaccine candidates induced multifunctional SFTSV-specific CD4 and CD8 T cell response as well as cross-reactive neutralizing antibody response. Immunization with vaccine candidates conferred full protection against lethal challenge with non-homologous SFTSV. This study provides a new insight into the development of an effective SFTS vaccine.

Keywords: SFTS, DNA Vaccine, Protective Immunity, Antibody, T cell

S13

Neuraminidase Inhibitor Resistance Markers among Avian Influenza Viruses N3~N9 subtypes

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Several subtypes of avian influenza viruses (AIVs) are emerging as novel human pathogens, and the frequency of related infections has increased in recent years. Although neuraminidase (NA) inhibitors (NAIs) are the only class of antiviral drugs available for therapeutic intervention for AIV-infected patients, studies on NAI resistance among NA subtypes of AIVs other than N1 and N2 have been limited, and markers of resistance are poorly understood. Here, we screened NAI resistance substitutions in NA genes of group 1 (N4, N5, and N8) and 2 (N3, N6, N7, and N9) and identified NA substitutions that confer NAI resistance using gene-fragmented random mutagenesis method. We generated libraries of NA mutant influenza viruses in the genetic background of A/Puerto Rico/8/1934 (H1N1) virus using reverse genetics (RG) and selected resistant variants in the presence of the NAIs, oseltamivir carboxylate (OS) and zanamivir (ZA), in MDCK cells. All of 72 substitutions found via OS and ZA screening were evaluated for susceptibility to available NAIs including OS, ZA, peramivir, and laninamivir. In addition, two substitutions, H274Y and R292K (N2 numbering), were introduced into each NA gene for comparison. We identified three categories of NA substitutions associated with reduced inhibition by NAIs (oseltamivir, zanamivir, and peramivir): (i) novel subtype-specific substitutions in or near the enzyme catalytic site (G/N147V/I, R152W, A246T, A246V, D293N, and I427L N2 numbering), (ii) subtype-independent substitutions (E119G/V and/or D and R292K in group 2), and (iii) substitutions previously reported in other subtypes (Q136K, I222M, R371K and E276D). Our data show that although some markers of resistance are present across NA subtypes, other subtype-specific markers can only be determined empirically. Therefore, knowledge of these substitutions in AIVs is important in facilitating antiviral susceptibility monitoring of NAI resistance in AIVs.

Keywords: Avian influenza virus, Neuraminidase inhibitor resistance, Random mutagenesis, N3~N9

S 14

진드기 매개 감염질환의 임상양상
Vector-borne Infectious Diseases

김동민

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감염병 중 모기, 진드기등 어떠한 매개체 혹은 숙주를 통해 사람에게 감염이 되는 것을 매개체 감염병 이라고 한다. 매개체감염병의 발생 원인은 다양하다. 기후변화에 의한 매개체 분포와 정도, 인간과 조류 및 야생동물의 이동과 분포, 숙주 밖에서의 병원체의 생존기간 등도 감염병 발생의 주요한 요인으로 지목되고 있다. 매개체 감염병(vector-borne infection)은 인간과 모기, 진드기, 물 등 미생물간의 직접적인 접촉(상호관계)를 통해서 발생하는 각종 질환을 말하며, 모기, 진드기 등과 같은 미생물 매개체는 세균, 바이러스 등과 같은 병원체와 숙주간의 오랜 기간에 걸친 상호 공생과 진화의 결과이다.

매개체 감염병의 발현과 전파는 지구온난화 등과 같은 기후변화와 교통수단의 발달로 인한 잦은 해외교류등과 밀접한 연관이 있는 것으로 밝혀졌다. 지구온난화(global warming)는 매개체 발생 및 서식 환경에 직접적으로 영향을 주고 있다. 이러한 기후 · 환경변화, 국제교류 및 여행객 증가 등으로 인하여 다양한 신종 감염병(지카바이러스. 에볼라바이러스, 중증열성 혈소판감소 증후군, 웨스트나일열 및 아나플라즈마증 등)들이 국제적으로 확산되고 있고 발생 빈도 또한 점차 증가 추세이다. 쯔쯔가무시병 이외의 매개체 감염병은 제4군감염병에 해당하는 질환이 대부분으로 과거에는 내국인의 국외 체류 중 감염된 경우가 대부분이었으며, 발생 환자 신고 수도 미미한 편이었으나 온난화로 인한 한반도 아열대화는 신종 매개체 서식이 가능 국외 유입 매개체 감염병의 한반도 토착화 및 풍토병화 등의 유행으로 이어질 가능성이 높아지고 있다. 한국은 기후변화가 가장 빠른 국가이며, 다양한 진드기 매개체가 전국에 널리 분포하고 있으므로 매개체 관련 감염병의 빠른 확산의 가능성이 크다.

모기 등이 매개체인 말라리아(malaria), 뎅기열(dengue fever), 치쿤구니야열(chikungunya fever)와 웨스트 나일열(west nile fever), 털 진드기가 매개체인 쯔쯔가무시증(scrub typhus), 참진드기가 매개체인 라임병(lyme disease)과 아나플라즈마증(anaplasmosis), 중증열성 혈소판 감소 증후군 (Severe fever thrombocytopenia syndrome)등이 있으며, 우리나라에서 가장 빈번하게 발현되는 매개체 감염병인 쯔쯔가무시병도 환자 발생이 점차 증가하여 매년 만명가량의 환자가 질병관리본부에 보고되고 있고, 중증열성 혈소판 감소 증후군, 아나플라스마증(anaplasmosis)등의 매개체 감염병이 2013년 보고된 이후 지속적으로 환자보고가 증가하고 있다. 기존에 우리나라에서 자체 발생이 보고되지 않은 뎅기열(dengue fever), 웨스트 나일열이나 진드기 매개체 뇌염은 향후 유입가능성이 크다는 점에서 이에 대비한 적극적인 감시 및 준비가 필요하다.

이번 강좌에서는 우리나라에서 발생하고 있는 매개체 감염병 특히 진드기 매개 감염병의 임상적 특징에 대해 이야기하고자 한다.

Keywords: 쯔쯔가무시병, 라임병, 아나플라즈마증, 중증열성 혈소판 감소 증후군

S15

Cytosolic Receptor Nod2 in Infectious Diseases

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Nod-like receptors (NLRs) are intracellular, cytoplasmic sensor for microbial components and danger signals. There are 23 NLR family members in humans and at least 34 genes in mice. NLRs are expressed in nonimmune cells including epithelial cells and mesothelial cells as well as immune cells. As first identified NLRs, Nod1 and Nod2 consist of N-terminal caspase recruitment domain (CARD), intermediate nucleotide-binding oligomerization domain (NOD), and C-terminal leucine-rich repeats (LRRs) domain. Nod1 and Nod2 recognize peptidoglycan derivatives, meso-diaminopimelic acid (meso-DAP) and muramyl dipeptide (MDP), respectively. After stimulated by their specific bacterial molecules, Nod1 and Nod2 associate with its adaptor molecule, RICK/Rip2/CARDIAK, through CARD-CARD interaction, which leads to activation of NF-κB and MAPK, followed by induction of numerous genes involved in inflammatory process. In this session, I will present a recent work about the role of Nod2 in host defense against *Mycobacterium abscessus* infection.

Keywords: Nod-like receptor (NLR), Nod2, RICK, *Mycobacterium abscessus*

S16

Role of the Microbiota and Its Potential in Mucosal Vaccination

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The role of symbiotic bacteria in the development of antigen-specific immunity remains poorly understood. We showed that the microbiota is critical for inducing antigen-specific IgG production after mucosal immunization. After nasal immunization with antigen and cholera toxin (CT), both antibiotic-treated and germ-free (GF) mice had reduced amounts of antigen-specific IgG, smaller recall-stimulated cytokine responses, impaired follicular helper T (T_{FH}) cell responses and reduced numbers of plasma cells. Recognition of symbiotic bacteria via the nucleotide-binding oligomerization domain containing 2 (Nod2) sensor in cells that express the integrin CD11c (encoded by Itgax) was required for the adjuvanticity of CT. Reconstitution of GF mice with a Nod2 agonist or monocolonization with *Staphylococcus sciuri*, which has high Nod2-stimulatory activity, was sufficient to promote robust CT adjuvant activity, whereas bacteria with low Nod2-stimulatory activity did not. Mechanistically, CT enhanced Nod2-mediated cytokine production in dendritic cells via intracellular cyclic AMP. These results show a role for the microbiota and the intracellular receptor Nod2 in promoting the mucosal adjuvant activity of CT. To extend these findings to oral vaccination, we examined the role of the microbiota in the adjuvant activity of CT after immunization via the oral route. In brief, like nasal immunization, our results indicated that Nod2 stimulation by symbiotic bacteria contributes to optimal CT-mediated antigen-specific oral vaccination through the enhanced production of IL-1β.

Keywords: Cholera Toxin, Microbiota, Nod2, Vaccination, IL-1β

S17

A Hepatitis B Virus-interacting Protein Selectively Regulates IRE1α and Protects Tumor Cells from ER Stress-induced Cell Death

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Unfolded protein response (UPR) is an adaptive mechanism that aims at restoring ER homeostasis under severe environmental stress. Malignant cells are resistant to environmental stress, which is largely due to an activated UPR. However, the molecular mechanisms by which different UPR branches are selectively controlled in tumor cells are not clearly understood. Here, we identified a novel hepatitis B virus (HBV)-interacting protein and provide evidence that it functions as a novel regulator for selective activation of the IRE1α branch of UPR. ER stress?triggered autophosphorylation and oligomerization of IRE1α requires its interaction with this protein. It contributes to the induction of tumor-promoting factors and to tumor resistance to ER stress-mediated cell death. Increased levels of this protein in various tumor tissues arepositively correlated with the expression of XBP1-target genes. Taken together, our data provide a molecular rationale for selective activation of the IRE1α branch by a HBV-interacting protein in tumors and adaptation oftumor cells to severe environmental stress.

Keywords: Hepatitis B virus, Unfolded protein response, ER stress, IRE1

S 18

Role of Nucleoprotein in the Pathogenesis of Influenza Virus

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Interaction between viral and host proteins plays an important role in the life cycle of viruses. Although influenza virus NS1 protein is well known to suppress a host immune response by inhibiting type I interferons, little has been demonstrated regarding the interaction of other influenza virus proteins with the host. In this study, we showed that influenza virus nucleoprotein (NP) contributes the pathogenesis of influenza virus by stimulating the innate immune system. Recombinant NP induced inflammatory cytokines and chemokines such as IL-6, keratinocyte chemoattractant, and IP-10 from bone marrow-derived macrophages via Toll-like receptors (TLR) 2 and 4. This activity was dependent on the self-oligomerization of NP monomers. In addition to TLR stimulation, NP activated NLRP3 inflammasome and caspase-1, resulting in IL-1beta secretion. When the mice were pre-treated with recombinant NP intranasally, the pathogenesis increased upon subsequent viral infection. The group injected with anti-NP serum after influenza virus infection, the levels of inflammatory cytokines, viral titer, and lethality significantly decreased. These results indicate that NP is closely involved in enhancing the pathogenesis of influenza virus through innate immune stimulation, suggesting that neutralization or inhibition of NP could be a new therapeutic strategy against the influenza virus.

Keywords: Influenza, Nucleoprotein, Toll-like receptor, Inflammasome, Pathogenesis

S19

Insights into Varicella Zoster Virus (VZV)-mediated Innate Immune Evasion Mechanisms

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Varicella Zoster Virus (VZV) is a human-restricted α-herpesvirus, which causes varicella (chickenpox) in its primary infection and zoster (shingles) upon reactivation following viral latency. Recently, several studies analyzed mutations found in several vaccine strains of VZV and 24 vaccine-type mutations were identified, including non-synonymous mutations in ORFs 0,6,31,39,55,62,and 64. In this study, we characterized VZV host receptors and downstream signaling pathways responsible for the antiviral innate immune response in the skin and VZV-mediated immune evasion mechanisms. Here, we show that stimulator of interferon genes (STING) mediates an important host defense against VZV infection in dermal cells including human dermal fibroblasts (HDFs) and HaCaT keratinocytes. Inhibition of STING using small interfering RNA (siRNA) or short hairpin RNA (shRNA)-mediated gene disruption resulted in enhanced viral replication but diminished IRF3 phosphorylation and induction of IFNs and pro-inflammatory cytokines. Pre-treatment with STING agonists resulted in reduced VZV glycoprotein E (gE) expression and viral replication. Additionally, we examined whether VZV virulence factors would interact with STING. VZV ORF39, which is an integral membrane protein localized in Endoplasmic Reticulum (ER), co-localizes with STING and co-immunoprecipitates with STING. Moreover, ORF39 overexpression modulates STING-mediated activation of type I and III IFN signaling pathways. Therefore, we propose an important insight into how VZV ORF39 can modulate STING-mediated induction of type I and III IFNs and subsequent antiviral signaling pathways.

Keywords: Varicella Zoster Virus (VZV), STING, Interferon (IFN), Vaccine-type mutations

S 20

CMV and Immunosenescence: Relevance to Cardiovascular Diseases

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Immunosenescence, defined as the age-associated dysregulation and dysfunction of the immune system, ischaracterized by impaired protective immunity and decreased ef?cacy of vaccines. Immunosenescence affects both the innate and adaptiveimmune systems; however, the most notable changes are inT cell immunity and include thymic involution, the collapse of T cell receptor (TCR) diversity, an imbalance in Tcell populations, and the clonal expansion of senescent Tcells. An increasing number of immunological, clinical and epidemiological studies suggest that persistent Cytomegalovirus (CMV) infection is associated with accelerated aging of the immune system and T cell immunosenescence especially. T cell responses to CMV are restricted to a limited number of immunodominant epitopes, as compared to responses to other chronic or persistent viruses. This response results in progressive, prolonged expansion of CMV-specific T cells, termed ‘memory inflation’. The expanded CMV-specific T cell population is extraordinarily large and is more prominent in the elderly. CMV-specific senescent T cells have the ability to produce largequantities of proinflammatory cytokines and cytotoxicmediators; thus, they have been implicated in the pathogenesis of many chronic inflammatory diseases. Recently, an increasing body of evidence has suggested thatsenescent T cells also have pathogenic potential in cardiovascular diseases, such as hypertension, heart failure,and myocardial infarction, underscoring the detrimentalroles of these cells in various chronic infiammatoryresponses. In this presentation, we will discuss thegeneral features of age-related alterations in T cell immunity and the possible roles of CMV induced T cellsenescence in thepathophysiology of cardiovascular disease.

법의학과 의료사고

Forensic Medicine and Medical Misadventure

대한법의학회

일시 : 6월 29일(금) 09:00-17:45

장소 : 교육관 강당 (401호)

2018 The 26th Federation Meeting of Korean Basic Medical Scientists

S21

의료사고의 판례 경향

노태헌

인천지방법원 부천지원

의료소송은 고도의 전문적 지식을 필요로 하는 분야에서 발생한 사고를 다루는 것으로서, 환자는 의료행위의 자세한 내용을 잘 모르고, 의사에게는 치료방법의 선택에 있어서 재량이 많이 주어지며, 증거도 의사에게 편재되어 있는 등의 특수성이 있다. 이에 대법원은 판례법리를 통하여 과실이나 인과관계의 증명책임을 완화하였고, 이러한 증명책임 완화 법리는 점점 구체화되어 비교적 합리적인 증명책임 완화 법리가 정리되었다. 예를 들어, 이미 잘 알려져 있는 합병증이 발생한 경우에도 의료소송상 과실 추정 법리를 적용할 수 있는지, 구체적으로 어떤 방식으로 과실을 인정할 것인지, 간접사실을 통하여 과실이나 인과관계를 추정할 수 있는 요건이나 추정의 한계 등에 관하여 구체적인 판례들이 나오고 있다. 이번 발표에서는 판례를 통하여 구체화된 증명책임 완화 법리에 대하여 소개하고, 여러 명의 의료인이 의료에 관여하는 경우 개별 의료인의 책임을 어떻게 인정하고 분배하는지에 관하여 법리를 소개하며, 진료기록의 변조가 인정되는 경우, 감정결과가 모순되는 경우, 하나의 감정결과 가운데 일부가 모순되는 경우에 이러한 상황이 과실이나 인과관계를 판단할 때 어떻게 작용하는지와 감정결과의 증명력 등에 관하여 발제하고자 한다.

Keywords: 의료소송, 과실, 인과관계, 증명책임, 판례, 감정

S22

사망환자의 의료사고 감정

박형천

한국의료분쟁조정중재원

한국의료분쟁조정중재원(이하 중재원)은 2012년 4월 개원 이후 의료사고에 대한 감정만을 전문적으로 수행하고 있으며 최근 5년간(2013.1.1.~2017.12.31.)의 통계연보를 발간하였다. 중재원의 의료사고 감정은 분쟁 조정을 위한 감정(조정중재감정)과 공공 기관으로부터 위탁 받는 수탁감정의 2가지 형태로 진행하고 있다. 위 기간 동안 조정중재감정은 총 4,143건으로 이중 사망에 따른 분쟁은 843건, 약 20.3%를 차지하고 있으며, 이중 부검이 이루어진 경우는 약 75건(약 9%)에 불과하였다. 연도별로는 사망 건수는 2013년 78건, 2014년 ~ 2016년 사이는 130건 미만이었으나 2017년은 388건으로 갑자기 증가하였으며, 이는 자동개시의 영향이 있었던 것으로 추정된다. 사망환자의 사인을 분석하기 위하여는 부검감정서가 매우 중요한 역할을 담당한다. 그럼에도 아직도 낮은 부검율은 사인과 의료사고의 인과 관계 여부에 대한 임상적 판단을 어렵게 하는 원인이다. 수탁감정의 경우는 위 5년간 총 2,264건중 사망 건은 922건으로 약 40.7%로 비율로는 조정중재건의 2배 가량을 차지하고 있고, 평균 부검 역시 410예로 부검율은 약 44%로 부검감정서가 작성되었다. 수탁감정의 의뢰기관으로는 사망건의 경우 경찰서가 가장 높은 의뢰기관으로 이는 초등 수사단계부터 부검 감정의 중요도를 인식하고 있다고 볼 수 있다. 사망건의 조정중재의 경우 진료과로는 산부인과(27예), 내과(23예), 외과(10예), 정형외과(6예)의 순이며, 수탁감정의 경우 내과(87예), 정형외과(50예), 산부인과(44예), 외과(38예), 응급의학과(23예)순이었다. 사망 환자의 의료사고의 인과관계여부는 사망에 이르기까지의 의료행위에서의 과실여부를 판단하는 것으로 부검감정의 결과가 결정적인 단서를 제공하는 것은 분명하다. 그러나 부검에도 불구하고 사인이 규명되지 않는 경우(약 4례의 조정중재감정)와 사인을 일으키는 임상과정이 고려되지 않은 부검 결과는 논란의 여지가 있으며, 특히 여러 장기가 사망의 원인이 되는 경우, 사망의 주원인에 대한 논란이 여전히 존재한다.

Keywords: 의료분쟁조정원, 조정중재감정, 수탁감정, 부검율, 사망

S23

의료사고의 민사적 해결

유현정

나음법률사무소

병원치료 중 의료분쟁이 발생한 경우 민사적 해결절차에는 당사자에 의한 합의, 조정/중재, 소송절차가 있다. 합의절차는 분쟁 당사자가 서로 양보하여 분쟁을 종결할 것을 약속하는 절차이고, 소송절차는 재판에 의하여 분쟁을 법률적으로 해결하는 절차이다. 조정/중재 절차는 시간과 비용이 많이 드는 소송절차에 비하여 간이하게 분쟁을 종결시키는 대체적 분쟁해결제도이다. 의료분쟁, 특히 사망사고의 경우에는 당사자간 감정의 골이 깊어진 상태로 사실상 합의가 쉽지 않은 경우가 많다. 소송절차, 즉 의료분쟁으로 민사소송을 제기할 경우 1심 판결까지 수백만 원의 비용과 평균 2년이 넘는 기간이 소요되는 반면, 대체적 분쟁해결제도인 조정과 중재절차를 이용할 경우 시간과 비용을 크게 단축하여 매우 효율적으로 분쟁을 종결할 수 있다. 우리나라의 의료분쟁에 관한 대체적 분쟁해결제도로는 한국의료분쟁조정중재원의 조정과 중재절차, 한국소비자원의 소비자분쟁조정위원회가 대표적이다. 한국의료분쟁조정중재원의 경우 조정절차는 일정한 자격을 갖춘 조정위원에 의한 조정절차 진행 후 양당사자 모두 조정결정에 동의할 때에는 재판상 화해와 동일한 효력이 있고, 중재절차는 당사자 쌍방이 합의한 중재인의 중재에 대한 판정으로 분쟁을 종결하는 절차로 확정판결과 동일한 효력이 있다. 한국소비자원의 경우 조정이 성립되면 조정서의 내용은 재판상 화해와 동일한 효력이 있다. 사망사고가 발생하여 부검이 이루어진 경우 민사적으로 병원과 유족과의 손해배상이 문제되는데, 손해배상책임 성립과 관련하여 부검결과가 의료진의 과실이나 의료행위와 환자의 사망 사이에 인과관계가 있는지 여부 판단에 중요한 역할을 하게 된다. 또한 의료진의 과실로 인하여 환자가 위중한 상태에 빠지게 되어 고가의 치료를 받던 중 사망하게 된 경우에는 국민건강보험공단의 의료기관에 대한 구상권 청구가 문제되고, 실제로 구상권 청구는 크게 증가하고 있는 추세이다. 국민건강보험공단뿐 아니라 국민연금공단에서도 유족연금을 지급한 경우 의료기관에 구상권을 청구하고 있다. 보험회사의 경우 통상 '의료진의 과실에 기한 의료사고는' 상해사고에 포함시키지 않고 보험금 지급을 거절하는 것이 실무였다. 의료사고와 직접적인 관련성은 낮은 편이나 자살에 의한 사망의 경우, 보험 가입 후 2년이 지나면 자살보험금을 지급한다는 약관에도 불구하고 보험회사가 자살보험금 지급을 거절하여 그에 대한 대법원 판결 및 금융감독원의 제재가 논란의 대상이 되었는바, 각 사례를 통해 이해를 돕는다.

Keywords: 의료분쟁, 합의, 조정, 중재, 소송, 손해배상, 과실, 인과관계, 구상

S24

의료사고에 대한 새로운 접근

이호

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한국의료분쟁조정중재원에 따르면 연 평균 10000건 이상의 의료사고가 발생하고 있다고 한다. 현재 의료분쟁조정중재원, 소비자보호원, 법원 등을 통해 의료사고에 대한 원인, 의료행위와의 인과관계, 과실여부 등을 입증하고 이에 대한 분쟁해결을 하고 있다. 그러나 의료는 매우 전문적인 분야로서 사고의 책임을 규명하는데 매우 어렵고, 해결과정에 상당한 시일이 소요된다는 점, 행위자-피해자(가족) 사이만의 법적 책임 규명으로만 그친다는 점 등과 함께 당사자간의 분쟁 해결이 아닌 제3자에 의한 해결이라는 점 등 여러 가지 현실적 한계로 인해 많은 문제점들이 노정되어 왔다. 의료사고가 고의성 없는 사고라는 관점과 의료현장에서 환자안전의 증진이라는 관점에서 접근하여, 과실여부, 인적/구조적 원인에 대한 분석, 사전 예방가능성 여부, 재발방지를 위한 교정을 위한 방편 마련의 책임성, 잠재된 위험요소 파악 등을 종합적으로 판단하는 해당 병원내 전문적 기구가 필요하다고 판단한다. 이를 위해 전북대학교병원 고객지원실의 운영실태에 대한 보고와 함께 독립성과 전문성, 신속성, 책임성이 담보될 수 있는 병원내 옴브즈만 형태의 기구의 필요성과 효율성, 가능성에 대해 종합적으로 모색하고자 한다..

Keywords: 의료사고, 의료분쟁, 해결

S25

의료사고 관련 부검 현황

박재홍, 박소형, 하홍일, 최인석, 유택균, 최병하, 이봉우, 최영식

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의학과 의술의 발달로 인해 의료행위가 다양하고 복잡해지면서 의료사고의 발생도 증가할 개연성이 있으며, 또한 일반인의 의학 지식과 국민의 권리의식이 신장됨에 따라 의료분쟁 발생의 가능성도 커지고 있다. 특히 환자의 사망을 초래하는 의료사고는 전체 의료사고 중 일부에 불과하지만, 환자 자신과 가족, 의료인 그리고 사회 전체적으로 미치는 영향은 매우 크다. 이에 저자들은 국립과학수사연구원에서 시행된 부검 중 의료행위와 관련된 사망 사례들을 분석함으로써 그 특징을 파악하고자 하였다. 2013년부터 2017년까지 5년간 국립과학수사연구원에서 시행된 부검 중 의료 관련 사건으로 집계된 사례는 총 572예였는데, 그 중 남성이 294예(51.4%), 여성이 278예(48.6%)였으며, 연령대별로는 10세 미만이 35예(6.1%), 10대가 14예(2.4%), 20대가 26예(4.5%), 30대가 44예(7.7%), 40대가 84예(14.7%), 50대가 117예(20.5%), 60대가 116예(20.3%), 70대가 99예(17.3%), 80대가 35예(6.1%), 90대가 2예(0.3%)였다. 사망의 발생과 직접 관련된 상황이나 의료행위를 유형별로 분석한 결과, 수술 또는 수술을 위한 마취 중 사망이 243예(42.5%), 수술 이외의 진단 및 치료처치 중 사망이 92예(16.1%), 약물과 관련된 사망이 49예(8.6%), 임신 및 분만과 관련되어 발생한 모성의 사망이 11예(1.9%), 신생아의 사망이 13예(2.3%), 침대에서의 낙상 등 병원 내 환자관리상의 문제로 인한 사망이 18예(3.1%), 기타 146예(25.5%) 등이었다.

Keywords: 의료사고, 부검

S 26

의료사고에서 법의학의 역할

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의료는 형식적으로 의사와 환자사이에서 일어나는 행위이지만, 사회 전체적으로 볼 때 여러 제도적인 사항들이 밀접하게 연결되어 있다. 한편 우리 사회가 발전해 감에 따라 사람의 권리에 대한 인식은 점점 더 강화되는 경향이며, 최근 의료의 영역에서도 이러한 움직임은 뚜렷하다. 소위 환자안전법의 시행이나 의료분쟁에서 조정중재원의 역할 확대 등은 이러한 경향을 반영하고 있다. 사람의 권리를 보호한다는 법의학의 학문적 소명뿐만 아니라 사망원인의 구명을 포함하여 여러 사실들을 밝히는데 의료사고에서 법의학의 역할을 매우 중요하다. 의료사고는 여러 측면에서 원만하게 해결하는 것이 환자나 의료진뿐만 아니라 사회적인 관점에서도 중요함에 비해, 우리 사회에서는 아직도 다양한 논란의 원인이 되곤 한다. 단순히 제도적인 문제가 있을 뿐만 아니라 이를 해결하는데 유능한 인력들이 충분하지 않은 것도 하나의 이유라고 생각한다. 법의학의 관점에서 의료사고를 다시 한번 조명해 보고, 전문적인 영역으로서 법의학의 역할을 다시 한번 생각해 보고자 한다.

Keywords: 의료분쟁, 의료사고, 법의학

S 27

우리나라 사망진단서 서식의 변천 과정과 개선의 필요성

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죽음을 증명하는 문서는 우리나라에서 시체검안서와 사망진단서라는 두 가지 이름으로 발급되고, 의료법시행규칙에 그 서식이 정해져 있다. 일본에도 시체검안서가 있는 반면, 영미권에서는 시체검안서라는 이름은 존재하지 않는다. 시체검안서를 만든 이유는 정확히 알려져 있지 않다. 우리나라에서는 일제강점기부터 시체검안서는 사망진단서와 동일한 서식으로 존재했다. 광복 이후 1951년 국민의료법이 제정될 때에도, 1962년 의료법이 제정되면서 의료법시행규칙이 마련되면서 사망진단서(시체검안서) 서식이 마련되었다. 의료법시행규칙의 개정과 더불어 사망진단서(시체검안서) 서식도 몇 차례의 큰 변화가 있었다. 사망진단서 서식의 제일 큰 변화는 사망의 원인과 사망의 종류 란이다. 일정한 서식이 있으면 서식에 맞는 작성 원칙이 있어야 하고, 이에 대한 교육도 있어야 한다. 역사적으로 법의학에서의 사망진단서 작성에 대한 교육은 불충분했고, 지금도 사망진단서 작성의 오류는 낯부끄러운 실정이다. 대한의사협회에서 마련한 사망진단서 작성 원칙 매뉴얼 때문에 교육이 활성화 된 것은 그나마 다행한 일이다. 시체검안서라는 이름의 서식이 정말 필요한 것인지에 대한 고찰은 필요하며, 사망진단서 서식도 크게 개선이 필요한 부분이 있다. 서식 변천의 역사적 변화 과정을 고찰하고, 새로운 서식의 개선을 제안한다.

Keywords: 사망진단서, 시체검안서, 역사, 법의학, 교육

S28

사망진단서 개선을 위한 제언

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사망진단서에 대한 작성원칙이 여러 경로를 통해 알려져 있음에도 불구하고, 아직도 많은 사망진단서가 다양한 유형의 오류를 지닌 채 발급되고 있다. 사망진단서는 단순히 하나의 문서로 끝나는 것이 아니라 망자 본인과 유족, 관계기관, 사회, 그리고 국가에 이르는 여러 대상에 적지 않은 영향을 미친다는 점에서 더욱 많은 관심과 노력이 필요하다. 그러나 의사 개인의 노력과 더불어, 사망을 다루는 사회 구성원들 역시 사망진단서에는 작성 주체나 작성 시점에 따른 필연적인 한계가 있음을 이해하고 이러한 한계를 적절히 해석하는 것에 관심을 가질 필요가 있다. 사망을 잘 관리할 수 있도록 관련 제도에 우리나라의 고유한 의료환경을 반영하는 것도 중요하다. 이를 위해서는 먼저 현재 형식상 차이가 없는 사망진단서와 시체검안서의 서식이 서로 구분되도록 조정하고, 특히 시체검안서의 경우에는 이를 작성할 수 있는 자격을 구체적으로 설정하여야 한다. 또한 유족 개인에게 맡겨져 있는 사망신고 의무를 제3자의 공적인 업무로 전환하는 것 역시 국가 사망관리체계의 보완에 도움이 될 수 있겠다.

S29

탄소 동위원소 분석을 통한 백골화 골격의 연대추정 사례 보고

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백골화 골격이 발견된 경우 변사자의 신원확인은 수사기관의 주요 관심사 중 하나이며, 신원확인을 위해 현재 유전자 검사, 법의인류학적 감정 및 법치의학적 감정이 실무에 활용되고 있다. 이에 더하여 백골화 골격의 연대추정을 위해 탄소 동위원소 분석을 활용한 연구가 진행 중이며, 이를 통해 백골화 골격의 출생연도 및 사망연도에 대한 정보를 확인할 수 있다. 아직 실무에 적용하기는 부족한 수준이나, 최근 탄소 동위원소 분석을 이용한 백골화 골격의 연대추정을 통해 수사상 필요한 정보를 제공한 사례가 있어 이에 대해 보고하고자 한다.

2017년 6월 강원도 속초시의 공사현장에서 약 1000 여점의 유골이 발견되어 국립과학수사연구원에 의뢰되었고, 이들 유골에 대해 법의인류학적 감정 및 법치의학적 감정이 시행되었다. 가장 많은 골격은 오른넙다리뼈로 총 29점이었고, 이중 넙다리뼈 머리와 몸통이 모두 채취가 가능한 골격은 7점이었으며, 이에 대해 연대추정을 위한 검체를 채취하였다. 아래턱뼈는 모두 10점으로 이중 아래턱 첫째큰어금니의 채취가 가능한 경우는 5점이었다. 이들 검체에 대해 탄소동위원소 분석이 시행되었고, 그 결과 모든 검체는 1950년 이전으로 결과가 분석되었고, 출생연도 및 사망연도도 다양하게 나타났다. 수사기관에서 제공된 정보에 따르면 골격이 발견된 장소는 1950년대에 공동묘지로 사용된 장소였거나 1968년에 해일이 발생하여 다수의 사망자를 매장한 장소일 가능성이 있다고 하였고, 분석결과에 따르면 1950년대 이전부터 존재하던 공동묘지에서 발견된 유골일 가능성이 높은 것으로 추정되었다.

탄소동위원소분석을 통한 백골화 골격의 연대추정은 다양한 분야의 전문가들이 참여해야 하는 연구이며, 연령 및 성별 변수에 대한 연구, 대퇴골 및 아래턱 첫째어금니를 제외한 다른 검체를 활용한 연대추정법 계발 등 추가연구가 필요한 상황으로, 아직까지는 수사실무에 적용하기에는 제한점이 있다. 그러나 현재까지의 연구결과로도 파악할 수 있는 정보가 있어 사안별로는 적용여부에 대한 검토가 필요하며, 향후 추가적인 연구를 통해 수사실무에 필요한 정보를 제공할 수 있을 것으로 기대된다.

Keywords: 탄소동위원소, 백골화, 연대추정

S 30

Study on Necrophagous Entomofauna Collected from Autopsies in Seoul, Incheon and the Part of Geonggi Area

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Knowledge of the necrophagous entomofauna attracted to human cadavers in each local area is a prerequisite for solving legal problems by insect evidence. As habitats of human cadavers are various, collecting at autopsies has advantages of reporting largescale insect cases. To expand the research on 35 autopsies with insects by Shin et al. (2015) and increase its credibility, insects collected at 556 autopsies in Seoul, Incheon and the part of Geonggi area from 2015 to 2017 were analyzed.

July and August show the highest frequency of insect cases. The body was mainly found indoors (79 %) and most of cause of death were unknown (75 %). Maggots were discovered at various sites, head (46.4 %), groin (25.1 %), around in body cloths (16.4 %) and so on. We performed morphological classification of all collected individuals (about 18,000) at least in Genus level and they were divided into 18 families, belong to Diptera, Coleoptera, Hymenoptera. Calliphoridae was the dominant family (76.0 %) and Phoridae was the subdominant family (12 %). Among collected 2nd and 3rd instar larvae, about 3,500 individuals of 383 autopsy cases (68.8 %) were also identified in species level by DNA barcoding methods (CO I) after vouchering. Total 30 fly species and 9 families were identified. *Lucilia sericata* showed the highest frequency (62.2 %) and only 4 other fly species showed more than 10 % frequency. In Coleoptera, 24 species and 7 families were identified and showed less than 5% frequency. In Hymenoptera, 2 speices and 2 families. Interestingly, only fly appearing cases were accounted for 92.5 %. Furthermore, the dominant species, *Lucilia sericata* appeared alone in 28 %, but more cases were found in combination with other fly species. Compared with the previous study in 2015, 24 species were newly recorded as forensically important species. The indoor preferences of *Sarcophaga crassipalpis* and *Megaselia scalaris* supported results of previous foreign studies.

These are thought to be results of various necrophagous flies adapting to various urban environments. We propose strategies to improve the applicability of insect evidence in survey area. First, new standard practice should be established according to refined indoor environments and insect activity seasons. Second, preferential studies should be performed for new species with indoor preferences.

Keywords: Case reports, Necrophagous entomofauna, Autopsy cases, DNA barcording, *Lucilia sericata*

S31

Impact of Pesticide Restriction on Pesticide Poisoning Death in South Korea : a 10-year Autopsy study (2008-2017)

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Pesticide poisoning death is the major problem worldwide as pesticides are usually used for a method of suicide. There have been reports of reduction in suicide mortalities following the pesticide bans. This study aimed to analyse the manner of pesticide poisoning deaths and investigate the influence of pesticide restrictions on pesticide poisoning deaths from autopsy cases of National Forensic Service(NFS) Institutes. Of 50479 autopsy cases in NFS from January 2008 to December 2017, the cases of 643 pesticide poisoning deaths were included in this study. We analysed the secular trend of usage of pesticide in pesticide poisoning deaths after paraquat ban in 2011. Before paraquat restriction, paraquat was the major pesticide in pesticide poisoning deaths. After this, glyphosate and glufosinate, herbicides with the class of organophosphate, have increased gradually. In conclusion, the restriction of pesticides has an impact on the type of pesticide used in pesticide poisoning deaths.

Keywords: Pesticide poisoning death, Paraquat ban, Pesticides restriction, Autopsy

S32

The Application of the Kvaal Method to Estimate the Age of Live Korean Subjects Using Digital Panoramic Radiographs

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Dental age estimation of the living is limited because observing the histological structure of teeth is difficult. Therefore, several methods have been proposed to estimate age by observing changes on dental radiographs of pulpal size because of secondary dentin deposition. This study's aim to evaluate the validity of the Kvaal method to estimate the ages of Korean subjects using digital panoramic radiographs and formulate a regression equation for use in Korean subjects. We included 266 Korean subjects (age, 21-69 years) visiting Chosun University Dental Hospital (Gwangju, South Korea). The pulpal size and width of six tooth types (maxillary central incisor, lateral incisor, second premolar, mandibular lateral incisor, canine, and first premolar) were measured on digital panoramic radiographs according to the Kvaal method. Statistical interobserver/intraobserver reliabilities were calculated to evaluate the reproducibility of the measured values and identify correlations with actual ages. The differences between the predicted ages and the actual age were analyzed. In addition, a regression equation series for the age estimation of Korean subjects was produced. When both the methods were applied directly to the teeth of the subjects, significant differences were observed between the estimated and chronological ages. The length-related parameters of the teeth of subjects calculated by the original Kvaal method showed no significant correlation, as with the Paewinsky' study. A regression equation derived from the width parameters without the length ratios is proposed for use in Korean subjects.

Keywords: Age estimation, Panoramic radiographs, Dental pulp, Secondary dentin

의료 빅데이터: 병리연구에서의 활용 가능성

Medical Big Data: Application in Pathology Research

대한병리학회

일시 : 6월 29일(금) 14:45-17:30

장소 : 행정관 대강당 (301호)

2018 The 26th Federation Meeting of Korean Basic Medical Scientists

S33

미토콘드리아 유전자에 대한 NGS의 적용 및 종양에서의 활용 가능성 탐색

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미토콘드리아는 핵과 별도로 16,569 bp의 짧지만 고유한 유전자를 갖는 세포 내 기관으로, 주로 세포의 ATP 생성에 중요한 역할을 한다. 미토콘드리아는 난자의 세포질을 통해 수정란에 전달되어 모계유전을 하게 된다. 미토콘드리아의 수는 세포나 조직마다 서로 다를 수 있고, 하나의 개체 또는 세포가 염기서열이 서로 다른 미토콘드리아 유전자를 동시에 가지기도 하는데, 이를 이형세포질성이라고 한다. 특히 미토콘드리아는 핵에 비하여 유전자 손상에 대한 수선 기전이 불완전하여 유전자 돌연변이율이 높은 편이어서, 후천적 이형세포질성도 드물지 않게 볼 수 있다. 그러나 대부분의 돌연변이는 단백질을 합성하지 않는 control region (또는 hypervariable region)에서 나타나므로, 기능에는 큰 영향이 없다.

법유전학계에서는 일찍이 이러한 미토콘드리아 유전자의 특성에 대해 주목하였다. 모계유전은 개인식별이나 친자관계의 확인, 출신 민족이나 지역의 구분, 인류의 이동과 이주 경로 등을 연구하는데 활용되고 있다. 또한 미토콘드리아 유전자는 복제수가 많아 불리한 환경에서도 남아있을 가능성이 상대적으로 높아, 오래된 시료나 머리카락, 뼈, 치아에서도 검출할 수 있다. 이러한 특징은 사건 해결과 범인 검거에 도움을 줄뿐만 아니라, 고고학이나 인류학에서도 광범위하게 활용되고 있다. 최근에는 차세대 염기서열 분석법(next generation sequencing, NGS)이 도입되면서 미토콘드리아의 전체 염기서열로 관심이 확대되고 있으며, Sanger sequencing으로 확인하지 못했던 범위의 이형세포질성에 대한 분석도 시도되고 있다.

한편, 임상의학 영역에서도 미토콘드리아 유전자에 대한 관심은 수십 년간 이어져 왔다. 대부분의 연구자들은 유전자 이상 - 단백질 합성 이상 - 기능 이상 - 질환의 발생이라는 전통적인 관점을 유지해 왔으며, 암 연구 역시 정상 조직과 종양의 대사적 기능에 어떠한 차이가 있는지, 혹은 종양의 발생에 영향을 주는 유전자가 있는지 알아보려는 시도에 집중되어 있었다. 본 연구에서는 이러한 관점에서 벗어나, 높은 돌연변이율이나 이형세포질성과 같은 미토콘드리아 유전자의 고유한 특성이 종양에서는 어떠한 결과를 나타내는지 확인하고 그러한 현상의 의미와 임상적 활용 가능성에 대해 알아보고자 한다. 이 과정에서 법유전학 연구를 통해 축적된 미토콘드리아 염기서열 분석에 대한 기술과 경험이 중요한 역할을 할 것으로 기대된다. 이번 발표에서는 한국인의 폐암 시료에서 확인한 미토콘드리아 전체 염기서열 분석 결과를 소개하고자 한다.

Keywords: 미토콘드리아, 차세대 염기서열 분석법, 돌연변이, 이형세포질성, 종양

S34

차세대염기서열분석법(NGS)를 이용한 법유전학 마커의 분석과 활용

신경진

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법유전학 분야에서는 짧은연쇄반복(STR) 유전자를 PCR 증폭한 후 그 증폭산물의 크기를 모세관 전기영동(CE)법으로 측정하여 사람을 식별하거나 혈연관계를 확인하는데 활용하고 있다. 이러한 분석방법은 매우 높은 민감도를 가지면서 절차가 간편하고, 표준화된 자료를 생성할 수 있어 법유전학 연구와 실무에서 널리 사용되고 있다. 하지만 CE 분석은 한번에 분석할 수 있는 마커의 수와 증폭산물의 크기에 제한이 있어 사건 현장에서 수집된 시료에서 충분한 정보를 획득하기 어려운 경우도 종종 있다. 최근에 각광 받고 있는 차세대염기서열분석법(NGS)으로 법유전학 마커를 분석하게 되면 대량의 염기서열로부터 변이 정보를 얻을 수 있어 보다 높은 식별력을 확보할 수 있고, 작은 크기의 증폭산물로 분석할 수 있어 분해된 시료를 대상으로 한 유전자분석 가능성도 증가될 수 있다. 또한 STR과 단일염기다형(SNP)과 같이 특성이 다른 마커도 동시에 분석할 수 있어 제한된 시료로부터 다양한 자료를 수집할 수도 있다. 이러한 NGS 분석을 이용한 법유전학 마커 분석의 효용성에 대한 기대에 따라 여러 연구가 진행되고 있고 관련 분석제품도 개발되고 있는 추세이다. 본 발표에서는 현재 법유전학 영역에서 NGS 방법에 기반하여 수행되고 있는 STR 혹은 SNP 분석을 통한 개인식별 정보의 획득, SNP 분석을 이용한 생물지리학적 기원 추정, 다중 SNP으로 구성된 microhaplotype의 분석과 활용성에 대해 소개하고자 한다. 나아가 DNA 정보를 분석하여 신원 불상자의 표현형을 추정하고자 하는 시도를 살펴 보고, 새로운 분석방법의 도입에 따르는 도전과 해결 과제에 대해서도 논의해 보고자 한다.

Keywords: 차세대염기서열분석법, 짧은연쇄반복, 생물지리학, 표현형

S35

의료 빅데이터와 기계학습을 이용한 정밀의료 응용

강재우

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정밀의료는 매우 도전적인 빅데이터 문제이다. 멀티오믹스 실험데이터, 환자 의료 기록, 생명의료분야 과학 문헌과 같은 대규모의 복잡한 이종 데이터로부터 파생 된 정보를 통합, 분석 및 해석해야하기 때문이다. 이 문제를 해결하기 위해 다양한 생명의료 빅데이터의 정보를 추출하고, 지식을 구조화하기 위해 정보를 연결하며, 이를 기반으로 새로운 지식을 추론하고 검증 가능한 가설을 생성하고, 데이터 기반 예측을 할 수 있는 새로운 컴퓨팅 플랫폼을 개발해야한다. 이번 강연에서는 이 목적을 달성하기 본 연구팀에서 현재 진행 중인 몇 가지 프로젝트를 소개하고, 최근에 참여한 두 개의 DREAM Challenge 국제 컴피티션 (약물조합시너지예측과 프로티오지노믹스)에서의 경험을 공유 하고자 한다.

Keywords: 정밀의료, 빅데이터, 인공지능, 기계학습

S36

분산형 생명의료 빅데이터 연구를 위한 서울대학교병원 CDM 구축 현황 및 향후 계획

김광수

서울대학교병원 임상의과학정보실

최근 전세계적으로 '분산형 바이오 빅데이터 플랫폼' 을 이용하여 의생명 빅데이터 연구를 진행하려는 움직임이 늘어나고 있다. '분산형 바이오 빅데이터 플랫폼' 이란 병원마다 서로 다른 형태로 구축되어 있는 전자의무기록(EMR) 데이터베이스를 국제적으로 표준화된 양식을 따라 공통된 형태로 변환하여 통합분석을 가능하게 하는 기술이라 할 수 있다. 국내에서는 가천길병원, 강원대병원, 분당서울대병원, 서울아산병원, 아주대병원이 공통데이터모델(Common Data Model, CDM) 변환을 완료하였고, 대다수의 상급병원들이 변환을 진행하고 있는 상황이다. 이러한 상황에서 서울대학교병원은 첫 번째 단계로서 2013년 1월부터 2018년 2월까지 약 5년간의 EMR 데이터를 CDM으로 변환하였고, 2013년 이전 데이터 및 새롭게 생성되는 데이터들을 추가로 변환하여 CDM을 지속적으로 확장시켜 나갈 계획이다. 본 발표에서는 서울대학교병원의 CDM 구축 방법 및 현황을 제시하고, 향후 계획으로서 유전체 및 생체신호 데이터 등으로 CDM을 확장하는 방안, CDM 기반 공동연구 활성화 방안 등을 제시할 것이다.

Keywords: 생명의료 빅데이터, 분산형 바이오 빅데이터 플랫폼, 공통데이터모델

S37

건강보험심사평가원 청구 자료의 이용

변선주

한림대학교 동탄성심병원

빅 데이터에 대한 정의는 Gartner 그룹에서 제시한 3V(자료의 크기와 관련된 volume, 자료의 빠른 변화 속도와 관련된 velocity, 자료 형식의 다양성과 관련된 variety)를 기반으로 하며, 여기에 자료의 불확실성과 관련된 veracity와 실질적 가치 창출과 관련된 value가 추가하여 5V로 정의하는 경우도 있다. 의료 분야에도 많은 빅 데이터가 있으며, 이번 강좌에서는 그 중 하나인 건강보험심사평가원(이하, 심평원으로 지칭) 청구 자료를 이용한 연구를 수행한 경험을 소개하고자 한다.

환자들이 치료 목적으로 의료 기관을 내원하였을 때, 의료 기관은 의료보험이 적용되는 다양한 의료 행위 및 여러 항목들을 국민건강보험공단(이하, 공단으로 지칭)으로 비용 지불을 청구하며, 심평원에서는 이 청구의 적절성을 평가한다. 이러한 청구 과정을 통하여 공단과 심평원에는 관련 자료가 축적된다. 이 두 기관에서는 연구자들이 자료를 요청하는 경우 환자 개인 및 의료 기관 식별 정보를 익명화 한 후, 해당 내용을 제공하고 있다. 본 연구자는 원격분석 시스템을 제공하고 있는 심평원 자료를 이용하기로 하였다.

내시경 점막하 박리절제술(endoscopic submucosal dissection, ESD)은 림프절 전이의 가능성이 매우 낮고, 점막에 국한되어 있을 것으로 예상되는 크기가 작고 분화도가 좋은(differentiated type) 위암에서 우선적으로 고려되는 치료 방법으로 2011년 후반기부터 급여가 결정되었다. ESD와 관련된 연구들은 대부분 단일 혹은 다기관 연구가 대부분이며, 연구를 제외한 자료들 중에서는 심평원의 위암 적정성 평가결과 보고서가 대표적이다. 위암 적정성 평가결과 보고서는 가장 대규모의 위암 환자들을 대상으로 하였지만, 병원에 내원한 모든 위암 환자들을 대상으로 하지 않았기 때문에 누락되는 환자들이 존재하게 된다.

본 연구에서는 심평원 청구 자료를 이용하여 2012년 이후 위암에 ESD를 시술 받은 모든 환자들을 파악하여, 의료기관 별로 해당 환자들의 현황 및 ESD와 관련된 지표들을 파악하고, 환자들이 ESD 시술 병원을 선택하기 위한 지표들을 선정하고자 하였다.

ESD 급여 청구 과정에서 ESD와 관련된 일부 의무 기록 정보를 포함하도록 되어 있지만, 심평원에서 연구자들에게 제공하는 자료는 관련 의무 기록 정보는 제공되지 않는다. 의무 기록 정보가 없는 상태로 ESD와 관련된 지표들을 평가하여야 하며, 이로 인한 한계점들 때문에 지표 분석을 위한 추가적인 조건 설정 과정이 필요하다.

심평원 청구 자료의 구성 및 한계점을 이해하고, 한계점을 극복하기 위한 추가 조건 설정 과정, 그리고 제공받은 청구 자료를 연구자의 분석 목적에 맞게 재구성하여 제한된 연구 기간 내에 연구자가 원하는 결과를 얻은 과정에 대하여 연구자의 경험을 소개하여 공유하고자 한다.

정밀의료시대의 베타세포 병태생리

Pathophysiology of Pancreatic β-cells in the Era of Precision Medicine

대한생리학회

일시 : 6월 29일(금) 14:45-17:45

장소 : 융합관 박희택홀 (101호)

2018 The 26th Federation Meeting of Korean Basic Medical Scientists

S 38

Trafficking vs Gating Regulation of K_{ATP} Channels in Pancreatic β-cells

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Glucose homeostasis of the body relies primarily on the ability of pancreatic β-cells to regulate insulin secretion in response to the changes in blood glucose concentrations, which is called "glucose-stimulated insulin secretion (GSIS)". Among the chain of reactions that underlie GSIS, K_{ATP} channels play a key role in the early steps of sensing glucose concentration changes and coupling these changes to the changes in beta cell membrane potentials. A high KATP channel activity in low glucose conditions contributes to the maintaining resting membrane potential at around -70 mV, whereas inhibition of K_{ATP} channels upon high glucose stimulation leads to membrane depolarization that leads to Ca^{2+} entry to initiate insulin vesicle exocytosis. A textbook knowledge about how K_{ATP} channels sense glucose concentration changes is ATP-dependent gating properties of K_{ATP} channels, in that K_{ATP} channel activities are regulated by changes in intracellular ATP concentrations by glucose concentration changes. We have been studying K_{ATP} channel trafficking mechanisms, and provided a line of evidence that shows glucose-dependent changes in membrane potential are mainly attributable to the changes in surface density of K_{ATP} channels. K_{ATP} channel proteins were mostly internalized in 11.1 mM glucose, but recruited to the plasma membrane by glucose deprivation without changes in total levels. The effects of glucose deprivation on K_{ATP}channels were abolished by an AMPK inhibitor or a knockdown of AMPK using siRNA, but mimicked by an AMPK activator. Activation of AMPK by leptin induced similar effects on K_{ATP} channel trafficking. Membrane potentials of ?-cells could be hyperpolarized by leptin even in high glucose conditions. These results indicate K_{ATP}channel are recruited to the plasma membrane via AMPK signaling. We then investigated whether glucose-stimulated membrane depolarization is driven by an increase in ATP concentration or a decrease in surface density of KATP channel, and quantitatively analyzed the contribution of the decrease in K_{ATP} channel density and the increase in intracellular ATP concentration ([ATP]i) to β-cell responses to high glucose (HG). Upon HG stimulation, resting membrane potential depolarized by 30.6 mV (from -69.2 to -38.6 mV) and K_{ATP} conductance (GKATP) decreased by 90% (from 0.243 to 0.024 nS/pF). HG-induced increase in [ATP]i was 47%, which is too small to explain GKATP decrease in HG. The surface level of K_{ATP} channel proteins decreased by 86%, and this decrease was abolished by dynasore, a dynamin-dependent endocytosis inhibitor. Interestingly, dynasore significantly inhibited glucose-stimulated membrane depolarization, while it did not affect the glucose-induced increase in intracellular ATP concentrations. These results suggest that decreased surface K_{ATP} channel density by endocytosis is a key mechanism that drives glucose-stimulated membrane depolarization, while ATP-dependent channel closure plays a minor role. We think that our discovery will open the new venue for β-cell researches. Detailed molecular mechanisms involved in glucose-dependent endocytosis of K_{ATP} channels need to be investigated in future studies, and each mechanism may become a good target for controlling insulin secretion from pancreatic β-cells.

S 39

Glucotoxicty and CD36 Signaling in Pancreatic Beta Cell

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Glucotoxicity in the pancreatic beta-cell is defined as nonphysiological and potentially irreversible cellular damage induced by chronic exposure to supraphysiologic glucose concentrations, which leads to defective insulin secretion and worsening glucose regulation. Preservation of beta-cells, through tight glycemic regulation, is an essential component of the treatment strategy for type 2 diabetes. It is well known that one of the main mechanisms of glucotoxicity is chronic oxidative stress.

Though free fatty acids (FFA) stimulate insulin secretion, chronically elevated FFA impairs pancreatic beta cell function *in vitro* and *in vivo*, which leads to the induction of lipotoxicity. FFAs move into cells through a passive concentration-dependent diffusion, and it has been reported that there are active transport systems to enhance FFA uptake. Fatty acid translocase cluster determinant 36 (CD36), which is part of the FFA transporter system, has been identified in several tissues such as muscle, liver, and insulin-producing cells. Several studies have reported that induction of CD36 increases uptake of FFA in INS-1 cells and Caco-2/15 cells, suggesting the functional interplay between glucose and FFA in terms of insulin secretion and oxidative metabolism. However, we do not currently know the regulating mechanism and physiological role of CD36 on glucotoxicity in pancreatic beta-cells. Also, the downstream and upstream targets of CD36 related signaling have not been defined. We would like to determine whether hyperglycemia enhances the expression of CD36, and whether the accompanying CD36 related signaling can affect pancreatic beta-cell function, and if inhibition of CD36 reverses the deteriorated beta-cell function.

S40

Pancreatic Beta-cell Neogenesis from Alpha-cells by Glucagon-like Peptide-1

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Glucagon-like peptide-1 (GLP-1) can increase pancreatic β-cells, and α-cells could be a source for new β-cell generation. We investigated whether GLP-1 increases β-cells through α-cell transdifferentiation. New β-cells originating from non-β cells were significantly increased in recombinant adenovirus expressing GLP-1 (rAd-GLP-1)-treated RIP-CreER;R26-YFP mice. Proliferating α-cells were increased in islets of rAd-GLP-1-treated mice and αTC1-9 cells treated with exendin-4, a GLP-1 receptor agonist. Insulin+glucagon+ cells were significantly increased by rAd-GLP-1 or exendin-4 treatment *in vivo* and *in vitro*. Lineage-tracing to label the glucagon-producing α-cells showed a higher proportion of regenerated β-cells from α-cells in rAd-GLP-1-treated Glucagon-rtTA;Tet-O-Cre;R26-YFP mice. In addition, exendin-4 increased the expression and secretion of fibroblast growth factor (FGF)21 in αTC1-9 cells and β-cell-ablated islets. FGF21 treatment of β-cell-ablated islets increased the expression of PDX-1 and neurogenin-3 and significantly increased insulin+glucagon+ cells. Generation of insulin+glucagon+ cells by exendin-4 was significantly reduced in islets transfected with FGF21 small interfering RNA or islets of FGF21 knockout mice. Generation of insulin+ cells by rAd-GLP-1-treatment was significantly reduced in FGF21 knockout mice compared with wild-type mice. We suggest that GLP-1 has an important role in α-cell transdifferentiation to generate new β-cells, which might be mediated, in part, by FGF21 induction.

Keywords: Diabetes, Pancreatic islet, Glucagon-like peptide-1, Transdifferentiation

S41

Essential Roles of PRMT1 in Pancreatic β-cell

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Although the progression of type 2 diabetes initiates with the development of insulin resistance, hyperglycemia does not develop as long as pancreatic β-cells compensate for insulin resistance. Type 2 diabetes can be diagnosed when β-cells fail to come up with the increased insulin demand due to insulin resistance. Thus, β-cell failure along with insulin resistance is an essential feature of type 2 diabetes. β-Cell death has been thought as a primary cause of β-cell failure. However, given that clear deficiency in glucose stimulated insulin secretion is observed in type 2 diabetes despite the absence of marked differences in β-cell mass, β-cell seems to experience more dynamic changes before β-cell death develops. In fact, recent studies in human and mice indicate that fully differentiated β-cell retains more plasticity than we appreciated before and the loss of β-cell identity results in dedifferentiation of β-cell into alternate endocrine cell fates. Although β-cell dedifferentiation is characterized by the changes in the expression of β-cell specific transcription factors as well as the decrease in insulin production, it remains to be elucidated how β-cell dedifferentiation develops.

Here, we propose a new model for β-cell dedifferentiation by knocking out protein arginine N-methyltransferase-1 (PRMT1). PRMT1 is a major type of protein arginine methyltransferase in mammalian cells. Knock out of *Prmt1* in developing pancreas (*Prmt1* PKO) showed severe defect in development of endocrine pancreas. β-Cell specific *Prmt1* knock out (*Prmt1* βKO) did not affect mice were grossly normal until they developed glucose intolerance at 12 weeks of age. Glucose stimulated insulin secretion and mitochondrial function were decreased in the islets of *Prmt1* βKO mice at 12 weeks of age. Moreover, high-fat diet induced β-cell dedifferentiation in *Prmt1* βKO mice. Inducible knock out of *Prmt1* in adult β-cell (*Prmt1* βiKO) resulted in marked down-regulation of mature β-cell genes and genes involved in mitochondrial function. In conclusion, PRMT1 plays essential roles in maintaining mature β-cell function and identity.

S42

Incretin Biology in Koreans

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Incretin hormones, such as glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), are secreted upon oral nutrient ingestion and regulate postprandial glucose homeostasis by conveying the signal of intestinal glucose flux. In East Asians, the secretion of GIP and GLP-1 is not reduced in type 2 diabetes relative to normal glucose tolerance (NGT). Although the incretin effect is blunted in European patients with type 2 diabetes, a few East Asian studies revealed no difference in the incretin effect between type 2 diabetes and NGT. Interestingly, the glucose-lowering efficacy of dipeptidyl peptidase-4 inhibitors or GLP-1 receptor agonists was reported to be greater in Asians than in non-Asians. The difference in the treatment responses could be ascribed to a different pathophysiology of type 2 diabetes (lower insulin secretory function and less insulin resistance), lower body mass index, different genetic makeups, preserved incretin effect, and different food compositions in East Asians compared to other ethnic groups. Based on the currently available data, incretin-based therapies appear to be safe and well-tolerated in East Asians. Nonetheless, continuous pharmacovigilance is required. The characteristics of incretin biology and treatment responses to incretin-based therapies should be considered in developing ethnicity-specific treatment guidelines and making patient-centered decisions for patients with type 2 diabetes.

S43

Targeting PGC-1α to Protect Glucose-toxicity in Beta-cells

Kun-Ho Yoon

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Glucolipotoxicity plays an important role in the development and progression of type 2 diabetes. Once chronic hyperglycemia and hyperlipidemia are established, it can affect pancreatic β-cell function and survival and finally deteriorate the hyperglycemia. After 3 days of exposure to high glucose concentrations, insulin and Beta2/NeuroD gene expression levels were downregulated significantly. Alteration of gene expressions in β-cells could reproduce by the overexpression of PGC-1α. Moreover, when highly expressed PGC-1α induced by an adenovirus vector, markedly suppressed Pdx-1 expression, whereas exposure glucolipotoxic conditions for 3 days did not. To clarify these discrepant results for Pdx-1 expression, we examined the effects of the dose of adenoviral PGC-1α and the time of exposure to glucolipotoxic conditions. Pdx-1 expression levels decreased gradually in dose- and time-dependent manners in parallel with the elevation of PGC-1α levels induced by exposure to glucolipotoxicity. These results strongly suggested that overexpression of PGC-1α play a pivotal role to induce glucose-toxicity induced β-cells dysfunction. Targeting the overexpressed PGC-1α by siPGC-1α, AMPK agonist treatment remarkably improved glucose-toxicity induced β-cell dysfunction and improved glucose metabolism in diabetic animal models. Recently our team found the miRNA which suppressed PGC-1α in hepatocyte and β-cell simultaneously and improved hyperglycemia in animal model of diabetes. Altogether, stabilization of metabolic changes induced by glucolipotoxicity in β-cells through targeting the PGC-1α represents a potential new avenue for treatment of patients with type2 diabetes mellitus.

섬유화 질환의 발병기전 및 치료

Pathogenesis and Treatment of Fibrosis-associated Diseases

대한약리학회

일시 : 6월 29일(금) 09:00–12:00

장소 : 행정관 대강당 (301호)

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S44

Role of Transglutaminase 2 in the Pathogenesis of Idiopathic Pulmonary Fibrosis

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Idiopathic pulmonary fibrosis is a chronic, progressive interstitial pneumonitis that leads to loss of alveolar cells, fibroblast proliferation, deposition of extracellular matrix and ultimately respiratory failure. This fibroproliferative process may be caused either by repeated lung injury and subsequent inflammation and repair responses or by an incomplete resolution of inflammation followed by persistent repair processes. Aberrant secretion of chemokines, proinflammatory cytokines and metalloproteinases from lung epithelial cells, fibroblast and immune cells contribute to the dysregulated repair processes in chronic inflammation. Interestingly, recent reports showed that cellular senescence is also implicated in the pathogenesis of lung fibrosis. However, the signals and molecular mechanisms leading to fibrotic development is still elusive. Transglutaminase 2 (TG2) is an enzyme that incorporates polyamine into substrate proteins or crosslinks proteins. TG2 is activated in response to various types of insult, including oxidative stress, DNA damaging injury, UV-irradiation, and hypoxic stress through increase of intracellular calcium or TGFβ signaling pathway. TG2-mediated modification of substrate proteins, such as NFkB, caspase-3 and collagen, contributes to inflammatory response, resistance to stress-induced apoptosis and extracellular matrix formation, respectively. In this symposium, I will talk about the current evidences for critical roles of TG2 in the pathogenesis of idiopathic pulmonary fibrosis.

Keywords: Lung, Fibrosis, Transglutaminase 2, Inflammation

S45

CST3 and GDF15 are Potential Therapeutics for Pulmonary Fibrosis

Young-Im Kim, Jong-Wan Park

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While wound healing is completed, the epithelium functions to normalize the interstitial context by eliminating fibroblasts excited during matrix reconstruction. If not, tissues undergo pathologic fibrosis. Pulmonary fibrosis is a fatal and hardly curable disorder. We here tried to identify epithelium-derived cytokines capable of ameliorating pulmonary fibrosis. Human lung fibroblasts were inactivated in epithelial cell-conditioned media. Cystatin C (CST3) and growth differentiation factor 15 (GDF15)were found to be enriched in the conditioned media and to inhibit the growth and activation of lung fibroblasts by inactivating the TGF-Smad pathway. In mouse and human lungs with interstitial fibrosis, CST3 and GDF15 expressions were markedly reduced, and the restoration of these cytokines alleviated the fibrotic changes in mouse lungs. These results suggest that CST3 and GDF15 are bona fide regulators to prevent excessive proliferation and activation of fibroblasts in injured lungs. These cytokines could be potential therapeutics for ameliorating interstitial lung fibrosis.

Keywords: Epithelium, Fibroblast, Lung Fibrosis, cystatin C, growth differentiation factor 15

S46

Oxidative Stress and Kidney Fibrosis: Recent Insights into Established Therapeutic Targets

Hunjoo Ha

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Chronic kidney disease (CKD) becomes epidemic worldwide, but the current pharmacological treatment for CKD is limited to renin-angiotensin system inhibitors. Kidney fibrosis, characterized by the accumulation of disorganized and stiff extracellular matrix, is the common final feature leading to end stage kidney disease regardless of the initial injury. Epithelial-mesenchymal transition (EMT) is an important mechanism involved in tissue fibrosis, and oxidative stress plays a key role in the development and progression of kidney fibrosis. Our recent network-based integrated analysis of transcriptomic and proteomic data on EMT suggest oxidative stress-related genes along with novel targets as the most significantly altered molecules during EMT. NADPH oxidases significantly contribute to intra-renal reactive oxygen species generation. While the downstream effectors of NADPH remains to be established, a considerable effort has been devoted to development of Nox inhibitors for the treatment of CKD. In this seminar, our ongoing studies on the development of Nox inhibitors as the first-in-class drug against CKD will be presented.

Keywords: Fibrosis, Diabetic Kidney Disease, Oxidative Stress

S47

Stem Cells as a Tool for the Treatment of Fibrotic Diseases and Screening of New Anti-fibrotic Drugs

Jong-Hoon Kim

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Fibrosis is a pathological feature of most chronic inflammatory diseases and caused by the formation of excessive fibrous connective tissue in organs, including the liver, lung, and kidney. The fibrosis creates scar-like tissue, disturbing normal architectures and functions of organs, and became a leading cause of morbidity and mortality worldwide. However, there is currently no effective therapeutic options or interventions for the treatment. Thus new anti-fibrotic strategies that can halt or reversethe fibrosis are urgently needed.Recently, it has become increasingly clear that mesenchymal stem cells (MSCs) have beneficial effects for the treatment of fibrosis, particularly in the liver, but the exact cellular dynamics and the related molecular mechanisms have remained enigmatic. We previously studied the anti-fibrotic effect of MSCs and found that the beneficial therapeutic outcome resulted from secreted proteins (secretome) of MSCs. We also identified a single glycoprotein in the secretome as a key anti-fibrotic factor, which contributedto the regression of fibrosis. This protein is profoundly secreted from MSCs obtained from different tissues, including bone marrow, umbilical cord, and teeth, and administration of the protein alone had a significant anti-fibrotic effect in animal models of fibrosis. This talk also introduce the molecular mechanism underlying the anti-fibrotic effect of the protein and potential applications of stem cell-derived organoids for the screening of new drug candidates to treat fibrotic diseases.

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Hepcidin as a Novel Anti-fibrotic Hepatokine to Inhibit HSC Activation

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Hepatic stellate cell (HSC) activation accelerates liver fibrosis upon liver injury. Despite the crosstalk between parenchymal cells and the neighboring HSCs, hepatokines affecting HSCs are largely unknown. This study investigated the potential role of hepcidin in HSC activation and liver fibrosis. The levels of hepcidin were inversely correlated with exacerbation of liver fibrosis in patients. The relationship between hepcidin repression and fibrosis progression was also verified in animal models. Adenoviral delivery of hepcidin to mice lessened liver fibrosis induced by hepatotoxicant treatment or bile duct ligation. In cell models, the activation of HSCs was suppressed by hepcidin derived from hepatocytes or exogenous hepcidin treatment. The inhibition of HSC activation was mediated by the blockade of transforming growth factor β1 (TGFβ1)-Smad3 signaling pathway through Akt. The levels of ferroportin (FPN, a target of hepcidin) were elevated in activated HSCs. FPN knockdown in HSCs inhibited TGFβ1-mediated Smad3 phosphorylation. Furthermore, HSC-specific FPN deletion also attenuated the development of liver fibrosis. In conclusion, hepcidin acts as an anti-fibrotic hepatokine by inhibiting TGFβ1-induced Smad3 phosphorylation in HSCs.

Keywords: Liver Fibrosis, Hepatic Stellate Cell, TGFβ1, Hepcidin, Ferroportin

4차 산업혁명, 헬스케어 3.0시대의 질병예방 전략

Disease Prevention Strategy of 4th Industrial Revolution and Heath Care 3.0

대한예방의학회

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S49

4차 산업혁명과 예방의학의 역할

이영성

한국보건의료연구원

현대 과학의 발달은 생명연장, 식품 과학, 환경 과학, 진단 기술의 진일보를 이루었으나, 이는 다시 인구고령화, 식품과 환경 건강과 관련된 문제, 과잉 진단 등의 문제를 양산하고 있다. 특히 의료정보기술은 고도화?다양화를 통해 개인맞춤형으로 진화하고 있으며 환자는 그 중심에 자리잡고 있다. 환자에게 가장 효과적이고 안전한 관리와 치료가 무엇인지 정밀하게 답을 주기 위한 정보 기술의 발달은 매우 빠르게 이루어지고 있다. 그러나 우리는 정보기술의 발달이 새로운 4차 산업혁명을 이끌어가고 있음을 인정하지만 한편으로는 거기에 따르는 위험도 충분히 인지하고 있다. 자동화, 초지능화와 함께 초연결성으로 특징지워지는 4차산업혁명 시대에서는 새로운 기술의 도입이 새로운 활용방안을 창출할 것으로 관측되는데 최근 이슈가 되고 있는 블록체인 등이 의료시스템에 도입되면 비용효과적이고 안전하게 데이터의 연계 및 활용이 가능하게 될 것이다. 특히 우리나라의 경우 전 세계에서 찾아보기 힘든 보건의료분야의 데이터를 보유하고 있으며 이러한 데이터를 현재 정부가 추진하고 있는 예비급여 평가에 활용한다면 의사결정을 위한 양질의 근거 생산에 기여할 것이다. 한국보건의료연구원은 예비급여의 재평가에 대한 정책적 업무를 부여받았으며 보건의료기술진흥법 제 26조에 의거 국내 유일하게 연구를 위한 데이터 연계가 가능한 법적 장치를 보유하고 있다. 2009년 설립 이후 약 90편의 건강보험 데이터베이스를 활용한 분석 연구를 수행해오고 있으며 특히 자료원을 연계하여 수행한 경우는 약 30건에 달한다. 한국보건의료연구원의 의료기술평가 데이터 플랫폼은 연구 신청에서 분석 및 결과 확산까지 원스탑 데이터 연계 서비스 제공이 가능하며, 의료기술평가방법론 지원 서비스, 보건의료분야 사업 평가 지원 정보 제공을 통해 국민 건강 향상과 보건의료자원의 효율적 활용이 가능할 것으로 기대된다. 향후 질병 예방 및 건강증진을 위한 다양한 분야에 한국보건의료연구원의 의료기술평가 데이터 플랫폼이 적극적으로 활용되길 바란다.

-저자는 본 초록에 부적절하게 영향을 줄 수 있는 경제적 또는 개인적 관계의 이해상충이 없습니다.

S 50

Distributed Research Network using Common Data Model

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Distributed Research Network (DRN) such as Observational Health Data and Informatics (OHDSI, pronounced "Odyssey") has gained popularity among clinical data partners worldwide. DRN uses the same data structure, called the Common Data Model (CDM), to run the same analysis program for participating organizations and then combine the results summarized over the network to provide results across the network. Data is stored in a CDM that achieves both syntactic and semantic interoperability, enabling consistent queries to be applied to databases around the world.

OHDSI is the international collaborators with more than 180 researchers committed to making this clinical big data analysis a reality. OHDSI has transformed more than 1.2 billion patient data from 64 databases in 17 countries into the OMOP (Observational Medical Outcomes Partnership) CDM format. In Korea, 5.5M patient data from 4 institutions has been converted to CDM v5. In addition. More than 42 Korean hospitals joined OHDSI to convert their data into CDM. By the end of 2018, more than 10M patient data are expected to be available in CDM v5 format in Korea.

The DRN will enable researchers to access a network of billions of patients to generate evidence about all aspects of healthcare. This collaborative analysis of clinical big data across the world will lead to medical innovation along with the 4th industrial revolution. Clinical big data analysis using DRN will serve as a key player to improve health, by empowering a community to collaboratively generate the evidence that promotes better health decisions and better care.

S51

4차 산업혁명, 무엇이 문제인가?

홍성욱

서울대학교

이 논문은 지금 우리나라에서 유행중인 4차 산업혁명론을 비판하려는 목적을 갖고 있다. 여기서 4차 산업혁명 "론" 이라 함은 4차 산업혁명에 대한 공론장에서의 담론과 좀 더 체계를 갖춘 학술적, 정책적 논의 모두를 의미한다. 나는 이런 4차 산업혁명론의 주장이 과장되었고, 편향되었으며, 철학적으로 진부한 것임을 주장할 것이다. 나는 우선 "4차 산업혁명" 이라는 용어가 현재 어떤 의미로 사용되며, 과거에는 어떤 의미들로 사용되었는가를 살펴보겠다. 그리고 왜 지금의 변화에 "산업혁명" 이라는 개념을 적용하는 것이 무리인지를 보이면서, 요즘 회자되는 4차 산업혁명이 "정치적 유행어" (political buzzword)에 가까운 것임을 주장할 것이다. 그리고 한국에서 이 개념이 유행하게 된 과정을 분석한 뒤에, 이것이 박근혜 정부 시절 정보통신분야에서의 지능정보기술 육성 정책이 발전한 것임을 보일 것이다. 지능정보기술 정책이나 4차 산업혁명론 모두 특정한 정보통신 기술을 발전시키면 우리나라가 행복하고 풍요로운 지능정보사회가 될 것이라는 기술결정론적에 근거하고 있는데, 이 글의 마지막 부분에서는 이런 기술결정론의 문제점을 지적하면서 상대적으로 진보적인 정부에서 표방해야 하는 대안적인 정책을 제안해 볼 것이다.

(이 논문을 쓰는 데 어떤 이해상충도 없었습니다)

S 52

소비자 중심 건강정보와 맞춤예방

강건욱

서울대학교 의과대학 핵의학교실

미래 의료 산업은 기존 치료 중심 질병 치료에서 예방 중심으로 이동하고 있으며 인공지능, 빅데이터, IoT 등 4차 산업혁명의 주요 요소들이 보건의료 전반에 큰 영향을 줄 것으로 예상된다. 유전체 검사의 가격이 급격히 내려가면서 개인 유전체 정보를 쉽게 얻을 수 있으며 보건소 및 병원의 전자의무기록과 건강검진센터의 검진정보, 건강보험공단 및 건강보험심사평가원에 디지털 형태로 구축된 개인의 보건의료 정보와 연계하면 소비자가 스스로 참여하는 맞춤예방이 가능하다. 그러나 정부가 주도하는 보건의료빅데이터 구축은 개인정보 유출에 대한 우려로 인해 진행이 어려우며 이에 대한 대안으로 익명화를 하여 개인이 맞춤서비스를 받는 혜택은 불가능하다. 블록체인 기술을 이용하면 본인 또는 타인에 의한 건강정보의 변조 등 부정사용을 방지하는 것이 가능하므로 안전하고 신뢰할 수 있는 개인의료정보의 활용이 가능하다. 의료소비자 개인이 여러 기관에 흩어져 있는 자신의 보건의료정보를 다운받을 수 있는 서비스 플랫폼 구축하고 유전자 검사결과와 IoT장비에서 생성된 건강정보를 탈중앙화한 보건의료 블록체인 DB 시스템에서 관리하게 함으로써 인공지능을 이용한 개인 맞춤형 예방서비스와 빅데이터 연구에 활용할 수 있는 시스템을 구축을 제안한다. 이를 통해 소비자는 참여와 동의에 기반을 둔 개인 건강정보 결정권을 확보할 수 있다. 이를 추진하기 위해서는 표준화를 이미 수행한 병의원간 진료정보교류 사업에서 개인이 자신의 정보를 다운로드할 수 있는 한국형 블루버튼 이니셔티브를 추가하고 소비자의 적극적인 참여를 유도하는 인식 변화가 필요하다.

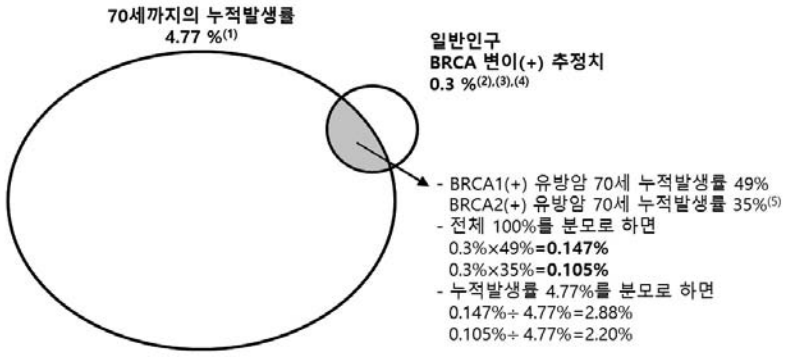
S 53

빅데이터의 공익적 활용: 허상과 실상 그리고 제안
Public Use of Public Big Data: Illusion, Reality and Suggestions

김재용

한양대학교 건강과 사회 연구소

빅데이터 활용을 강조하는 근래 기사들 중에 하나는 배우 안젤리나 졸리가 예방적인 유방절제술을 받았다는 것이다. 하지만, 유방암과 관련성이 높다고 알려진 BRCA 변이의 일반인구 유병률은 최저 0.07%에서 0.33% 사이로 보고되고 있다. 요약하면, (1) 유방암 유전자 검사에서 음성이 나올 확률은 99.7%다. 하지만 음성이 나왔다고 결코 안심할 수는 없다. 이 결과는 단지 70세까지 유방암에 걸릴 누적확률을 4.77%에서 0.147% 낮은 4,62%로 낮추는 것에 불과하다. (2) 유방암 유전자 검사에서 전체인구의 0.3%에 속하는 양성이 나오면 100만원 전후의 확진 검사를 한다. 유방암에 걸릴 확률이 49%(일부에선 70%)라는 결과를 통지받으면 악성종양이 발생하지도 않은 유방이나 난소를 절제할 것인지 여부를 결정해야 한다. 본인뿐만 아니라 자식과 부모까지 모두 검사를 해보라는 권유를 받을 것이고 결과에 따라서는 죄책감이나 원망에 시달릴 가능성도 배제할 수 없다.



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졸리 효과라는 신조어까지 만들어낸 유방암 분야는 현재 유전자 맞춤형 의료 연구가 집중되고 있는 영역이다. 하지만 4차 산업혁명과 빅데이터 맞춤형 의료를 옹호하는 측은 유방암 유전자변이의 유병률이 기껏 0.3%에 불과하다는 사실을 의도적으로 무시하거나 또는 그 의미를 깨닫지 못하는 것 같다. 지난 정부에서 대거 급여범위에 진입한 신기술들에 대해 합리적인 재평가와 후속조치가 필요하다.

불필요한 고가진료의 남발과 사회적 형평성 악화, 공공재원의 소진에 기여할 이런 시장을 개발하기 위해서 국가가 나서서 국민의 진료기록과 유전자 정보까지 포함된 빅데이터를 제공해야할 이유가 무엇일까? 공공 자료는 개별적 동의여부를 떠나 마땅히 공익적으로 활용되어야 한다. 제한적으로 허용되는 사익조차도 공익이라는 큰 틀의 일부이기 때문에 허용된다는 점을 이해해야 한다. 앞서 기술한 유방암 유전자 검사와 같이 기만 또는 무지에 의거한 공익론에 대응하기 위한 사회적 논의가 절실하다.

1987 민주화와 한국 의료계의 역할

1987 Democratic Transition and the Role of Health Professions in Korea

대한의사학회

일시 : 6월 29일(금) 14:10-18:10

장소 : 융합관 GDR1 (107-1호)

2018 The 26th Federation Meeting of Korean Basic Medical Scientists

S54

구술사로 본 의료인의 민주화운동: 의사 양길승 사례를 중심으로

이현숙

연세대학교 의학사연구소

구술사란 '과거의 기억을 구술한 기록에 근거한 역사 기술' 로서, 밑으로부터의 역사라고 할 수 있다. 구술이란 역사적 현상에 대한 구술자 개인의 기억을 대담자를 통해 역사 자료를 생성하는 과정이며, 기존 문헌 자료를 보완 또는 재해석할 수 있는 근거가 된다. 근현대 의학사에서 사회를 개혁하고자 하였던 의료인의 다양한 활동 가운데 독립운동과 민주화운동은 주목할 만하다. 20세기 전반기 의료인의 독립운동에 대해서는 사료발굴과 함께 연구가 상당히 진척되었지만, 20세기 후반기 민주화운동 속에서 이루어진 의료인의 역할에 대한 연구는 시작 단계라고 할 수 있다. 의료인 가운데 의사의 경우, 현재 보건의료운동과 인도주의실천의사협의회를 중심으로 개괄적 정리가 이루어진 상태이다. 한국 현대사에서 산업화와 민주화가 이루어졌을 때, 이 시기 의료인은 어떠한 역할을 하였는지 밝히는 것은 앞으로 중요한 주제가 될 것이다. 본 발표는 의료인의 민주화 운동에 관한 본격적인 연구 토대를 위하여 구술을 통한 역사자료의 생산과 함께 본 연구가 가지는 학문적 의미를 살펴보는 기회를 제시하고자 한다. 또한 본 발표를 통해 앞으로 민주화 운동에 헌신하였던 다양한 의료인들을 발굴하고 그들의 구술을 어떻게 역사화할 것인지에 대해 공론화하는 장을 제공할 것이다. 그 첫 걸음으로 인도주의실천의사협의회가 1987년 발족할 때 기획국장으로 참여하였던 의사 양승길의 구술작업 과정과 그 의미를 소개할 것이다.

키워드: 민주화운동, 의사, 의료인, 구술사

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한 의료인이 겪은 한국의 민주화과정

양길승

녹색병원 이사장

1. 들어가며

한 개인으로서 과거를 돌아보는 것이 익숙하지 않다. 그래서 그동안 사회의학연구회에 대한 책을 낼 때나 인도주의실천의사협의회 창립 30주년을 맞아 기록을 위한 자리가 마련되었을 때에도 늘 사양하고 빠졌다. 이제는 "지나간 일"(過去)이라는 생각으로, 그리고 확실히 과거가 되기를 바라는 마음으로 돌아본다.

2. 개인사 약력

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2003년 녹색병원 개원, 원장, 15년 원진직업병관리재단 이사장

3. 돌아보기1 학생운동

의예과 시절부터 홍사단에서 서울대 아카데미 활동을 통해 역사와 사회현실문제를 공부하기 시작했고 의예과에서 잔디회란 토론모임을 만들어 함께 공부하다가 서울의대 사회의학연구회 모임을 같이 하였다. 일반적인 써클활동이 당시에는 자연스럽게 학생운동의 한부분이 되었다. 당시 박정희 군사독재는 억압과 검열이 노골적이었고 부당함에 저항하는 것은 당연한 일이었다. 학생들은 부정선거반대, 교련반대 시위 등 항의하고 반대하는 운동 이외에도 농촌봉사, 환경인식조사, 판자촌실태조사 등을 하였고 후배들은 방학기간동안 노동자로서 일하는 공장활동 등을 하였다. 유신헌법이 공포된 후 1974년 1월 긴급조치에 반대하는 시험거부를 하였고 나는 도피하였으나 3명의 학우들이 군사재판에서 각 10년형을 받았다.

나는 75년 겨울에 김지하 양심선언을 대학가에 뿌린 것과 소위 서울의대 재일교포간첩사건에 연루되어 육군 보안사에 붙잡혀 3년에 집행유예 5년을 대법에서 확정되었다.

80년 "서울의 봄" 때 복학을 하였으나 다시 제명을 당해 해외 의과대학에 편입하여 학업을 마치고 의사시험을 통해 의료인 되었다.

4. 돌아보기2 보건의료운동

구로공단 오거리에서 우리의원을 하면서 노동자들의 건강실태와 산재실상을 매일 접하게 되면서 1987년 6월항쟁을 만나고 후배들이 호헌철폐 성명서를 발표하는 활동과 접했고 민주항쟁이후 부문별 활동을 담당할 조직건설이 화두가 되어 보건의료계도 부분별로 민주화운동단체들이 만들어진다. 운동이 불법이었던 시대가 가고 합법공간이 열리면서 활동이 활발하게 추진되면서 부문운동이 형태를 갖추기 시작했다. 노동자들의 안전과 건강의 문제, 빈민들의 문제, 환경피해 조사 등 요구가 쏟아지고 의료제도개혁을 위한 노력이 시작되었다.

5. 내일을 위하여

의료의 문제는, 그리고 의료의 성패는 신뢰에 있다. 믿음을 얻기 위해서 싸워온 것이, 아니 믿을 수 있는 세상을 만들기 위한 과정이 민주화였다고 생각한다. 6월항쟁이후에서도 일상의 민주화가 이루지지 않았다. 의료계가 진정한 민주화로 내일을 만들기를 기원한다.

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한국 민주화운동 속 부검논쟁

최규진

인하대학교 의과대학 의학교육학교실

격동의 한국 현대사에서 적지 않은 부검 논쟁이 있었다. '1987' 영화를 통해 잘 알려진 박종철군 고문치사 사건이 대표적이다. 그러나 박종철 고문치사 사건에서 부검이 사건의 진실을 밝히는 데 어떤 역할을 했는지 좀 더 명확히 짚어볼 필요가 있다.

87년이 지나면서 민주화운동 과정에서 더 많은 부검논쟁이 들끓었다. 80년대말과 90년대초 이철규, 강경대 그리고 이경현, 김귀정 등 죽음의 행렬이 이어졌다. 그리고 이러한 죽음들마다 계속된 부검논쟁을 낳았다.

이처럼 한국 민주화운동 속에서 끊이지 않았던 부검논쟁을 통해, 부검이라는 의학적 행위가 한국 민주화운동 역사에서 어떤 역할을 했고, 또 그것을 사회적 논쟁은 어떤 모습으로 어떤 의미를 낳았는지 살펴보고자 한다.

키워드: 1987, 박종철, 이철규, 부검, 민주화운동

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한국과 일본에서 노동안전보건운동의 전개와 안전보건 시민권

김직수

사회공공연구원

노동안전보건 영역은 '생산의 지점' 안팎에서 무엇이 '재해'인가의 규정을 둘러싸고 '생산의 정치'와 '전문성의 정치'가 동시에 작동하는 독특한 영역이다. 생산과정에서 노동자의 안전과 건강은 임금과 더불어 핵심적인 노동조건으로서 노동과 자본 간의 구조적인 권력 비대칭 속에서 투쟁과 협상을 통해 결정되는 '경합적 교환'의 대상이다. 동시에 노동안전보건 영역의 주요 이슈들은 생산방식 및 생산과정과 관련되는 기술적 요소들과 밀접히 관련되어 있으며, 노동자의 안전과 건강에 대한 규정은 종종 의학 및 인간공학과 같은 고도의 과학기술적 전문지식과 결합되어 있다.

때문에 노동안전보건 영역은 노동과정에 대한 통제와 긴밀히 연결되어 있으면서도 계급적 이해관계나 노동자 의식의 발달 정도만으로 설명되지 않는 특수성을 지닌다. 예컨대 노동조합이 상대적으로 강한 교섭력과 현장 통제력을 지닌 작업장의 사례에서도 일반 노동자들은 안전보건 문제와 관련하여 적극적으로 사고하고 행동하기보다는 감히 건드릴 수 없는 '전문적 영역'으로 남겨두는 경우가 많다. 그런데 전문성이 구축되고 유지되며 재구축되는 정치과정을 '전문성의 정치'라 한다. 전문성의 정치는 의료시스템과 같은 전문성의 영역 '내부'에서 전개될 수도 있지만, 전문성 자체에 대해 문제를 제기하는 방식으로 이루어질 수도 있다.

본 연구에서는 한국과 일본의 사례를 통해 전문성의 정치를 경유하여 안전보건에 관한 '시민권'이 어떻게 형성되고 변화하는지를 분석하고자 한다. 시민권의 개념은 공동체의 구성원 자격을 의미하는 개념으로부터 시민적 권리, 나아가서는 정치적 주체로서 참여의 의무 및 덕성의 의미로 확장되어 왔다. 노동안전보건 영역에서 시민권은 생산과정에서 안전과 건강이 사회적 문제로서 인정되며 형성되는지, 노동자들이 그러한 노동안전보건 문제에 관해 개별적 또는 집단적으로 참여할 권리를 지니는지, 나아가서는 다른 노동자들 및 사회집단의 안전과 건강에 대한 관여가 시민적 의무로서 제기되는지 등과 관련된다.

키워드: 노동안전, 건강권, 시민권, 전문성의 정치

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조선의 유행성 열병 대응 - 16, 17세기 온역 전문의서

김상현

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한국의학사 연구에서 유행병(혹은 전염병)은 충분히 주목할만한 주제이다. 무엇보다 실록의 기록을 통해 질병의 유행이라는 사건을 확인할 수 있고 그에 대응되는 간이의서가 사료로서 남아있기 때문이다. 조선시대에 유행했던 대표적인 전염병으로 두창(천연두), 마진(홍역)이 있고, 그 외에 온역(瘟疫)이라는 질병 범주가 있었음을 사료를 통해 확인할 수 있다. 온역이라는 명칭을 현대의 병명으로 특정지어 설명하는 데에는 한계가 있지만 보편적으로 발열을 주 증상으로 하는 전염성, 유행성 질환이었다는 것을 유추할 수 있다. 현전하는 사료로서 국가에서 편찬한 온역 전문의서는 『간이벽온방』, 『분문온역이해방』, 『신찬벽온방』, 『벽온신방』, 『벽역신방』 총 다섯 권이다. 해당 서적의 간행 시기가 16, 17세기에 국한되어 있지만 이 사료를 바탕으로 당시에 유행성 열병에 어떻게 대응하였는지 다각도로 분석하고자 한다.

우선 이러한 온역 전문의서가 국가적으로 간행된 배경에 대해 살펴본다. 조선 건국 이래로 의료 정책이 어느 단계로 시행되었으며, 그 중 이러한 서적의 간행과 배포는 어떤 성격을 지니는지 고찰하도록 하겠다. 다음으로 이런 일련의 사료를 중심으로 형성된 의학지식을 온역학이라고 정의할 때, 그 학술적, 사회적 특징을 고찰해본다. 기본적으로 각 의서에 수록된 내용의 성격을 분석하고, 이러한 간이의서의 속성과 유행병 대응 시책간의 관계를 분석하도록 하겠다. 마지막으로 동아시아 의학의 흐름에서 조선의 온역학이 어떠한 위상을 지니는지 고찰해본다. 주류 의학이라 할 수 있는 대륙의 의학 사조에 비견해 볼 때 온역학이 어떻게 한반도의 사정을 반영하여 형성되었는지를 살펴보도록 하겠다.

이상의 고찰을 바탕으로 조선의 유행성 열병 대응의 의학적, 역사적 가치를 조망해보고 나아가 고대나 근현대 전염병 연구의 연결점으로써 활용되기를 기대한다.

키워드: 유행병, 전염병, 열병, 온역, 온역학

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조선시대 전염병 대책과 활인서 운영

김성수

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조선은 건국과 동시에 국가를 운영하기 위한 다양한 정부기구의 직제를 개편한다. 그 중에는 고려의 제도를 그대로 답습하는 경우도 있으며, 때로는 새로운 관제를 창설하기도 하였다. 의료와 관련하여서는 대체적으로 고려의 유제를 따르는 편이었지만, 관서의 명칭을 바꾸거나 혹은 직제를 구체화하는 것으로 정리하였다. 질병의 치료를 위한 제반 정책 수립과 운영을 담당하는 기관은 애초에 전의감과 혜민서, 동서대비원만이 존재하였다. 이후 전의감에서 내의원이 독립하였고, 혜민서와 함께 대민의료를 담당할 관서로는 대비원 이외에 제생원이 창설되기도 하였다.

전의감이 관료들의 치료를 담당하였지만, 기본적으로는 의료정책의 전반을 관할하는 의료의 핵심이었다고 할 수 있다. 한편 혜민서와 활인원, 제생원은 의료 현장의 최전선에 있었다. 그러나 이들 관서의 성격은 매우 달랐다. 혜민서가 국가에서 사용되는 약재의 출납, 즉 전국에서 중앙정부로 올라오는 향약을 관장하면서 동시에 향약을 기반으로 병자에게 판매하는 역할을 하였다. 반면 활인원은 병자들을 수용하여 치료하며, 기민의 구휼에도 관여하고 있었다. 둘 사이의 차이를 관리 중심 대상이라는 관점에서 거칠게 말한다면, 혜민서는 약 위주이며 활인원은 대상이 사람이었다고 할 수 있다. 그리고 이 가운데에 위치하였던 것이 제생원이었다.

조선의 국정을 운영하였던 국왕 및 위정자들이 의약정책을 시행하면서 특히 관심을 가졌던 부분이 전염병 대책이었다. 온역을 비롯하여 두창, 마진 등으로 이어지는 전염병의 유행은 대규모 인명 피해로 이어졌고, 이는 사회 · 경제 전반에 걸쳐 커다란 타격을 주었다. 따라서 전염병자들을 구휼하고 치료를 주로 하였던 활인원(활인서)은 매우 중요한 부서였다. 수사적인 표현임에도 불구하고, 그러한 이유로 격이 낮은 활인원을 일러 "훌륭한 정치의 큰 일(王政之大事)"을 하는 부서라고 말하였다.

그러나 격리치료 및 구휼을 담당하는 활인서를 운영하기 위해서는 재정 문제가 절실하였다. 많은 환자를 수용하고 치료하는 데 드는 비용 대부분을 국가에서 부담하였기 때문에, 운영인력과 필요한 치료에서 발생하는 비용을 획기적으로 줄일 필요가 있었다. 승려를 참여시키고 한증요법 등을 이용한 이유이기도 하였다. 그럼에도 병자를 수용하는 시설이 항구적이지 못하고 전염병 발생에 따라 유동적이고 임시적으로 운영되는 한계를 지니고 있었다. 게다가 전염병을 제외한 일반적인 의료행위가 환자가 거주하는 곳에서 행해졌던 관례와 다른 격리수용은 당시로써는 부정적 인식을 강화시킴으로써 활인서의 기능을 약화시키기는 요인이었다.

무엇보다 조선후기에 이르러 전염병 유행의 양상이 변화하면서 활인서의 중요도는 약화되었던 것으로 보인다. 여전히 온역과 같은 전염병이 유행하고 있었지만 두창이나 마진과 같은 질병이 대체로 소아전염병으로 정착하면서, 소아과 혹은 두창 전문 의사들이 출현하기 시작하였다. 이는 활인서의 활동 영역을 축소시켰고, 정부 의료기구가 감축되는 경향 속에 활인서 인원 축소로 반영되었다. 그러나 존폐와 병합의 논란 속에서도 1882년 혁파되어 전의감 소속될 때까지 활인서는 조선의 주요 의료기관으로 존속하였고, 활인서가 갖고 있었던 대빈민구료 정신은 1905년 대한국 적십자병원의 설립으로 계승되었다.

키워드: 활인서, 전염병, 격리, 병상, 의료정책

S60

미국 보건권력의 상호작용: 20세기초 결핵 요양소를 중심으로

김서형

인하대학교 인경교양교육연구소

인류 역사상 가장 오래된 질병 가운데 하나였던 결핵은 산업화 이후 더욱 심각한 영향을 미쳤다. 많은 의사들은 과도한 노동과 도시의 비위생적 환경, 그리고 불균형적인 식사 때문에 결핵이 발생했다고 생각했고, 신선한 공기와 균형 잡힌 식사를 통해 결핵을 치료하고자 했다. 미국사회도 예외는 아니었다. 19세기 말 결핵균이 발견된 이후에도 특별한 결핵 치료법이 없었기 때문이다. 하지만 20세기 이후 결핵의 치명성이 더욱 심각해지면서 이는 다른 어떤 전염병보다도 미국사회의 공중보건과 위생을 위협하는 치명적인 요인이었다. 이러한 사회적 분위기 속에서 사적 영역을 넘어 공적 영역에서 결핵을 치료해야 한다는 주장들이 제기되었고, 이제 결핵은 미국사회 전체가 적극적으로 해결해야 할 문제로 부상했다.

공적 영역에서 결핵을 적극적으로 통제하고자 하는 시도는 버지니아 주에서 가장 먼저 시작되었다. 당시 버지니아 주에서는 매년 1만 명 이상의 결핵 환자가 발생했고, 5천 명 이상이 사망했다. 이와 같은 심각한 문제를 해결하기 위해 버지니아 주정부는 미국역사상 최초로 주정부가 후원하는 결핵 요양소를 설립했다. 1909년 로어노크에 설립된 카토바 요양소가 바로 그것이다. 결핵 요양소에 수많은 환자들이 몰려들면서 버지니아 주정부는 블루리지 요양소를 설립했고, 가난한 흑인들을 위해 피드몬트 요양소를 설립하기도 했다. 이와 같은 결핵 요양소는 질서유지 권력을 행사함으로써 역학과 질병 관리를 통해 공중보건을 유지하고 향상시키고자 했던 버지니아 주정부의 정책의 상징이었다.

미국사회에 만연했던 결핵에 관심을 가졌던 것은 비단 주정부뿐만이 아니었다. 연방정부 역시 결핵 통제를 통해 생명 권력을 행사하고자 했다. 공중보건법을 통해 미국사회의 위생과 공중보건을 향상시키고자 했던 연방정부는 아메리카 원주민 결핵 환자들을 위한 요양소를 설립하고, 여러 가지 정책들을 시행했다. 이와 같은 연방정부의 정책들은 무엇보다도 바람직한 사람들을 미국시민으로 수용하기 위한 것이었다. 이와 같은 과정 속에서 주정부의 질서유지 권력과 연방정부의 생명 권력은 중첩되면서 공중보건과 관련된 통제 권력의 주체를 둘러싼 갈등을 야기했다. 그럼에도 불구하고, 서로 다른 층위의 보건권력의 궁극적인 목적은 결핵이라는 치명적인 유행성 전염병을 효과적으로 통제하는 것이었다. 이러한 점에서 20세기 초 미국사회의 결핵 요양소는 이중적인 보건 권력의 갈등과 마찰, 그리고 얽힘을 단적으로 보여주는 공간이었다고 할 수 있다.

키워드: 결핵, 결핵요양소, 버지니아 주정부, 연방정부, 질서유지 권력, 공중보건 권력

S61

1894년 홍콩 페스트의 유행과 동화의원의 공간변화

신규환

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동아시아 각국은 서양의학의 도입과정에서 질병인식과 의학인식에 기초하여 엄청난 병원공간의 변화를 경험했다. 특히 1880년대부터 1900년대 초까지 서양의학계는 미아즈마설에서 세균설을 거쳐 실험의학으로 나아가는 급격한 변화의 시기였고, 병원공간 역시도 이러한 변화에 민감하게 대응했다. 홍콩의 대표적인 중의병원인 동화의원은 개원 직후인 1872년 평면도와 개축 이후인 1903년 평면도를 비교해 볼 때, 무려 30년의 시간 차이에도 불구하고 병원의 공간구성과 배치에 있어 별다른 차이가 발견되지 않는다. 동화의원 설립부터 개조에 이르기까지 식민정부 내외에서 엄청난 논쟁과 대립이 있었던 것과 달리 평면도상에서는 수술실, 예방접종실, 전염병실 등 서양의학의 영향을 찾아볼 수 없다. 그것은 홍콩 식민당국의 방역정책이 미아즈마설에 근거한 것이어서 병원의 폐쇄 이외에는 별다른 대안을 제시하지 않은 점, 동화의원에서 서양의학의 도입이 전면적인 것이 아니라 절충적이었던 점 등과 관련된다.

평면도상으로는 서양식 병원의 특징을 찾아보기 어렵다. 당초 동화의원에는 근대식 서양병원에서 중요한 공간이었던 수술실, 실험실, 접종실, 전염병실이 별도로 구축되지 않았다. 페스트 유행 이후 식민당국으로서는 동화의원을 통해 단순히 질병을 치료하는 것에 그치지 않고 서양의학의 도입을 통해 질병을 분류하고 전염병을 관리하는 것이 중요했다. 동화의원에 전염병 전문병동은 설치되지 않았지만, 수증방 제도를 운영하여 전염병 관리에 신경을 썼으며, 서의의 고용을 통해 외과수술을 본격적으로 도입했다. 수증방이란 일종의 예비 격리병실을 뜻한다. 주치의가 1차 진단을 통해 질병에 따라 환자를 분류하고, 순회의관의 2차 진단을 통해 질병을 확진하는 제도였다. 수증방 제도가 전염병 관리에 필요한 실험실과 검사장비의 부실을 근본적으로 만회할 수는 없었지만, 2차례에 걸친 진단으로 오진의 가능성을 줄이고자 했다는 점, 서양의학을 전면적으로 실시할 수 없었던 제한적인 환경에서 전염병관리를 유지했다는 점은 평가할 만하다. 아울러 동화의원은 서양식 외과수술의 도입을 통해 서양식 감염관리와 서양의학의 점진적 확산에도 공을 들였다.

키워드: 홍콩 페스트, 동화의원, 공간변화, 수증방

S62

한국전쟁 이후 한센병 정책의 전환-코크레인 보고서를 중심으로

김원중

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일제 강점기 조선에서의 한센병 정책은 크게 두 가지로 구분 된다. 서구 선교사들에 의한 상대적 격리 모델과 일제에 의한 강제 격리 모델이 있다. 이는 1930년대 이후 강제적 격리로 통합되면서 일본 파시즘의 본질을 가장 잘 드러내게 된다. 강제적 격리 정책은 일본 본국의 정책과도 크게 다르지 않았다. 한국에서는 대형 수용소에 모아 상황이 더욱 열악했던 반면 일본의 한센병 요양소는 여러 곳에 분산되어 있었던 차이였다. 해방 후 한국의 한센병 정책은 일본과 뚜렷한 차이를 보인다. 일본은 1931년 제정된, 제국주의 시기의 한센병 정책의 근간이었던 나예방법은 1953년 라이예방법으로 개정되었지만 강제 격리 정책은 그대로 유지되어 1996년까지 지속되었다. 반면, 한국의 경우 1950년대의 재활정착운동, 특히 1962년 이후의 국가적 정착사업으로 식민지 시기와 결별하였다. 이런 차이를 보이게 된 원인은 다음과 같다. 한국전쟁 이후 한센병 정책은 보건의료체제의 일부로서 살펴볼 필요가 있다. 특히, 한센병은 당시 보건부예산의 40%를 사용할 정도로 비중있는 질환이었다. 한미재단은 한국전쟁으로 붕괴된 공적 보건의료체제의 기반을 재건하는데에 중추적 역할을 한 기관이다. 그 중의 하나가 한센병 관리를 위한 코크레인 박사의 초빙이었다. 1955년 방한한 코크레인은 한국 한센병 관리의 실태를 파악하고 권고안을 제시하였는데, 이는 추후 한국 한센병 정책의 중요한 지침이 되었다. 코크레인은 다음을 제안하였다. 첫째, 외국인 공중보건의에게 나병을 교육시켜 역학조사를 실시하여 그 실태를 파악하고 사업을 점차 내국인에게 넘겨 주어야 한다. 둘째, 남부 4개도에서 표본 사업(pilot project)을 권유한다. 셋째, 한센병 환자에 대해서 강제적으로 경찰력을 동원하여 시설에 넣으려는 시도는 중단되어야 한다. 넷째, 내국인 공중보건 전문가를 시급히 양성해야 하고 외국인은 그들을 지휘할 것을 권유한다. 다섯째, 경기도의 한 집단마을이 자활을 위하여 노력하는 것을 보고 그 가능성을 엿보고, 시책의 초점을 자급자족에 두기를 권유한다. 여섯째, 나병의 치료에 DDS 투여를 권장하고 예방적으로도 투여함이 바람직하다. 보건부는 이 같은 코크레인의 권고에 따라 한미재단의 후원으로 1956년 나이동진료반을 운영함으로써 기존의 격리 위주였던 소극적인 한센병 관리에서 벗어나, 직접 환자를 찾아나섰고 그들의 거주지에서 치료를 시행하였다. 이는 한국 특유의 재활정착운동이 성공적으로 자리잡게 하는데에 큰 역할을 하였다.

키워드: 한센병, 식민지시대, 코크레인 보고서, 한국전쟁

S63

1987년 에이즈예방법 제정과 반미주의

김택중

인제대학교 의과대학 인문사회의학교실

1979년 미국에서 처음 보고된 뒤 6년이 지난 1985년 한국에 모습을 드러낸 후천성면역결핍증(이하 에이즈)은 1980년대 한국의 반미주의를 심화시킨 여러 요인들 가운데 하나였다. 그러나 정작 1987년 11월 28일 공포된 한국의 후천성면역결핍증예방법(이하 에이즈예방법) 제정에 직접적인 영향을 미친 것은 반미주의가 아니었다.

에이즈를 대상으로 한 세계 최초의 법제화라는 점에서 1987년 당시 각국의 관심을 받았던 에이즈예방법 제정의 직접적인 동력은 반미주의가 아니라 1986년 서울 아시안게임과 1988년 서울 하계 올림픽의 성공을 위해 전두환 정부가 1982년부터 본격화한 통제 위주의 성병 정책이었다. 정부가 1987년 3월 특별법 형태의 에이즈예방법 제정을 천명하면서 위반자에 대한 처벌 수위를 기존 전염병예방법(현 감염병의 예방 및 관리에 관한 법률) 처벌 규정보다 훨씬 강화할 방침임을 예고한 점, 1987년 10월 30일 국회 본회의에서 의결된 에이즈예방법안이 의원 제출안이 아닌 정부 제출안이었고 이 정부 제출안이 원안대로 국회를 통과한 점, 그리고 1987년 9월 대한의학협회(현 대한의사협회)와 1987년 10월 대한변호사협회가 각각 인권 침해를 이유로 정부가 입법 예고한 법안에 반대 의견을 제출한 점 등은 전두환 정부의 통제 위주 성병 정책이 신종 성병인 에이즈에도 그대로 관철되었음을 말해 준다.

에이즈예방법은 제정된 지 불과 1년만인 1988년 12월 31일 1차 개정이 이루어졌다. 반미주의는 이 시기에 이르러 예방법 개정의 주요한 사회적 배경으로서 분명하게 가시화되었다. 역으로 얘기하면 에이즈의 국내 확산이 뜻하지 않게 한국의 반미주의를 심화시킨 한 사회적 요인으로 작용하였다는 것이다. 즉, 에이즈 국내 확산의 가장 큰 책임이 주한 미군과 타락한 미국 문화에 있으며 이로부터 우리 민족의 자주성을 지켜야 한다는 당시 한국 사회 내부의 인식이 결과적으로 검역 주권이 제대로 작동할 수 없었던 기존 예방법의 개정과 보완이라는 정치적 성과를 이끌어 내었다는 의미이다. 이는 한편으로는 1980년 5월 17일 군사 쿠데타로 집권한 신군부의 광주민주화운동 폭력 진압 이후 사회 저변에 깔린 반미감정과 친미 일변도 독재정권에 대한 저항의식, 그리고 1987년 6월 민주항쟁으로 권위주의 체제가 침식되면서 사회 전반에 형성된 민주화 분위기에 에이즈라는 전대미문의 신종 감염병에 대한 사람들의 공포심이 어우러진 결과였다고 할 수 있다.

키워드: 후천성면역결핍증예방법, 에이즈예방법, 에이즈, 반미주의, 1987년

해부학에서의 차세대 융합연구
(나노, 센서, 플랫폼)

Next Generation Convergence Research in Anatomy
(Nano, Sensor, Platform)

대한해부학회

일시 : 6월 29일(금) 14:30-18:00
장소 : 종합실습동 함춘강의실

2018 The 26th Federation Meeting of
Korean Basic Medical Scientists

S64

Bio-inspired Nanomedicine

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Nanotechnology have attracted great attention to molecular biology and translational medicine because life processes are maintained by the action of a series of molecular nanomachines in the cell machinery. Recent advances in nanoscale materials that possess emergent physical properties and molecular organization hold great promise to impact human health in the diagnostic and therapeutic arenas. In order to be effective, nanomaterials need to navigate the host biology and traffic to relevant biological structures, such as diseased or pathogenic cells. Moreover, nanoparticles intended for human administration must be designed to interact with, and ideally leverage, a living host environment. Inspired by nature, we use peptides to transfer biological trafficking properties to synthetic nanoparticles to achieve targeted delivery of payloads. In this talk, development of nanoscale materials will be presented with a particular focus on applications to three outstanding health problems: bacterial infection, cancer detection, and traumatic brain injury. A biodegradable nanoparticle carrying antibacterial agents trafficked to the bacterial surface has antimicrobial activity in a pneumonia model. Trafficking of a tumor-homing nanoprobes sensitively detects cancer via a high-contrast time-gated imaging system. A neuron-targeted nanoparticle carrying siRNA traffics to neuronal populations and silences genes in a model of traumatic brain injury. Unique combinations of material properties that can be achieved with nanomaterials provide new opportunities in translational nanomedicine. This framework for constructing nanomaterials that leverage bio-inspired molecules to traffic diagnostic and therapeutic payloads can contribute on better understanding of living systems to solve problems in human health.

Keywords: Nanoparticle, Drug delivery system, Bioimaging, Antibacterial, Nano-bio interface

S65

Micro/Nanotechnology-based Biosensor Platforms for Biomedical Applications

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Recently, there has been growing interest of highly sensitive biomolecule detection technology based on miniaturized system for detection of disease biomarkers ranging in sub-ng/mL level. The detection limit of most of detection system in clinical laboratory stayed down at ng/mL concentration level in spite of the concentration range of newly discovered biomarkers (proteins, enzymes and so on) in several body fluids is under ng/mL level. Moreover, detection system with better sensitivity and detection limit definitely need understanding for neurotransmitter function in a brain. In this point of view, micro/nanotechnology-based biosensor platforms have new opportunity because these are able to satisfy detection performance (sensitivity and detection limit)for new target molecules detection. In this presentation, we introduce our developed two biosensor platforms, such as microelectrode-based biosensors and reduced graphene oxide-based biosensors, with detection limit of sub-ng/mL to apply a number of clinical and biological applications.

Keywords: Biosensors, Biomarkers, Microelecgtrode, Graphene

S66

RNAi-based Nanoparticle for Neuropathic Pain

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Central sensitization results from changes in the properties of neurons in the central nervous system and produces pain hypersensitivity by changing the sensory response elicited by normal inputs. Although numerous mechanisms have been implicated in central sensitization, three mechanisms have been well established: alteration in glutamatergic neurotransmission / NMDA receptor-mediated hypersensitivity, loss of tonic inhibitory controls (disinhibition), and glial-neuronal interactions. In particular, activated microglia in the spinal dorsal horns have been shown to secrete a variety of cytokines and other diffusible factors involved in re-sensitizing neurons and the surrounding glia, thereby further exacerbating disease symptoms.

Thus, regulation of microglial activation (M1, M2) has been the subject of intensive research efforts aiming to ameliorate pain hypersensitivity. Recently, gene therapies based on small interfering RNA (RNAi) silencing of disease-related genes has received significant attention due to its potential to cure painful disorders. In this study, we applied nanoparticles (PLGA) encapsulated RNAi targeted microglia activation regulating factors (p38, CD200, Foxp3) as a powerful strategy for the treatment of neuropathic pain.

Keywords: Neuropathic pain, Nanoparticle, Central sensitization, Microglia, Spinal cord

S67

A Calcium- and Light-gated Switch to Induce Gene Expression in Activated Neurons

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Despite recent advances in optogenetics, it remains challenging to manipulate gene expression in specific populations of neurons. We present a dual-protein switch system, Cal-Light, that translates neuronal-activity-mediated calcium signaling into gene expression in a light-dependent manner. In cultured neurons and brain slices, we show that Cal-Light drives expression of the reporter EGFP with high spatiotemporal resolution only in the presence of both blue light and calcium. Delivery of the Cal-Light components to the motor cortex of mice by viral vectors labels a subset of excitatory and inhibitory neurons related to learned lever-pressing behavior. By using Cal-Light to drive expression of the inhibitory receptor halorhodopsin (eNpHR), which responds to yellow light, we temporarily inhibit the lever-pressing behavior, confirming that the labeled neurons mediate the behavior. Thus, Cal-Light enables dissection of neural circuits underlying complex mammalian behaviors with high spatiotemporal precision.

Keywords: Optogeneitics, Neuronal ensembles, Synthetic biology, Gene expression, Neuronal labeling and manipulation

S68

What Drive us to Eat- The Neuroscience of Appetite

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Modern rapid rise of obesity is mainly due to modern lifestyle and modern environment with overwhelming exposure to highly hedonic food cues. The cognitive response to these hedonic food cues and behavior consequences are the key pathogenic drivers of obesity. Recent researches have enlightened important insights into the neural circuits controlling energy balance and glucose homeostasis. By translating these neural circuits to clinical therapies, numerous approved drugs and devices are already in clinical use and many promising novel approaches are under development. Novel advances in basic and clinical neurosciences have broadened the classical view of homeostatic regulation of body weight primarily by the hypothalamus to include hedonic appetite controls. Hedonic mechanisms are driven by cortical and subcortical brain areas that process external sensory information, reward, cognition, and executive functions. These hedonic mechanisms interact with homeostatic mechanisms to regulate appetite and body weight in a flexible, adaptable and dynamic equilibrium. This equilibrium build basis for, so called, body weight set-point (or more precisely settling point). This set-point is not a rigid inborn genetic number, but more like a flexible point of compromise, influenced by environmental conditions. The current hypotheses on the cause of obesity includes, genetics, increased availability of palatable energy-dense foods, increased exposure to food cues, stress-induced overeating and habit-driven food intake. The modern obesity is driven by gene?environment interactions whereby recent changes in palatable food industry and environment trigger overeating and/or sedentary life style in individuals with genetic predisposition. Many of these predisposition genes are expressed in the brain, the master controller of food seeking, food memory, food emotion, food motivation, ingestive behavior, locomotor behavior and regulator of body weight. Novel anti-obesity and/or anti-diabetes drugs targeting brain are continuously in development. Current approved anti-obesity drugs target noradrenaline, serotoninergic, GLP-1, dopaminergic, GABAergic, and opioid pathways in the brain. Current approved anti-obesity devices/surgery target vagus nerve and/or stomach. Deep brain stimulation and current stimulation targeting hypothalamus or cortex are under development. Because the neural pathways controlling food intake and energy expenditure are complex and involve redundant mechanisms controlled by a multitude of genes and neural circuits, optimal therapeutic strategy will likely require combination approaches. Certainly, future researches on the brain pathways regulating energy balance and glucose homeostasis will provide insights that will facilitate the development of multi-faceted approaches to combat both obesity and diabetes.

대사 경로의 연구 – 최신 동향과 리뷰

Metabolic Pathways - Latest Research and Review

생화학분자생물학회

일시 : 6월 29일(금) 14:45–17:45

장소 : 학생관 제1강의실 (101호)

2018 The 26th Federation Meeting of Korean Basic Medical Scientists

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The Nuclear Receptor SHP is a Critical Regulator of Nutrient Sensing, Basal Autophagy, and Energy Homeostasis

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The atypical nuclear receptor small heterodimer partner (SHP, also known as NR0B2), which lacks a DNA binding domain, is a key transcriptional corepressor of bile acid synthesis and its related metabolic pathways. SHP is also a tumor suppressor because *Shp*$^{-/-}$ mice develop spontaneous liver tumors. Bile acid signaling is activated in the fed state of the liver, when bile acids return to the liver via the enterohepatic circulation. Here we show a role for SHP in nutrient sensing in the fed state of the liver. Livers of *ad libitum* chow-fed *Shp*$^{-/-}$ mice show multiple features of nutrient deprivation, with an increase in upstream signaling of autophagy, autophagosome formation, and fatty acid oxidation. Despite these phenotypes, hepatic p62, a well-known substrate of autophagic degradation, is elevated in the fed state of *Shp*$^{-/-}$ mice. This is also observed in liver-specific knockouts of the essential macroautophagy genes, Atg7 or Atg5, and indicates a blunted basal autophagic flux. *Shp*$^{-/-}$ mice also have dramatically elevated hepatic glycogen depositions, probably due to a deviation of hepatic glucose into glycogenesis pathway rather than glycolysis. In compensation, *Shp*$^{-/-}$ mice show increased fatty acid oxidation to generate ATP. Taken together, *Shp*$^{-/-}$ mice mimic a constant fasting status with a dysfunction of basal autophagy activity in the fed state. These results reveal a critical role of the nuclear receptor SHP as a fed state nutrient sensor.

Keywords: Metabolism, Nuclear Receptor, Glycogen, Autophagy

S70

How Metabolic Stress Leads to Chronic Diseases - Role of TonEBP

Hyug Moo Kwon

UNIST

TonEBP belongs to the Rel family of DNA binding proteins which include NFκB and NFAT. The physiological function of TonEBP appears to be the induction of inflammation in response to infection by bacteria or viruses. Infection elevates TonEBP expression in macrophages which elicits inflammation and fights infection. TonEBP is a transcriptional cofactor for inflammatory transcription factors NFκB and AP-1. Elevated expression of TonEBP enhances M1 gene expression and cell migration in macrophages leading to systemic inflammation.

Our recent studies reveal that TonEBP is induced by a variety of metabolic stresses leading to immunometabolic and chronic diseases:

1) Hyperglycemia directly elevates TonEBP expression in macrophages leading to systemic inflammation which results in vascular (atherosclerosis) and renal injury (diabetic nephropathy).

2) Hepatocellular carcinoma (HCC) is a major cancer with very high recurrence (70%) and mortality. TonEBP expression in hepatocytes is elevated by a variety of etiological agents for HCC: hepatitis B virus, hepatitis C virus, fatty liver, alcohol abuse and septicemia. Elevated hepatic TonEBP drives hepatocellular carcinogenesis indicating that TonEBP represents a common pathway of tumorigenesis in response to diverse etiological agents. Analyses of hepatic tissues from 296 patients who received a complete resection of HCC (primary tumors) reveal that elevated TonEBP expression in areas adjacent to tumor predicts recurrence and metastasis. Our preliminary data indicate that TonEBP promotes self-renewal of cancer stem cells by regulating DNA repair pathways. This can provide mechanisms basis for the role of TonEBP in cancer recurrence and chemoresistance.

3) When subcutaneous adipocytes accumulate triglycerides in response to excess calorie intake, TonEBP expression rises to a very high level. The elevated TonEBP blocks the expression of the β adrenergic receptor (adrb3) using an epigenetic mechanism involving methylation of the promoter. The lack of adrb3 leads to blocked lipolysis and thermogenesis, which, in turn, results in obesity and insulin resistance.

We are making headway in developing therapeutic agents targeting TonEBP. We have lead compounds which exhibit potent anti-inflammatory activity and block self-renewal of cancer stem cells. These data demonstrate that TonEBP is an attractive therapeutic target for immunometabolic and chronic diseases.

Keywords: Macrophage, Hepatocellular Carcinoma, Lipolysis, Thermogenesis

S71

Hepatic Steatosis and Insulin Resistance via Endocytosis of TLR4/NOX2 in Macrophage

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Reactive oxygen species (ROS) contribute to the development of non-alcoholic fatty liver disease. ROS generation by infiltrating macrophages involves multiple mechanisms, including Toll-like receptor 4 (TLR4)-mediated NADPH oxidase (NOX) activation. Here, we show that palmitate-stimulated $CD11b^{+}F4/80^{low}$ hepatic infiltrating macrophages, but not $CD11b^{+}F4/80^{high}$ Kupffer cells, generate ROS via dynamin-mediated endocytosis of TLR4 and NOX2, independently from MyD88 and TRIF. We demonstrate that differently from LPS-mediated dimerization of the TLR4-MD2 complex, palmitate binds a monomeric TLR4-MD2 complex that triggers endocytosis, ROS generation and increases pro-interleukin-1β expression in macrophages. Palmitate-induced ROS generation in human $CD68^{low}CD14^{high}$ macrophages is strongly suppressed by inhibition of dynamin. Furthermore, Nox2-deficient mice are protected against high-fat diet-induced hepatic steatosis and insulin resistance. Therefore, endocytosis of TLR4 and NOX2 into macrophages might be a novel therapeutic target for non-alcoholic fatty liver disease.

Keywords: Nonalcoholic fatty liver disease, Kupffer cell, Reactive oxygen species, Palmitate

S72

Lessons from Hepatocyte-specific Sirtuin 6 Knockout Mice: Activation of All Three Canonical Pathways of the UPR is Not a Prerequisite for the Development of NAFLD

In-Hyuk Bang and Byung-Hyun Park

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Endoplasmic reticulum (ER) stress has been proposed to be involved in the pathophysiology of nonalcoholic fatty liver disease (NAFLD). Sirtuin 6 (Sirt6), an NAD^+-dependent deacetylase, is known to improve NAFLD. Here, we hypothesized that Sirt6 can protect against NAFLD by alleviating ER stress response in the liver. Hepatocyte-specific Sirt6 knockout (KO) mice and wild type (WT) mice were challenged with tunicamycin (Tm) to induce ER stress. Primary cells isolated from WT and KO mice and HepG2 cells were also used for the *in vitro* experiments. Tm treatment increased ER stress markers and pro-apoptotic proteins and decreased anti-oxidative capacity, leading to hepatic steatosis and insulin resistance; these effects were augmented in KO mice. Conversely, administration of Sirt6 adenoviruses in mice alleviated Tm-induced hepatic steatosis and insulin resistance, in parallel with reduced expression of ER stress markers. Analysis of three canonical unfolded protein response (UPR) branches indicated that Sirt6 deficiency activated inositol-requiring enzyme 1α (IRE1α)-X-box-binding protein 1 (XBP1) pathway. Similar observations were made in cell culture experiments. Mechanistically, Sirt6 directly interacted with and deacetylated XBP1s, which decreased its protein stability and transcriptional activity. Finally, we showed that pharmacological activation of Sirt6 inhibited the ER stress-induced steatosis *in vivo*. Taken together, these results suggest that Sirt6 is an integral component of hepatic UPR program and exerts beneficial effects on lipid metabolism and insulin signaling through counteracting IRE1α-XBP1s pathway.

Keywords: Sirtuin 6, ER stress, XBP1, NAFLD

S 73

A Journey to Explore Glucose Homeostasis

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I have been exploring the roles of transcription factors regulating the genes involved in glucose metabolism for over 30 years. The main field of study can be summarized as (1) identification of promoters of genes in glucose metabolism, (2) exploration of interaction between promoters and transcription factors leading to tissue-specific gene expression, and (3) changes in these interactions in metabolic diseases such as diabetes or obesity. Particularly, we have clarified the gene regulation of glucose sensor, GLUT2 and glucokinase, in the liver and pancreatic β-cells.

Keywords: Glucose Sensor, Glut2, Glucokinase, Type 2 Diabetes, Obesity, Transcriptional Regulation

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계명대학교 의과대학 미생물학교실

P-052 **인테그론과 IncF 복제단위를 보유한 CTX-M 산생 대장균의 다약제 내성 획득 기전**
양유이, 백원기, 서성일, 서민호
계명대학교 의과대학 미생물학교실

P-053 **Anti-obesity and Anti-diabetic Effects of Mixed Cultures of Sanghwang, Chaga and Youngji Mushroom Mycelia Germinated Naked Barley (MC-SCY) in Mice**
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P-054 **Effect of Chunggukjang Fermented with *Bacillus subtilis* (SRCM 101336) to Enhance Immune Responses in Murine Immune Cells**
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P-055 **Epidemiology and Genetic Characterization of Human Adenovirus in Korea, 2013-2017**
Heui Man Kim, Anna Lee, Namjoo Lee, Mi-Seon Kim, Jun-Sub Kim, Min Gu Kang, Jeong-Min Kim, Yoon-Seok Chung, Chun Kang
Division of Viral Diseases, Center for Laboratory Control of Infectious Diseases, Korea Centers for Diseases Control and Prevention

P-056 **A Human Hepatoblastoma Cell Line Susceptible to Hepatitis B Virus**
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P-057 **Genetic Analysis of Severe Fever with Thrombocytopenia Syndrome Viruses Isolated from Korea in 2017**
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P-058 **Laboratory Surveillance of Human Acute Respiratory Virus Infections in Korea, 2017**
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P-059 **Congenital Rubella Syndrome: A laboratory-confirmed, Import-related Case in the Republic of Korea, 2017**
Jin-Sook Wang[1], Hye Min Lee[1], Su Jin Kim[1], Yoon-Seok Chung[1], Chae won Jung[2], Hye kyung In[2], DongHee Seo[2], Dong Han Lee[2], and Chun Kang[1]
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P-060 **An Improved Infectious Hepatitis B Virus Cell Culture System Supporting the Entire Viral Life is Suitable to Perform Chemical and Functional Genomic Studies**
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P-061 **KSHV vIRF3 Promotes Angiogenesis of Lymphatic Endothelial Cells by Deregulating HDAC5 Activity**
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P-062 Transmembrane Protein pUL50 of Human Cytomegalovirus Inhibits ISGylation by Downregulating UBE1L

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P-063 Surveillance of Acute Falaccid Paralysis (AFP) in the Republic of Korea(ROK), 2017

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P-065 Genetic and Antigenic Characterization of Influenza Viruses for Recent Four Seasons (2014/2015~2017/2018) in Korea

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P-066 A Study of Immune Enhancement by Co-administration of Interleukin-2 and Foot-and-Mouth Disease Vaccine

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P-067 Evolution and Persistence of the Resistance-Associated Substitutions of Hepatitis C Virus after Direct-Acting Antiviral Treatment Failures

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P-068 Analysis of IE62 Mutations Found in Varicella-Zoster Virus Vaccine Strains for Transactivation Activity

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P-069 Multiplex PCR-based Next-generation Sequencing Reveals Global Distinct Genotypes of Seoul Virus

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P-070 **Novel Triple-Reassortant Influenza A(H1N2) Viruses isolated from pigs in Korea**
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P-071 **KH29 추출액의 PKB/AKT Signal 활성을 통한 수족구병 유발 엔테로바이러스 증식 억제**
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P-072 **Lumbar Artery Injury During Posterior Spinal Surgery Detected by Postmortem CT-angiography: An Autopsy Case**
Hyelin Kim[1], Hong-il Ha[1], Kyungmoo-Yang[1], Sookyoung Lee[2], In-Soo Seo[1], Se-Min Oh[1], Bonggu Kang[1], Ki-Su Park[1], Heon Lee[3], Jang Gyu Cha[3], Taehwa Baek[1]
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P-073 **Os Odontoideum Mimicking Odontoid Fracture of the Axis**
Hyelin Kim[1], Hong-il Ha[1], Kyungmoo-Yang[1], Sookyoung Lee[2], In-Soo Seo[1], Se-Min Oh[1], Bonggu Kang[1], Ki-Su Park[1], Heon Lee[3], Jang Gyu Cha[3], Taehwa Baek[1]
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P-074 **Postmortem Interval Study of Potassium and Magnesium by Vitreous Humor**
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P-075 **Death After Bronchoscopic Biopsy of a Pulmonary Artery Aneurysm Mimicking Bronchial Polyp: Report of 2 Cases and Review of the Literature**
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P-076 **Study for Lists of Forensic Autopsy Request: Quantitative Analysis about Documents relating to Autopsy Request**
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P-077 **Acute Myocardial Infarction Secondary to Acute Aortic Dissection: An Autopsy Case**
Seung Jin Yoo, Myung Seok Sim, Ho Lee and Sang Jae Noh
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P-078 **Analysis of Morphometrical Relationship between Nostril and Nasal Aperture Employing Three-dimensional Post-mortem Computed Tomography Images of Heads**
Ki-Su Park[1], Ji-Su Yun[1], Min-Ji Kim[1], U-Young Lee[2], Sang-Seob Lee[3], Byung-Yoon Roh[3], Jeong-Uk Seo[3], Chang-Un Choi[1], In-Su Seo[1] and Won-Joon Lee[1]*
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P-079 **Estimation of Postmortem Interval based on Developmental Gene Expression Profiling in Necrophagous Fly**
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P-080 Identification of Forensically Important Calliphoridae and Sarcophagidae Species Using Multiplex Real-time PCR Assay
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P-081 Forensic Entomological Analysis of Puparia (Diptera: Calliphoridae) from Ancient Tomb in South Korea
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대한병리학회

P-082 Encapsulated Papillary Carcinoma of the Breast with an Ipsilateral Synchronous Invasive Ductal Carcinoma
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P-083 T-cell Immunoglobulin Mucin 3 Expression on Tumor Infiltrating Lymphocytes in Breast Cancer
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P-084 Loss-of-function of IFT88 Determines Metabolic Phenotypes in Thyroid Cancer
Junguee Lee[1], Shinae Yi[2], Minho Won[3], Young Shin Song[4], Hyon-Seung Yi[2], Young Joo Park[4], Ki Cheol Park[5], Jung Tae Kim[2], Joon Young Chang[2], Min Joung Lee[6], Hae Joung Sul[1], Ji Eun Choi[1], Koon Soon Kim[2], Jukka Kero[7], Joon Kim[8], Minho Shong[2]*
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P-085 Loss of Primary Cilia Results Development of Cancer in Murine Thyroid Gland
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P-086 Primary Cutaneous Adenoid Cystic Carcinoma
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P-087 The Cytologic and Histologic Findings of Cribriform-Morular Variant of Papillary Thyroid Carcinoma
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P-088 Primary Extramammary Paget's Disease with Colonic Metastasis: A Rare Aggressive Feature
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P-089 Human Leukocyte Antigen Class I and Programmed Death-ligand 1 Co-expression is an Independent Poor Prognostic Factor in Adenocarcinoma of the Lung
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P-090 Mesenchymal Stem Cells Promotes Tumor Formation in a Mouse Model of Fibrosarcoma
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P-091 화순전남대학교병원 인체자원 단위은행 운영에 관한 보고
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P-092 계명대학교동산병원 인체자원단위은행 운영실제
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P-093 Impact of Tissue Ex-Vivo Ischemia Time and Storage Period on DNA Quality in Biobanked Human Colorectal Cancer Tissue
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P-094 IDH2 Deficiency Induces Vascular Endothelial Cell Senescence in HUVECs
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P-095 Tetrahydrobiopterin is Key Factor to Endothelial Nitric Oxide Synthase Uncoupling in CR6 Interacting Factor-1 Deficiency Endothelial Cell
Ikjun Lee[1,2,3], Shuyu Piao[1,2,3], Seonhee Kim[1,2,3], Harsha Nagar[1,2,3], Su-Jeong Choi[1,2,3], Sung-min Kim[1,2,3], Saet-byel Jung[1,4], Byeong Hwa Jeon[1,3], Hee-Jung Song[1,5], Cuk-Seong Kim[1,2,3]*
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P-096 CR6-interacting Factor 1 Deficiency Induces Senescence by Impairment of Anti-oxidant System in Endothelial Cells

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P-097 DGLHT Inhibits Imiquimod-Induced Psoriasis-Like Skin Inflammation by Suppressing IL-22 Production

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P-098 Somatotype Analysis of Korean Combat Sport Athletes Based on Weight Divisions

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P-099 Somatotype Analysis of Both Sides Body in Stroke Patients

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P-100 Analysis of the Pressure-related Sensory Changes in Supine Position with Pillow

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P-101 Effect of Orthopaedic Manual Physical Therapy on Patients with Total Knee Replacement in Early Stage

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P-102 Development of Nanofiber-based Conjunctival Stroma for 3D Reconstructed Human Conjunctiva

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P-103 Ginsenoside Rk1 Induces Apoptosis in Neuroblastoma Cells through Loss of Mitochondrial Membrane Potential and Activation of Caspases

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P-104 Ginsenoside Rk1 Inhibits Epithelial-mesenchymal Transition (EMT) and Invasion of Neuroblastoma by Down-regulating Survivin

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P-105 Apoptotic Cells Trigger the ABCA1/STAT6 Pathway Leading to PPARγ Activation in Macrophages

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P-106 Gas6/Axl or Mer Signaling Inhibits Epithelial-mesenchymal Transition in Lung Alveolar Epithelial Cells through HGF Secretion

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P-107 The APE1/Ref-1 Inhibits Inorganic Phosphate-Induced Vascular Calcification and the Loss of the Smooth Muscle Phenotype in Vascular Smooth Muscle Cells

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P-108 Chronic Exposure of Ethylenethiourea Induces Nephritic Toxicity and Polycystogenesis in Male C57BL/6 Mouse

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P-109 Open-state Inhibition of Kv channels by Dapoxetine, a Selective Serotonin Reuptake Inhibitor, on Voltage-gated K^+ channels in Coronary Vascular Smooth Muscle Cells

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P-110 Nortriptyline-induced Inhibition of Voltage-gated K^+ Channels in Rabbit Coronary Arterial Smooth Muscle Cells

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P-111 Inhibitory Effect of Tricyclic Antidepressant Clomipramine on Voltage-dependent K^+ Current in Rabbit Coronary Arterial Smooth Muscle Cells

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P-112 The Direct Effect of Desipramine on Voltage-gated K^+ Current in Rabbit Coronary Arterial Smooth Muscle Cells

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P-113 A Meglitinide Class of Anti-diabetic drug, Repaglinide Induces Vasodilation by Activation of Protein Kinase A and Protein Kinase G in Aortic Smooth Muscle

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P-114 Changes of ATP-sensitive K^+ Channels Expression in Human Umbilical Smooth Muscle during Gestational Diabetes Mellitus

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P-115 The Vasodilatory Effect of Nateglinide, a Meglitinide Class of Anti-diabetic Drug, via Activation of Voltage-gated K^+ Channels in Rabbit Aortic Smooth Muscle

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P-116 The Dipeptidyl Peptidase-4 Inhibitor Vildagliptin Induces Vasodilation via Activation of Kv Channel and SERCA Pump in Aortic Smooth Muscle
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P-117 Role of JHDM in the Development of Non-alcoholic Fatty Liver Disease
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P-118 Role of SREBP 1c NEDDylation Pathway in Non Alcoholic Fatty Liver Disease and the Discovery of Therapeutic Agents
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P-119 Comparative Effects of Angiotensin A and Alamandine on Cardiac Functions and ANP Secretion in Rats
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P-120 Augmentation of Sodium Hydrosulfide-induced ANP Secretion During Hypoxia via K_{ATP} Channel Pathway
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P-121 Isocitrate Dehydrogenase 2 Mediated Mitophagy by mtUPR in Endothelial Cells
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P-122 The Role of RhoGDI2 in Cell Migration of CR6- Interacting Factor 1 Deficient HUVECs
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P-123 Nitric Oxide Modulates Stability of Lipocalin-2 Protein under Inflammatory Condition in RINm5F Beta Cells
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P-124 STIM2 and STIM1 Have Similarities and Differences, but Both Regulate Ca^{2+} Movement in Skeletal Muscle
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P-125 Regulation of Slow Delayed Rectifier K^+ Current by Protein Arginine Methyltransferase 1
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P-126 Effect of Carbon Monoxide on Ca^{2+}-activated K^+ currents of Human Cardiac Fibroblasts through the Protein Kinase Pathways

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P-127 Effects of Nitric Oxide on L-Type Voltage-gated Ca^{2+} Currents of Human Cardiac Fibroblasts

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P-128 Effects of Polychlorinated Biphenyl 77 on Kv1.3 Channel

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P-129 Anoctamin1 Does Not Function as Ion Channel in Head and Neck Squamous Cell Carcinoma Due to Lack of Surface Expression

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P-130 The Cellular Chloride Channels CLIC1 Inhibition Enhances Ca^{2+} and Reactive Oxygen Species Signaling in A549 Human Lung Cancer Cells

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P-131 Effects of Alprenolol on Kv1.3 Channel

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P-132 Effects of Paroxetine on Kv1.3 Channel

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P-133 Effects of Carteolol on hERG Current and Cardiac Action Potential

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P-134 Effects of Pindolol on hERG Current and Cardiac Action Potential

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P-135 Effects of Acebutolol on Action Potential in Guinea Pig Ventricular Myocytes and hERG K^+ Current

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P-136 The role of CACC and ENaC in Epithelial Barrier Disruption During Bacterial Infection
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P-137 High Glucose Increases Aβ Production through Endosomal Traffic Jams in Neuronal Cells: Involvement of CHC/AP2A1/PICALM-and mTOR-Pathway
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P-138 Best-1 Mediated GABA Release from Reactive Astrocytes Sustain Tonic Inhibition in Epileptic Hippocampus
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P-139 Glucocorticoid-mediated Aβ and SCG10 Upregulation Promotes Microtubule Destabilization and Memory Impairment: Involvement of ER-Mitochondria Interaction
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P-140 Extra-synaptic NMDA Receptors Antagonist Ameliorates Gait Deficits in MPTP-induced Parkinson' s Model Mice
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P-141 The Effect of Early Social Experience on Social Functions
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P-142 Gonadotropin Releasing Hormone (GnRH) Neurons Experience less Glutamate Receptor-Mediated Excitation than Non-GnRH Neurons of Preoptic Area in Immature Mice
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P-143 Geraniol Activates GABA and/or Glycine Receptors?on the Substantia Gelatinosa Neurons of the Trigeminal Subnucleus Caudalis in Mice
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P-144 Serotonin Increases Inhibitory Synaptic Transmission through Glycinergic and GABAergic Receptors in the Substantia Gelatinosa Geurons of Medullary Dorsal Horn
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P-145 Trim69 E3 Ubiquitin Ligase Regulates Neuronal Excitability by SK Channels in Hippocampal Dentate Granule Cells

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P-146 Effect of Electrical Stimulation on Reserpine-induced Pain-Depression Dyad in Mice

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P-147 Allopregnanolone Effects on Transmission in the Brain Stem Solitary Tract Nucleus (NTS)

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P-148 The E3 Ligase C-CBL Inhibits Cancer Cell Migration By Neddylating the Proto-oncogene c-Src

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P-149 Hydrogen Peroxide Inhibits the Growth of Lung Cancer Cells via the Induction of Cell Death and G1 Phase Arrest

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P-150 Inhibition of Neddylation Facilitates Cell Migration through Enhanced Phosphorylation of Caveolin-1 in PC3 and U373MG Cells

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P-151 HN1 Stimulates Tumorigenesis by Promoting Lipogenesis through SREBP Signaling in Hepatocellular Carcinoma

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P-152 Synergistic Effect of Ursolic Acid with Paclitaxel Inhibit Proliferation of Esophageal Cancer Cells

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P-153 Panobinostat Dimishes Metastasis and Invasion of Gastric Cancer Cells

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P-154 Downregulation of HN1 Induced Alteration of Cell Growth and Autophagy in Colorectal Cancer

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P-155 Valproic Acid Induces Caspase-dependent Apoptosis and GSH Depletion in Calu-6 Lung Cancer Cells

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P-156 Combined Anti-cancer Effects of Arsenic trioxide and Valproic acid in Human Large Cell Lung Cancer Cells

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P-157 Loss of CR6 Interacting Factor 1 Exerts Anticancer Effects by Inducing Mitochondrial Dysfunction and Inhibiting Pentose Phosphate Pathway in Breast Cancer

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P-158 The Role of Sirt5 in Preventing TNF-α-induced Mesenchymal Stem Cell Senescence and Lipid Droplet Formation

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P-159 Novel Role of Bicaudal D Homolog 1 as a HIF1α Nuclear Transport Modulator in Human Mesenchymal Stem Cells under Hypoxia

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P-160 Protective effect of 17β-Estradiol on High Glucose-induced Mitochondrial Reactive Oxygen Species through ERα-dependent Sirt3 and Nrf2 Expression in Human Umbilical Cord Blood-Derived Mesenchymal Stem Cells

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P-161 Effect of Histone Deacetylase Inhibitors on the Neurogenic Differentiation of Human Mesenchymal Stem Cells

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P-162 Effects of PCB77 and PCB126 on PKC Activation in Ventricular Myocytes

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P-163 The Inhibitory Effects of Pulsed Radiofrequency (RF) Stimulation on Acute Knee Joint Pain in Rats

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P-164 ***In Vitro* and *in Vivo* Anti-inflammatory Action of Anthocyanin-Rich Extract from Red Chinese Cabbage**
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P-165 **Crif1 Deficiency Inhibits the Invasive Growth of Keloid Fibroblasts via TGF/SMAD Signaling Pathway**
Sungmin Kim[1,2,3,4], Su-jeong Choi[1,2,3], Harsha Nagar[1,2,3], Shuyu Piao[1,2,3], Seonhee Kim[1,2,3], Ikjun Lee[1,2,3], Byeong Hwa Jeon[1,3], Cuk-Seong Kim[1,2,3], Sang-Ha Oh[4]*
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대한약리학회

P-166 **Activation of $P2Y_2R$ by Extracellular ATP Induces OxLDL-mediated Mitochondrial Damage and Inflammasome Activation in Endothelial Cells**
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P-167 **Cysteine Export Triggers Copper-dependent Cell Death**
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P-168 **Plant Lignan A from Natural Product Could Sensitize TRAIL Resistance in TRAIL-Resistant Glioblastoma Cells**
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P-169 **Cyclic Hexapeptides from Rubiaceae Prevents Inflammatory Responses in Rheumatoid Fibroblast-like Synoviocytes**
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P-170 **The Significance of Non-Drug Factors Involved in Drug Responses**
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P-171 **Coumarins from *Paramignyatrimera* Prevents Inflammatory Responses in Raw264.7 Macrophages**
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P-172 **Association of MicroRNA 72a with Colon Cancer in a Korea Population**
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P-173 **Action of Fluvoxamine, a Selective Serotonin Reuptake Inhibitor, on the Potassium Channel**
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P-174 Effects of Acidic pH on Hyperpolarization-Activated and Cyclic Nucleotide-Modulated Cation Channels in Dural Afferent Neurons

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P-175 Mosapride, Gastrokinetic Agent, Inhibits 5-Hydroxytryptamine 3 Receptor Function in NCB-20 Neuroblastoma Cells

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P-176 Anesthesia and Cognition: Memory Formation During General Anesthesia and Development of Preclinical Model for the Prevention of Postoperative Cognitive Decline (POCD)

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P-177 $P2Y_2R$-mediated Inflammasome Activation Regulates Tumor Progression in Breast Cancer Cells and Radiotherapy-resistant Breast Cancer Cells

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P-178 Oleandrin and Odososide A Exhibit Anti-cancer Effects via Suppressing the p-STAT3 Signaling Pathway

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P-179 Incidence of Dementia in Patients with Type 2 Diabetes Mellitus by the Nationwide Population-Based Cohort Study

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P-180 Association between Oxidative Stress and PRMTs Levels on Childhood Asthma

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P-183 Cost-Minimization Analysis of Rotavirus Vaccination in South Korea

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P-184 Estimating the Cost-Effectiveness of Inactivated Quadrivalent Influenza Vaccination in the Prevention of Influenza and Related Complications in South Korean Individuals with Co-Morbid Conditions

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P-185 Prediction of Metabolic Syndrome Severity According to Body Fat Mass
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P-186 어린이에서 뇨중 프탈레이트 노출수준과 갑상선 호르몬과의 연관성 연구
박보현, 한혜진, 박보미, 박혜숙
이화여자대학교 의과대학 예방의학교실

P-187 5세에서 12세까지의 한국 소아 코호트에서 K-CBCL을 통한 행동 발달 장애 추적
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P-188 Analysis of Co-morbidities between Various Types of Cancers and Ovarian Cancer Using National Health Insurance Database in Korea
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P-189 위암환자의 10년 생존율과 관련 예후인자 및 역학적 특성
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P-190 도시규모 및 주택유형에 따른 알레르기 비염 진단 경험률과 영향요인에 관한 연구
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P-191 북한이탈 가정내 아동 및 청소년 성장
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P-192 소비자 암 정보 요구도 체계적 문헌고찰
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P-193 The Association between Handgrip Strength and Cardiometabolic Risk in Korean Adults: Findings from the Korea National Health and Nutrition Examination Survey (KNHANES) VI (2014, 2015) VII (2016)
Mee-Ri Lee[1], Sungroul Kim[2], Hyuk Bang[1], Won Gi Jhang[1], Young Hwangbo[1], Hwa Sung Kim[1], Sung Soo Lee[1], Yoon Hyung Park[1], and Yong Bae Kim[1]
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P-194 The Association between Handgrip Strength and Type 2 Diabetes Mellitus in Korean Adults: Results from the Korea National Health and Nutrition Examination Survey (KNHANES) VI
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P-195 The Association between Handgrip Strength and Depression in Korean Adults: Results from the Korea National Health and Nutrition Examination Survey (KNHANES) VI
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P-196 **Association between Body Mass Index and Gastric Cancer Risk: A Pooled Analysis of Over 400,000 Asians in the Asia Cohort Consortium**

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P-197 **Auto-reporting System for Notifiable Infectious Diseases in Korea: IT-based System Capable of Reporting in Real Time**

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P-198 **후지나미 아키라의 학술적 궤적 — 의사학적 활동을 중심으로**

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P-199 **4차 산업혁명을 계기로 맞은 한국의 의료일원화**

김재식, 박언휘, 서영익, 정승필, 김인겸, 김대현, 여상희, 김학균, 김건엽
경북대학교 의과대학 경북대동서의학연구회

P-200 **한국과 일본의 기생(寄生) 혐오 담론과 기생충 박멸운동**

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P-201 **윌리엄슨 대 리 옵티컬 사건을 통하여 분석한 현대 미국의 안경 관련 업무 영역 분쟁**

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대한해부학회

P-202 ***Puerariae Radix* Extract Stimulates Cell Proliferation via Phosphorylation of ERK and Akt in Human Dermal Papilla Cells**

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P-203 **응집-유도 형광방출 분자의 분해에 기반한 금 이온 검출 프로브 개발 및 생체영상화 연구**

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P-204 **다공성 실리콘 나노입자와 이광자 현미경을 이용한 암 특이적 생체영상화 연구**

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P-205 **파장대 조절이 가능한 신규 분자 프로브의 개발 및 이를 이용한 생체내 세포막 영상화 연구**

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P-206 **EnGel™-Based 3D Cell Culture System as an *in Vitro* Prostate Cancer Model**
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P-207 ***In Vitro* 3D Culture Model of Thymic Epithelial Cells on Bioactive Electrospun Nanofibrous Scaffolds**
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P-208 **Regulation of Necroptotic Factors in Gastric Cancer Cells through miR-93-5p and EBV-miR-BART 18-3p**
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P-209 **Role of KLF4 in Controlling Proliferation and Survival of Periovulatory Granulosa Cell**
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P-210 **사람 다형성아교모세포종 세포주인 U87-MG와 T98G에서 할미꽃 추출 사포닌 D의 항암효과에 관한 연구**
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P-211 **The Effects of High Peripubertal Caffeine Exposure on the Adrenal Gland in Immature Male and Female Rats**
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P-212 **Prognostic Value of TZAP Expression in Various Cancers: TCGA Data Analysis**
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P-213 **Age Estimation of Children Using Tomography-based Volumetric Quantification of the Ossification Centers**
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P-214 **한국인의 얼굴비례계측 및 개인의 미적만족도 간의 상관관계**
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P-215 **Variations in Branching Pattern of the Anterior Circumflex Humeral Artery**
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P-216 **Quantification of Intraepidermal Nerve Fiber Density Using Three-dimensional Microscopy**
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P-217 **The Pathogenic Role of Interleukin-22 and its Receptor during UVB-induced Skin Inflammation**
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P-218 Alloferon Alleviates Dextran Sulfate Sodium-induced Colitis

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P-219 Anti-inflammatory Effect of Alloferon on Ovalbumin-induced Asthma

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P-220 Efficacy of a pan-NADPH Oxidase Inhibitor on Streptozotocin-induced Rat Models

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P-221 mTOR Mediates Neuronal Death Following Transient Global Cerebral Ischemia in the Striatum of the Chronic High-fat diet-induced Obese Gerbils

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P-222 Pretreated Fucoidan Confers Neuroprotection against Trainset Global Cerebral Ischemic Injury in the Hippocampal CA1 Area via Reducing Glial Cells Activation and Oxidative Stress

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P-223 Optimizing Tissue Clearing Method for Human Brain Tissue: Preparing Methods, Clearing Efficiency, Staining Methods, and Imaging Strategy

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P-224 Chemogenetic Activation/Inhibiton of Dorsal Vagal Complex (DVC) Regulates Feeding and Energy Homeostasis

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P-225 Early Exposure to High Fat Diet Affects Feeding Related Behavior

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P-226 Neuroanatomical Change of Colon Enteric Nervous System in Inflammatory Bowel Disease Mouse
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P-227 Activation of Leptin Receptor-expressing Neuronsin Lateral Hypothalamus Enhances Food-seeking without Altering Food Intake in Mice
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P-228 The Relationship between Circulating Adiponectin and Arterial Stiffness is Associated with *ADIPOQ* 276G〉T Polymorphisms
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P-229 Secretory Protein PRELP Mediates Mitotic Clonal Expansion During Adipogenesis
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P-230 Up-regulated Expression of Quinolinate Phosphoribosyltransferase (QPRTase) was Revealed in Colorectal Adenocarcinoma Tissues
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P-231 Calpain-dependent Beclin1 Cleavage Stimulates Senescence-associated Cell Death in HT22 Hippocampal Cells under the Oxidative Stress Conditions
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P-232 Serotonin Regulates β-cell Proliferation During Perinatal Period
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P-233 Proteasome Inhibition Attenuated Diet-induced Gallstone Formation by Modulating Cholesterol and Bile Acid Homeostasis
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P-234 Ceramide Synthases Modulate Hepatic Triglycerides by Regulating Endoplasmic Reticulum Stress-induced SREBP-1 Activation
Eun-Ji Lee[1], Ye-Ryung Kim[2], Min Hee Kim[1], Joo-Won Park[2], and Woo-Jae Park[1*]
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P-235 Wilms Tumor 1 (WT1) Inhibits the p53-induced Transcription of *p21WAF1* via Recruitment of TLE1-HDAC1 Complex

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P-236 Aberrant Hypometnylation of *sortilin1* is Associated with Moyamoya Disease

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P-237 *Passiflora incarnata L.* has Potential Effects on Anti-Alzheimer' s Disease

Gwang-Ho Kim[1], Hyekyung Baek[1], Kyunghyun Lim[1], Hae sung Yang[1], Ji-kwang Lee[1], Min-A Lee[1], Sang Kyu Park[2], In Koo Hwang[3], Sun shin Yi[1,4]*
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P-238 *Passiflora incarnata L.* has Potential Effects against Insomnia

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P-239 Protective Mechanism of Vitamin C in Neuronal Cell Death by Streptozotocin

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P-240 Aberrant Hypermetnylation of *α-N-acetylgalactosaminidase* Enhances Cisplatin Resistance in Ovarian Cancer

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P-241 Autophagy-dependent SNAI1 Degradation Regulates the Epithelial to Mesenchymal Transition and Metastasis in Cancer Cells

Sahib Zada, Jin Seok Hwang, Mahmoud Ahmed, Trang Huyen Lai, Trang Min Pham and Deok Ryong Kim

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P-242 Efficient Production of Enhanced Functions of Hepatocytes Derived from Human Pluripotent Stem Cells Using Size-controlled 3D Culture System

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P-243 Purification of Hepatocytes Derived from Multiple Human Pluripotent Stem Cell Lines using Chemically Modified Compound

Ji Young Park[1], Soo Jin Uhm[2], Jiyou Han[1], Jeong Sang Son[1], Jae Hun Lee[1], Gyunggyu Lee[1], Hyo Jin Kim[1], Kijung Park[1], Jong Seung Kim[2], Jong-Hoon Kim[1]
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▶▶▶M-001

Changes in Antimicrobial Peptide Expression in Small Intestinal Organoid Stimulated by LPS

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An organoid is a cell cluster that has similar structures and functions to organs by culturing stem cells three-dimensionally *in vitro*. AMP(antimicrobial peptide) is part of the innate immune response and is expressed during pathogen infection, killing bacteria and viruses. PAMP(Pathogen-associated molecular patterns) such as LPS are recognized by PRR (pattern recognition receptors) of intestinal epithelial cells and express AMP (antimicrobial peptide) through a series of reactions. We will investigate how the expression of AMP can be altered by treating LPS in the small intestinal organoid. Small intestinal organoid preparations were made using mouse small intestine and treated with LPS. After that, cDNA was synthesized from the extracted RNA and Real-Time PCR (qPCR) is performed. Immunocytochemistry is used to identify the changes in the amount of AMP expression in the cells by fluorescence In small intestinal organoids treated with LPS, the expression level of AMP is low or almost unchanged. In the case of mBD3, the expression level is increased. In ICC, the expression level of lysozyme slightly increased or did not change during LPS treatment. In this experiment, it was confirmed that the expression level of AMP such as lysozyme, mBD1, reg3β and Reg3γ except mBD3 was reduced when LPS was treated in small intestinal organoid. In previous experiments in this lab, it was confirmed that the expression of lysozyme increased. But in this experiment, it was confirmed that the expression of lysozyme was lowered or not changed. This is due to the fact that the organoid state is different from the previous experiment, and the contamination in the organoid prep can be another factor. If the results are consistently the same, it will be necessary to change the conditions such as the time of LPS treatment or the treatment of LPS concentration differently.

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Keywords: Organoids, Small Intestine, AMP(Antimicrobial Peptide), LPS

▶▶▶M-002

명의(名醫)를 찾아서: 한국 대중매체의 명의 담론 분석

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한국에서 명의(名醫)란 어떤 의사를 의미하는가? 일반적으로 명의란 병을 잘 고치기로 이름 난 의사를 지칭한다. 오늘날에도 수많은 명의들이 '명의예감' , '대한민국 명의를 찾아라' 등의 언론 기사를 통해 소개된다. 명의에 대한 정보가 공식적인 의료 질 평가 기관이 아닌 통로를 통해 유통되고 있음에도 불구하고, 현대 한국 사회에서 명의에 대한 인기는 끊이지 않고 있다. 표준적인 의학지식과 의료행위가 널리 공유되고 있는 현대의 과학적 의학에서도 그와 같은 명의에 대한 선호가 유지되고 있는 점은 흥미로운 현상이다. 그러나 명의 현상을 단순히 개인의 선호 문제로 파악하기보다는 명의에 대한 선호를 낳는 제도적 문제라는 관점에서 살펴볼 필요가 있다. 의료와 관련된 사회적인 현상에서, 의사와 환자는 완전히 자율적 행위자로만 존재하는 것이 아니라 역사적, 구조적 산물인 제도와의 관계 속에서 존재하기 때문이다. 여기서 제도적 환경은 크게 대한민국의 의료 제도, 명의에 대한 담론, 그리고 그 외 사회적 담론(의료전문주의와 유교적 근대성을 바탕으로 한 실력주의)으로 구성된다. 이 연구에서는 2000년 1월 1일부터 2014년 12월 31일까지 3대 중앙 일간지에 실린 명의 소개 기사를 대상으로 하여 담론 분석을 수행하였다. 기사에 나온 의사들 중 최종 분석 대상인 390명의 명의는 주로 남성, 외과계, 수도권 3차 병원 소속으로 나타났다. 명의에 대한 담론이 좋은 의사의 여러 특징 중 어떤 측면을 부각하는지 살펴본 결과, 의사-환자 간의 상호관계나 의사의 사회적 책무와 관련된 특징들보다는 지식적인 측면과 학술적인 능력이 강조되는 경향이 있었다. 이러한 명의에 대한 담론은 대중이 생각하는 바람직한 의사 상은 물론이고 의학교육과 의사 수련의 규범적 기준에 영향을 미칠 수 있으며, 더 나아가 사회적으로 의료제도에 대한 특정한 가치 체계를 형성하고 현 의료제도를 정당화하는 기제가 될 수 있다.

Keywords: 명의, 선호, 제도주의, 담론, 생태적 합리성

▶▶▶M-003

Drug Repositioning of Angiogenesis Inhibitors Using Database-based Analysis System

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Drug repositioning, which is the application of known drugs and compounds to treat new indications, has attracted much attention in the global pharmaceutical market. On average, it takes up to 10 to 17 years to develop a new drug and more than 90% of drugs fail during development. A significant advantage of drug repositioning is that it can be used to skip this costly and time-consuming process. In addition, GEO (Gene Expression Omnibus), an open gene expression database, allows for quick rediscovery of drugs approved by the FDA and EMA. Because tumor cells are known to stimulate the growth of new vessels, we analyzed a network of bioinformatics database built on the GEO site to rediscover drugs that effectively counteract the angiogenic effects of tumor cells. From these candidate substances, already known angiogenesis inhibitors were excluded and the remaining candidate substances and their efficacy were further investigated on human umbilical vein endothelial cells. Our data showed that treatment with these drugs effectively inhibited HUVEC vascularization in a dose-dependent matter. All in all, the newly rediscovered angiogenesis inhibitors have the potential to be quickly applied in the medical field and used in clinic compared *de novo* drug development.

Keywords: Drug repositioning, angiogenesis inhibitor, GEO, HUVEC

▶▶▶M-004

Evaluation of Epigenetic Toxicity for Dithiocarbamate Fungicide *in Vivo*

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Mancozeb, a polymeric complex of zinc and manganese salts of ethylene bisthiocarbamate(EDBC), is used widely in agriculture as fungicides. In mice, mancozeb induces embryo apoptosis, affects oocyte meiotic spindle morphology and impairs fertilization rate even when used at very low concentrations. In the present study, we evaluated the mancozeb-induced thyroidal and gonadal toxicity, and epigenetics for miRNA profiles. When the chronic administrated mancozeb at 800 mg/kg body weight per day for 30 days in SD rats, body weight slightly decreased, however, liver, thyroid, and testis weight per 100 g body weight were not changed. Histologic studies of the testis of the male rat treated with mancozeb revealed spermatogenesis inhibition reflected by significant decrease in the number of spermatogoniums, primary spermatocytes, spermatids, and sperms, when compared with that of controls. Chronic exposure of mancozeb induced gonadal hormone disturbance. Estradiol, progesterone, and testosterone levels in serum were significantly decreased in mancozeb-treated rats. Also, the volume and histopathology of thyroid gland were distinctly altered, whereas thyroid weight per 100 g body weight was not changed. Disruption of thyroid follicles reflected in nucleus-to-cytoplasm ratio (N/C) in epithelial and stromal cells, epithelial cell hypertrophy and altered colloid volume. To functional correlation, we tested the T3 and T4 levels in serum that were significantly decreased in mancozeb treated rats (0.96±0.05 ng/mL and 3.33±0.32 mg/dL, n=8) compared with control (1.18±0.09 ng/mL and 5.80±0.64 mg/dL, n=8). Thus, the dithiocarbamate fungicide mancozeb exposure could affect the thyroid homeostasis and male reproduction. Microarray was also performed on the serum and liver of the mancozeb diet group compared to the control for assessment of epigenetic toxicity. Mancozeb diet results in altered expression oncogenic, liver injury, ischemia, and insulin resistance-related miRNAs.

Keywords: Dithiocarbamate, Endocrine disrupter, Gonadal toxicity, Oncogenic miRNA, Liver injury

▶▶▶M-005

Effect of Stemness and Invasive Properties of Glioblastoma Tumorsphere by Treatment with 2'-Hydroxycinnamaldehyde and 2'-Benzoyloxycinnamaldehyde

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Glioblastoma multiforme(GBM) is the most common and aggressive human primary brain malignancy, which is associated with a dismal prognosis. The standard therapy of GBM is Temozolomide(TMZ), a prodrug of anti-cancer drug Temodar. Since epithelial mesenchymal transition(EMT) plays a critical role in GBM progression, it emerges as a potential therapeutic target. 2'-Hydroxycinnamaldehyde (HCA) isolated from the stem bark of *Cinnamomum cassia* and its derivative 2'- benzoyloxycinnamaldehyde (BCA) were reported to have anti-angiogenic, anti-proliferative, and anti-inflammatory effects in several human cancer cells (colon cancer, breast cancer) and RAW 264.7 macrophage cells. HCA and BCA is a potential therapeutic agent of GBM, as they have known to affect EMT by programming transcriptional level of breast cancer cell. In this study, HCA/BCA and TMZ, in combination, are used in order to affect EMT of GBM. Biological functions before and after the treatment were evaluated in GBM Tumorospheres (TSs). In vivo anticancer efficacy of drug was examined in a mouse orthotopic xenograft model. Combined treatment of GBM-TSs with HCA/BCA and TMZ significantly reduced stemness, invasiveness and cell viability. Our findings suggest that HCA and BCA, in combination with TMZ, are novel and effective therapeutic regimen against GBM.

Keywords: 2'-Hydroxycinnamaldehyde, 20-benzoyloxycinnamaldehyde, EMT(Epithelial Mesenchymal Transition), glioblastoma, tumorsphere

▶▶▶M-006

3차원 *in vitro* 모낭 배양을 이용한 AQP3 유전자결핍생쥐의 모발 증식 속도 측정

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세포막을 통해 수분 뿐 아니라 글리세롤 등 작은 용질의 이동을 촉진시키는 Aquaglyceroporin의 일종인 Aquaporin 3(AQP3)은 표피 뿐 아니라 모낭(hair follicle)에도 발현하는 것으로 밝혀져 모발 증식에 중요한 역할을 담당할 것으로 추측되나, 아직까지 이에 대해 보고된 바는 없다. AQP3가 모발 증식에 미치는 효과를 알아보기 위해 *in vitro* 모낭 배양을 통해 AQP3 유전자결핍생쥐와 야생형 생쥐의 모발 증식 속도를 조사하였다. 생쥐 콧수염 모낭에서 AQP3의 발현을 면역형광법으로 관찰한 결과 AQP3는 모낭의 하부과 중간부의 내모근초세포에서 발현되며, 모낭의 상부에서 AQP3 발현세포는 표피 기저각질세포와 연결되는 외모근초세포에 발현되었다. 증식기(생후 3-4주)에 있는 생쥐의 콧수염(Vibrissae) 모낭을 분리한 후 일반적인 액상배지로 배양하는 2차원 조직 배양법과 collagen을 함유한 hydrogel에 심어서 배양하는 3차원 조직 배양법으로 2주 동안 배양하면서 모발의 길이를 계측하였다. 콧수염 모낭은 2차원 액상배지 환경 및 3차원 hydrogel 환경에서 모두 모발의 길이 증가가 관찰되었으나, 2차원 액상 환경에서는 털망울(hair bulb)의 위축으로 인해 7일 이후 모발의 길이는 오히려 감소하였다. 첫 성장기 동안 분리한 콧수염 모낭을 2차원 환경에서 7일 배양한 경우 야생형생쥐는 처음 길이의 121%로, AQP3 유전자결핍생쥐는 115%로 중가 하였으나 유의한 차이는 없었다. 3차원 겔 환경에서 배양된 첫 성장기 콧수염 모낭은 14일 동안 지속적인 모발 증식이 관찰되었으며, 14일째 야생형생쥐는 처음 길이의 156%로 증가한 반면, AQP3 유전자결핍생쥐는 132%의 증가에 그쳐 2 그룹 간 유의한 차이를 보였다. 이상의 결과를 종합하면 AQP3 유전자결핍생쥐 콧수염 모낭은 야생형생쥐에 비해 모발 중식 속도가 감소되었으며, 이러한 차이는 3차원 모낭 배양 환경에서 털망울의 위축 없이 2주 이상 장기간 배양한 경우에만 관찰될 수 있어, *in vitro* 3D 모낭 모델은 향후 모낭 및 모발을 표적으로 하는 새로운 개발 약물의 검증에 도움이 될 수 있을 것으로 기대된다.

* 2017년도 정부(교육부)의 재원으로 한국과학창의재단(2017년도 학부생연구프로그램)의 지원을 받아 수행된 연구임(2017-0485).

Keywords: 3차원 모낭 배양, 콧수염(Vibrissae) 모낭, Aquaporin 3(AQP3), 모발 증식 속도, Hydrogel

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▶▶▶ P-001

Anti-obesity Effect of Whole Body Vibration Exercise: A Clinical Pilot Trial

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Background: It is well known that exercise is effective in overcoming obesity. Recent studies have focused on various types of exercise and vibration exercise was found to be one of them. In this study, we investigated the effect of exercise through the bed type vibrator. **Methods:** Twenty clinical trial participants were carefully recruited and were treated on a vibrating bed with an automatic program developed in 6-8 steps for 1 hr. Blood pressure, body indices, blood tests, oxidative stress markers, cytokines and obesity related biomarkers such as adiponectin, resistin and irisin were measured. **Results:** Results shows that blood pressure was significantly lowered ($p< 0.05$) after 1 hr of using the vibrating bed. In lipid tests, total cholesterol and low-density lipoprotein cholesterol were found to decrease ($p<0.01$). Reactive oxygen species and nitric oxide, which are factors of oxidative stress, were slightly increased ($p<0.05$), and the activity of glutathione peroxidase also increased ($p<0.01$). Interleukin (IL)-6, IL-10, and tumor necrosis factor-α were decreased. Adiponectin secreted from adipocytes was slightly increased, while resistin, which was reported to be involved in insulin resistance, showed a decreasing trend after the exercise. In addition, irisin levels were decreased after the use of the vibrating bed, which showed consistent result with the reports that irisin decreased in the early period of exercise in relation to glucose metabolism and increased by increased muscle activity during continuous exercise. **Conclusion:** Collectively, our result showed that exercise using WBV decreased the blood pressure level, lipid level in the blood, and showed favorable response to obesity biomarkers such as adiponectin, resistin, irisin and immune redox markers. Besides that, level of oxidative stress was observed to be stable as exercise naturally increases those markers. Allergic and inflammatory response was not observed. Taken together, results importantly imply that exercise with WBV bed can be used as an easy, safe and effective exercise therapy especially to heart and lower back disability patient and could be an alternative therapy for obesity. However, further studies are needed to confirm and elucidate the specific anti-obesity mechanism.

Keywords: Obesity, Exercise, Vibration

▶▶▶ P-002

Protective Effect of Enzyme-Treated *Rhus verniciflua* Sap Extract through Immune-Redox Modulation against Hepatotoxicity *in Vivo*

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Aim: This study was done to evaluate the hepatoprotective effects of enzyme treated *Rhus verniciflua* sap extract (RVsE) and hot water-refined *Rhus verniciflua* stoke extract (RVstE) drinking supplementation against acetaminophen (APAP)-induced hepatotoxicity in C57BL6 mice. Beyond that, we also investigated the nontoxic effects of RVsE, RVstE and the mixture of RVsE+RVstE (1:1) (M) and the hepatoprotection efficacy on APAP-induced hepatotoxicity. **Methods:** In this study, 70 mice were assigned randomly into 7 groups (n=10/group): normal control (NC), APAP only (AP), RVstE, RVsE, RVstE with APAP toxicity (RVstE+AP), RVsE with APAP toxicity (RVsE+AP) and the mixture of RVsE+RVstE+AP (M+AP) to exert the effects of RVE drinking supplementation continuously for 14 days. After then, all APAP groups were intoxicated with APAP (500mg/kg/mice) 24 hr before sacrifice. Blood and liver tissue samples were subjected to biochemical and histological examinations. Hepatoprotective effect was analyzed by redox profiling, liver function test (LFT), cytokine assay and histopathological examination. **Results:** Firstly, we confirmed the APAP intoxication by histopathology of liver from APAP-treated group. Secondly, the production of higher ROS and NO enhanced the antioxidant enzyme (GPx and CAT) activity in RVsE+AP and M+AP groups. In line, the result of LFT also showed the evidence of hepatoprotective ability of M+AP by lowering ALT, AST and bilirubin. RVsE group showed least self-toxicity, which was expressed through its positive immune-redox balance and LFT. Lastly, RVsE+AP and M+AP had less extensive hepatotoxicity than that shown in AP group. **Conclusion:** Collectively, RVsE+AP and M+AP might be a safe, effective, anti-oxidative and immune enhancing agent against drug-induced hepatotoxicity.

Keywords: *Rhus verniciflua* sap extract, Immune-Redox, Hepatotoxicity, Acetaminophen

▶▶▶ P-003

Protective Effect of Enzyme-Treated *Rhus verniciflua* Extract on Alcohol-induced Hangover in Human

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Background: Alcohol-induced hangover and liver diseases are considered as a cause of serious health morbidity, mortality and socio-economic burden worldwide. In recent years, many researchers explored abundant numbers of natural products related with hepatoprotective effect against oxidative damage. *Rhus verniciflua* Stokes (RV) is an ancient traditional deciduous tree widely used by people in East Asia including Korea for its therapeutic properties including anti-oxidant, anti-bacterial, anti-allergic and anti-inflammatory effects. This study was performed to investigate effect of enzyme-treated RV sap extract (RVSE) on alcohol-induced hangover in human. **Methods:** Total of 20 participants was orally administered with 100 ml urushiol-free RVSE once a day for 1 week. After 1 week of RVSE administration 0.78 g of alcohol per kg body weight was given to participants and blood samples were collected after 0, 1, 2 and 4 h. Further, we evaluated the drinking effect of RVSE extract on alcohol-induced hangover by checking hangover symptoms, biochemical profiles in blood, ethanol concentration, liver toxicity markers, cytokines and reactive oxygen species (ROS). **Results:** According to the survey result, RVSE-administered group showed significant reduction of hangover symptoms like severe thirst, drowsiness, headache, whirl, throw up, lethargy and colic after 1 week treatment. Moreover, serum ethanol concentration, acetaldehyde and liver toxicity markers such as sorbital dehydrogenase and 5'-Nucleotidase significantly were inhibited in experimental group. Additionally, inflammatory cytokine (TNF-α, GM-CSF and IL-13), and Th1 and Th_2 cytokines (IL-4, IL-5 and IL-10) were significantly decreased in RVSE group compared to control group time dependently. In line, ROS level was significantly decreased in RVSE group. Likewise, drinking RVSE showed elevation of blood acetate level. **Conclusion:** Overall these findings suggest that drinking enzyme-treated RVSE has relieving effect on alcohol-induced hangover in human by suppressing hangover markers. The effects might be related to enzymatic treatment of RV sap and the presence of anti-oxidant components in RVSE.

Keywords: Anti-hangover, Urushiol-free *Rhus verniciflua* Stokes, Hepatoprotective

▶▶▶ P-004

PHMB와 클로로퀸에 의한 가시아메바의 세포자멸사

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가시아메바의 살충제로서 여러 가지 약제가 보고되고 있으나, 그 살충기전에 대해서는 아직 정확하게 밝혀지지 않은 상태이다. 본 연구에서는 현재 가시아메바성 각막염 치료제로 사용되고 있는 polyhexamethylene biguanide (PHMB)와 자가포식억제제인 클로로퀸을 가시아메바에 처리하여, 가시아메바의 사멸기전을 확인해 보고자 하였다. 0.02%의 PHMB, 0.02% chlorhexidine digluconate, 100 μm 클로로퀸 및 100 μm 2,6-dichlorobenzonitrile을 가시아메바의 영양형 및 포낭형에 처리한 결과, PHMB와 클로로퀸을 처리한 아메바에서 세포 수축과 막 변화가 관찰되었다. Annexin V로 염색하여 가시아메바 막에서 phosphatidyle serine이 방출되는 것을 확인하였고, DAPI 염색으로 핵의 용해가 확인되었다. FACS 분석을 통해 PHMB를 처리한 가시아메바 영양형에서 98.3%, 포낭형에서 96.9%의 세포자멸사 유도를 확인 할 수 있었고, 클로로퀸을 처리한 포낭형에서 47.2%의 세포자멸사 유도를 확인 할 수 있었다. 이 결과들로 PHMB가 가시아메바의 영양형 및 포낭형 모두에게 세포자멸사를 일으키고, 클로로퀸은 미성숙 포낭형에게 세포자멸사를 일으키는 것을 알 수 있다. 이는 세포자멸사 유도를 통한 아메바성 각막염 치료제의 효과적인 활용 및 새로운 치료제 개발에 중요한 정보를 제공할 것으로 생각된다.

Keywords: 가시아메바, 세포자멸사, PHMB, 클로로퀸

▶▶▶ P-005

자가포식 억제제인 클로로퀸이 첨가된 다목적 용액의 가시아메바 살충력 증가

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최근 콘택트렌즈 착용과 관련하여 가시아메바성 각막염이 증가되고 있다. 콘택트렌즈의 소독, 세척 및 보관을 위해 다수가 다목적용액을 사용하고 있으나, 다목적용액의 가시아메바 살충력은 충분하지 않은 것으로 보고되어 있다. 본 연구에서는 국내생산 및 해외수입을 통해 시판되고 있는 다목적 용액 20종에 대해 가시아메바 살충력을 확인한 후, 자가포식 억제제를 첨가하여 가시아메바의 살충력 증가를 확인해 보고자 하였다. 국내생산 다목적 용액 15종은 모두 가시아메바의 영양형 및 포낭형에 대한 살충력이 충분하지 않은 것으로 확인이 되었고, 해외수입 다목적 용액 5종 중 일부는 가시아메바 영양형에 대해 살충력을 보였으나, 대부분이 포낭형에 대한 살충력은 불충분한 것으로 확인되었다. 자가포식체 형성을 저해함으로써 가시아메바의 포낭 형성을 억제하여 살충력을 증가시키는 클로로퀸을 일부 다목적용액에 100 μM씩 첨가하여 24시간 동안 관찰 한 결과, 미성숙 포낭형에 대한 가시아메바 살충력이 현저하게 증가되는 것이 확인되었다. 또한 100 μM의 클로로퀸이 첨가된 다목적 용액을 인체 각막세포에 반응시켜 보았을 때, 30분 배양에도 독성이 나타나지 않는 것으로 확인되었다. 이 결과들로 다목적 용액에 자가포식 억제제인 클로로퀸을 첨가하면 가시아메바 살충력은 증가되고, 인체 각막세포에는 독성이 없는 것을 알 수 있다. 이는 콘택트렌즈 착용에 의한 가시아메바성 각막염 예방에 큰 역할을 할 수 있을 것으로 생각된다.

Keywords: 가시아메바, 자가포식억제제, 다목적용액, 아메바살충력

▶▶▶ P-006

Protective Effects of Omega-3 Fatty Acid against *Toxoplasma gondii* Infection in Primary Macrophages

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Omega-3 fatty acids are a group of polyunsaturated fatty acids that are important for a number of functions in the body. Previous studies also demonstrated that Docosahexaenoic acid (DHA), the most abundant omega-3 fat in our brains, is an attractive agent to inhibit the survival of various cancer cells through the activation of autophagic cell death. Despite this, the roles of DHA during protozoa infection have not been investigated. Here, we showed that DHA treatment attenuated intracellular survival of *Toxoplasma gondii* (*T. gondii*) in bone marrow-derived macrophages (BMDMs). Moreover, intracellular proliferation of *T. gondii* was also significantly reduced in BMDMs isolated from FAT1 transgenic mice as compared with wild type mice. Furthermore, FAT-1 mice infected with *T. gondii* ME49 strain had markedly reduced cyst burden in brain tissue, compared with wild type mice. In primary macrophages, DHA treatment led to the significant induction of autophagy that is crucial for the reduced intracellular survival of *T. gondii*. Moreover, we found that DHA-induced autophagy activation and decrease of intracellular *T. gondii* is mediated by AMPK signaling pathway. Overall, these results strongly suggested that Omega-3 fatty acid contributes to host protective immunity through the AMPK-mediated the activation of autophagy.

Keywords: DHA, *Toxoplasma gondii*, Autophagy, AMPK, FAT-1

▶▶▶ P-007

Diversifying Selection at the Thrombospondin-Related Adhesive Protein (TRAP) Gene of *Plasmodium knowlesi*

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Plasmodium knowlesi a parasite of the macaques is currently the most common cause of human malaria in Malaysia. The thrombospondin-related adhesive protein (TRAP) gene is pre-erythrocytic stage antigen however, no study has been done in the orthologous gene of *P. knowlesi*. We analysed forty full-length *pktrap* sequences from clinical isolates of Malaysia along with the reference H-strain were downloaded from published databases. Comparison of 40 full-length *pktrap* sequences along with the H-strain identified 74 SNPs (53 non-synonymous and 21 synonymous substitutions) resulting in 29 haplotypes. Analysis of the full-length gene showed that the nucleotide diversity was lower compared to its nearest ortholog *pvtrap*. Domain-wise analysis indicated that the proline/asparagine rich region had higher nucleotide diversity compared to the von Willebrand factor domain and the thrombospondin-type-1 domain. McDonald-Kreitman test of *pktrap* with *pvtrap* as an ortholog sequence identified significant positive selection within the von Willebrand factor domain. These results indicate that TRAP in *P. knowlesi* could be a major target of human immune response to pre-erythrocytic stages of *P. knowlesi*. Phylogenetic analysis of full-length genes identified 3 distinct sub-clusters of *P. knowlesi*, one originating from Peninsular Malaysia and two originating from Malaysian Borneo.

Keywords: *Plasmodium knowlesi*, thrombospondin-related adhesive protein (TRAP), natural selection

▶▶▶ P-008

Seasonal Prevalence and Species Composition of Mosquitoes (Culicidae) Collected from Gangwondo in South Korea

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Recent global climate changes affect the habitat characteristics of various species and the density of vectors of pathogens that transmit diseases to humans is rapidly increasing in various regions. In South Korea, 54 mosquito species have been recorded, of which Culex tritaenior- hynchus and Anopheles Hyrcanus Group have caused many illnesses, because they carry Japanese encephalitis virus and Plasmodium vivax Malaria, respectively. As the habitat changes in Korea due to climate change, the emergence of disease-mediated vectors is increasing rapidly. Thus for the surveillance of mosquito seasonal prevalence and species composition were investigated at three sites in Wonju, at 3 sites in Taebaek and at 4 sites in Hoengseong. Mosquitoes were collected twice every month from ten collection sites using a black light and BG sentinel traps in Wonju, Taebaek and Hoengseong from March through November. A total number of female mosquitoes collected during 9 months total 2,817, 6 genera and 10 species. Among the species of mosquitoes Aedes vexans collected 1,646 and were the most dominant 58.3%, followed by Armigeres subalbatus and Och. Koreicus accounted for 13.3% and 8.9% respectively. The distribution of mosquitoes during the period showed that mosquitoes began to collect from the end of April, and the number of collected mosquitoes increased from early May to early September. In November collected 8 mosquitoes. Zikavirus and other flavivirus-mediated mosquitoes Ae. Albopictus collected 98 and were 3.5%. A malaria mediated mosquito was collected in 133 and were 4.7% of the total mosquito species. Cx. tritaeniorhynchus the leading mosquito that spread Japanese encephalitis accounted for 0.1%.

Keywords: Culicidae, Wonju, Taebaek

P-009

호흡기 세포 융합 바이러스의 선 감염이 선모충 감염에 미치는 저항성

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윤충류들에서는 다른 병원체와 공동 감염될 경우, 숙주의 면역반응 변화를 유발하고 윤충의 생존률이 높아진다는 보고가 있다. 그러나 아직까지 바이러스 감염에 의한 기생충에 대한 숙주의 면역력 변화에 대한 내용은 상세하게 보고된 바 없다. 본 실험에서는 마우스의 호흡기 세포 융합 바이러스의 선 감염이 선모충 감염에 대한 면역반응 및 저항성을 분석하였다. 호흡기 세포 융합 바이러스 선 감염 후 선모충에 감염된 마우스에서 선모충 분비배설항원 특이 면역 글로불린 IgG 반응이 증가한다는 것을 알 수 있었다. 또한 기생충에 대응하는데 필요한 호산구의 수치도 증가하였다. 마우스 횡경막에서 검출된 선모충 유충은 호흡기 세포 융합 바이러스 선 감염에서 선모충 단일 감염에 비해 현저하게 감소 된 것이 확인되었다. 호흡기 세포융합 바이러스 감염으로 생성된 항체가 선모충 항원을 인식하는 것도 확인되었다. 이러한 결과는 호흡기 세포융합 바이러스와 선모충에는 공동 항원이 존재하는 것으로 사료되며, 호흡기 세포 융합 바이러스 선 감염으로 인해 증가한 호산구 및 선모충 특이 IgG 항체가 선모충 감염에 대한 저항성이 생성 되었을 것으로 사료된다.

Keywords: 호흡기 세포 융합 바이러스, 선모충, IgG, 저항성

P-010

톡소포자충 inner membrane complex, rhoptry protein 18 및 microneme protein 8을 발현하는 바이러스 유사입자 백신 효능

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톡소포자충은 전 세계의 약 20-50% 인구에서 감염보고가 되어있다. 톡소포자충의 inner membrane complex (IMC), rhoptry protein 18 (ROP18) 및 microneme protein 8 (MIC8)은 톡소포자충이 숙주내로 침입하고 증식하기 위한 필수 요소이다. 본 연구에서는 톡소포자충의 IMC, ROP18 및 MIC8을 각각 발현하는 조합 바이러스 유사입자(VLPs)와 하나의 입자에 IMC, ROP18 및 MIC8을 모두 발현하는 다중 항원 바이러스 유사입자(VLPs) 백신에 의해 유도되는 백신효능을 동물모델(마우스)에서 비교분석 하였다. Baculovirus expression system을 이용하여 곤충세포에서 톡소포자충의 IMC와 인플루엔자 바이러스 matrix protein 1 (M1)을 포함하는 VLP (IMC VLPs), ROP18과 M1을 포함하는 VLP (ROP18 VLPs), MIC8과 M1을 포함하는 VLP (MIC8 VLPs) 및 IMC, ROP18, MIC8과 M1을 포함하는 VLP (IMC+ROP18+MIC8 VLP)를 생성하였다. 제조된 VLPs를 전자현미경 및 western blot으로 확인하였다. 단일 VLPs (IMC VLPs, ROP18 VLPs 및 MIC8 VLPs)를 1:1:1의 비율로 혼합한 조합 VLPs (IMC1/ROP18/MIC8 VLP)와 다중 항원 VLPs (IMC+ROP18+MIC8 VLP)를 마우스의 비강내로 접종하였으며 그룹은 조합 VLPs 접종군, 다중 항원 VLPs 접종군 및 비접종군으로 나누었다. 백신은 2번 접종 하였으며, 접종 후 마우스의 혈청과 비장에서 면역반응을 관찰하였다. 다중 항원 VLPs 접종군은 조합 VLPs 접종군에 비해 세포성 면역($CD4^+$, $CD8^+$ T cell) 및 germinal center B cell의 반응이 증가하였다. 결론적으로, IMC, ROP18 및 MIC8을 동시에 발현하는 다중 항원 바이러스 유사입자 백신은 조합 VLPs 보다 우수한 면역반응을 유도하는 것을 알 수 있었다.

Keywords: 톡소포자충, 바이러스 유사입자, 백신

P-011

Comparison of Co-stimulatory Molecules and Cytokine Production in *Toxoplasma gondii*-infected Dendritic cells from C57BL/6 and BALB/c Mice

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Toxoplasma gondii (*T. gondii*) is an intracellular parasitic protozoan that can cause infection in most warm-blooded animals, including humans. C57BL/6 and BALB/c mice are prototypical Th1- and Th2- type immune responses mouse strain, respectively. Despite the Th1 immune response, C57BL/6 are highly susceptible than BALB/c mice to *T. gondii* infection. Previous studies have reported that the difference in susceptibility between C57BL/6 and BALB/c mice to *T. gondii* infection was due to the decrease of $CD4^+$ T cells and the occurrence of necrosis. However, there was no study on the characteristics of dendritic cells derived from these mice. So we investigated the functional differences of susceptibility to *T. gondii* by using BMDCs from C57BL/6 and BALB/c mice. In *T. gondii*-infected BMDCs, the expression levels of co-stimulatory molecules (CD40, CD86, MHC II and CD80) were higher in the BMDCs of BALB/c mice than those in C57BL/6 mice at all the times. The TNF-α, INF-γ, IL-12p40, IL-1β, IL-10 and TGF-β productions were increased in both *T. gondii*-infected BMDCs of C57BL/6 and BALB/c mice, but there were higher in the BMDCs of BALB/c mice than those in C57BL/6 mice. The mRNA levels of surface antigen 1 (SAG-1) of *T. gondii* in the BMDCs of C57BL/6 mice than those in BALB/c mice. These results showed that the BMDCs of BABL/c mice showed better control of *T. gondii*, which is likely to be affected by the maturation of DCs and the cytokine produced by these cells.

Keywords: *Toxoplasma gondii*, Dendritic cells, Co-stimulatory molecules, Cytokines

P-012

HIF-1α /GSK3β-dependent Regulation of Anti-parasite Effect of 4-Hydroxyacetophenone

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In recent years, more and more medicinal plants or their active compounds have been revealed as novel candidate for drugs to control parasite development or growth. *Cynanchi atrati Radix* (*C. atrati*) has been traditionally used as an anti-inflammatory agent to treat hectic fevers, acute urinary infection or subcutaneous pyogenic infection with invasion of the pathogenic factors. Nevertheless, the bioactivity of *C. atrati* remains to be identified in order to confirm its importance in preventing parasites proliferation. Here, we reportes that *C. atrati* suppresses *T. gondii* (an obligate intracellular protozoan pathogen) proliferation without side effect to host. From the *C. atrati* extracts, the presence of 4-HAP (4-Hydroxyacetophenone) was confirmed and it revealed similar effect with *C. atrati* to suppress *T. gondii* growth. In the activity of anti-inflammatory signaling pathway analysis, 4-HAP significantly inhibited HIF-1α pathway, and loss of HIF-1α stability was responsible for the effect since protease inhibitor MG-132 reversed the inhibiting effect of 4-HAP on *T. gondii* proliferation. Gene silencing of HIF-1α restrained the growth of *T. gondii* and inhibition of GSK3β, which is known to directly mediates HIF-1α degradation improved *T. gondii* proliferation. The results suggest that GSK3β/HIF-1α is indispensable for *T. gondii* growth and survival. *C. atrati* especially 4-HAP is capable of suppressing *T. gondii* growth by activating HIF-1α. Our results indicates the pharmaceutical potential of this plant, *Cynanchi atrati Radix*, and its chemical compound 4-HAP, as candidate for anti-parasytic drug for *Toxoplasma gondii*.

Keywords: *Cynanchi atrati Radix*, 4-Hydroxyacetophenone, HIF-1α, GSK3β, *T. gondii*

▶▶▶ P-013

Proliferation of Prostatic Stromal Cell Infected with *Trichomonas vaginalis* via Crosstalk with Mast Cell Tryptase

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Chronic inflammation has a role in the pathogenesis of benign prostatic hyperplasia (BPH) and prostate cancer. In our previous study, we demonstrated that the proliferation of prostate stromal cell (PSC) was induced by BPH epithelial cells stimulated with *Trichomonas vaginalis* (Tv) via crosstalk with mast cells. Tryptase, which is produced by activated mast cells, is known to involve in the proliferation and angiogenesis of epithelial cells and fibroblasts by protease-activated receptor-2 (PAR-2). In this study, we investigated whether tryptase released from mast cells affects on proliferation of prostate stromal cell infected with *T. vaginalis*. We used the WPMY-1 cell line as the prostate stromal cell and the HMC-1 cell line as the human mast cell. Conditioned media were prepared as follows; Culture supernatant of PSC infected with live Tv was named TCM (Trichomonad-conditioned medium), and culture supernatant of mast cell incubated with TCM was M-TCM (mast cell-TCM). Proliferation of PSC was measured by CCK8 assay and wound healing assay after treatment of M-TCM. Cytokine (CCL2, CXCL8) production was increased when stromal cells were infected with Tv, and TCM from the stromal cell caused migration of mast cells. When the mast cells were stimulated with TCM, β-hexosaminidase, CXCL8 and tryptase were increased. When M-TCM pretreated with tryptase inhibitor was added to stromal cells, proliferation of the stromal cells was significantly decreased compared with M-TCM alone. Expression of PAR-2 was confirmed by RT-PCR, and treatment of PSC with PAR-2 inhibitors reduced the proliferation of PSC in response to M-TCM. Therefore, the crosstalk between prostate stromal cell infected with Tv and mast cell (tryptase) may cause proliferation of the stromal cell through PAR-2.

Keywords: *Trichomonas vaginalis*, Prostate stromal cell, Mast cell, Tryptase, Proliferation

▶▶▶ P-014

톡소포자충의 ROP18과 ROP4를 발현하는 바이러스 유사입자 백신 효능 비교

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톡소포자충은 전세계적으로 분포하는 기생원충으로서 톡소포자충증을 유발한다. 일반적으로 톡소포자충에 감염되면 증세가 전혀 나타나지 않거나 가벼운 몸살감기 정도 증세만 나타난다. 하지만 임산부가 임신 기간 중에 톡소포자충에 감염될 경우 태반을 통해 태아로 톡소포자충이 감염될 수 있고 태아, 신생아의 유산과 기형아발생이 나타난다. 현재로써 톡소포자충증을 예방할 수 있는 방법이 없어 다양한 후보물질 탐색을 통한 백신 개발이 필요한 상황이다. 본 연구에서는 인플루엔자의 핵심단백질인 M1에 톡소포자충유래 ROP4와 ROP18단백질을 발현하여 생성한 두 가지 바이러스 유사 입자 백신의 효능을 비교하였다.마우스에 비강 경로를 통하여 백신을 접종하였고 백신 접종 후에 톡소포자충(ME49 cyst) 치사량을 마우스에 경구 감염시켰다. 이후 두가지 백신의 방어 효능을 비교하기 위하여 ELISA를 통한 항체 반응을 관찰하였고, 몸무게 감소율과 마우스 뇌에서의 ME49 cyst의 개수 변화를 확인하였다. 결과, 톡소포자충 특이 항체 IgG와 IgA의 반응에서 ROP4보다 ROP18에서 더 높게 나타났으며, 분리한 마우스 뇌에서의 cyst 개수와, 몸무게 감소율 또한 ROP18에서 적게 나타났다.본 연구를 통해 톡소포자충의 ROP18 바이러스 유사 입자 백신은 ROP4 바이러스 유사입자 백신보다 높은 방어 효능을 보였으며, 이는 톡소포자충증 백신개발에 적합한 후보 물질이 될 수 있다.

Keywords: 바이러스유사입자, 백신, 톡소포자충, Rhoptry protein 4, Rhoptry protein 18

▶▶▶ P-015

말라리아(*Plasmodium berghei*, ANKA)의 선 감염이 톡소포자충(*Toxoplasma gondii*, ME49) 감염에 미치는 저항성

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말라리아는 학질모기가 옮기는 전염병으로, 매년 2억에서 3억 명의 사람이 감염되고 수백만 명이 사망하는 위험한 질병이다. 톡소포자충은 전 세계 인구 중 약 20% 정도가 감염되어 있다고 보고되고 있으며, 특히 임산부에게 감염 시 태아에게 치명적인 영향을 준다. 유전자분석에서 말라리아와 톡소포자충의 inner membrane complex (IMC)의 아미노산 서열이 33%가 유사한것으로 나타났다. 본 연구에서는 말라리아 감염이 톡소포자충 감염에 미치는 영향을 알고자 말라리아(*Plasmodium berghei*, ANKA)를 마우스(BALB/c)에 감염시킨 후 4주 후에 톡소포자충(*Toxoplasma gondii*, ME49)를 감염시키고, 톡소포자충에 미치는 저항성을 분석하였다. 마우스에서 혈청을 분리하여 항체 반응을 확인하였고, 감염된 마우스의 뇌를 관찰하여 ME49 크기 및 감염 정도를 측정하였다. 또한 비장 세포를 분리하여 유세포분석기(flow cytometry)로 면역반응을 분석하였다. 그 결과 말라리아에 감염 된 마우스에서 톡소포자충의 특이 IgG, IgG1 및 IgG2a에서 항체 반응이 나타났으며, 몸무게 측정 결과 톡소포자충만 감염시킨 마우스보다 몸무게가 덜 감소된 것으로 나타났다. 또한 비장 세포의 면역반응을 분석한 결과 말라리아를 감염시킨 마우스에서 많은 수의 CD4+ T cell, CD8+ T cell 및 Total B cell이 검출되었으며, 마우스의 뇌에서 톡소포자충의 cyst가 현저히 감소하였고, 크기도 많이 줄어들었다. 결론적으로, 말라리아의 선 감염은 톡소포자충 감염에 저항성을 가지고 있으며, 이는 두 원충의 유전자가 유사성이 있는 것으로 사료된다.

Keywords: 말라리아, 톡소포자충, 유세포분석, ELISA, Antibody

▶▶▶ P-016

Inhibition of Breast Cancer Growth by *Toxoplasma gondii* through Down-regulating MMP2 and Induction of Autophagy

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Recently, the development of tumor immunology has revealed many new facts about the characteristics of human tumors, and most cancer patients are known to have decreased immune function. *Toxoplasma gondii* is an intracellular parasitic protozoan that can cause infection in almost all warm-blooded animals, including humans. The activation of immune cells by *T. gondii* infection has been reported to inhibit the growth of cancer cells. In this study, the inhibitory effect of breast cancer growth by *T. gondii* or *T. gondii* excretory secretory products (ESPs) was investigated at the experimental animal model and cell line level. *T. gondii*-infected mice were subcutaneously injected with mouse breast cancer cell line E0771 and observed the tumor mass and survivals for 3 weeks. As a result, the size of tumor masses was significantly decreased in *T. gondii* pre-infected group as compared to the only cancer-injected group, however the survival periods were not shown significant differences between infected and uninfected group. After E0771 cell line was treated with *T. gondii* ESA or live *T. gondii* tachyzoites, the expression levels of MMP2 and MMP9, which are indicators related to the metastasis of cancer cells, were observed. The levels of MMP2 mRNA expressions were markedly decreased. Also the levels of LC3 expression, which is an autophagy indicator, was increased, however apoptosis was not induced in the E0771 cells infected with *T. gondii*. These results suggest that the proliferation of breast cancer cells was inhibited in *T. gondii*-infected mice, and this effect is thought to be induced by the down-regulating MMP2 and induction of autophagy, however further detailed follow-up studies are required.

Keywords: *Toxoplasma gondii*, Breast cancer, E0771 cell line, MMP2, Autophagy

▶▶▶ P-017

The Role of PI3K/AKT Pathway and NADPH Oxidase 4 in Host ROS Manipulation by Protozoan Parasite, *Toxoplasma gondii*

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Dendritic cell (DC) is one of the first innate immune cell to encounter *T. gondii* after the parasite crosses the intestinal epithelium. Being an early source of IL-12, which drive protective Th1 responses, ablation of DCs results in the failure of mounting protective immunity and the lethal outcome in murine toxoplasmosis. In the aspect of parasite, *T. gondii* requires intact DC as a carrier to infiltrate into host central nervous system (CNS) without being detected or eliminated by host defense system. The mechanism by which *T. gondii* avoids innate immune defense of host cell, especially in the dendritic cell is unknown. Therefore, we examined the role of host PI3K/AKT signaling pathway activation by *T. gondii* in its proliferation in dendritic cell. *T. gondii* infection or *T. gondii* excretory/secretory antigen (*Tg*ESA) treatment to the murine dendritic cell line DC2.4 induced AKT phosphorylation, and PI3K inhibitor treatment effectively inhibited the *T. gondii* proliferation but did not have effect on infection rate and invasion rate. Furthermore, it is found that *T. gondii* or *Tg*ESA can reduce H_2O_2-induced intracellular reactive oxygen species (ROS) as well as host endogenous ROS via PI3K/AKT pathway activation. While searching for the main source of the ROS, we found that NADPH oxidase 4 (NOX4) expression was controlled by *T. gondii* infection or *Tg*ESA treatment, which is in correlation with previous observation of the ROS reduction by identical treatments. These findings suggest that the manipulation of the host PI3K/AKT signaling pathway and NOX4 expression is an essential mechanism for the down-regulation of ROS, and therefore, for the survival and the proliferation of *T. gondii.*

Keywords: *Toxoplasma gondii*, DC2.4 cell, PI3K-AKT pathway

▶▶▶ P-018

Th17 Cells Induced by Prostate Epithelial Cells Stimulated with *Trichomonas vaginalis* Promote Progression of Prostate Cancer Cells

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Trichomonas vaginalis (*Tv*) have been associated with urethritis and prostatitis as well as benign prostatic hyperplasia (BPH) and prostate cancer (PCa) in male. Many inflammatory immune cells may play critical roles in development and progression of PCa. Among these infiltrating immune cells, Th17 cells known as key mediators in a number of autoimmune diseases may play a role in inflammation-associated cancer. Interestingly, increased IL-17 mRNA level was shown in tissue from both PCa and BPH. Here, we investigated whether the inflammation induced by *Tv* infection in human prostate epithelial cells could induce the differentiation of Th17 cells and promote progression of PCa by the differentiated Th17 cells. Conditioned medium of prostate epithelial cells (RWPE-1) was prepared by infection without (CM) and with *Tv* (TCM). Human $CD4^+$ T cells were isolated using the $CD4^+$ isolation kit from human peripheral blood. Conditioned medium of $CD4^+$ T cells was prepared by incubation with CM (T-CM) or TCM (T-TCM). RWPE-1 cells infected with *Tv* produced IL-6 and IL-1β. When isolated $CD4^+$ T cells were treated with conditioned medium of RWPE-1 cells co-cultured with *Tv* (TCM), it resulted in differentiation of Th17 cells by increased production of IL-17 and IL-22, and the expression of IL-21, RORγt and STAT3 mRNA known as Th17 cell markers. However, blockade of IL-6 and IL-1β signaling with IL-6 receptor antibody and IL-1 receptor antagonist inhibited differentiation of Th17 cells. To determine progression of prostate cancer cells by crosstalk between Th17 cells and inflamed prostate epithelial cells by *Tv* infection, PCa cell lines (LNCaP and PC3) were treated with conditioned medium of $CD4^+$ T cells stimulated with TCM (T-TCM). Proliferation of PCa cells were significantly increased by T-TCM than T-CM. In conclusion, our findings suggest that *Tv* infection in men may be responsible for altering the tumor microenvironment for progression of PCa through differentiation of Th17 cells by inducing IL-6 and IL-1β production of prostate epithelial cells.

Keywords: *Trichomonas vaginalis*, Prostate, Inflammation, T helper 17 Cell, Tumor Microenvironment

▶▶▶ P-019

성대에서 발견한 국내 미기록 단생흡충 1 종 보고

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성대는 선명한 주홍색의 몸과 큰 가슴 지느러미가 특징적인 바다물고기로 주로 서해안에서 잡히며 대상어로 할 만큼 어량이 풍부하지 않지만 고급 생선으로서 일본에서는 행사때 올릴 정도로 귀하게 여기는 어종이다. 성대의 아가미에서 단생흡충 1 종을 발견하였으나 국내에서는 기록을 찾을 수 없어서 이를 동정하였다. 2017년 5월 3일에 포항시 죽도시장에서 구입한 성대의 아가미에서 수집한 충체를 10% 포르말린에 고정한 후 Semichon' s Acetocarmin 염색을 하여 형태관찰을 하였다. 몸체는 길쭉한 타원형이며 앞뒤로 잘 발달된 흡착 기관이 있다. 구형인 고환 2 개는 몸통 중간에 대칭으로 위치한다. 고환 바로 앞쪽으로 구형의 난소가 자리잡고 있다. 후방 햅터는 원반모양으로 10 개의 근육성 셉터로 나뉜어 있다. 후방 햅터 중앙에 3 쌍의 후크를 가지고 있으며 후크 사이로 셉터가 없는 것을 특징으로 하여 *Trochopus hobo*로 동정하였다. *Trochopus hobo*는 일본에서 1942년 Yamaguti에 의해 처음 발표되었다. 지금까지 *T. hobo*는 일본에서만 보고되었지만 한국에서도 보고가 됨으로서 분포 지역이 더 넓을 것으로 파악된다. 단생흡충목에 대한 국내 연구가 미흡한 상황에서 추가적인 조사가 이뤄져야할 대상으로 판단한다.

Keywords: 미기록종, 단생흡충, *Trochopus hobo*, 성대

▶▶▶ P-020

청줄돔에서 발견한 흡충 4종의 국내 첫 보고

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충북대학교 의과대학 기생충학교실

현재까지 청줄돔(*Chaetodontoplus septentrionalis*)에서는 *Paragyliauchen chaetodontis* Yamaguti, 1934, *Hurleytrematoides japonicus* Kamegai 1970, *Antorchis tsushimaensis* (Machida, 1971) Machida, 1975 등 총 3종의 장흡충이 보고되었다. 이 연구에서는 제주에서 채집된 청줄돔을 대상으로 연충류 기생충 조사를 하여 보고하고자 한다.
2016년 3월 4일부터 2017년 5월 24일까지 해양환경 및 어획시험조사를 통해 제주연안에서 해역별(신창, 신흥, 사계, 가파도)로 채집한 청줄돔을 대상으로 기생충 조사를 실시하였고, 장에서 3종의 흡충류 기생충을 발견하였다. 충체의 일부를 10% 포르말린에 고정한 후 아세토카민 염색하여 광학현미경으로 내부형태를 관찰하였다. 4개 해역에서 잡힌 총 11마리의 청줄돔에서 *P. chaetodontis*와 *Antorchis sp*. 를 각각 239마리, 1300마리 발견하였고, 신창과 사계 지역에서 잡힌 총 8마리의 청줄돔에서 *H. japonicus* 115마리를 발견하였다. *H. japonicus*의 경우 신흥과 가파도에서는 발견되지 않았다. 발견된 4종의 흡충은 형태학적 특징을 기반으로 각각 *Paragyliauchen chaetodontis, Hurleytrematoides japonicus, Antorchis tsushimaensis, Antorchis pomacanthi*로 동정하였다. 이상 4종의 흡충은 모두 일본에서만 발견되었으며 국내에서는 보고되지 않았다. 이번 결과에서 토대로 청줄돔이 *A. pomacanthi*의 추가적인 숙주로서 처음으로 기록되었다.

Keywords: 청줄돔, 장내기생충, *Paragyliauchen*, *Hurleytrematoides*, *Antorchis*

▶▶▶ P-021

Myeloid SIRT1 is Essential for Host Defense against *Toxoplasma gondii* Infection by Activation of Autophagy via AMPK Signaling Pathway

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Toxoplasma gondii is an obligate intracellular protozoan capable of manipulation at diverse cellular responses related to the activation of host defense system. Previous studies suggested that Sirt1 is required for AMP-activated protein kinase (AMPK) activation and plays a key role of host innate defense by activation of autophagy in macrophages. However, the roles of SIRT1 in the regulation of protective immune responses against *T. gondii* have been largely unknown. Here, we first examined that myeloid-specific deletion of SIRT1 resulted in enhanced survival of the *T. gondii* ME49 strain in brain tissues. Moreover, deficiency of myeloid SIRT1 highly increased intracellular *T. gondii* survival in bone marrow-derived macrophages (BMDMs) through impaired regulation of AMPK signaling. Resveratrol (RSV), a SIRT1 activator, significantly increased antiparasitic activity and the phosphorylation of AMPK in *T. gondii*-infected BMDMs. Furthermore, our results showed that RSV induced the colocalization of *T. gondii* and autophagosome via SIRT1 in BMDMs. And SIRT1 is critical for the increase in the formation of autophagosomes and autolysosomes in *T. gondii*-infected BMDMs in response to resveratrol. Taken together, our findings indicate that myeloid Sirt1 plays a central role for the regulation of antiparasitic autophagy via AMPK-dependent signaling during *T. gondii* infection.

Keywords: *Toxoplasma gondii*, SIRT1, AMP-activated protein kinase, Autophagy, Resveratrol

▶▶▶ P-022

Molecular Detection and Characteristics of *Cryptosporidium suis* and *C. scrofarum* from Pigs in Korea

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Cryptosporidium is a widespread parasite with a wide host range and can be classified into a variety of host-dependent species. It is found in the intestinal tract of many vertebrate animals, including humans. Cryptosporidiosis is a water-borne infectious disease, and is known to cause lethal diarrhea in immunocompromised hosts. This study investigated the molecular characteristics of *Cryptosporidium* based on the 18S rRNA sequence using DNA extracted from pig feces in Korea. Stools from 585 pigs were collected in Gyeongsangnam-do province of Korea from May to November 2017. DNA samples were extracted, and nested PCR was performed using *Cryptosporidium* genus-specific primers. Of 585 samples, 76 (13.0%) were positive for *Cryptosporidium* spp. The age group with the highest infection rate was the grower/finisher group (21.2%), followed by weaners (11.0%). The rate was much higher in fall (20.0%) than in spring (1.7%) and summer (3.3%). The phylogenetic analysis identified *C. suis* and *C. scrofarum*. Fortunately, the *C. suis* and *C. scrofarum* species identified in this study do not pose a major threat to public health. Overall, the infection rate was somewhat lower than the infection rates in other countries. However, this is a result limited to the southern region, so it is unclear to what extent it can be applied nationwide. The study found a significantly higher infection rate in certain areas, which indicates that continuous monitoring of the breeding environment may be required in these areas.

Keywords: *Cryptosporidium*, Pig, PCR, Korea

P-023

Molecular Detection and Genetic Characteristics of *Giardia duodenalis* from Pigs in Korea

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Giardia duodenalis (syn. *Giardia intestinalis, Giardia lamblia*) is an important zoonotic parasite that infects livestock species, including pigs, through the ingestion of cysts contained in food or water. It has been classified into eight different genetic assemblages, A to H. Assemblages A and B have been detected in a variety of species. Because their host range is wide, the type detected in humans also belongs to this group. This study examined the infection rate of *Giardia* in domestic pig farms and confirmed the specificity by comparing the genotypes.

Samples were collected from Gyeongsangnam-do, southern province of Korea, during the period from May to November 2017. DNA was extracted directly using a commercial kit from a total of 585 pig fecal specimens. PCR was carried out targeting the *β*-giardin gene sequences of *G. duodenalis*. Of 585 samples tested, 2 (0.3%) were positive for *G. duodenalis*. The infection was detected in Goseong and Hapcheon area and fall season only. Phylogenetic analysis showed that the genetic assemblage was E. Fortunately, in this study, the zoonotic types of assemblages A and B were not found. The infection rate was also low compared to that observed in previous studies. Although there is a limit to comparability because the number of positive samples was very small, the present results suggest that the environment of pig farms is well-managed but will require continuous management and monitoring.

Keywords: *Giardia duodenalis*, Pig, PCR, Korea

P-024

Molecular Detection and Phylogenetic Analysis of *Cryptosporidium canis* from Dogs in Korea

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Cryptosporidium is a ubiquitous intestinal parasite that causes enteric disease in humans and animals. It has a wide host range, and several different genotypes have been identified. Dogs may harbor this pathogen and represent a potential risk of transmission to humans. In this study, we tested for *Cryptosporidium* infection using PCR based on the 18S rRNA sequence, analyzed the molecular characteristics, and examined the potential zoonotic risk. Feces were collected from 597 dogs from animal hospitals from August 2016 through February 2018. DNA samples were extracted and subjected to PCR with *Cryptosporidium* genus-specific primers. Of 597 samples tested, only three samples were positive for *Cryptosporidium* spp., an infection rate of about 0.5%. One companion dog and two shelter dogs were infected, all falling into the junior (less than 7 m) and unknown aged groups. The phylogenetic analysis identified three *C. canis* in dogs. In this study, we identified *C. canis*, a dog-specific type of *Cryptosporidium*, and no *Cryptosporidium* infection was detected in special-purpose dogs. It could be concluded that their management is adequate. However, because of the low overall number of infections, the generalizability of our results is limited, and further investigation with more individuals and a longer follow-up is needed since the potential reservoirs of the zoonotic pathogens are not completely understood.

Keywords: *Cryptosporidium*, Dog, PCR, Korea

▶▶▶ P-025

Molecular Detection and Subtyping of *Giardia duodenalis* from Dogs in Korea

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Giardia duodenalis (syn. *G. intestinalis*, *G. lamblia*) is the only *Giardia* species that infects humans, as well as most other mammals. A recent study showed that it can be classified into at least eight different assemblages (A to H), based on genetic characteristics and host range. Assemblages A and B have been reported not only in humans but also in many other animals, including dogs, so they are potentially zoonotic. This study broadens the scope of the previous study to a nationwide analysis and analyzes the status of *Giardia* infections and phylogenetic characteristics in companion dogs and special-purpose dogs as well as shelter dogs. DNA was extracted, using a commercial kit, from fecal samples collected from 597 dogs throughout Korea from August 2016 through February 2018 and PCR was performed with G7/G759 and G7n/G759n primers. The phylogenetic assemblages were determined using *β*-giardin gene sequences. Of the 597 fecal samples, 3 (0.5%) were positive for *G. duodenalis*, indicating an unexpectedly low infection rate. However, all positive samples were detected in shelter dogs (3/198, 1.5%) in the northern region in the spring season. The phylogenetic analysis indicated assemblages C and D. Unlike the previous results, assemblages A and B, which are mainly found in humans, could not be identified in our study. In addition, no infections were found in companion dogs or special-purpose dogs, the main types of dogs that are commonly in contact with humans. The unexpectedly low infection rates may indicate that the living environment of the dogs is well-managed. However, it is possible that the results are not representative, so continuous follow-up studies will be needed.

Keywords: *Giardia*, Dog, PCR, Korea

▶▶▶ P-026

Molecular Identification of Human Taeniid Cestodes in Northern Lao PDR

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Taenia saginata, *T. solium*, and *T. asiatica* are identified to cause human taeniasis. The morphological identification is available, but it is not always typical to identify the human taeniids and needs to be confirmed by molecular diagnosis. Previous studies have shown 1.5% of egg positive rate by Kato-Katz methods and 27.9% of positive rate by copro-antigen ELISA in northern Lao PDR. The present study investigated human taeniasis by molecular identification of human taeniids. In Oudomxay, a province of northern Lao PDR, four villages (Namchim, Hwei Hung, Nangua, and Na Kham), where mass drug administration was not previously conducted, were selected. The village residents with a history of discharging *Taenia* worm segments from their feces were identified by questionnaire and medicated with praziquantel for treatment and discharge of the worms. The isolated worms were identified by PCR using cox1 gene and DNA sequencing. A total of 203 individuals were examined and 22 (10.8%, 22/203) complained for a history of discharging worm segments. Worms were collected from nine of 22 individuals (40.9%) after medication. Among the 9 worms, two were identified to be *T. solium* and rest seven were *T. saginata*. In northern Lao PDR, 4.4% (9/203) of individuals were positive for human taeniids and 22.2% were identified as *T. solium* infection and the rest were identified as *T. saginata* infection by PCR and DNA sequencing.

Keywords: Taenia, Lao PDR, Molecular diagnosis

▶▶▶ P-027

Genetic Polymorphism and Antigenicity of *Plasmodium vivax* 34 kDa Rhoptry Protein of Korean Isolates

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The *Plasmodium vivax* 34 kDa rhoptry protein (Pv34) plays an important role in parasitophorous vacuole formation sharing homology with proteins from other *Plasmodium* spp. Although Pv34 is a *P. vivax* malaria vaccine candidate antigen, genetic variability and antigenicity of Pv34 have not been studied. In this study, genetic variability of the Pv34 gene and naturally acquired humoral immune responses against recombinant Pv34 in South Korea (SK) were investigated. The Pv34 gene was amplified from DNA extracted from blood samples of 40 SK patients with *P. vivax* infection between 1998-2012. Genetic diversity and polymorphism analyses were performed and sequences of each SK isolate were compared to Sal-1, P01, and VCG-1. For the antigenicity study, total IgG responses of 56 naturally infected sera were evaluated using ELISA against recombinant Pv34 expressed in a prokaryotic system. In contrast to the 6 sets of repeats found in Sal-1, SK isolates had 7 sets of a 5-amino-acid repeat. Single point mutations with a low frequency were also detected at 33 positions. We identified two types (C970T) of SK isolates based on a variant in the 6th repeated region. Further, the nucleotide diversity of Pv34 (0.00199) was lower compared to other vaccine candidate antigens found in SK isolates, and we identified two haplotype groups using phylogenetic analysis. In addition, IgG antibody against recombinant Pv34 antigen was significantly high (optical density of 1.833 ± 0.1172) in naturally infected patient sera ($P < 0.0001$) with a 71.4% seropositive rate. We discovered sequence differences in Pv34 between strains of *P. vivax*, and identified 23 unique haplotypes in the Pv34 gene using single nucleotide polymorphisms. The distinct change in the distribution of rare haplotypes during a 10-year period suggests that the genetic variability of Pv34 in SK isolates may be because of population expansion directly after a bottleneck event, which is a common characteristic of purifying selection. Considering the functional importance of Pv34 in malaria infection and our findings in the present study of low genetic variability and strong antigenicity, Pv34 may be a useful candidate antigen to develop a blood-stage vaccine against *P. vivax*.

Keywords: *Plasmodium vivax*, 34 kDa Rhoptry protein, Genetic polymorphism, Antigenicity, Natural selection

▶▶▶ P-028

Involvement of Adipocyte Leptin in Proliferation of Prostatic Cells Induced by *Trichomonas vaginalis* Infection

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Obesity induces chronic low-grade inflammation and increases the risk of benign prostatic hyperplasia (BPH). Adipocytes influence not only the endocrine system but also the immune response through several cytokine-like mediators known as adipokines including leptin. Leptin is an adipokine that was originally identified as a key molecule in the regulation of food intake and body weight. Abdominal obesity and serum leptin level are known to associate with prostate growth, and reported as high risk factors for clinical BPH. However, it is not known that leptin could induce proliferation of prostate. In this study, we investigated whether adipocyte reacted with the culture supernatant of BPH epithelial cells infected with *T. vaginalis* (*Tv*) may induce the proliferation of prostate stromal cells. BPH epithelial cells incubated with live *Tv* released pro-inflammatory cytokines, and induced the migration of pre-adipocytes. When the culture supernatant of BPH epithelial cells stimulated with *Tv* (TCM) was added to mature adipocytes, they produced adipokines such as CXCL1, IL-6, CCL2 and leptin. Prostate stromal cells incubated with the culture supernatant of adipocyte stimulated with TCM (ATCM) showed increased proliferation and expression of leptin receptor (OB-R). However, blocking the leptin receptor reduced the proliferation of prostate stromal cells. Therefore, leptin from adipocytes may be involved in proliferation of prostate stromal cells. In summary, the inflammatory mediators released by BPH epithelial cells in response to infection with *Tv* induced the migration and activation of adipocytes. The activated adipocytes induce the proliferation of prostate stromal cells through adipokine containing leptin. Our results therefore show the inflammatory response by BPH epithelial cells stimulated with *Tv* induce the proliferation of prostate stromal cells via crosstalk with adipocyte leptin.

Keywords: *Trichonomas vaginalis*, Benign Prostatic Hyperplasia, Proliferation, Adipocyte, Leptin

▶▶▶ P-029

국내산 다슬기에서 발견된 pleurolophocercous cercariae의 분자생물학적 구분

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다슬기(Semisulcospira libertina)는 다양한 Metagonimus 종의 제 1 중간숙주로 알려져 있다. 다슬기에서 검출되는 Metagonimus 의 꼬리유충 동정은 흡반 주변 소극의 배열, 화염세포식과 같은 형태학적 특징을 기반으로 이루어지지만, 이 방법에는 훈련된 전문가가 필요하고, 형태적으로 유사한 종의 경우 오동정 될 수 있는 단점이 있다. 이 연구에서는 다슬기에서 검출한 pleurolophocercous cercariae를 분자생물학적인 방법으로 구분해 보고자 하였다. 2017년 4월에서 7월까지, 충북 영동군 황간면 금강 상류, 경남 밀양시 동천천, 전남 구례군 간문천에서 다슬기(n=1243, 474 및 242)를 확보하였다. 각 다슬기는 페트리접시에 0.5% saline과 함께 담아 파쇄한 후 실체 현미경으로 관찰하여 pleurolophocercous cercariae를 검출하였다. 지역별 5~7시료에서 DNA를 추출하였고, 28S rRNA 및 Mitochondria의 COI partial gene 염기서열을 확보, GenBank 상에 제공된 염기서열을 이용하여 계통수를 분석하였다. 각 지역의 다슬기에서 pleurolophocercous cercariae는 각각 7/1243, 6/474, 112/242 마리에서 양성이었다. 계통수 분석결과는 DNA의 분석 위치에 상관 없이 비슷한 양상을 나타냈다. 금강에서 검출된 꼬리유충은 모두 Metagonimus 에 속하지 않았으며, GenBank상에 부합되는 염기서열이 없이 2개의 독립적인 그룹을 이루었다. 간문천의 경우 모두 M. yokogawai와 일치하였다. 동천천에서 확보한 염기서열의 대부분은 금강에서 확인된 그룹 중 하나와 함께 clade를 이루었으나, 한 시료에서 기존의 Metagonimus 종들의 염기서열과 명백히 구분되는 새로운 염기서열을 얻을 수 있었다. Pleurolophocercous cercariae의 경우 전문가의 형태학적 동정 없이도 염기서열 분석을 통한 종 구분이 가능함을 밝혀내었으며, 기존에 알려지지 않았던 새로운 장흡충 종이 국내 생태계에 존재하고 있음을 확인하였다.

Keywords: 꼬리유충, 다슬기, Metagonimus

▶▶▶ P-030

Distribution of Freshwater Snails and their Cercarial Infection Status at Some Regions in Sejong and Daejeon

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To investigate the fauna and larval infection status of freshwater snails living in water stream and rice paddy, we collected 925 freshwater snails at 7 regions in Sejong and Daejeon at 2016 and 2017. From the survey, a total of 925 freshwater snails were identified as 6 families, 9 genuses and 9 species. The collected ten species of freshwater mollusks were identified as *Lymnaea pervia, Radix (Lymnaea) auricularia, Physa acuta, Cipangopaludina chinensis, Gyraulus convexiusculus, Hippeutis cantori, Segmentina hemisphaerula, Semisulcospira libertina*, and *Parafoussarulus manchuricus*. The most populated snails were *L. pervia* and the second one was *P. acuta*. The cercariae of *Paragonimus, Metagonimus* and *Echinostoma* species were isolated from *Semisulcospira, Gyraulus, Hippeutus, Parafoussarulus, Segmentina, Lymnaea and Radix* collected at 3 regions among 7 surveyed regions. Collectively, this study presented that various species of freshwater snails and cercaria-infected snails are distributed at water stream and rice paddy at Sejong and Daejeon, and further investigation needs to be carried out to identify the fauna of freshwater snails in detail.

Keywords: Freshwater snails, Cercaria, Water stream, Rice paddy, Korea

대한미생물학회

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▶▶▶ P-031

Interaction of Bif-1 with PHB2 during Apoptosis Facilitates OPA1 Cleavage for Inner Membrane Fission of Mitochondria

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Mitochondrial fragmentation is a critical process during the intrinsic pathway of apoptosis. Emerging studies have documented lots of proteins participate in both mitochondrial inner (IMM) and outer (OMM) membrane changes regarding to fission or fusion of mitochondria. Drp1, Fis1, Mfu1/2, and Opa1 have a major function in morphological change of IMM or OMM, respectively. Besides, several Bcl-2 family proteins including Bax and Bak, take part in this kind of apoptotic procede through pore formation of OMM for release of cytochrome c. Moreover, Bif-1 had been also documented to involve in change of mitochondria by interacting with Bax and inducing its translocation to OMM in response to apoptotic stresses. However, it is not crystal clear how fission of IMM associating with Opa1 occurs so far. Here, we highlights that Bif-1 might trigger a proteolytic cleavage of OPA1 by directly contacting with PHB2 in IMM under cell stress

Keywords: Bif-1, PHB2, Apoptosis

▶▶▶ P-032

Characterization of *Mycobacterium tuberculosis* Protein Rv32XX Induces Macrophage Apoptosis in RAW264.7 Cells

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Macrophages infected with *Mycobacterium tuberculosis* undergo increased rates of apoptosis. Important objectives are to define the microbial factors that cause apoptosis, the mechanisms involved and the impact on infection. In this study, using multidimensional fractionation, we identified mycobacterial proteins, which induced macrophage apoptosis in *Mycobacterium tuberculosis* culture filtrates. The Rv32XX is candidate virulence factor. We investigated whether the recombinant Rv32XX protein could effectively induce apoptosis in macrophages. The annexin V binding to membrane phosphatidylserine was used to measure apoptosis. The results show that Rv32XX induce apoptosis in a dose-dependent manner in macrophage cells. DNA fragmentation, caspase activation, and poly (ADP-ribose) polymerase (PARP) cleavage were observed in apoptotic macrophages treated with Rv32XX. Enhanced ROS production was essential for Rv32XX -induced apoptosis, and pretreatment with N-acetylcysteine (NAC), a potent ROS scavenger, brought restoration of the viability of macrophages. In addition, ROS-mediated activation of JNK pathway was especially associated for Rv32XX -induced apoptosis. The loss of $\Delta\Psi$m, mitochondrial translocation of (Bax, BID) and release of cytochrome *c* from mitochondria were occurred in Rv32XX -treated macrophages. Interestingly, Rv32XX induced apoptosis was significantly reduced in TLR4-deficient macrophages. Altogether, the results suggest that Rv32XX may act as a strong pathogenic factor to cause apoptosis of macrophages.

Keywords: *Mycobacterium tuberculosis*, Apoptosis, ROS, RAW264.7 cells

▶▶▶ P-033

Differential Effect of Silver Nanoparticles on the Glucose Consumption and the Reactive Oxygen Species Generation by *Candida albicans* and *Saccharomyces cerevisiae*

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Silver nanoparticles (AgNPs) inhibit the proliferation of various fungi, however, the inhibitory mechanisms remain poorly understood. We investigated whether 5 nm AgNPs differentially exert the inhibitory effect in pathogenic *Candida albicans* and non-pathogenic *Saccharomyces cerevisiae*. AgNPs suppressed the proliferation of both yeast cells through G1 phase delay in the concentration dependent manner. However, AgNPs increased cell death and glucose consumption only in *C. albicans*. Further, AgNPs together with glycolysis pathway inhibition synergistically increased cell death only in *C. albicans*. AgNPs enhanced ROS production significantly in *C. albicans* but negligibly in *S. cerevisiae*. Concordantly, the proliferation of *S. cerevisiae* harboring deletion of genes involved in oxidative or cell wall stress response (ΔSKN7, ΔYAP1, ΔHOG1 or ΔSLT2) was similarly inhibited by AgNPs treatment compared with *S. cerevisiae* wild type. ROS scavenger treatment reduced AgNPs-induced G1 phase delay in *C. albicans* but not in *S. cerevisiae*. Our results suggest that the differential mechanisms underlie the AgNPs-mediated growth suppression of *C. albicans* and *S. cerevisiae*.

Keywords: Metal Nanoparticles, Yeasts, Reactive Oxygen Species, G1 Phase, Cell Death, Cell Proliferation

▶▶▶ P-034

Eosinophils Accelerate Pathogenesis of Psoriasis by Supporting Inflammatory Milieu that Promotes Neutrophil Infiltration

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Eosinophils are proinflammatory granulocytes that are involved in the pathogenesis of various inflammatory reactions. However, their roles in psoriasis remain largely unknown. In this study, by examining the inflammatory features of the eosinophilic cell line EoL-1 and an imiquimod (IMQ)-induced murine model of psoriasis, we showed that eosinophils provide inflammatory signals that accelerate the pathogenesis of psoriasis. EoL-1 cells constitutively expressed TLR7, which mediates acute and rapidly developing psoriatic inflammation. The activation of TLR7 on EoL-1 cells using R837 resulted in the secretion of inflammatory mediators that support the migration, activation, and survival of neutrophils. The underlying pathologic role of eosinophils in psoriatic inflammation was further substantiated by markedly decreased psoriasiform inflammation in IMQ-treated ΔdblGATA mice, which have a systemic eosinophil deficiency. While IMQ-treated wild-type mice showed a significant increase in the eosinophils in their skin, neutrophils remarkably outnumbered the eosinophils in the skin, lymph nodes, and spleen in wild-type mice after IMQ application. In addition, lesional skin samples from psoriasis patients also showed upregulated eosinophil cytotoxic granules, accompanied by marked neutrophil infiltration. Based on these collective data, we propose that eosinophils accelerate psoriatic inflammation by supporting inflammatory microenvironments to favor the activation and infiltration of neutrophils.

Keywords: psoriasis, imiquimod, TLR7, eosinophil, neutrophil

▶▶▶ P-035

Effect of The Saccharide Fraction of Codonopsis lanceolata (S-CL) on LPS-Induced Inflammation in RAW 264.7 Macrophages and Metabolic Syndromes in Mice

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It is known that Codonopsis lanceolate has the same effect as ginseng because of its high content of bitter saponins. However, there is no information about biological activity of the leaves and stems of Codonopsis lanceolate. Therefore, in order to examine the biological activity of the leaves and stems of this plant, we extracted the saccharide fraction from Codonopsis lanceolata (S-CL), and investigated it inhibitory effect on lipopolysaccharide (LPS)-stimulated inflammation in RAW-264.7 macrophages metabolic syndromes such as diabetes and obesity in mice. We dried nodule leaves and stems naturally on the shade and then grinded them into a blender to extract crude polysaccharides. Inhibitory effect of S-CL on diabetes and obesity was carried out using ICR mice at 6-7 weeks of age. Mice were administered orally with 0.5 or 1 mg/mouse of S-CL, and the anti-obesity and anti-diabetic effects were measured weekly by measuring weight and tail blood glucose, respectively. Treatment of S-CL markedly inhibited the production of inflammatory medoators such as nitric oxide, IL-6, and TNF-α form LPS-stimulated RAW 264.7 cells. In addition, oral administration of S-CL significantly suppressed the level of blood glucose in alloxan-induced diabetic mice and body weight gains of high-fat diet-fed mice. These results suggest that S-CL has a biological activity to inhibit inflammation and suppress metabolic syndromes such as diabetes and obesity.

Keywords: Codonopsis lanceolata, diabetes, obesity, inflammation

▶▶▶ P-036

새로운 배양촉진성분을 이용한 액체배양배지시스템에서의 결핵균(Mycobacterium tuberculosis) 신속배양

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Tuberculosis is a chronic infectious disease caused by Mycobacterium tuberculosis (M. tuberculosis). Various culture media have been used for the culture of M. tuberculosis. Bacteriologic culture still remains as an obstruction in the diagnosis of tuberculosis. Growth-Enhancing Media were included a series of concentration of culture-promoting ingredient, 0.0, 0.2, 0.4, 1.0, and 2.0 mg in 7H9 broth. Growth of M. tuberculosis was analyzed by counting CFU using 7H10 agar plates. The effect on the growth of M. tuberculosis was measured in a Liquid Mycobacterial Culture System, MGIT. The Time to Position Detection (TTD) in the media containing growth-enhancing ingredient was reduced by 13.6%, 21.4%, 22.7%, 32.6%.

Keywords: 결핵, 신속배양, 액체배양시스템

▶▶▶ P-037

안전하면서 신뢰성있는 Acid Fast Staining(AFB) 검사기기 개발

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호흡기 감염질환인 결핵(Mycobacterium tuberculosis)을 신속히 치료하기 위한 전략은 조기 진단에 있으며, 전통적으로 염색법(AFB)이 결핵 유병율이 높은 대부분의 국가에서는 검사실 진단방법으로 필수적이다. 하지만 검사자의 AFB 염색을 실시하는 기술의 차이로 검사 결과의 재현성이 확보되어 있지 않아 재현성 및 신뢰도가 확보된 새로운 방식을 필요로 하여 결핵균을 확인하는 측정 결과의 동일하게 제시할 수 있는 결핵균 자동염색기를 개발하고자 하였다. 결핵균 염색시험방법의 정확한 비교 분석을 위해 검사자가 직접 수행하는 방법(수동), 수입품(W사)과 자사에서 개발한 자동염색기로 자동염색하는 3가지 방법을 실시하였다. 자동염색과 수동염색(검사자 실시) 검사 결과는 미국 CDC 기준(-, +/-, +, ++, +++)으로 측정하였다. 각 군별로 50개씩 설정하여 인공객담과 결핵균을 혼합하여 도말하여 AFB 염색사진에서 수동염색 대비 자동염색의 결과가 선명하면서 균 개수의 확인도 우수한 것을 확인하였고, 수동 염색방식은 전처리 및 1차 염색에서 Heating 방식으로 염색을 실시하는 방법으로서 염색 결과, 음성이 13개 관찰되었고, +/- 이상이 37개 관찰되어 양성율이 74%이었다. W사 기기의 염색방식은 전처리를 검사자가 Heating을 직접해야하며, 그 후 염색방식은 Heating을 실시하지 않고 검체에 직접 타격하는 분사방식으로 염색을 실시하였을 때 염색에서 음성이 19 개 관찰되었고, +/- 이상이 31 개 관찰되어 양성율이 62% 이었다. 본 연구에서 개발한 자동염색기는 자동으로 전처리 및 1차 염색에서 Heating 방식으로 염색하는 방법으로서 염색 결과, 음성이 14 개 관찰되었고, +/- 이상이 31 개, 양성율이 72% 이었다. 본 연구에서 개발된 자동염색기와 수동작업에서 검체의 전처리 및 1차 염색에서 Heating 방식이 동일하면서도 수동염색의 결과보다 정성(사진 비교)/정량적 분석으로 우수한 결과를 획득하였다. 미생물검사가자 독성이 있는 염색액 및 병원성 세균에 대한 노출을 줄일 수 있을 것이다.

Keywords: 결핵, 자동염색기기, AFB

▶▶▶ P-038

Reclassification of *Borrelia* spp. of the Strains Isolated in South Korea Using Multilocus Sequence Typing

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To understand the epizootic spread and to predict the evolutionary propensity of *Borrelia*, accurate information on the population structure and the evolutionary relationships of the pathogen is important. Therefore, we validated the multilocus sequence typing (MLST) scheme on *Borrelia spp*. specimens from South Korea. These data were compared with sequences for the commonly used genetic markers 16S rRNA, 5S-23S intergenic spacer (IGS) region and the gene encoding the outer surface protein A (ospA) gene (abbreviated as multilocus sequence analysis, MLSA). The study demonstrates that the concatenated sequences of the 8 housekeeping genes of *Borrelia spp*. provide highly resolved phylogenetic signals and that the housekeeping genes evolve differently compared with the MLSA. In results, HN7, HN9, HN17, HNM17, and KM4 were identified *B. afzelii*. And HN12 was identified as *B. yangtzensis*. HN13 was identified as *B. garinii* and KW3 was identified as *B. bavariensis*.
The aim of all molecular genotyping is to assess relationship between *Borrelia* and its reservoir hosts and vectors as well as to clarify molecular background of pathogenicity.

Keywords: *Borrelia*; MLST; 16S *rRNA*; 5S-23S IGS; *ospA*; MLSA

P-039

Modulation of Autophagy by Heme Oxygenenase-1 in *Mycobacterium abscessus* Infected Bone Marrow-derived Macrophage

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Mycobacterium abscessus (M.abs) is a rapidly growing non-tuberculous mycobacterial species that infects macrophages of the lung and skin which are cause a variety of clinical syndromes in human. The heme oxygenase-1 (HO-1) acts as the cytoprotective stress protein, and provides defense against oxidative stress by accelerating the degradation of pro-oxidant heme and hemoproteins to the radical scavenging bile pigments, biliverdin and bilirubin. This protein is also induced in response to variety of stimuli such as free iron, inflammation, heavy metals, UV radiation and various oxidative stress conditions including hypoxia or conditions that produce ROS. The role of HO-1 in M.abs infection is not well known. In this study, we are investigating the role of the HO-1 on M.abs infection in macrophage. The murine bone marrow-derived macrophage (BMDM) was infected with M.abs ATCC19977 and UC22 (clinical isolates, BioProjectID 80959). Extracellular bacteria were killed by gentamicin. Intracellular bacteria were measured by serial dilution from cell lysate. HO-1 enzymatic activity measured by using mouse HO-1 ELISA kit. The M.abs infected cells were immunoblotted with anti-HO-1 and anti-LC3 (autophagic marker). The HO-1 inhibitor, Tin protoporphyrin IX dichloride (SnPP) was utilized to confirm the HO-1 effects to infected macrophage. Also, TNF mRNA expression level was quantified by qRT-PCR. BMDM infected with different M.abs strains exhibited different intracellular bacteria growth and HO-1 expression. Intracellular bacteria number and HO-1 expression were significantly higher in M.abs UC22 compared with M.abs ATCC19977. Intracellular bacterial growth was suppressed in SnPP pretreated BMDM. Expression of TNF mRNA expression level were decreased in SnPP pretreated BMDM. SnPP inhibits HO-1 activity in M.abs infected BMDM. However, LC3 and HO-1 protein expression was increased in SnPP pretreated BMDM. These results suggest that different intracellular bacteria growth of M.abs is influenced by HO-1 activity, and that increased HO-1 activity and expression may enhance autophagy to control of M.abs infection.

Keywords: HO-1, Autophagy, *M.abcessus*

P-040

Molecular Characterization of *Rickettsia* in South Jeolla Province in the Republic of Korea

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Spotted fever group rickettsiosis is a common infectious disease mediated by ticks. It is a disease that requires continuous domestic surveillance due to changes in the habitat and distribution pattern of mediators. However, clinical features and infection pathways are inferred. To investigate the distribution and molecular biology of *Rickettsia* spp., environmental samples and human samples were collected in South Jeolla provinces of ROK. We collected specimens from ticks during May to December, 2017 and human blood (Rickettsia infections or similar symptoms) from Chungnam National University Hospital. The partial citrate synthase (gltA) and outer membrane protein B (*ompB*) genes of *Rickettsia* were amplified and confirmed by the nested PCR method. PCR products of the Rickettsial agents were compared with the sequence specific to each genotype of *Rickettsia* in the BLASTN database (Sequence analysis), and sequencing was performed with MEGA 6.0, MegAlign, and Seqman program. The mortality rate of ticks were found to be *gltA* genes were found to be high in 10 *H. flava* tick pools (5.59%, MPR), and the *ompB* gene was high in 10 *H. flava* tick pools (1.96%, Minimum Positive Rate, MPR) in the Jeolla provinces. Positivity of *gltA* was detected in 9 samples (15.52%, n = 58) of the human blood samples. The isolation rate of *gltA* gene was 3.03% and *ompB* gene was 2.27% in South Jeolla province. *Rickettsia* in the RBC layer was 13.79% (8/58) and the recirculation rate of the buffy coat layer was 5.17% (3/58) of Chungnam National University Hospital. Subsequently, the result of sequencing analysis of *gltA* and *ompB* were showed to be closely related to *R. heilongjiangensis*-like or *R. japonica*-like and *R. monacensis*. In this study, we confirmed the distribution and characteristics of Rickettsia species in South Jeolla Provinces in the ROK.

Keywords: *Rickettsia*, GltA, OmpB

▶▶▶ P-041

결핵균으로 자극된 큰포식세포의 L-plastin

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L-plastin(LPL)은 조혈세포에서 유래한 세포에 발현되는 단백이다. 이 단백은 액틴 섬유골격이 다발을 형성하게 하는 것으로 칼슘의 영향을 받는다. 칼슘이 LPL에 결합하는 부위는 아미노 말단에 있다. 칼슘농도가 높으면 LPL이 액틴에 결합하는 능력이 낮아진다. 그러나, 큰포식세포의 포식작용에서 세포질의 칼슘농도 변화에 따라 LPL이 어떻게 수식되는지 잘 밝혀져 있지 않다. 이 연구에서 큰포식세포를 결핵균으로 자극하여 칼슘신호 발생을 확인한 다음, 그 신호 경과에 따른 LPL의 5-serine 인산화 정도를 특이항체로 측정하였다. 그 결과 LPL의 Ser5 인산화는 칼슘신호 경과에 따라 특징적으로 변하였다. 이러한 결과는 포식작용에서 세포막의 역동적 움직임에 적어도 LPL의 Ser5 인산화의 지속적인 변화에 따른 세포골격의 다발형성이 작용할 수 있음을 암시한다.

Keywords: L-plastin, 큰포식세포, 칼슘신호, 인산화

▶▶▶ P-042

악성 간암세포주의 L-plastin

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L-plastin(LPL)은 세포운동성과 관련이 있는 액틴과 결합하는 것으로 칼슘에 영향을 받는 단백이다. 이 단백은 주로 조혈세포에서 유래한 세포에 발현된다. 그런데, 정상세포를 전이 암세포로 형질전환시키면 이 LPL이 발현되며, 일부 암세포의 경우 조기 발견에 표식자로 이용되기도 한다. 이러한 보고들은 LPL이 암세포의 침습과 세포부착에 중요한 역할을 할 수도 있음을 시사한다. 그러나, 간암세포의 악성정도에 따라 LPL이 어떠한 양태로 발현 및 수식되는지 잘 밝혀져 있지 않다. 이 연구에서 양성 또는 악성 간암세포주를 대상으로 LPL의 발현 정도와 세포내 분포, phorbol 12-myristate 13-acetate (PMA) 자극 후 LPL의 동태를 측정하였다. LPL은 악성 간암세포주에 발현되지만 양성 간암세포주에서는 발현되지 않았고, 세포막과 연관되어 검출되었다. PMA로 악성 간암세포주를 자극하면 세포막 연관 정도가 증가되었으며, LPL의 5-serine 인산화도 증가하였다. 이러한 결과는 LPL이 악성 간암세포에서 액틴의 역동성에 개입하여 암의 전이과정에 기여할 수 있음을 시사한다.

Keywords: 악성 간암세포주, L-plastin, 인산화

▶▶▶ P-043

Study on MALDI-TOF Peaks of Methicillin Susceptible and Resistant *Staphylococcus aureus* Isolated in Korea

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MALDI-TOF-MS in clinical laboratory provides an easy and rapid identification of bacteria. *Staphylococcus aureus* is an important bacterial pathogen that cause pneumonia, bacteremia, endocarditis and toxic shock. For proper antibiotic treatment, it is necessary to obtain the peak for the characterization of methicillin-resistant *S. aureus*. Therefore, we compared the MALDI-TOF peaks for the methicillin resistance of *S. aureus* (MRSA). A total of 359 *S. aureus* strains isolated from Kangdong Sacred Heart Hospital and analyzed by Tinkerbell MALDI-TOF instrument (ASTA, Korea). MALDI-TOF peak identification was performed by MALDI-TOF instrument and SPSS software. It was compared the MALDI-TOF peak of MRSA and MSSA strains to find specific peaks for methicillin resistance clone. Among the 359 isolates, 23 peaks were statistically different. The 19 peaks of MRSA and 4 peaks of MSSA were found to be specific for each group. It was observed for two peaks of 2978.5 m/z (MSSA 3% vs. MRSA 25%) and 3015.3 m/z (MSSA 27% vs. MRSA 7%) more than 20% differences of frequency. We demonstrated that specific peaks of methicillin resistance. The identification of MRSA or MSSA by MALDI-TOF might be helpful for the treatment for the patients because of the rapidity and ease performance of MALDI-TOF analysis.

Keywords: *S. aureus*, Methicillin-resistant, MALDI-TOF MS

▶▶▶ P-044

A Pathogenic Role of the A1S_3412 Gene Encoding D-alanyl-D-alanine Carboxypeptidase in *A. baumannii* ATCC 17978

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Acinetobacter baumannii is a notorious nosocomial pathogen that commonly infects severely ill patients in intensive care units. However, the pathogenesis of *A. baumannii* has not yet been fully characterized. This study was investigated the pathogenic role of the A1S_3412 gene, a zinc uptake regulator-regulated gene, using the wild-type *A. baumannii* ATCC 17978, ⊿A1S_3412 mutant, and A1S_3412 gene-complemented strains. The A1S_3412 gene was predicted to a D-alanyl-D-alanine carboxypeptidase (DD-CPase) and was highly conserved among the A. baumannii strains with 98-100% homology. Bacterial growth was not different between the wild-type and ⊿A1S_3412 mutant strains under the zinc-replete and -deplete conditions. The ⊿A1S_3412 mutant displayed reduced biofilm production in polystyrene tubes, surface motility in agar plates, and adherence and invasion in A549 cells in comparison to the wild-type strain. The ⊿A1S_3412 mutant showed significantly lower bacterial number in the blood than the wild-type strain in a mouse pneumonia model. These virulence traits of ⊿A1S_3412 mutant were restored when the A1S_3412 gene was complemented. The recombinant protein of the A1S_3412 gene showed a specific DD-CPase activity. The chaperon-usher system *csuCDE* genes that were responsible for the biofilm production, surface motility, and adherence to host cells were significantly down-regulated in the ⊿A1S_3412 mutant under sessile condition than the wild-type strain. In summary, our results indicate that the A1S_3412 gene encoding DD-CPase plays a role in *A. baumannii* pathogenesis *in vitro* and *in vivo*, suggesting the potential target for the development of anti-virulence agents.

Keywords: *A. baumannii*, Carboxypeptidase, Virulence, Biofilm, Chaperon-Usher System

▶▶▶ P-045

Thymol Suppresses the Inflammatory Responses Induced by *Staphylococcus aureus* Membrane Vesicles in Cultured Keratinocytes

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Staphylococcus aureus membrane vesicles (MVs) deliver effector molecules to host cells and induce host cell pathology. This study investigated whether thymol could disrupt *S. aureus* MVs and suppress the pathology of the keratinocytes induced by *S. aureus* MVs. Membrane disruption of the *S. aureus* MVs treated with thymol was determined using transmission electron microscopy. Human keratinocyte HaCaT cells were incubated with either intact or thymol-treated *S. aureus* MVs and then analyzed for cytotoxicity and pro-inflammatory cytokine gene expression. Thymol inhibited the growth of *S. aureus* strains and disrupted the membranes of the *S. aureus* MVs. Thymol-treated *S. aureus* MVs inhibited the cytotoxicity of HaCaT cells when compared to intact *S. aureus* MVs; however, the cytoprotective activity differed between the MVs derived from two *S. aureus* strains. Intact *S. aureus* MVs stimulated the expression of the pro-inflammatory cytokine and chemokine genes, whereas thymol-treated *S. aureus* MVs did not stimulate the expression of these genes. Thymol-treated *S. aureus* MVs delivered lesser amounts of the MV component to host cells than intact MVs. Our results suggest that the thymol-induced disruption of the *S. aureus* MVs inhibits the delivery of effector molecules to host cells, resulting in the suppression of inflammatory responses in keratinocytes. Thymol may attenuate the host cell pathology induced by an *S. aureus* infection via both the antimicrobial activity against the bacteria and the disruption of the secreted MVs.

Keywords: Membrane Vesicle, Thymol, *S. aureus*, Inflammation, Cytotoxicity

▶▶▶ P-046

Enhancement of Intracellular Survival of *Brucella abortus* in Professional Phagocytes, RAW 264.7cells, by Mutagenesis of BruA2_1031 gene

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Since recognizing the interaction between *Brucella* and host cells is crucial to the elucidation of the infectious process, priority tasks in *Brucella* researches is investigation of genes related to pathogenicity. To demonstrate the roles of Brucella genes, RAW 264.7 cells were infected with the *Brucella abortus* wild-type and mutant strains (generated using transposon mutagenesis), after which the different transcriptional responses of the infected cells were determined using microarray. Following infection, enhanced strategies for intracellular survival, such as down-regulation of genes associated with cytokine responses and apoptosis, were observed in RAW 264.7 cells infected with C3 mutant strain, when compared to the transcriptional responses of wild-type infected cells. The mutation site of C3 mutant strain was determined as the ATP-binding cassette transporter permease (BruAb2_1031) using sequence analysis. These results were evidenced by an increased level of intracellular survival of the C3 mutant strain. Our results indicate that the BruAb2_1031 gene might be closely related with intracellular survival of *B. abortus* in RAW 264.7 cells.

Keywords: BruAb2_1031 gene, Intracellular survival, *Brucella* mutant, *Brucella abortus*

P-047

The Uncharacterized Transcription Factor AcrR Controls the AcrAB Efflux Pump and Plays a Role in Biofilm Formation and Virulence in *A. nosocomialis*

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Multidrug efflux systems constitute to antimicrobial resistance and pathogenicity in bacteria. Here, we report the identification and characterization of a transcriptional regulator AcrR controlling the yet uncharacterized multidrug efflux pump, AcrAB in *Acinetobacter nosocomialis*. *In silico* analysis revealed that the homologues of AcrR and AcrAB are reported in the genomes of many other bacterial species. We confirmed that the genes encoding the AcrAB efflux pump, *acrA* and *acrB* forms a polycistronic operon which is under the control of acrR gene upstream of *acrA*. Bioinformatic analysis indicated the presence of AcrR binding motif in the promoter region of *acrAB* operon and the specific binding of AcrR was confirmed by electrophoretic mobility shift assay (EMSA). The EMSA data showed that AcrR binds to -89 bp upstream of the start codon of *acrA*. The mRNA expression analysis depicted that the expression of *acrA* and *acrB* genes are elevated in the deletion mutant compared to that in the wild type confirming that AcrR acts as a repressor of *acrAB* operon in *A. nosocomialis*. The deletion of acrR resulted in increased motility, biofilm/pellicle formation and invasion in *A. nosocomialis*. We further analyzed the role of AcrR in *A. nosocomialis* pathogenesis *in vivo* using murine model and it was shown that *acrR* mutant is highly virulent inducing severe infection in mouse leading to host death. In addition, the intracellular survival rate of *acrR* mutant was higher compared to that of wild type. Our data demonstrates that AcrR functions as an important regulator of AcrAB efflux pump and is associated with several phenotypes such as motility, biofilm/pellicle formation and pathogenesis in *A. nosocomialis*.

P-048

N-acyl Homoserine Lactone of *Acinetoabcter baumannii* Induces Apoptosis via Mitochondria Dysfunction and ER Stress

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Objectives: *Acinetobacter baumannii* possesses a quorum sensing system comprising of the genes, *abaI* and *abaR*, encoding an autoinducer synthase and a putative LuxR-type regulator respectively. Quorum sensing (QS) is a cell to cell communication system that coordinates gene expression in bacteria. QS plays an important role in mediating biofilm formation and bacterial virulence. N-(3-hydroxydodoecanoyl)-L-homoserine lactone (OH-dDHL) is produced by *A. baumannnii* to function as a QS molecule. QS molecule is known for multiple effects on host cells including induction of host cell death. However, a little is known about the effects of *A. baumannii* QS molecule OH-dDHL on host cells. We investigated the influence of QS molecule on cell viability, apoptosis in macrophage and epithelial cells. **Methods:** We utilized OH-dDHL to assess the effect of QS molecule on host cell death. Cells were treated with OH-dDHL and cell death was determined by DNA fragmentation assay, microsocpic analysis and flow cytometry with annexinV/PI stain and nuclear staning with DAPI. To determine whether apoptosis of cultured cells is associated with caspase-dependent pathway, the enzyme activity of caspase and western blot analysis were performed. Mitochondrial and ER damage was determined by using cellular ROS detection kit and western blot analysis. Pro-inflammatory cytokine was quantified by qRT-PCR. In addition, the pathogenesis of *A. baumannii* 17978 wild type, isogenic *aba*R mutant strain and complementary abaR mutant was determined by neutropenia mouse infection model and *in vitro* experiments. **Result:** OH-dDHL significantly decreased cell viability in macrophages, epithelial cell by triggered apoptosis that was accompanied by the mitochondrial dysfunction and ER stress. OH-dDHL induced high level of pro-inflammatory cytokine mRNA expression. The survival rate of infected mice with the *aba*R mutant strain was significantly higher than that of those infected with the *A. baumannii* wild-type. **Conclusion:** Our data suggests that OH-dDHL of *A. baumannii* plays an important role in the pathogenicity of bacterial including intracellular survival and growth.

▶▶▶ P-049

Mycobacteria-induced Apoptosis is Associated with Hypertension

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It is well known that inflammation plays an important role in the pathogenesis of hypertension and tuberculosis. To explore the role of hypertension in tuberculosis, we compared pathophysiological characterization of lungs between wild type mice (control group) and angiotensin II-induced hypertensive mice (hypertension group) after mycobacterial infection. We found that inflammatory lesions and severe fibrosis were increased in hypertension group compared with the control. We found that ER stress responses were increased in hypertensive mice lung tissue. Severe inflammatory lesions and fibrosis were increased in hypertension group compared with controls. Mtb infection was severe in hypertensive mice lung comparing to the control. These results suggest that hypertension might be harmful for host protection from mycobacterial infection.

Keywords: *Mycobacterium tuberculosis*, Hypertension

▶▶▶ P-050

임상가검물 유래 ESBL산생 대장균 CTX-M유전자의 유전적 환경의 다양성

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최근에 CTX-M효소들이 ESBL류 항균제 내성의 주류를 차지하고 있으며, 전세계적으로 주목을 받고있다. CTX-M형 베타락탐 분해효소들이 성공적으로 전세계적으로 확산되게 된 유전적 기반은 아직 잘 규명되어 있지 않다. 이 연구에서는 CTX-M형 베타락탐 분해효소를 산생하는 대장균들의 분자역학 및 확산 기전을 규명하기 위해 중합효소연쇄반응 및 유전자 염기서열 분석법을 이용하여 임상 가검물 유래 CTX-M 산생 대장균들의 유전적 기반구조를 분석하였다. 총 100주의 대장균 중에서 35주가 CTX-M 산생균들이었다. 19주의 균이 CTX-M9군 (CTX-M14형 14주, CTX-M27형 5주)이었고, 16주의 균이 CTX-M3군 (CTX-M15형 12주, CTX-M3형 4주)이었다. CTX-M3/15형 대장균의 68.8%에서 CTX-M3/15 유전자의 상위부에 이동성 DNA ISEcp1B가 발견되었고, CTX-M3/15형 대장균의 62.5%에서 ISEcp1B의 상위부에 IS26이 발견되었다. 모든 CTX-M3/15형 대장균은 CTX-M3/15 유전자의 하위부에 orf477유전자를 가지고 있었으나 mucA유전자는 관찰되지 않았다. CTX-M14/27형 대장균의 79%에서 CTX-M14/27 유전자의 상위부에 ISEcp1B가 발견되었고, CTX-M14/27형 대장균의 26.3%에서 ISEcp1B의 상위부에 IS26이 발견되었다. 대부분의 CTX-M14/27형 형 대장균은 CTX-M14/27 유전자의 하위부에 IS903D를 가지고 있었고, IS26을 가진 것도 한주가 발견되었다. ISEcp1B의 우측 역 반복서열과 유사한 DNA서열들이 CTX-M유전자들의 하위부에서 발견되는 점으로 보아 CTX-M유전자들이 전좌단위들에 의해 전좌 이동되었음을 알 수 있었다. 이 연구를 통해 CTX-M유전자들의 유전적 환경이 매우 다양함을 알 수 있었고, ISEcp1B, IS26, IS903 등의 이동성DNA들이 CTX-M유전자들의 이동 및 확산에 중요한 역할을 수행함을 알 수 있었다.

Keywords: 대장균, CTX-M유전자, 이동성 DNA, ISEcp1B, IS26

▶▶▶ P-051

CTX-M 산생 대장균의 플라스미드 안정성과 유전자 중독계의 분자유전적 특성

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CTX-M형 ESBL을 산생하는 대장균의 확산이 전세계적으로 문제가 되고 있다. 국내에서 CTX-M유전자의 확산과 안정적인 유지 기전을 파악하기 위하여 이 연구에서는 CTX-M유전자를 보유하고 있는 R 플라스미드들의 분자역학적 특성을 조사하였다. 중합효소연쇄반응과 염기서열 분석 및 접합실험을 이용하여 R 플라스미드들을 분석하였다. 또한 5종의 단백질성 항독소 조절계와 3종의 antisense RNA 조절계를 대상으로한 유전자중독계 형별검사와 DNA 복제단위분석을 실시하여 특정 CTX-M유전자들과 플라스미드의 특정replicon형 및 특정 유전자 중독계와의 관련성과, 플라스미드가 균체내에서 안정적으로 유지되는 분자적 기전을 규명코자 하였다. 8종의 유전자 중독계 분석에서 pemK, ccdAB 및 srnB가 가장 흔히 발견되었고, 이어서 vagCD, hok-sok, pndCA, RelE 순서였고, parDE는 발견되지 않았다. CTX-M3/15산생균과 CTX-M14/27산생균의 평균 중독계 보유수는 각각 3.2와 2.8이었다. 80%의 플라스미드들이 IncF replicon들 (IncF1A, F1B)을 보유하고 있었다. replicon형별검사가 불가능한 균들은 모두다 유전자 중독계도 검사가 불가능하였다. CTX-M15산생균에서 IncI1과 IncN replicon이 각각 하나씩 발견되었다. 3개의 replicon을 동시에 보유한 플라스미드들이 가장 많았다. Southern 블롯 분석을 통하여 모든 다중 replicon들은 모두 하나의 플라스미드 안에 존재함을 알 수 있었다. 이상의 사실을 고려해볼 때 CTX-M유전자는 다수의 유전자 중독계를 보유한 전달성 IncF군 플라스미드 체계 위에 존재하고 있기 때문에 이질적인 다양한 숙주내에서도 유전적 안정성을 유지할 수 있으며, 타 균으로 쉽게 확산될 수 있을 것으로 사료된다.

Keywords: 플라스미드 안정성, 유전자 중독계, Replicon형별, CTX-M, 대장균

▶▶▶ P-052

인테그론과 IncF 복제단위를 보유한 CTX-M 산생 대장균의 다약제 내성 획득 기전

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다약제 내성 대장균(MDREC)은 의학적으로 중요한 문제를 일으키며 CTX-M형 ESBL 산생균이 전세계적으로 급속히 증가하고 있다. 다약제 내성은 전달성 내성 플라스미드와 깊이 관련되어 있으며 특히 다양한 내성유전자를 특정 위치에 재조합시켜 채집하는 자연적인 유전자 클로닝 장치인 인테그론이 중요한 역할을 할 것으로 생각되고 있다. 이 연구에서는 전세계적인 확산과 높은 유병율을 보이고 있는 CTX-M형 MDREC의 다약제 내성 획득 기전을 규명하기 위하여, 35주의 임상가검물 유래 CTX-M형 MDREC를 대상으로 접합실험, 중합효소연쇄반응 및 염기서열 분석을 실시하여 이들이 보유하고 있는 인테그론의 분자유전적 특성을 조사하였다. 12주 (34.3%)의 균이 제1군 인테그론을 보유하고 있었는데, 3주는 CTX-M3/15 산생균이었고, 9주는 CTX-M14/27산생균이었다. 12주 모두가 전달성 내성 플라스미드를 보유하고 있었으며, 접합에 의해 피전달균 J53으로 다약제 내성이 높은 빈도로 전달되었다. 11주 (91.7%)의 균이 IncF 복제단위들(IncFrep, IncF1A, IncF1B)을 가지고 있었다. CTX-M14산생균 중의 하나는 IncF군 이외에도 IncI1복제단위도 함께 보유하고 있었다. 모든 인테그론들은 한 개 이상의 다양한 조합의 유전자 카세트들을 가지고 있었다. 모든 내성유전자들은 라이보좀 부착부위(RBS)가 잘 보존되어 있었으며, 항상 표현형으로 발현되고 있었다. 인테그론이 보유하고 있는 다양한 내성유전자들 중에서는 CTX-M, TEM, SHV 등의 베타-락탐계 내성유전자들과 sul1 등의 설폰아마이드 내성유전자 뿐 아니라 아미노배당체 내성유전자들(aadA1, aadA5)과 트리메토프림 내성유전자(dfrA7) 등이 관찰되었다. 인테그론의 5' -보존서열과 3' -보존서열 사이에는 attI 및 59-be 재조합 서열이 잘 보존되어 있었다. 이상의 결과를 종합해 볼 때, MDREC들의 다약제 내성 획득의 주된 기전은 IncF를 포함한 다수의 복제단위와 인테그론을 보유하는 전달성 내성 플라스미드들이 대장균 사이에 수평적 유전자 전달(HGT)에 의해 높은 빈도로 전파되어 내성이 발현되기 때문인 것으로 사료된다.

Keywords: 다약제 내성 대장균, 인테그론, 유전자 카세트, CTX-M

P-053

Anti-obesity and Anti-diabetic Effects of Mixed Cultures of Sanghwang, Chaga and Youngji Mushroom Mycelia Germinated Naked Barley (MC-SCY) in Mice

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The inhibitory effects of MC-SCY on high-fat diet-induced obesity and alloxan-induced diabetic mice were investigated. MC-SCY was produced by germinating the mixture of three different mushroom mycelia (Sanghwang, Chaga and Youngji) on naked barley solid medium. First, for induction of obesity, ICR mice were given high fat diet for 4 weeks. Mice were orally administered with 2 mg / mouse of MC-SCY every day for 4 weeks, and the body weight was measured to evaluate the anti-obesity effect. Secondly, antidiabetic effect was evaluated by oral administration of 2 mg / mouse of MC-SCY for 14 days in ICR diabetic mouse model induced by alloxan (50 mg / kg), and blood glucose level was measured every 3 days. Oral administration of MC-SCY significantly reduced the body weight of the mice compared to the control group receiving the high fat diet only. In addition, oral administration of MC-SCY also significantly reduced glucose and water consumption in alloxan-induced diabetic mice. These results indicate that MC-SCY is an excellent reagent applicable to the development of anti-obesity and anti-diabetic nutritional foods and drugs.

Keywords: MC-SCY, Mushroom mycelium, Obesity, Diabetic, Mice

P-054

Effect of Chunggukjang Fermented with *Bacillus subtilis* (SRCM 101336) to Enhance Immune Responses in Murine Immune Cells

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This study conducted to examine the immunostimulating activities of Chungkukjang fermented with *Bacillus subtilis* (SRCM 101336). To investigate the immune-enhancing activity of Chungkukjang, the experiment was carried out using ethyl alcohol extract. Experiments were performed using RAW 264.7 macrophage cells and murine splenocytes. To evaluate the activity of immune cells, cytokines such as nitric oxid (NO) and tumor necrosis factor (TNF-α) was measured. Also confirmed that the phosphorylation of neclear factor (NF)-κB and inhibitory (I) κB and mitogen-activated protein kinase (MAPK) as the positive control was treated. LPS was used as a positive control, and the treatment time varied depending on the type of experiment. In addition, the extract of SRCM 101336 enhanced the level of cytokines like IL-2 and interferon-g (IFN-g) from ConA-stimulated splenocytes. Therefore our traditional fermented food, chungkukjang fermented with *Bacillus subtilis* (SRCM 101336), may be effective in enhancing the immune system.

Keywords: Chungkukjang, Fermentation, *Bacillus subtilis* (SRCM 101336), Innate immunity, Immune cells

대한바이러스학회

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▶▶▶ P-055

Epidemiology and Genetic Characterization of Human Adenovirus in Korea, 2013-2017

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Human Adenovirus (HAdV) causes not only respiratory diseases but also various diseases such as enteritis, conjunctivitis and cystitis according to their types. Generally, HAdV B species (3, 7, 12, 14 and 55), C species (type 1, 2, 5 and 6) and E species (type4) are closely related in upper respiratory tract infections. The notorious HAdV type 55 recombinated type 11 and 14 have been reported in China as a sporadic cases with a high virulence since 2008. Furthermore, HAdV type 55 infection in new recruit associated with severe clinical sings was reported in febrile respiratory illness surveillance in South Korea military, 2016. Concerning the emergence of HAdV type 55 in Korea, we retrospectively analyzed epidemic and genetic characterization of HAdV detected by real-time PCR in KINRESS (Korea Influenza and Respiratory Surveillance System) for recent 5 years. We analyzed hexon gene sequence of HAdV for typing using randomly selected twenty positive specimens in each year and compared clinical symptoms of HAdV infected patients depending on types. HAdV was identified in 1,730 (11.5%), 490 (4.9%), 537 (4.8%), 700 (6.3%) and 438 (3.7%) respectively from 2013 to 2017 and did not show district seasonality unlike influenza in KINRESS. HAdV detection rate was the highest in children under 6 year-old and did not show gender difference. HAdV type 2 (29.4%), 5 (17.6%), 1 (15.7%) and 3 (15.7%) were prevalent in influenza like illness patients, followed by type 55 (9.8%) and type 4 (8.8). Interestingly, HAdV type 55 was detected in 2013 and the detection rate gradually increased after 2015. Most common clinical symptoms were fever, runny nose and coughing in HAdV infected patients. Although we could not compared the severity of each symptoms depending on types, confirmed higher incidence in coughing, sore throat, myalgia and anorexia in HAdV type 55 infected cases. However, our study has limitation to understand HAdV epidemics in Korea because KINRESS focused on outpatients with acute reparatory infection. Therefore, it is necessary to evaluate HAdV infected cases in sentinel surveillance systems including both outpatients in KINRESS and inpatients in SARI (Severe Acute Respiratory Infection).

This study was supported by the intramural fund in Korea CDC (4851-304).

Keywords: Human Adenovirus (HAdV), Molecular epidemiology, HAdV type 55, KINRESS

▶▶▶ P-056

A Human Hepatoblastoma Cell Line Susceptible to Hepatitis B Virus

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The lack of a suitable cell culture system to study the entire HBV life cycle hampered research for decades. The identification of NTCP, enabled to generate HBV-susceptible cell culture systems. Mainly, human hepatocellular carcinoma derived cell lines, e.g. HepG2 and Huh-7, are being used to investigate the still poorly understood HBV life cycle. Here, we report on a new host cell line for HBV infection. We demonstrate that a human hepatoblastoma (hHB) cell line, stably overexpressing NTCP (hHB-NTCP), supports HBV and hepatitis delta virus (HDV) infection, and the efficient formation of HBV cccDNA. Interestingly, despite robust cccDNA formation, comparable to HBV-infected HepG2-NTCP cells, subsequent viral DNA replication was not detectable. However, transient transfection of hHB cells with an genomic HBV plasmid resulted in the secretion of progeny virus, which was used to infect HepG2-NTCP cells. Together, hHB cells represent a valuable new host cell line for HBV. Despite high cccDNA level after infection, HBV DNA replication is limited in hHB-NTCP cells. This observation indicates a lack of epigenetic regulation of cccDNA. Consequently, hHB-NTCP cells can serve as a useful tool for identification of crucial host factors associated with the transition from the early- to the late stages of the HBV life cycle.

P-057

Genetic Analysis of Severe Fever with Thrombocytopenia Syndrome Viruses Isolated from Korea in 2017

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Severe fever with thrombocytopenia syndrome (SFTS) is an emerging tick-borne viral disease caused by the SFTS virus (SFTSV) which is a member of the *Phlebovirus* genus in the *Phenuiviridae* family. The major clinical symptoms of SFTS are fever, vomiting, diarrhea, thrombocytopenia and leukopenia. To investigate SFTSV infections in Korea, the clinical specimens from the suspected cases of SFTS in 2017 were examined. SFTSV infection was confirmed in 270 patients by using reverse transcription PCR and IFA by acute-phase and convalescent-phase serum samples. We have isolated SFTSV in cell culture and analyzed the complete genome sequences of two isolates of SFTSV. One isolate of SFTSV was from the first SFTS case in 2017 and another isolate of SFTSV from the first case of death with STFS in 2017. Genetic and phylogenetic analysis were conducted by aligning published full genome sequences of SFTSV obtained from Japan, China and Korea isolates. Phylogenetic analyses of these sequences revealed that these two isolates of SFTSV in 2017 were clustered into genotype B, the most prevalent genotype in Korea. The isolate of SFTSV from the first SFTS case in 2017 was clustered with Korean SFTSV strain in 2013 which was belonged to genotype B. The isolate of SFTSV from the first case of death with STFS showed low nucleotide sequence identity with other genotype B SFTSVs.

This study was supported by the intramural fund (4837-301-210) from the Korea CDC.

Keywords: SFTSV, full-sequencing, phylogenetic analysis

P-058

Laboratory Surveillance of Human Acute Respiratory Virus Infections in Korea, 2017

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The prevalence of eight respiratory viruses detected in patients with acute respiratory infections (ARIs) in Korea was investigated through analysis of data recorded by the Korea Influenza and Respiratory Viruses Surveillance System (KINRESS) in 2017. Throat swab specimens were collected from 11,903 patients with ARIs, and viral nucleic acids were detected by real-time (reverse-transcription) polymerase chain reaction for eight respiratory viruses, including human respiratory syncytial viruses (HRSVs), influenza viruses (IFVs), human parainfluenza viruses (HPIVs), human coronaviruses (HCoVs), human rhinovirus (HRV), human adenovirus (HAdV), human bocavirus (HBoV), and human metapneumovirus (HMPV). The overall positive rate of patient specimens was 51.3% (6,104/11,903), 4.9% of which carried two or more viruses simultaneously. HRV (19.4%) was the most predominantly detected virus, followed by IFVs (10.9%), HPIVs (6.3%), HMPV (5.3%), HRSVs (4.6%), HCoVs (4.5%), HAdV (3.7%) and HBoV (2.0%). Most of the ARIs were significantly correlated with clinical symptoms of fever, cough, and runny nose. Although HRV and HAdV were frequently detected throughout the year in patients, other respiratory viruses showed apparent seasonality. HRSVs and IFVs were the major causative agents of acute respiratory diseases in infants and young children. Overall, this study demonstrates a meaningful relationship between viral infection and typical manifestations of known clinical features as well as seasonality, age distribution, and co-infection among respiratory viruses. Therefore, these data could provide useful information for public health management and to enhance patient care for primary clinicians.

This study was supported by the intramural fund (4851-304-210) from the Korea CDC.

Keywords: Surveillance, Acute respiratory infections, Respiratory Viruses

▶▶▶ P-059

Congenital Rubella Syndrome: A laboratory-confirmed, Import-related Case in the Republic of Korea, 2017

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Maternal rubella infection can lead to miscarriage, stillbirth or an infant born with congenital rubella syndrome (CRS) in the early stages of gestation. Under continuous strengthening of NIP, the 2-dose MMR vaccine coverage rate is 97% in the Republic of Korea (ROK) 2017. A suspected CRS case was reported to Korea CDC in August 2017. Epidemiologic investigation for the mother and the neonate was done. Serum, throat swap and urine samples for virus identification were collected. In order to confirm the pathogen of the suspected case, rubella IgM, IgG, realtime-RT PCR, virus isolation and genotyping were performed. The CRS case was confirmed based on Rubella-specific IgM detection and Rubella RNA detection directly in the urine and throat swab. Rubella virus was isolated in throat swab and the strain was classified into genotype 2B. A phylogenetic analysis indicated that the genotype 2B was imported in Vietnam. Rubella IgM persisted up to 5 months, while urine and throat swab showed rubella RNA negative in specimens after 5 months. The mother of CRS case is a Vietnamese and stayed in Vietnam during pregnancy before delivery. She was interviewed reporting that screening of rubella in early stage was negative but diagnosed as rubella infection at the late stage of pregnancy. At birth, the baby had a whole body rash and showed symmetric intrauterine growth restriction. Corneal opacity was observed in the left eye. This is the first report on a laboratory-confirmed, import-related CRS with virus isolation in the ROK. Laboratory surveillance have played a critical role in rubella elimination by providing laboratory data; virus isolation and characterization of circulation strains.

This study was supported by the intramural fund (4837-301) from the Korea CDC.

Keywords: Rubella, Congenital rubella syndrome (CRS), National immunization program (NIP)

▶▶▶ P-060

An Improved Infectious Hepatitis B Virus Cell Culture System Supporting the Entire Viral Life is Suitable to Perform Chemical and Functional Genomic Studies

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Hepatitis B virus (HBV) is a global health concern, responsible for severe liver diseases. Current therapies are unsuitable to cure, because addressing these unmet medical needs had been hampered due to the lack of infectious cell culture models to study the entire HBV life cycle. With the recent discovery of sodium taurocholate cotransporting polypeptide (NTCP) as a functional receptor for HBV, the development of a robust in vitro infection system to investigate viral entry and subsequent early infection steps became effectively applicable. However, current infectious cell culture systems do not support the generation and spreading of progeny HBV. Consequently, we aimed to establish an in vitro HBV infection system, robustly supporting the entire viral life cycle, suitable to perform chemical and functional genomics studies. Here, by using an HepG2-NTCP cell line and an optimized HBV infection protocol, combined with a viral cell culture supernatant transfer step from HBV infected cells to naïve target cells, viral entry as well as the secretion of maturated, infectious progeny virus can be monitored. In addition, this infectious HBV cell culture system was employed to develop an assay suitable to identify novel cellular restriction factors. Following an RNAi approach utilizing lentiviral particle expressing short hairpin RNAs (shRNAs) targeting NTCP. In conclusion, our results demonstrate for the first time a robust and easy to handle infectious HBV cell culture system, unifying viral entry as well as the efficient secretion of infectious particle. This assay can serve as an important tool to accelerate the discovery of novel viral interventions, as well as host drug targets and will shed light on the poorly understood HBV life cycle.

Keywords: Hepatitis B virus (HBV), Entire viral life cycle, Short hairpin RNAs (shRNAs)

▶▶▶ P-061

KSHV vIRF3 Promotes Angiogenesis of Lymphatic Endothelial Cells by Deregulating HDAC5 Activity

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Kaposi's sarcoma-associated herpesvirus (KSHV) is the causative effector of Kaposi's sarcoma (KS), an angioproliferative disease characterized by a prominent compartment of spindle cells (SCs) that are considered to be the tumor cells of KS. Remarkably, SCs are derived from endothelial origin and it is known that endothelium plays an important role in processes, such as regulation of inflammation and vasculogenesis/angiogenesis. In accordance with the hypervascular nature of KS, it has been shown that several KSHV-encoded proteins stimulate angiogenesis. Nevertheless, none of angiogenic-associated KSHV proteins could recapitulate KSHV-mediated hyper-sprouting in the lymphatic endothelial cells (LECs). Here, we reported viral interferon regulatory factor 3 (vIRF3) as a pro-angiogenic factor together with HDAC5 that coordinates with LEC transcriptome, thus resulting in hyper-sprouting formation and ultimately leading to the abnormal lymphangiogenesis. Using mass-spec analysis, we identified HDAC5, a single-responsive regulators of gene expression involved in the vasculogenesis, as a novel binding partner of vIRF3. Using various vIRF3 and HDAC5 mutants, we identified that the double helix-loop-helix region of vIRF3 and c-terminal region of HDAC5 are responsible for their interaction. Interestingly, vIRF3 blocks the translocation of phosphorylated HDAC5 in the nucleus, thus maintaining its activity, suggesting that the vIRF3-HDAC5 interaction reshapes physiological vascular homeostasis. Surprisingly, we found that vIRF3 leads to the spindle morphology and hyper-sprouting formation in the LECs, but not in the blood endothelial cells (BECs) via HDAC5 interaction. Remarkably, our RNA-seq analysis data shows that expression of vIRF3 dramatically changes the genes expression profiles in the LECs but not in the BECs. Using vIRF3 knockout recombinant KSHV, we also confirmed that vIRF3 is a critical factor of KSHV-mediated hyper-sprouting formation in primary LECs. Collectively, our data indicated that KSHV has evolved to carry the vIRF3 gene to cooperate with HDAC5 to accelerate lymphangiogenesis and it may contribute KSHV-associated pathogenesis.

Keywords: Tumor virus, lymphangiogenesis, HDAC5, sprouting formation, RNA-Seq

▶▶▶ P-062

Transmembrane Protein pUL50 of Human Cytomegalovirus Inhibits ISGylation by Downregulating UBE1L

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Interferon-stimulated gene (ISG) 15 encodes a ubiquitin-like protein that can be conjugated to proteins via an enzymatic cascade involving the E1, E2, and E3 enzymes. ISG15 expression and protein ISGylation modulate viral infection; however, the viral mechanisms regulating the function of ISG15 and ISGylation are not well understood. We recently showed that ISGylation suppresses the growth of human cytomegalovirus (HCMV) at multiple steps of the virus life cycle, and that the virus-encoded pUL26 protein inhibits protein ISGylation. In this study, we demonstrate that the HCMV UL50-encoded transmembrane protein, a component of the nuclear egress complex, also inhibits ISGylation. pUL50 interacted with UBE1L, an E1-activating enzyme for ISGylation, and to a lesser extent ISG15, as did pUL26. However, unlike pUL26, pUL50 caused proteasomal degradation of UBE1L. The UBE1L level induced in human fibroblast cells by interferon-β treatment or virus infection was reduced by pUL50 expression. This activity of pUL50 involved the transmembrane (TM) domain within its C-terminal region, although pUL50 could interact with UBE1L independent of the TM domain. Consistently, colocalization of pUL50 with UBE1L was observed in cells treated with a proteasome inhibitor. Furthermore, we found that RNF170, an ER-associated ubiquitin E3 ligase, interacted with pUL50 and promoted pUL50-mediated UBE1L degradation via ubiquitination. Our results demonstrate a novel role for the pUL50 transmembrane protein of HCMV in the regulation of protein ISGylation.

Keywords: Human cytomegalovirus, ISG15, UL50, UBE1L

▶▶▶ P-063

Surveillance of Acute Falaccid Paralysis (AFP) in the Republic of Korea(ROK), 2017

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Acute flaccid paralysis (AFP) is described as sudden onset of flaccid paralysis in one or more limbs in children and may be caused by poliovirus infection. AFP surveillance was undertaken by the World Health Organization (WHO) to monitor the progress of poliomyelitis eradication, since 1998, the Korea Center for Diseases Control and Prevention has conducted its surveillance system. One of WHO' s indicators for polio elimination is strengthening of surveillance maintaining the number of reported non-polio AFP cases per 100,000 children aged less then 15 years equivalent or more than one. The number of non-polio AFP cases were 68 in 2017 in the ROK. This study was an overview of the surveillance of AFP conducted in the ROK in 2017. The AFP surveillance was conducted through reporting and laboratory testing according to WHO recommendations. Conventional tube cell culture method was used for virus isolation and the isolates were identified by real-time RT-PCR, semi-nested RT-PCR. The molecular methods were used for further characterization to improve specificity. For genotyping, semi-nested RT-PCR was used to amplify part of the viral protein 1 gene. Of 68 patients(non-polio AFP rate were 1.00 in 2017) whose samples were tested, 8 samples were positive for non-polio enterovirus(NPEV) as diagnostic methods improved, the rate of positive results increased. Patients below ten years of age accounted for the largest proportion(77.9%) of cases. Among the total of 68 cases, Guillain-Barré Syndrome(n=25, 36.8%) was the major leading cause of AFP. Moreover, meningoencephalitis(n=18, 26.5%), transverse myelitis(n=8, 11.8%) acute demyelinating encephalomyelitis(n=2, 2.9%) and other paralysis symptoms(n=14, 20.6%) showed in some patients. Enterovirus 71, Coxsackievirus(C) B2, Echo(E)3 was detected in cell culture method and CA5, CA24 and E12 were detected in semi-nested RT-PCR and real-time RT-PCR. The present study represented a country-based survey of AFP in the ROK. This surveillance could provide better understanding of the epidemiologic pattern and clinical manifestations associated with specific genotypes of AFP in the ROK.

Keywords: AFP, Poliomyelitis, Poliovirus, NPEV

▶▶▶ P-065

Genetic and Antigenic Characterization of Influenza Viruses for Recent Four Seasons (2014/2015~2017/2018) in Korea

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The influenza surveillance based on epidemiology and laboratory diagnosis was carried out through Korea Influenza and Respiratory Viruses Surveillance System (KINRESS) every influenza season since 2009 pandemic in Korea. We screened samples of patient signing influenza like illness within real-time PCR for detecting and subtyping influenza. The genetic characterization of influenza isolates was analyzed based on HA sequence and antigenic features of isolates were evaluated by Hemagglutination inhibition assay using ferret antisera to WHO recommended vaccine strains. Influenza detection rates were 14.5% in 2014/2015, 12.1% in 2015/2016, 10.3% in 2016/2017 and 22.6% in 2017/2018(18weeks) season respectively. The influenza A virus was the most prevalent virus in the early and middle of influenza season, and influenza B virus was dominant in the later season in the previous three seasons. However, in 2017/2018 season, influenza B virus was detected from the 38th week along with influenza A(H3N2). A(H1N1)pdm09 dominantly detected in 2015/2016 season and low in other season. Genetically A(H1N1)pdm09 isolates were divided into 6b.1 and 6b.2 clade since 2015/2016 season. However, most of A(H1N1)pdm09 belonged to 6b.1 clade since 2016/2017 season. Antigenically, A(H1N1)pdm09 isolates were well inhibited by ferret antisera to vaccine strains of each season. The evolution of A(H3N2) isolates was faster than update of vaccine strains in Korea. Especially, A(H3N2) isolates in 2014/2015 season mostly belonged to 3C.3a clade were genetically and antigenically far from A/Texas/50/2012 which was Northern hemisphere vaccine strain. Although, two lineages (Yamagata and Victoria) of influenza B were co-circulated from 2015/2016 season to 2017/2018 season, most isolates were not matched with vaccine stains which was component of trivalent influenza vaccine except for 2014/2015 season. The continuous laboratory monitoring of influenza isolates is important crucial to figure out epidemic and prevent pandemic.

This study was supported by the intramural funds (2017-NI43002-00 and 4834-303-210) from the Korea CDC.

▶▶▶ P-066

A Study of Immune Enhancement by Co-administration of Interleukin-2 and Foot-and-Mouth Disease Vaccine

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Foot-and-Mouth Disease(FMD) is a highly contagious, acute viral infectious disease of livestock such as cattle, swine and other cloven-hoofed ruminants. When pigs are infected with FMDV or FMD vaccinated, neutralizing antibodies begin to form about 7 days after infection or inoculation. However, viruses in the blood of livestock infected with FMD begin to increase immediately after infection and peak at 4 days. Since FMD spreads during these four days, the blocking of disease spreading within the first 4 days is the most important step to prevent nationwide occurrence. For this reason, there has been a need to develop a method for improving the immune effect early in the vaccine inoculation. In this study, recombinant adenovirus expressing porcine interleukin-2(IL-2) was constructed to develop a new immunoadjuvant for increasing the efficacy of FMD vaccine. Expression of porcine IL-2 was confirmed by Indirect Immunofluorescence Assay(IFA), and Western blot. To conform the effect of Ad.IL2 in vivo, the animal experiments were conducted. In the mouse experiment, 2 days after inoculation, the FMD specific antibody titer in the experimental group co-inoculated Ad.IL-2 with commercial FMD vaccine was increased at a faster rate than that of the commercial FMD vaccine alone. The antibody titer on the third day of inoculation was maintained at 1: 128. Similarly, in the pig experiment, on the second day after inoculation, the FMD specific antibody titers of the co-inoculated group were significantly increased. While all of the FMD specific antibody titers in the group vaccinated with FMD vaccine only did not reach the level that could prevent FMD. Thus, it was confirmed that the FMD specific antibody titers of co-inoculated group were relatively higher than that of FMD vaccine only group. Through this study, as an immunoadjuvant, recombinant adenovirus expressing swine interleukin-2 gene has been shown to enhance antigenicity and the immune response to the antigen within the first 4 days co-administrated with FMD vaccine. Therefore, when FMD occurs, it would be effective as an immune enhancer for early defense.

Keywords: Adenoviral vector, Porcine Interleukin-2, Molecular cloning, Immunostimulant, Adjuvant

▶▶▶ P-067

Evolution and Persistence of the Resistance-Associated Substitutions of Hepatitis C Virus after Direct-Acting Antiviral Treatment Failures

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Daclatasvir plus asunaprevir (DCV+ASV) treatment is an all-oral direct-acting antiviral (DAA) therapy for the genotype 1b HCV-infected patients. In this study, we investigated how resistance-associated substitutions (RASs) evolved after treatment failures and assessed the effect of those substitutions on viral fitness. Sequencing of NS5A and NS3 revealed typical RASs after treatment failures. Interestingly, the RASs of NS3 reverted to the wild-type amino acid within one year after treatment failures. However, the RASs of NS5A were stable and did not change. The effect of NS5A and NS3 RASs on viral RNA replication was assessed after mutagenic substitution in the genotype 1b HCV RNA. Among the single substitutions, the effect of D168V was more substantial than the others and the effect of the triple mutant combination (D168V+L31V+Y93H) was the most severe. The RAS at NS5A Y93 affected both viral RNA replication and virus production. Finally, the effect of *trans*-complementation of NS5A was demonstrated in our co-transfection experiments and these results suggest that such *trans*-complementation effect of NS5A may help maintain the NS5A RASs for a long time even after cessation of the DAA treatment. In conclusion, the results from this investigation would help understand the emergence and persistence of RASs.

Keywords: Hepatitis C virus, Daclatasvir, Asunaprevir, Resistance-associated substitution, Viral fitness

▶▶▶ P-068

Analysis of IE62 Mutations Found in Varicella-Zoster Virus Vaccine Strains for Transactivation Activity

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Live attenuated vaccine strains have been developed for Varicella-Zoster virus (VZV). Compared to clinically isolated strains, the vaccine strains contain several non-synonymous mutations in open reading frames (ORFs) 0, 6, 31, 39, 55, 62, and 64. In particular, ORF62, encoding an immediate-early (IE) 62 protein that acts as a transactivator for viral gene expression, contains six non-synonymous mutations, but whether these mutations affect transactivation activity of IE62 is not understood. In this study, we investigated the role of non-synonymous vaccine-type mutations (M99T, S628G, R958G, V1197A, I1260V, and L1275S) of IE62 in Suduvax, a vaccine strain isolated in Korea, for transactivation activity. In reporter assays, Suduvax IE62 showed 2- to 4-fold lower transactivation activity toward ORF4, ORF28, ORF29, and ORF68 promoters than wild-type IE62. Introduction of individual M99T, S628G, R958G, or V1197A/I1260V/L1275S mutations into wild-type IE62 did not affect transactivation activity. However, the combination of M99T within the N-terminal Sp transcription factor binding region and V1197A/I1260V/L1275S within the C-terminal serine enriched acidic domain (SEAD) significantly reduced the transactivation activity of IE62. The M99T/V1197A/I1260V/ L1275S mutant IE62 did not show considerable alterations in intracellular distribution and Sp3 binding compared to wild-type IE62, suggesting that other alteration(s) may be responsible for the reduced transactivation activity. Collectively, our results suggest that acquisition of mutations in both Met 99 and the SEAD of IE62 is responsible for the reduced transactivation activity found in IE62 of the VZV vaccine strains and contributes to attenuation of the virus.

Keywords: Varicella-Zoster virus, ORF62, transacrivator

▶▶▶ P-069

Multiplex PCR-based Next-generation Sequencing Reveals Global Distinct Genotypes of Seoul Virus

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Hantaviruses (Genus *Orthohantavirus*, Family *Hantaviridae*, and Order *Bunyavirales*), negative-sense single-strand RNA viruses, pose a worldwide public health threat. Hantavirus infections are the causative agent of hemorrhagic fever with renal syndrome (HFRS) in Eurasia and hantavirus pulmonary syndrome in the Americas. Seoul virus (SEOV) is a worldwide Old World hantavirus harbored by *Rattus norvegicus* and *R. rattus*. In human, SEOV is responsible for an urban mild HFRS with significant morbidity and mortality in the lack of good medical care. Pet rat markets and urbanization are positively associated with SEOV-induced HFRS cases due to the increase of human-rat contacts. However, the epidemiologic surveillance and phylogenetic diversity of SEOV remain to be investigated for disease risk assessment and mitigation. Here, a total of 1,269 rats were captured in the urban HFRS-endemic area, Republic of Korea (ROK), during 2000-2016. Serological prevalence of SEOV demonstrated an enzootic infectious cycle during a year regardless of sex, weight (age), and season. The loads of SEOV RNA showed wide dissemination in various tissues and dynamic circulation among the rat populations. Using multiplex PCR-based next-generation sequencing, nearly whole-genome sequences of SEOV were complete from HFRS patients and natural reservoirs in the ROK. Phylogenetic analyses demonstrated the distinct genotypes of SEOV from East Asia, Southeast Asia, Western Europe, and North America. The phylogenetic patterns of SEOV M and S segments suggested a possible genomic configuration of genetic exchanges. In conclusion, this study provides significant insights into continued surveillance, whole-genome sequencing, and genetic diversity of SEOV.

Keywords: Hantavirus, Seoul virus, Multiplex PCR-based Next-generation sequencing, Genetic diversity

▶▶▶ P-070

Novel Triple-Reassortant Influenza A(H1N2) Viruses isolated from pigs in Korea

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Three subtypes (H1N1, H1N2, and H3N2) of influenza A virus are predominantly circulating in pigs worldwide. In Korea, eight different subtypes (H1N1, H1N2, H3N1, H3N2, H5N2, H7N2, H9N2, and H11N6) of swine influenza A virus (SIV) have been reported thus far. However, due to the lack of genomic sequence resources of SIVs and public database archiving these data in Korea, our understanding of genetic diversity and reassortment events of SIVs remains limited. To this end, here we investigated molecular evolution and genetic shift of SIVs. From 241 nasopharyngeal clinical specimens collected from farmed pigs during the 2016-17 season, we isolated four different H1N2 viruses and obtained their whole-genome sequences using a next generation sequencing (NGS) method. Given the phylogenetic relationships of SIV genetic segments, it was revealed that the PB1, PA, NP, M, and NS genes of the isolated SIVs are clustered into those of 2009 pandemic (PDM) H1N1-like virus strains. Notably, the PB2 and NA genes of the isolated H1N2 SIVs belong to be the North American triple-reassortant (TR) lineage whereas the HAs of these SIVs are all grouped with those of Eurasian Avian-like (EA) lineage. Co-circulation of PDM, TR, and EA lineage SIVs has been recognized worldwide. However, the exact triple-reassortment pattern of the isolated SIVs has been never reported. Along with the amino acid substitutions identified at the HA antigenic sites, such as Sa (L178I, S179N), Sb (S203R, D204G/V), and Ca1 (G187E, G219E), genetic reassortment events might eventually affect genetic and antigenic divergence of SIVs in Korea. Considered all, these results demonstrate the circulation of novel triple-reassortant SIVs in Korea and suggest the need for year-round, nation-wide surveillance network for SIVs.

Keywords: Antigenic site; Genetic lineage; Phylogeny; Reassorment; Swine influenza virus

▶▶▶ P-071

KH29 추출액의 PKB/AKT Signal 활성을 통한 수족구병 유발 엔테로바이러스 증식 억제

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엔테로바이러스71(Enterovirus71, EV71)은 피코르나바이러스에 속하는 양성단일가닥 RNA 바이러스로 수족구병의 주요 병원균이다. 수족구병은 입 안과 손발에 작은 물집이 생기는 질병으로 소아와 어린이에서 흔하게 발생하며 감염 후 1-2주일 만에 물집이 사라지면서 병에서 회복되지만 환자에 따라 뇌염이나 마비성 질환을 일으키는 심각한 질병이다. 하지만 대표적인 백신과 치료제는 아직 개발되지 않은 실정이다. KH29는 *Actinomycetes* 목의 *Streptomyces*과에 속하는 균으로 다양한 항바이러스 효능 물질을 생산하는 것으로 알려져 있다. 본 연구에서는 EV71에 대한 치료제 개발을 위한 후보물질을 찾고자 하였으며 여러 물질 중 KH29 배양액의 일부 성분의 EV71에 대한 항바이러스 효과를 HeLa 세포를 이용하여 확인 하였으며 세포 작용 원리를 밝히고자 하였다. EV71 감염에 대한 세포에서의 항바이러스 작용을 MTT assay를 통해 세포 생존을 분석한 결과, KH29는 100ug/ml, 10ug/ml 농도에서 세포의 cytopathic effect를 억제하여 EV71 감염에 대한 항바이러스 효과를 확인하였다. EV71의 증식은 바이러스의 증식 첫 과정인 유전자 증폭유무를 RT-PCR을 수행하여 양성, 음성가닥 RNA 유전자의 증폭을 확인하였으며 KH29의 처리는 100ug/ml의 농도에서 EV71 음성가닥 RNA 증폭을 유의하게 억제하였다. 또한 Western blot analysis 수행을 통해 EV71 막단백질 VP1(viral capsid protein 1)의 발현과 세포 전사개시인자 eIF4G1의 절단을 효과적으로 억제하였다. 특히 KH29의 처리가 EV71 감염 세포의 생존 및 세포자살 억제 조절과 밀접한 관계가 있는 AKT 세포신호의 활성을 유의하게 증가시킴을 확인하였다. 이러한 결과를 통해, KH29 추출액은 AKT signaling 활성을 통해 세포의 생존을 증가시키고 EV71의 감염과 증식을 효과적으로 억제하였다. 본 물질은 차후 수족구병에 대한 치료제 개발을 위한 유효물질로 이용 될 것으로 기대가 된다.

Keywords: 엔테로바이러스, 수족구병, 항바이러스, 스트랩토마이스, 세포신호

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▶▶▶ P-072

Lumbar Artery Injury During Posterior Spinal Surgery Detected by Postmortem CT-angiography: An Autopsy Case

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Postmortem computed tomography angiography (PMCTA) has become increasingly important process for postmortem investigation especially in cases with vascular injuries. Vascular injury during spinal surgery is potentially life threatening although it is uncommon, however, It might be hard to identify the injured vessels clearly in routine autopsy. Here, we report a fatal case of vascular bleeding during posterior fusion from T10 to L4 for correction of kyphosis in a 48-year-old man. PMCTA was performed to identify the exact source of significant bleeding prior to autopsy. At subsequent autopsy, a bleeding focus could not be identified grossly but PMCTA detected the bleeding focus at the posterior branch of right lumbar artery. PMCTA is useful and could be considered as an essential technique in identifying the bleeding focus, particularly when the injured vessels are too small to be detected visually or located in areas that are difficult to access.

Keywords: Postmortem computed tomography angiography (PMCTA), Vascular injury, Lumbar artery, Autopsy

▶▶▶ P-073

Os Odontoideum Mimicking Odontoid Fracture of the Axis

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Os odontoideum(OO) or separate odontoid is a rare anomaly of the second cervical vertebra(axis), defined as an ossicle with independent, smooth margins and no osseous connection to the body of axis. It remains controversial whether the etiology of OO is congenital or traumatic. It can lead to atlanto-axial instability, even under physiological loads in some individuals, and can cause various symptoms from mild progressive myelopathy to sudden death even after minor trauma. Here we report a case of 53-year-old man found dead outside his home. The police report suggested the possibility of fall from the second floor terrace. However, on autopsy, external examination revealed no evidence of trauma. The internal examination of the neck revealed a sepatation of odontoid process from the body of the axis with hemorrhage of the adjacent tissue. Postmortem computed tomography(PMCT) showed presence of smooth, well-corticated ossicle, accompanied by the findings of ossification of posterior longitudinal ligament(OPLL) of the cervical vertebra, therefore, we assumed dead by traumatic cervical injury. This case suggests that radiographs especially PMCT may play a significant role in autopsy of cervical trauma cases.

Keywords: Postmortem Os odontoideum, Cervical trauma, Fall, Autopsy

P-074

Postmortem Interval Study of Potassium and Magnesium by Vitreous Humor

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This study aimed to identify the association of postmortem elapsed time and the changes in potassium, magnesium relationships with the postmortem elapsed time by chemical analysis of vitreous humor. We collected the samples of 10 cases without trauma and medical history from autopsy cases in Seoul institute National Forensic Service from 26th February 2018 to 4th April 2018. potassium and magnesium levels were measured by collecting each vitreous humor, prior to and an hour afterward the autopsy from the body with the relatively clear time of death, no putrefaction, and within 72 hours after death. Both level of Potassium and magnesium were increased with postmortem elapsed time. Vitreous humor makes enclosed environment after death and does not get contaminated easily. Therefore vitreous humor can be considered as a useful indicator for estimation of postmortem elapsed time because It changes with certain time. Based on these findings, multiple chemistry analysis with potassium and magnesium measurement may contribute to improved examination reliability of postmortem elapsed time.

Keywords: Postmortem Interval, Magnesium, Potassium

P-075

Death After Bronchoscopic Biopsy of a Pulmonary Artery Aneurysm Mimicking Bronchial Polyp: Report of 2 Cases and Review of the Literature

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Pulmonary artery aneurysms (PAAs) are rare, and massive hemoptysis can lead to death if appropriate diagnosis and treatment is not provided. PAAs can be of congenital, acquired, or idiopathic origin, and the clinical symptoms are various. Among all reported cases, one-third of the patients died due to rupture. Optimal treatment or guidelines for PAAs remain uncertain. Herein, we report two autopsy cases about PAA. The patient 1 was taking medication for tuberculosis. The patient 2 has no medical history about lung disease. Bronchoscopy revealed a polypoid lesion in both patients, suspected to be an inflammatory polyp. Biopsy was performed and massive bleeding into the airway occurred. The bleeding could not be controlled by bronchoscopic suction, and cardiac arrest occurred 30 minutes after biopsy; the patients subsequently died. In one patient's case, autopsy revealed a round, calcified PAA in the bronchus of the right middle lobe; the end of the PAA was torn. In another patient's case, autopsy revealed a round, calcified PAA in the bronchus of the right lower lobe; the neck of the PAA was torn. Hypovolemic signs, including weak postmortem lividity and pallor of the skin and conjunctivae, were observed in both patients. Visual inspection and histopathological examination of the right lung revealed tuberculosis and congestion in both patients. Cases related PAA are not uncommon, but autopsy cases of death occurring after biopsy of PAA mimicking bronchial polyps are rarely reported.

Key words: Pulmonary Artery Aneurysm; Tuberculosis; Biopsy; Bronchoscopy; Autopsy

▶▶▶ P-076

Study for Lists of Forensic Autopsy Request: Quantitative Analysis about Documents relating to Autopsy Request

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In the Republic of Korea, relevant documents are submitted to a forensic doctor or agency when the court grants a confiscation warrant for autopsy, and then autopsy is performed according to the procedure. If the essential data about unusual death is not submitted at the time of the autopsy, it may difficult to understand the situation of the unusual death properly prior to the autopsy, which may reduce the accuracy of the autopsy. An analysis was performed on 6,133 out of 6,610 autopsy data (92.8%) in Korea during 2015. Most of autopsy appraisal request (99.8%) were submitted, unusual death occurs report (86.0%) and command recommendations of unusual death (70.3%) were submitted in many cases. However prosecutor command of unusual death (27.8%) was submitted in small cases and confiscation warrant was not submitted at 7.4%. Postmortem inspection report (29.3%) and death scene investigating report (34.1%) were submitted in small cases. In addition to the above two documents, death certificate and record of statement of relational person had significant regional variations. For postmortem inspection and death scene photos, 2.7% and 3.2% were submitted in black and white, respectively. Authors propose a list of forensic autopsy request that autopsy appraisal request, unusual death occurs report, command recommendations of unusual death, prosecutor command of unusual death and confiscation warrant should be included as an essential document reflecting the progress of the investigation, and postmortem inspection report and photos, death scene report and photos, death certificate should be included as the postmortem investigation data.

Keywords: Autopsy; List, Autopsy request; Quality analysis, Autopsy; Data interpretation, Statistical; Korea

▶▶▶ P-077

Acute Myocardial Infarction Secondary to Acute Aortic Dissection: An Autopsy Case

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Aortic dissection is a relatively uncommon, life-threatening medical emergency. Aortic dissection is associated with a high mortality rate, and death from the aortic dissection is related to the pericardial tamponade, severe aortic regurgitation, and occasionally acute myocardial infarction. Aortic dissection involving the coronary artery results in coronary obstruction, and these coronary lesions can be classified according the their morphological characteristics, 1) ostial dissection; 2) dissection with a coronary false channel; and 3) circumferential detachment with an inner cylinder intussusception. In this report, we describe a case of acute myocardial infarction secondary to acute aortic dissection resulting in sudden death. A 48 year-old man unexpectedly died during in the shower. Autopsy examination reveals the intimal tearing of the ascending aorta and type A aortic dissection. Moderate atherosclerosis and peri-coronary hemorrhage were observed in the left anterior descending branch of the coronary artery. Grossly, there were patches of marked dark mottling appearance in the internal wall of the left ventricle, and the microscopic examination showed the extensive hemorrhage of the myocardium. There was no alternative lethal disease or injuries for cause of death, and no toxic agents were detected.

Keywords: Acute myocardial infarction, Aortic dissection, Coronary artery, Sudden cardiac death

P-078

Analysis of Morphometrical Relationship between Nostril and Nasal Aperture Employing Three-dimensional Post-mortem Computed Tomography Images of Heads

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Craniofacial reconstruction (CFR) has been utilized in forensic identification. For the accurate CFR, reliable prediction methods for facial components must be studied and developed by scientific approaches. The purpose of this study was to investigate the methods for the prediction of the morphology and location of nostrils from the morphometrical analysis into nasal apertures on skulls. For the study, three-dimensional (3D) Post-mortem Computed Tomography (PMCT) images of the heads were utilized, that had been scanned by Multi-detector Computed Tomography (MDCT) being operated in National Forensic Service (NFS) Seoul Institute. The 3D head images were scanned from a total of 65 corpses (52 males and 13 females) which were autopsied in NFS Seoul Institute during the research term. 3D conversions and measurements were processed in an image processing software (Mimics, Materialise Mimics Research version 20.0, Materialise NV, Leuven, Belgium). For measurements, 13 bony landmarks on skull and 12 facial landmarks on nostril were established. From the 25 landmarks, a total of 91 distances were measured. Descriptive statistics and sex differences in mean values were compared statistically for each set of measurement values. The results demonstrated that the maximum nasal aperture width correlates with the width of nostril, and that the height from the insertion point of inferior nasal concha to the lowest point of nasal aperture correlates with the heights of nostrils. From these results, it has been concluded that the nostril might be predicted by morphometrical analysis on the nasal aperture.

Keywords: Craniofacial reconstruction, Nasal aperture, Nostril, Landmark, Measurement, Three-dimension, Prediction
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P-079

Estimation of Postmortem Interval based on Developmental Gene Expression Profiling in Necrophagous Fly

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Determining a postmortem interval using the weight or length of blow and flesh fly larvae to calculate the insect's age is well established. However, to date, there are only a handful studies dealing with age estimation of post-feeding larva and pupae, in which weight or length cannot be used as a relevant parameter. The analysis of genetic markers, which indicate a certain developmental stage, can be used to rapidly and precisely determine the developmental stage. In order to break new ground in the field of age determination of forensic relevant necrophagous flies, we performed a de novo transcriptome analysis at 9 different developmental stages of *Sarcophaga peregrina* and *Lucilia sericata*. Obtained data serve as base to establish molecular age determination techniques. We generated 20 libraries out of 9 developmental stages, with about 4 Gbp per library. In total, 32,711 and 13,824 distinct transcripts were detected, and 30,929 and 13,348 were annotated to known insect genes. Based on transcriptome sequencing results, we describe the first high resolution analysis of the transcriptome dynamics of distinct developmental stages of both flies. The larva developmental stages from two flies were accompanied by the greatest number of differentially expressed genes (DEGs), including the upregulation of cellular component organization or biogenesis and genes related to metamorphosis. The pupa stages revealed changes the upregulation of genes associated with multicellular developmental and morphogenesis process. The number of common DEGs between *S. peregrina* and *L. sericata* were 647 genes. Among them, 40 genes were selected to identify differentially expressed genetic markers as candidates for a molecular age estimation of two flies. Therefore, the present study is expected to provide the new forensic technology can determine the developmental stage of key necrophagous flies through RNA biomarker studies and greatly contribution to the application of forensic entomology in estimating PMI.

Keywords: necrophagous fly, postmortem interval, transcriptome, developmental clock, molecular network

▶▶▶ P-080

Identification of Forensically Important Calliphoridae and Sarcophagidae Species Using Multiplex Real-time PCR Assay

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Medicolegal entomology, a sub-field of forensic entomology, is mainly used for estimation of PMI (postmortem interval) and to determine whether movement of corpse happened or not for medicolegal investigation. Calliphoridae and Sarcophagidae flies, are the dominant necrophagous taxa in most temperate climate zones. The PMI of corpse invaded by necrophagous immature insects hatched on that could be estimated because minimum PMI would be near or earlier than the age of the larvae fed on the corpse. As growth speed of larvae differs depending on temperature and species, minimum PMI could be estimated by using species-specific growth data. While morphological identification of adult necrophagous flies could be done by well-trained entomologist, identifying larvae is difficult relatively. Larvae only could be identified up to family level and developmental stage (1st-instar, 2nd-instar, 3rd-instar and post-feeding) by observing posterior spiracles. For these disadvantages, the molecular biological method, DNA barcoding using DNA sequences has been researched. Especially DNA barcoding targeting mitochondrial COI (cytochrome c oxidase subunit I) gene is being most commonly used. The COI sequences are acquired using normal PCR (polymerase chain reaction) and Sanger's sequencing method, which are time-consuming and complex to use for medicolegal investigation in practice. To overcome this limitation in using medicolegal entomology for medicolegal investigation, authors designed a multiplex real-time PCR system to identify nineteen species of forensically important Calliphoridae and Sarcophagidae flies collected in South Korea. Instead of time-consuming Sanger's nucleotide sequencing process, this technology only requires one-step real-time PCR with analyses of the melt curves of the amplicons generated by primers targeting the species-specific single nucleotide polymorphisms (SNPs). These multiplex real-time PCR reactions were performed by 4 reactions for 12 species of Calliphoridae and 3 reactions for 7 Sarchophagidae. The accuracy of this assay was confirmed by the blind tests on the voucher specimens confirmed by expert entomologists and cross reactions among Calliphridae, Sarcophagidae and Muscidae. The sensitivity was confirmed by serially diluted samples with template concentrations of 5 ng/ul, 1 ng/ul, 0.1 ng/ul, and 0.01 ng/ul. This study is expected to make it easier and faster for the investigating authorities to identify major species of necrophagous flies and to increase the utilization of entomological evidence in forensic investigations.

Keywords: DNA barcoding, Calliphoridae, Sarcophagidae, Multiplex Real-time PCR

▶▶▶ P-081

Forensic Entomological Analysis of Puparia (Diptera: Calliphoridae) from Ancient Tomb in South Korea

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At excavated Tomb of Naju Bogam-ri Jungchon (Naju City Native Cultural Heritage No. 13) in South Korea, about a dozen puparia of blowfly were found around gilt-bronze shoes and heel of skeletal human remains which are inside of the wooden coffins. Although blowflies are the most important necrophagous insect in this region, it is very unusual that fly remains are found with almost original shape even after 1,500 years. Unlike the case where insects were utilized for decoration of artificially created ornaments in South Korea, it is the first case where buried insects were found in relation to the funeral process. The shape of the puparia were Calliphoridae-type, but identification of species or genera was impossible. Therefore, using the widths of puparia to estimate the most similar species, it was presumed to be Chrysomyia spp. Rearing experiments on larval Diapause of Lucilia sericata in one control group and three experimental groups were performed to observe at which condition puparia had appeared using the control condition of 24℃, 70 % relative humidity and 16:8(L:D) and the estimated tomb condition of 16℃, 90% RH and all day darkness. As a result, among three experimental groups only pupa stage group was able to produce puparia like the control group when entered the tomb. In order to estimate the reason for the placement of puparia on the heel of the gilt-bronze shoes, we performed simulations using a dummy and post-feeding maggots with positive thigmotaxis(taxis by physical contact). As a result, we were able to see maggots moving along the edge, soon to be located in heels of virtual gilt-bronze shoes. In conclusion, above experiments support that the gilt-bronze shoes had been worn before 3rd post feeding stage of larvae occurred. After the fly larvae had grown up eating the body, the post feeding larvae move into the shoes and turned into pupae. When the body was moved for burial, the developmental stage of Calliphorids was at least at the pupal stage outside the tomb. This excavation provides a scientific basis for the funeral culture, secondary burial, in Naju, South Korea about 1,500 years ago. Secondary burial is a burial ceremony that laying skeleton remains in tomb after decomposition on the ground (primary burial). It is the first discovery of fly remains in an ancient tomb in South Korea, which provided valuable information illuminating archaeo-entomological features of past culture and environment.

Keywords: Archaeo-entomology, Ancient tomb, Secondary burial, Fly remains

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▶▶▶ P-082

Encapsulated Papillary Carcinoma of the Breast with an Ipsilateral Synchronous Invasive Ductal Carcinoma

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Encapsulated papillary carcinoma is a recently defined variant of papillary carcinoma of the breast. Pathologically, it lacks both intralesional and peripheral myoepithelial cell layer. However, on contrary to our common knowledge, it is considered an "in situ" lesion according to the world health organization (WHO) classification. We present a case of this rare lesion with an ipsilateral synchronous invasive ductal carcinoma.

Keywords: Encapsulated papillary carcinoma, papillary carcinoma

▶▶▶ P-083

T-cell Immunoglobulin Mucin 3 Expression on Tumor Infiltrating Lymphocytes in Breast Cancer

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T-cell immunoglobulin and mucin domain-containing molecule 3 (TIM-3) is an emerging immune response molecule, related with T cell anergy. There have been tremendous interests in breast cancer targeting immune checkpoint molecules, especially in triple-negative subtype (TNBC). This study was designed to investigate expression of TIM-3 on tumor infiltrating lymphocytes (TILs), analyses of relationships with clinic-pathological parameters, together with expressions of programmed cell death protein 1 (PD-1), and PD1 ligand 1 (PD-L1) and its prognostic role. Immunohistochemistry with tissue microarray blocks produced from 109 samples of invasive ductal type TNBC was processed with anti-TIM-3, PD1, PDL1, ER, PR, CK5/6, Ki-67, EGFR and HER2 antibodies. Associations between their expressions and clinicopahological parameters and survival analyses were performed. TIM-3 expressed in TILS of all 109 TNBCs, consisting of 17 (<5%, 15.6%), 31 (6-25%, 28.4%), 48 (26-50%, 44.0%) and 13 (>51%, 11.9%). High TIM-3 was significantly related with younger patients (p=0.0101), high TILs (p=0.0029) and high tumor stage (p=0.0018), high PD-1 (P=0.0001) and high PD-L1(P=0.0019), tended to be associated with higher histologic grade, absence of extensive in situ components and microcalcification. Significantly, TIM-3 expression was increased in combination group of high PD-L1 and high PD-L1 (p<0.0001). High TIM-3 demonstrate a significantly better DFS (p<0.0001) and OS (p=0.0001), together with TIL, and inversely with PD-1. In univariate survival analysis, high TIM-3 showed reduced relapse risk (p<0.0001) and better OS (p=0.0003), together with high tumor stage, nodal metastasis and advanced stage, and inversely with PD-1. In multivariate analysis, high TIM-3 was significantly associated with better DFS (p=0.0002) and OS (p=0.0259) , and high PD-1 with worse DFS (p=0.0207). This is the first study to demonstrate that TIM-3 expression is an independent positive prognostic factor in TNBC, despite its association with poor clinical and pathologic features

Keywords: Triple negative breast cancer, TIM-3, Prognostic factor, Immunohistochemistry

▶▶▶ P-084

Loss-of-function of IFT88 Determines Metabolic Phenotypes in Thyroid Cancer

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Primary cilia are microtubule-based, dynamic organelles characterized by continuous assembly and disassembly. The intraflagellar transport (IFT) machinery, including IFT88 in cilia, is involved in the maintenance of bidirectional motility along the axonemes, which is required for ciliogenesis and functional competence. Cancer cells are frequently associated with loss of primary cilia and IFT functions. However, there is little information on the role of IFT88 or primary cilia in the metabolic remodeling of cancer cells. Therefore, we investigated the cellular and metabolic effects of the loss-of-function (LOF) mutations of IFT88/primary cilia in thyroid cancer cells. IFT88-deficient 8505C thyroid cancer cells were generated using the CRISPR/Cas9 system, and RNA-sequencing analysis was performed. LOF of the IFT88 gene resulted in a marked defect in ciliogenesis and mitochondrial oxidative function. Gene expression patterns in IFT88-deficient thyroid cancer cells favored glycolysis and lipid biosynthesis. However, LOF of IFT88/primary cilia did not promote thyroid cancer cell proliferation, migration, and invasion. The results suggest that IFT88/primary cilia play a role in metabolic reprogramming in thyroid cancer cells.

Keywords: Primary cilia, IFT88, Defective ciliogenesis, Energy metabolism, Mitochondrial dynamics

▶▶▶ P-085

Loss of Primary Cilia Results Development of Cancer in Murine Thyroid Gland

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Primary cilia observed in apical membrane of thyroid epithelial cells, but its role *in vivo* remained to be determined. We generated mice model which has devoid of primary cilia through thyroid epithelial cell-specific deletion of *Ift88* gene. Thyroid-specific *Ift88*-deficient mice (*Tg-Cre;Ift88*$^{flo/flox}$) showed normal folliculogenesis and hormonogenesis. However, Tg-Cre;Ift88flo/flox mice over 7 weeks old showed an appearance of irregularly dilated and degenerated follicles in thyroid gland. More interestingly, the malignant featured cells which have characteristic nuclear features of human thyroid carcinomas were appeared and formed solid and papillary proliferative nodules from degenerated follicles. Furthermore, malignant tumor cells were observed as tumor emboli in thyroid vessels. Transformed thyroid follicular cells displayed activated canonical Wnt/β-catenin and PI3K/AKT/mTOR signaling. In conclusions, loss-of-function of *Ift88*/primary cilia in thyroid follicular cells prevents the maintenance of normal follicle structure, resulting in irregularly dilated and destroyed follicles. In these structurally abnormal follicles, the function of thyroid-specific genes is lost and the malignant transformation is induced by aberrant activations of Wnt/β-catenin as well as PI3K/AKT/mTOR signaling pathways. Furthermore papillary-solid proliferative thyroid nodules progress to aggressive and dedifferentiated thyroid carcinomas.

Keywords: Primary cilia, Defective ciliogenesis, Dilated and destroyed thyroid follicle, Malignant transformation

P-086

Primary Cutaneous Adenoid Cystic Carcinoma

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Adenoid cystic carcinoma (ACC) is a rare, slowly growing neoplasm, commonly occurs in the minor salivary glands. Uncommonly it can also involve major bronchi, breast, uterine cervix, and lacrimal glands. However, less than a hundred of cases from the skin as a primary tumor has been described in the literature. Herein, we describe the clinical and pathologic features of primary cutaneous ACC from the forearm of an 82-year-old man.

Keywords: Adenoid Cystic Carcinoma; Cutaneous; Primary

P-087

The Cytologic and Histologic Findings of Cribriform-Morular Variant of Papillary Thyroid Carcinoma

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Cribriform-morular variant of papillary thyroid carcinoma (CMVPTC) is a recently introduced, rare subtype of PTC, characterized by typical cribriform growth pattern with morules. A subset of the tumor shows the clinical association with familial adenomatous polyposis (FAP) and CTNNB1 other than BRAF mutation is known to be associated with the pathogenesis. Here we report a case of CMVPTC from a patient with FAP. A 21-year-old woman presented our hospital with hemorrhagic stool and two thyroid nodules in both lobes on a routine health checkup. The cytologic findings show many irregular sheets of follicular cells with typical nuclear features of PTC. Pathologically, tumors were well-defined encapsulated masses with variable growth patterns including solid, papillary, cribriform, acinar and spindle patterns with multiple morules, which immunohistochemically showed strong positivity for b-catenin. Following gastroduodenoscopy and colonoscopy showed multiple adenomatous polyps throughout the duodenum and colon. APC gene mutation analysis revealed a novel nonsense mutation (c.2140A>T) and 7 known single nucleotide variations while V600E BRAF mutation was wild-type. Thus we present the cytologic and histologic features of CMVPTC with the literature review.

Keywords: Cribriform-Morular Variant, Papillary Thyroid Carcinoma, Familial Adenomatous Polyposis

P-088

Primary Extramammary Paget's Disease with Colonic Metastasis: A Rare Aggressive Feature

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Primary extramammary Paget's disease (EMPD) is adenocarcinoma of apocrine sweat glands that involves the overlying squamous epithelium, commonly in the perineal area. Pathologically, it should be differentiated from secondary Paget's disease (PD) that is an intraepidermal metastasis of underlying anorectal, urothelial or cervical carcinomas. Unlike secondary PD, primary EMPD does not often metastasize to distant organs that secondary PD often presents in an end-stage disease. However, EMPD can also have distant metastasis in a very limited number of cases. Herein, we report a case of primary EMPD that metastasize to the colon and present as polypoid lesions from an 84-year-old man and review the aggressive cases of EMPD described in the literature.

Keywords: Primary Extramammary Paget's Disease; Distant Metastasis; Apocrine Intraepidermal adenocarcinoma

P-089

Human Leukocyte Antigen Class I and Programmed Death-ligand 1 Co-expression is an Independent Poor Prognostic Factor in Adenocarcinoma of the Lung

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Background & Objective: Both human leukocyte antigen (HLA) class I and programmed death-ligand 1 (PD-L1) molecules are known to play important roles in cancer immunity. In this study, we evaluate HLA class I expression in resected adenocarcinoma of the lung, and investigate its prognostic impact in correlation with PD-L1 expression. **Methods:** HLA class I and PD-L1 expression was evaluated by immunohistochemistry in a total of 403 resected lung adenocarcinomas using tissue microarray. Correlations between the expression of HLA class I/PD-L1 and clinicopathologic features and prognostic significance were analyzed. **Results:** HLA class I expression was reduced in 91.6%, and more frequently reduced in patients with younger age, absence of vascular invasion, and low pathologic stage (p=0.023, p=0.007 and p=0.012, respectively). Positive PD-L1 expression in tumor cells was 16.1% (1% cut-off), and associated with poor differentiation, presence of vascular invasion and nodal metastasis (p<0.001, p=0.002 and p=0.032, respectively). On survival analysis, HLA class I or PD-L1 expression alone did not showed any statistical significance. On the integrated analysis, HLA class I (+)/PD-L1 (+) subgroup showed a significant shorter overall survival than others (p=0.001). Multivariable analysis revealed that co-expression of HLA class I and PD-L1 was an independent poor prognostic factor of lung adenocarcinoma. (p=<0.001, Hazard ratio=5.657 with 95% confidence interval 2.179-14.688) **Conclusion:** Lung adenocarcinoma with co-expression of HLA class I and PD-L1 was associated with poor prognosis. This subgroup may evade immune attack by expressing PD-L1 protein despite of HLA expression.

Keywords: Human leukocyte antigen class I, Programmed death-ligand 1, lung adenocarcinoma

▶▶▶ P-090

Mesenchymal Stem Cells Promotes Tumor Formation in a Mouse Model of Fibrosarcoma

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Mesenchymal stem cells (MSCs) have the potential to act as microenvironmental factors in tumor and to promote tumor growth and metastasis. Although the potential of tumorigenesis is one of the critical risk factors for MSC therapy, the conditions for evaluating have not been extensively studied. To investigate the tumorigenesis of MSC, a dose that not form tumors when administered alone (5×10^3 HT1080 cells), and two different origins of MSCs at various doses (3×10^5, 1×10^5, 3×10^4 and 1×10^4 cells) were administered subcutaneously into BALB/c-nude mice. In the adipose tissue-derived mesenchymal stem cells-injected group, tumors developed in 14/15(93%), 12/15(80%), 5/15(33%) and 3/15(20%), the bone marrow-derived mesenchymal stem cells-injected group showed tumor formation in 13/15(86%), 10/15(66%), 4/15(26%), 1/15(6%) respectively. When 5×10^3 HT1080 cells and 3×10^3 MSCs were administered at the same time, tumor formation was not observed. In addition, 1×10^5 and 2×10^7 MSCs were injected subcutaneously and it was confirmed that no tumors were developed by itself. These results suggest that MSCs capable of mimicking the tumor microenvironment may affect susceptibility to tumorigenesis.

Keywords: Mesenchymal stem cells, Tumorigenicity, Tumor-promotion, Safety

▶▶▶ P-091

화순전남대학교병원 인체자원 단위은행 운영에 관한 보고

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화순전남대학교병원 인체자원 단위은행은 악성종양 환자의 조직과 혈액성분을 중점적으로 수집하는 암 전문 거점은행이다. 백혈병, 유방암, 대장암 등 한국인에 호발하는 암을 대상으로 수집한 지난 10년간(2008년 2월 - 2017년 12월)의 운영결과를 보고하고자 한다. 인체자원의 수집은 한국인체자원은행사업의 취지에 공감하고 인체유래물등의 기증동의서를 작성한 환자를 대상으로 하였다. 환자의 혈액을 채취하여 혈청(5 vials), 혈장(5 vials), 연막(2 vials)을 분리 수집하였고, 병리의사는 수술로 적출된 검체에서 정상과 종양조직을 일정한 크기(0.2 × 0.2 × 0.2 ㎤)로 각각 6개씩 만들었다. 수집된 인체자원은 cryovial에 넣어 오랫동안 보관하여도 서로 오염되지 않도록 액체질소의 기체층에 보관하였다. 환자의 모든 역학 및 임상자료는 BIMS(Biobank Information Management System)프로그램을 통해 관리하였다. 10년간 조혈계암을 비롯한 대장암, 위암, 간암, 유방암, 폐암, 뇌종양, 간담췌암 및 기타질환 환자 26,994명으로부터 자원이 수집되었다. 12,549명의 혈액(혈청, 혈장, 연막) 및 조직이 확보되었으며 백혈병의 경우 6,292명의 혈액(혈청, 혈장, 골수세포)이 수집되었다. 유방암, 위암, 대장암, 전립선암 4,949예를 대상으로 정상 및 종양을 포함하는 조직미세배열(TMA)을 제작하였다. 혈액 및 조직이 함께 수집된 예는 조직부위에 대한 광학현미경 검사를 통해 검체의 적절성을 평가하였으며, 1년에 2번 냉동보관 조직의 RNA에 대한 정기적인 안정성 검사를 실시하였다. 또한 적극적인 홍보와 자원활용위원회를 통한 합리적인 운영을 통해 내부 및 외부기관 연구자들에게 138과제 20,874건의 검체(외부 및 공동분양 54%)를 분양하여 인체자원을 이용한 임상 및 기초연구를 하는데 기여하였다. 화순전남대학교병원 인체자원 단위은행은 10년 간의 지역거점은행 운영을 통해 양질의 인체자원을 확보할 수 있는 절차를 마련하였으며, 수집된 자원에 대해서는 정기적인 정도관리를 통해 자원의 질을 보증하고 있다. 화순전남대학교병원 인체자원 단위은행은 이들 자원을 많은 연구자 들이 적극 활용할 수 있는 방안을 마련하여 한국인체자원은행 사업이 의학연구의 발전에 크게 기여할 수 있도록 할 예정이다.

Keywords: 인체자원, 단위은행, Biobank

▶▶▶ P-092

계명대학교동산병원 인체자원단위은행 운영실제

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유전자의 기능과 질병과의 관계를 연구하기 위해서는 고품질의 인체자원을 확보하여 연구자들에게 제공할 수 있도록 하는 인체자원은행의 역할이 중요해 지고 있다. 이와 관련하여 다양한 인체자원을 국가차원에서 수집 관리하여 연구자들에게 제공하기 위하여 한국인체자원은행사업을 질병관리본부에서 주축이 시행하고 있다. 계명대학교동산병원 인체자원은행은 17개 한국인체자원은행 단위은행 중 하나로 2009년도부터 한국인에서 흔히 발생하는 위암, 폐암, 자궁 및 난소암, 간암, 대장암 등 주요 종양과 만성사구체질환, 만성간질환, 만성기도질환과 대사성질환을 대상으로 조직, 혈액 및 이차자원을 수집하고 있다. 자원수집의 효율성을 높이기 위해 특성화분야를 중심으로 각 분야별 임상교수를 팀장으로 둔 팀제운영을 실시하고 있으며 양질의 인체자원을 수집, 분양하기 위한 표준작업지침(SOP)을 확립하였다. 2017년 까지 19,186바이알의 종양성 질환 검체를 수집하였으며 비종양성 질환은11,490바이알을 수집하였다. 주요 수집된 인체 자원은 급속동결조직과 혈액의 경우 혈청, 혈장, buffy coat 등으로 분리하여 보존하며, 모든 인체자원에 대해 각 환자의 동의서를 확보하고, 주요 임상 및 역학소견을 함께 보유하고 있다. 은행 설립 이후 적극적으로 분양에 노력하고 있으며 2017년에도 19건의 연구를 위하여 1719 바이알의 인체자원을 분양하였다. 질적으로 최상의 자원을 수집, 분양함을 은행의 중요 목표로 설정하여 철저한 품질관리를 시행하고 있다. 조직자원의 경우 적출된 후 동결저장까지 30분 이내 완료함을 원칙으로 하며, 모든 인체자원을 수집 할 때 소요되는 시간을 기록하고 있다. 정기적으로 RNA(1회/월), DNA(2회/년) 자원의 품질검증을 통해 조직자원의 질을 평가하고 있으며, 동결조직의 적절성 판정을 위해 mirror image를 제작하고 있다. 이러한 노력을 인정받아 조직 자원의 정도관리에 대하여 위탁교육도 시행하고 있다. 혈액자원의 경우 실온보관 할 경우 2시간, 냉장 보관할 경우 12시간 이내에 처리하는 것을 원칙으로 하고 있다. 질관리 업무의 전산화를 통해 정확한 기록 및 통계를 유도하고, 실무직원에 대한 효율적인 교육을 통해 오류를 최소화하고 있다. 또한 한국인체자원중앙은행과의 전산 업무망 연계를 통해 보다 활발하고 효율적으로 검체를 분양할 것으로 기대하고 있다.

Keywords: 한국인체자원단위은행사업, 자원수집 및 관리, 분양

▶▶▶ P-093

Impact of Tissue Ex-Vivo Ischemia Time and Storage Period on DNA Quality in Biobanked Human Colorectal Cancer Tissue

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Biobanking plays an important role in future translational cancer research. Assessing and controlling the preanalytical handling of biospecimens is fundamental for the optimal future use of biospecimens. Forty-five, fresh-frozen colorectal cancer (CRC) tissues (tumor cell content higher than 80%) stored at -80℃ in Bio-Resource Bank of Dong-A University Hospital were evaluated in order to define the influence of tissue ischemia time (TIT) and storage period (SP) on DNA quality in biobanked CRC tissue. Three TITs (less than 30 minutes (TIT-1), 30-45 minutes (TIT-2), and 45-60 minutes (TIT-3)) and three SPs (less than 1 year (SP-1), 2-3 years (SP-2), and 4-5 years (SP-3)) were chosen and then the samples were assigned to nine groups of five tissues per group. A Nanodrop spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA) was used to determine concentrations (ng/ul) and the A260/A280 of DNA samples. DNA integrity was confirmed by an ultraviolet transilluminator following electrophoresis with 3% agarose gel. All DNA samples had a A260/A280 ratio ranging between 1.8 and 2.0 with the exception of one sample (TIT-2/SP-2 group). DNA remained stable in CRC tissues kept at room temperature up to 60 minutes (mean purity: 1.89 in TIT-1 group, 1.83 in TIT-2 group, and 1.90 in TIT-3 group) and long-term storage up to 5 years did not negatively influence DNA purity (A260/A280) (mean purity: 1.88 in SP-1 group, 1.87 in SP-2 group, and 1.87 in SP-3 group). For DNA integrity, DNA appears as a compact, high-molecular-weight band with no or scanty low-molecular-weight smears. In conclusion, no significant difference was found in DNA purity and integrity of different TITs and SPs. Storage conditions of our biobank are suitable for long-term (at least five years) sample preservation with high DNA quality. The presented data should be considered in attempt to further standardize tissue biospecimen collection and banking.

Keywords: Biobank, Colorectal Cancer, Quality Evaluation, DNA, Ischemia

대한생리학회

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▶▶▶ P-094

IDH2 Deficiency Induces Vascular Endothelial Cell Senescence in HUVECs

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Aging is a progressive decay of the physiologic efficiency of an organism as well as a major cardiovascular disease risk factor. Accumulation of reactive oxygen species (ROS) with age is known to be associated with age related diseases. Mitochondrial NADP(+)-dependent isocitrate dehydrogenase (IDH2) is an enzyme to regulate the mitochondrial redox balance, and mediates the cellular defense system against oxidative damage. The redox enzyme p66shc is a key factor in regulating the level of ROS in endothelial cells. Previously, we demonstrated that the IDH2 knockdown caused increased mitochondrial ROS (mtROS), stimulated p66shc phosphorylation, and increased cytosolic ROS in endothelial cells. In this study, we investigated whether downregulation of IDH2 induced cell senescence in human umbilical vein endothelial cells (HUVECs). Protein markers of stress-induced senescence (p53, p21, and p16) were analyzed as regulators of ROS. We confirmed that IDH2 deficiency increased mRNA and protein levels of p66Shc, p53, p21, p16 expression in HUVECs using western blotting and RT-qPCR, respectively. Thus, our study demonstrated that IDH2 deficiency induced vascular endothelial cell senescence.

Keywords: IDH2, Senescence, ROS, Mitochondria, Endothelial cells

▶▶▶ P-095

Tetrahydrobiopterin is Key Factor to Endothelial Nitric Oxide Synthase Uncoupling in CR6 Interacting Factor-1 Deficiency Endothelial Cell

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Tetrahydrobiopterin (BH4) has responsibilities as a cofactor for the reaction of many enzymes. One is the biosynthesis of the neurotransmitters in brain. Tetrahydrobiopterin also related to catalyst for the production of nitric oxide. BH4 is synthesized by two pathways, de novo and recycling pathway. In vascular endothelium, de novo pathway is the primary pathway for BH4 synthesis. Endothelial nitric oxide synthase (eNOS) generates NO in blood vessels, which plays a major role in regulating vascular function. eNOS is composed of two kinds of domains, a reductase domain and an oxidase domain. Oxidative domain displays binding sites for heme group, zinc, BH4, and the substrate L-arginine. Reductase domain and Oxidase domain are linked by calmodulin-binding sequence. In the vascular endothelium, NO is synthesized by eNOS from L-arginine and molecular oxygen, which binds to the heme group of eNOS, is reduced and finally incorporated into L-arginine to from NO and L-citrulline. Without BH4, the structure of the eNOS becomes unstable and the substrate L-arginine cannot bind. Then the oxygen in the heme group receives the electrons instead of the substrate and canges to reactive oxygen species. eNOs that forms ROS instead of NO is called uncoupling eNOs. CR6 interacting factor 1 (CRIF-1) is essential for the translation and integration of mitochondrial oxidative phosphorylation complex, CRIF-1 deficiency induces mitochondrial dysfunction and mitochondrial reactive oxygen species. Our previous studies shown that NO generation and vasodilation decrease and ROS production increases in CRIF-1 knockout endothelial cell. So, we investigated eNOS and its cofactor BH4 in CRIF-1 knockout endothelium. First, eNOS inhibitor L-NAME and substrate L-arg were treated to confirm eNOS uncoupling in CRIF-1 knockout endothelial cells. It was confirmed that eNOS was uncoupled through reduction of ROS by L-NAME and lack of reactivity to L-arginine in CRIF-1 deficiency endothelial cells. Next, the amount of BH_4 in endothelium was determined by high pressure liquid chromatography (HPLC). In CRIF-1 deficiency endothelial cell, total biopterin, BH4, BH4/Total ratio was decreased. To determine the effect of ROS induced by CRIF-1 deficiency on BH_4, we treated N-acetylcysteine (NAC), a ROS scavenger. Reduction of ROS restored NO production and reactivity to L-arginine. In addition, total biopterin, BH_4, and BH_4/Total ratio were restored. In conclusion, ROS induced by CRIF-1 deficiency is major factor on BH4 declined and eNOS uncoupling.

Keywords: eNOS uncoupling, BH4, CRIF-1, ROS

▶▶▶ P-096

CR6-interacting Factor 1 Deficiency Induces Senescence by Impairment of Anti-oxidant System in Endothelial Cells

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CR6-interacting factor 1 (CRIF1) is a protein that exists in mitochondria and interacts with large ribosomal subunit, the deficiency of CRIF1 induces mitochondrial dysfunction and mitochondrial reactive oxygen species (mtROS). Oxidative stress, which is defined as a disturbance between mtROS and anti-oxidant molecules, is one of the most critical factors contributing to endothelial dysfunction. The consequence of mitochondrial dysfunction is cellular apoptosis and senescence. The aorta SA-b-gal staining ratio in endothelium-specific CRIF1 knockout mice was increased compared with wild-type mice. Sirtuin 3 (SIRT3), a mitochondrial deacetylase, plays a major role in mitochondrial biogenesis and is related to oxidative stress. Furthermore, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1a), which is a downstream protein of SIRT3, plays a major role in apoptosis, inflammation, and proliferation in endothelial cells. Our data confirmed that CRIF1 downregulation destroyed the anti-oxidant system in mitochondria by decreasing SIRT3 expression. SIRT3 downstream gene, mRNA and protein level of SOD2 were level dramatically decreased in CRIF1 deleted endothelial cells. SOD2 is an important antioxidant against oxidative stress. Thus, CRIF1-mediated SOD2 reduction may accumulate mtROS production in mitochondria. CRIF1 deficiency induced apoptosis and senescence progression in HUVECs by altering their morphology, β-galactosidase activity, expression of molecular senescence marker (P-p53 (S15), p21) and apoptosis marker (bcl-2, bax, caspase-3). In addition, we proved that SIRT3 overexpression could attenuate CRIF1 deficiency induced senescence in endothelial cells. We also demonstrated the same results in CRIF1 knockout mice. Our data identify a distinct senescence response and provide a mechanism by which mitochondrial dysfunction can drive aging. The final purpose of the study is to delay the development of senescence already in vascular damage.

Keywords: CRIF1, mtROS, SIRT3, Senescence

▶▶▶ P-097

DGLHT Inhibits Imiquimod-Induced Psoriasis-Like Skin Inflammation by Suppressing IL-22 Production

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Herbal formula, DGLHT has been previously shown to inhibit T lymphocyte proliferation and suppress dendritic cell function. An in vivo mouse model of IMQ-induced psoriasis-like inflammation was used to investigate the effect of DGLHT. The anti-inflammatory effects of an extract of DGLHT and the responsible mechanism were examined in an in vitro model using M5 stimulated HaCaT cells. The anti-proliferative effect of DGLHT-E was examined by analyzing the expression levels of K16, K17 and Ki67 in IL-22 stimulated HaCaT cells. Topical application of 1% DGLHT-E significantly reduced psoriasis-like symptoms including scaling and epidermal hyperplasia in IMQ-treated mice. Immunohistochemical studies showed that DGLHT-E exerted potent anti-inflammatory effects by inhibiting IL-22 production in local skin lesions. DGLHT-E also attenuated the productions of CXCL10 and CCL20 in M5-stimulated HaCaT cells by suppressing the ERK1/2, JNK and STAT3 signaling pathways. Furthermore, berberine hydrochloride, a primary constituent of DGLHT-E inhibited the expressions of the proliferation markers K16 and K17 in IL-22 stimulated HaCaT cells. These results suggested that DGLHT-E offers a possible treatment for psoriasis, and that berberine hydrochloride might be a useful component of ointment-based treatments for psoriatic lesions.

Keywords: Psoriasis, Dang-Gui-Liu-Huang Tang, Berberine hydrochloride, IL-22, K16

▶▶▶ P-098

Somatotype Analysis of Korean Combat Sport Athletes Based on Weight Divisions

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It is well established that somatotypes are defined by the physical characteristics of the body. However, the somatotype results of combat sport athletes have not yet been established. The purpose of present study was to evaluate somatotype analysis by comparing between combat sport athletes based on body weight to determine physical characteristics and to establish a reference for studies of training and sport rehabilitation. This study consisted of 40 judo, 32 ssireum, 31 taekwondo (gyorugi), 20 taekwondo (poomsae), 23 boxing, and 13 wrestling elite athletes. The participants were divided into four weight divisions: light weight (-55 ~ -74 kg), middle weight (-75 ~ -94 kg), heavy weight (-95~ -114 kg), and super heavy weight (+115 kg). Somatotypes measurements were performed using a Heath and Carter's modified somatotype method. Ssireum athletes had higher endomorphic and mesomorphic characteristic values and lower ectomorphic characteristics compared to other athletes. Somatotype component values for judo and wrestling athletes were similar. Gyorugi athletes had higher ectomorphic values than other athletes and were taller. Values of all components among the poomsae athletes were balanced. Boxing athletes had the same endomorphic and ectomorphic values and higher mesomorphic characteristic values. Differences between the sports were more significant in the lower- and middle-weight categories compared to the heavy- and super-heavy-weight categories. For all sports, higher weight divisions included higher endomorphic and mesomorphic values and lower ectomorphic values compared to lower weight categories. Correlations between endomorphic characteristics and body weight were significant among all athletes except for gyorugi athletes. Correlations between mesomorphic characteristics and body weight were significant among judo, ssireum, boxing, and wrestling athletes, but taekwondo athletes did not show any correlation. The correlation between ectomorphic characteristics and body weight were significantly negative among judo, ssireum, gyorugi, boxing, and wrestling athletes and negative among poomsae athletes. Almost all combat sport athletes have mesomorph body types except for taekwondo athletes, and the somatotypes of athletes were influenced by the type of sport and weight divisions. Therefore, injured or ahead-of-the-game elite combat athletes require different methods of rehabilitation and training based on sport type and body weight, and further studies are required to assist in proper training for athletes returning from injury and to aid in sport rehabilitation.

Keywords: Somatotype analysis, Korean combat sport athletes, Weight divisions

▶▶▶ P-099

Somatotype Analysis of Both Sides Body in Stroke Patients

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The purpose of this study is to establish the difference between the somatotype of the paretic side and the non-paretic side of the hemiplegia patient and to establish the difference according to the ambulation function. The participants of this study include 50 hemiplegic patients. They were divided into independent gait group (IG) and gait with assistive device group (GA). Somatotype measured according to Heath-Carter's modified somatotype method. These results compared paretic side and non-paretic side of hemiplegic patients. Data analysis was used a paired t-test to compare between both side and independent t-test to compare between group. Mesomorphic component in IG group was a statistically significant difference. Mesomorphic component of paretic side was 4.71±0.29, but non-paretic side was 5.34±0.32. There was also a statistically significant difference in the mesomorphic component of the GA group (paretic side - 2.98±0.22, non-paretic side ? 4.19±0.25). This difference was 1.20±0.11, which was statistically significant higher than IG group. Mesomorph of paretic side in IG group (4.71±0.29) was higher than GA group (2.98±0.22). There was no difference in endomorphic components of all groups (IG group: paretic side - 4.70±0.23, non-paretic side - 4.76±0.28, difference - 0.07±0.12, GA group: paretic side - 3.90±0.19, non-paretic side - 3.81±0.23, difference - -0.09±0.07). Hemiplegia patients have muscular body in non-paretic sides than paretic sides, and this difference is higher gait with assistive device group than independent group.

Keywords: Stroke, Somatotype, Gait

▶▶▶ P-100

Analysis of the Pressure-related Sensory Changes in Supine Position with Pillow

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The purpose of this study was to analysis of the body pressure-related sensory changes between the male and female in a supine position with pillow for healthy science research. The Body Pressure Measurement System was used to analyze body pressure. To evaluate, body pressure sensors were attached to mattresses beneath the subjects. Pain score tools was used to evaluate the level of pain before the supine position with pillow position was adopted, at 1, 5, 10, and 15 min, and in total for specific body points. In analysis of digitized images, the head pressure intensity and shoulder pressure intensity was significantly higher than that of the other body parts. And, in head pressure intensity, supine with pillow was significantly higher non pillow group. Each parts total pain score value in supine group were higher than supine with pillow group. Especially, the value of pelvis pain in supine group was significantly higher than supine with pillow group. And all value was significantly increased than before. These results suggest that properties that change in a time-dependent manner and postural changes need to be carefully considered when applying physiotherapy.

Keywords: Sensory, Supine position, Pillow

▶▶▶ P-101

Effect of Orthopaedic Manual Physical Therapy on Patients with Total Knee Replacement in Early Stage

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The purpose of this study was to investigate effectiveness of orthopaedic manual physical therapy on restore of joint and function on acute total knee replacement (TKR) patients. The participants of this study include 30 patients with total knee replacement who are receiving admission treatment in P rehabilitation center. All subjects were acute stage patients within 4 weeks of surgery. Patients were randomly allocated to a conventional physical therapy group (CPT) and an orthopaedic manual physical therapy group (OMPT). Conventional physical therapy is consisted of cold therapy, electrical therapy, continuous passive motion (CPM) and group exercise program. OMPT group was received additional manual therapy used slow eccentric isotonic stretch technique (SEIS) of muscle energy technique (MET). After 2 weeks of intervention, the outcomes were measured. The primary outcomes were pain, active range of motion (ROM) of knee flexion and knee extension, swelling. The secondary outcomes were timed up and go test (TUG), step length, step speed. Pain, active ROM in flexion, reduction of swelling in the primary outcomes was improved in both groups. However, active ROM in knee extension was significantly increased in the only OMPT group. Also, decrease of swelling was greater in OMPT group than CPT group. TUG was improved in all groups, but other gait parameters were not significant. Orthopaedic manual physical therapy is positively effectiveness on the recovery of early TKR patients. The SEIS technique is effective in reducing edema and improving ROM in early TKR patients. Therefore, we suggest that using the SEIS technique, which is a gentle manual therapy for early TRK patients, will help in the early recovery of TKR patients.

Keywords: Total knee replacement, Range of motion, Orthopaedic manual physical therapy

▶▶▶ P-102

Development of Nanofiber-based Conjunctival Stroma for 3D Reconstructed Human Conjunctiva

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Bioengineered 3D tissue models have become valuable tools for medical research and clinical applications. In vitro biomimetic human conjunctiva model might be helpful to determine drug delivery and safety of novel ophthalmic drugs, but 3D culture models based on human conjunctiva-derived cells have not yet been developed. With the aims of development of the 3D reconstructed human conjunctiva, 3D culture of human primary conjunctival fibroblasts using nanofibrous scaffold was performed to establish the proper stroma for growth and maturation of human conjunctival epithelial cells. Bilayered poly(ε-caprolactone) scaffolds with upper aligned nanofibers and lower randomly-oriented microfibers were fabricated to recapitulate *in vivo* human bulbar conjunctiva. A primary culture of human conjunctival fibroblasts and epithelial cells was prepared form surplus tissue obtained from surgical resection using the explant culture technique. For the adhesion assay, human conjunctival epithelial cells were seeded into 96-well plates which had been precoated with the cell culture supernatants from human conjunctival fibroblasts cultured either in PCL micro/nanofibrous scaffold (3D) or on the traditional polystyrene plastic surface (2D). For reconstruction study, human conjunctival epithelial cells were grown in transwell chambers for 3 days on the top of 3D micro/nanofibrous scaffold in which human conjunctival fibroblasts had been cultured for 6 days. For z-stack acquisition of confocal images, fibroblasts and epithelial cells were labeled with Cell Tracker Green CMFDA and Red CMTPX, respectively. The cell culture supernatants from human conjunctival fibroblasts cultured on 3D displayed a greater growth promoting effect on human conjunctival epithelial cells than those from 2D cell culture supernatants or pre-coated with poly-L-lysine. Stacked confocal images of co-cultured human conjunctival epithelial cells and fibroblasts revealed that epithelial cells were grown to confluence and aligned in several rows beneath the upper surface of micro/nanofibrous scaffold whereas fibroblasts distributed below the epithelial cell layer. These data suggest that 3D culture of human primary conjunctival fibroblasts using PCL micro/nanofibrous scaffold create more suitable biomimetic microenvironments for microenvironments for conjunctival epithelial cells to reconstruct 3D human conjunctiva *in vitro*.

Keywords: Human primary conjunctival fibroblasts, human conjunctival epithelial cells, 3D culture, poly(ε-caprolactone) nanofibrous scaffold

▶▶▶ P-103

Ginsenoside Rk1 Induces Apoptosis in Neuroblastoma Cells through Loss of Mitochondrial Membrane Potential and Activation of Caspases

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Neuroblastoma (NB) is the most common childhood cancer, with a very poor prognosis. More than 60% of children with NB die within 5 years; therefore, a more effective therapy for NB is required. As a more tolerable cancer drug and natural product, ginsenosides have been shown to significantly inhibit the growth of some types of cancer, but the effect of ginsenoside Rk1 on neuroblastoma has not been previously shown. Here, we obtained highly pure Rk1 from Korean ginseng and investigated its anticancer effects on a neuroblastoma cell line, and the results suggested that Rk1 concentration-dependently inhibited SK-N-BE(2) cell viability. The effects of Rk1 were determined by flow cytometry and cell staining; Rk1 increased apoptosis through nuclear condensation and mitochondrial membrane potential loss, and induced cell cycle arrest at the G0/G1 phase. Rk1 also inhibited the metastatic ability of SK-N-BE(2) cells. Moreover, Rk1 (30 mg/kg) injections markedly inhibited xenograft tumour growth. These findings demonstrate that Rk1 might be valuable in the development of anti-cancer agents for neuroblastoma treatment.

Keywords: Neuroblastoma, Ginsenoside RK-1, Apoptosis, MMP ($\Delta\Psi$m)

P-104

Ginsenoside Rk1 Inhibits Epithelial-mesenchymal Transition (EMT) and Invasion of Neuroblastoma by Down-regulating Survivin

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The epithelial-mesenchymal transition (EMT) is an important factor in neuroblastoma metastasis, which targeting EMT is a potential therapeutic strategy. Survivin was abnormally elevated in many cancers. In this study, we investigated minor ginsenoside Rk1 inhibits EMT and invasion in neuroblastoma cell lines and the relevance of survivin. We found that Rk1 treatment (0, 10, 20, and 30 μM) inhibited cell migration and invasion by wound-healing and transwell assays. Rk1 significantly altered EMT marker proteins with increased E-cadherin, but decreased Snail, N-cadherin, Slug and Vimentin expression. Rk1 also down-regulated survivin gene and protein expression in neuroblastoma cells by qPCR, Western blot and immunofluorescence. After survivin down-regulated with siRNA survivin, EMT was obviously inhibited. In conclusion, Rk1 inhibits EMT and invasion of neuroblastoma by down-regulating survivin mediated blocking MAPK pathways. Rk1 may be a potentially effective agent for the treatment of neuroblastoma

Keywords: Neuroblastoma, Ginsenosides, Survivin, EMT

P-105

Apoptotic Cells Trigger the ABCA1/STAT6 Pathway Leading to PPARγ Activation in Macrophages

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We investigated proximal membrane signaling that was initiated in macrophages after exposure to apoptotic cells that led to enhanced PPARγ expression and activity, using specificsiRNAs for ABCA1, STAT6, and PPARγ or their antagonists. The interactions between mouse bone marrow-derived macrophages or RAW 264.7 cells and apoptotic Jurkat cells, but not viable cells, resulted in the induction of STAT6 phosphorylation as well as PPARγ expression and activation. Knockdown of ATP-binding cassette transporter A1 (ABCA1) after the transfection of macrophages with ABCA1-specific siRNAs reduced apoptotic cell-induced STAT6 phosphorylation as well as PPARγ mRNA and protein expression. ABCA1 knockdown also reduced apoptotic cell-induced liver X receptor α (LXRα) mRNA and protein expression. Moreover, inhibition of STAT6 with specific siRNAs or the pharmacological inhibitor AS1517499AS reversed the induction of PPARγ, LXRα, and ABCA1 by apoptotic Jurkat cells. PPARγ-specific siRNAs or the PPARγ antagonist GW9662 inhibited apoptotic cell-induced increases in LXRα and ABCA1 mRNA and protein levels. Thus, these results indicate that apoptotic cells trigger the ABCA1/STAT6 pathway, leading to the activation of the PPARγ/LXRα/ABCA1 pathway in macrophages.

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Keywords: The ABCA1, STAT6, PPARγ, macrophages

▶▶▶ P-106

Gas6/Axl or Mer Signaling Inhibits Epithelial-mesenchymal Transition in Lung Alveolar Epithelial Cells through HGF Secretion

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We have demonstrated that macrophages can be re-programmed by growth arrest-specific protein 6 (Gas6) to promote epithelial proliferation and wound repair via a paracrine role of HGF. However, a direct role of Gas6 in epithelial homeostasis remains largely unknown. Here, we investigated a role of growth arrest-specific protein 6 (Gas6) and its underlying mechanisms in prevention of EMT process in alveolar type II epithelial cells (AT II). Pretreatment with Gas6 inhibited TGF-β1-induced EMT process in primary mouse AT II or LA-4 cells, based on morphologic cellular alteration, changes in EMT marker expression profiles, including loss of E-cadherin, synthesis of N-cadherin and α-smooth muscle actin, and induction of EMT-activating transcription factor, such as *Snai1/2*, *Zeb1/2*, and *Twist1*. Gas6 induced phosphorylation of Axl and Mer receptor tyrosine kinase, and enhanced RhoA activation and HGF production. The Rho kinase inhibitor (Y27632) or siRNA of RhoA inhibited Gas6-induced anti-EMT effect in LA-4 cells. The antagonist of c-Met (PHA-665752) also reversed EMT inhibition by Gas6. Additionally, we found that Axl-or Mer- specific siRNA inhibited Gas6-induced RhoA/Rho kinase-dependent HGF production, and consequently blocked anti-EMT effect of Gas6 in LA-4 cells. Our data suggest Gas6/Axl or Mer signaling events play a potential role in resistance to TGF-β1-induced EMT process via production of RhoA/Rho kinase dependent HGF.

▶▶▶ P-107

The APE1/Ref-1 Inhibits Inorganic Phosphate-Induced Vascular Calcification and the Loss of the Smooth Muscle Phenotype in Vascular Smooth Muscle Cells

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Vascular calcification plays a role in the pathogenesis of atherosclerosis, diabetes, and chronic kidney disease; however, the role of apurinic/apyrimidinic endonuclease 1/redox factor-1 (APE1/Ref-1) in inorganic phosphate (Pi)-induced vascular smooth muscle cell (VSMC) calcification remains unknown. In the present study, we studied a novel role of apurinic/apyrimidinic endonuclease 1/redox factor-1 (APE1/Ref-1) in Pi-induced vascular calcification and vascular smooth muscle cell (VSMC) phenotype changes and showed that the redox function of APE1/Ref-1 was involved in the inhibition of inorganic phosphate (Pi)-induced oxidative stress and vascular calcification in VSMCs. To determine the role of APE1/Ref-1 in the Pi-induced VSMC calcification, we studied the effect of adenoviral overexpression of APE1/Ref-1 (200 MOI) on the Pi-induced VSMC calcification. Adenoviral-transfected cells were exposed to Pi (5 mM) in the presence of 10% FBS for 6 days. The overexpression of APE1/Ref-1 inhibited Pi-induced loss of the alpha-smooth muscle actin and smooth muscle protein 22-alpha, and VSMC calcification, which was examined by alizarin red staining and a calcium content assay. In the ex vivo system overexpression of APE1/Ref-1 suppressed the Pi-induced aortic calcification (alizarin red staining) and phosphate precipitation (von Kossa staining). We demonstrated that Pi-induced VSMC calcification is associated with decreased APE1/Ref-1 expression. APE1/Ref-1 overexpression suppressed the Pi-induced VSMC calcification and prevented a loss of the smooth muscle phenotype.

Keywords: APE1/Ref-1; Inorganic Phosphate; Vascular Smooth Muscle Cells; Vascular Calcification

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Chronic Exposure of Ethylenethiourea Induces Nephritic Toxicity and Polycystogenesis in Male C57BL/6 Mouse

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Ethylenethiourea (ETU) was firstly produced in the United States in 1951. ETU was mainly used as a vulcanizing catalyst for polychlorophrene and polyacrylate rubbers and used in dyes, synthetic resins, pharmaceuticals, and intermediate in antioxidant production. ETU is also one of the main metabolite of ethylenebisdithiocarbamate (EDBC) fungicides including maneb, zineb, and mancozeb. Therefore, potential occupational exposure to ETU is greatest for workers involved in machine and metal manufacturing, rubber production, and manufacture of EDBC fungicides. The pathways of potential human exposure to ETU are dermal contact, ingestion, and inhalation. The toxicological study of ETU were extensively investigated to the endocrine disruption, teratogenesis, goiter, and carcinogenicity. Extensive study on the carcinogenicity demonstrates that ETU increases adenocarcinomas and thyroid follicular adenomas in rodents. ETU has also demonstrated developmental toxicity including central nervous system and skeletal structure. Recently, it has been reported that high dose of ETU(300 mg/L) resulted in ultrastructure alteration in proximal tubular epithelial cells. In the present study, we evaluated that the changes of visceral organ weight, cholesterol levels in serum, renal and liver function index, and epigenetic miRNA expression levels in C57BL/6 mouse with chronic exposure of ETU for 58 weeks. Chronic exposure of low dose ETU(250 ppm) induced toxicological effects which as followed; 1) lowered body weight, 2) increased triglyceride and cholesterol in serum, 3) increased blood urea nitrogen(BUN) and creatine levels, 4) induced extreme malfunction of kidney including decreased number and size of glomerulus, 5) and induced severe hydronephrosis or poly-cystogenesis compared to the control. Also, ETU diet increased expression levels of miR-1971, miR-155, miR-135, miR-125, and miR-21, as known to biomarker for renal injury and fibrosis, in kidney. In the cause of polycystic kidney disease, ETU diet increased expression levels of miR-17~92 cluster, known as an oncogenic miRNA cluster and renal cyst growth, and miR-182, an novel regulator of actin cytoskeleton and cyst progression. Taken together, these data suggest that chronic exposure to ETU, at low concentration without causing acute toxicity, evoked renal dysfunction such as glomerular dysfunction and renal cyst development.

Keywords: Ethylenethiourea, Polycystic kidney disease, miRNA 17~92 cluster, miR-18, Renal dysfunction

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Open-state Inhibition of Kv channels by Dapoxetine, a Selective Serotonin Reuptake Inhibitor, on Voltage-gated K^+ channels in Coronary Vascular Smooth Muscle Cells

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We investigated the inhibitory effect of dapoxetine, a selective serotonin reuptake inhibitor (SSRI), on voltage-dependent K^+ (Kv) channels using native smooth muscle cells from rabbit coronary arteries. Dapoxetine inhibited Kv channel currents in a concentration-dependent manner, with an IC_{50} value of 2.68 ± 0.94 μM and a slope value (Hill coefficient) of 0.63 ± 0.11. Application of 10 μM dapoxetine accelerated the rate of inactivation of Kv currents. Although dapoxetine did not modify current activation kinetics, it caused a significant negative shift in the inactivation curves. Application of train step (1 or 2 Hz) progressively increased the inhibitory effect of dapoxetine on Kv channels. In addition, the recovery time constant was extended in its presence, suggesting that the longer recovery time constant from inactivation underlies a use-dependent inhibition of the channel. From these results, we conclude that dapoxetine inhibits Kv channels in a dose-, time-, use-, and state (open)-dependent manner, independent of serotonin reuptake inhibition.

Keywords: Dapoxetine, Voltage-dependent K^+ channel, Coronary artery, Serotonin reuptake inhibitor

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Nortriptyline-induced Inhibition of Voltage-gated K^+ Channels in Rabbit Coronary Arterial Smooth Muscle Cells

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We demonstrated the effect of nortriptyline, a tricyclic antidepressant drug and serotonin reuptake inhibitor, on voltage-dependent K^+ (Kv) channels in freshly isolated rabbit coronary arterial smooth muscle cells using a whole-cell patch clamp technique. Nortriptyline inhibited Kv currents in a concentration-dependent manner, with an apparent IC_{50} value of 2.86 ± 0.52 μM and a Hill coefficient of 0.77 ± 0.1. Although application of nortriptyline did not change the activation curve, nortriptyline shifted the inactivation current toward a more negative potential. Application of train pulses (1 or 2 Hz) did not change the nortriptyline-induced Kv channel inhibition, suggesting that the effects of nortiprtyline were not use-dependent. Preincubation with the Kv1.5 and Kv2.1/2.2 inhibitors, DPO-1 and guangxitoxin did not affect nortriptyline inhibition of Kv channels. From these results, we concluded that nortriptyline inhibited Kv channels in a concentration-dependent and state-independent manner by changing the steady-state inactivation curves independently of serotonin reuptake.

Keywords: Nortriptyline, Voltage-dependent K^+ channel, Coronary artery

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Inhibitory Effect of Tricyclic Antidepressant Clomipramine on Voltage-dependent K^+ Current in Rabbit Coronary Arterial Smooth Muscle Cells

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We investigated the effect of the tricyclic antidepressant clomipramine on voltage-dependent K^+ (Kv) channels in native rabbit coronary arterial smooth muscle cells. Our results showed that clomipramine inhibited vascular Kv channels in a concentration-dependent manner, with an IC_{50} value of 8.61 ± 4.86 μM and a Hill coefficient (*n*) of 0.58 ± 0.07. The application of 10 μM clomipramine did not affect the activation curves of the Kv channels; however, the inactivation curves of the Kv channels were shifted toward a more negative potential. The clomipramine-induced inhibition of Kv currents was not changed by the application of train pulses (1 or 2 Hz), which demonstrated that clomipramine inhibited Kv current in a state (use)-independent manner. Pretreatment with the Kv1.5 and Kv2.1 inhibitors, DPO-1 and guangxitoxin, respectively, did not affect clomipramine-induced inhibition of Kv currents. Therefore, we concluded that clomipramine inhibited vascular Kv channels in a concentration-dependent, but state (use)-independent manner, regardless of its own function.

Keywords: Clomipramine, Voltage-dependent K^+ channel, Coronary artery

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The Direct Effect of Desipramine on Voltage-gated K^+ Current in Rabbit Coronary Arterial Smooth Muscle Cells

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We describe the effect of a tricyclic antidepressant drug, desipramine on voltage-dependent K^+ (Kv) currents in freshly isolated rabbit coronary arterial smooth muscle cells using a conventional whole-cell patch clamp technique. Application of desipramine rapidly decreased the Kv current amplitude in a concentration-dependent manner, with an IC_{50} value of 5.91 ± 0.18 μM and a Hill coefficient of 0.61 ± 0.09. The steady-state inactivation curves of the Kv channels were not affected by desipramine. However, desipramine shifted the steady-state inactivation curves toward a more negative potential. Application of train pulses (1 or 2 Hz) slightly reduced the Kv current amplitude. Such reduction of the Kv current amplitude by train pulses increased in the presence of desipramine. Furthermore, the inactivation recovery time constant was also increased in the presence of desipramine, suggesting that desipramine-induced inhibition of the Kv current was use-dependent. Application of a Kv1.5 inhibitor (DPO-1) and/or a Kv2.1 inhibitor (guangxitoxin) did not change the inhibitory effect of desipramine on Kv currents. Based on these results, we concluded that desipramine directly inhibited the Kv channels in a dose- and state-dependent manner, but the effect was independent of norepinephrine/serotonin reuptake inhibition.

Keywords: Desipramine; voltage-dependent K^+ channel; coronary artery; smooth muscle

▶▶▶ P-113

A Meglitinide Class of Anti-diabetic drug, Repaglinide Induces Vasodilation by Activation of Protein Kinase A and Protein Kinase G in Aortic Smooth Muscle

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We investigated the vasorelaxant effect of repaglinide and its related signaling pathways using phenylephrine (Phe)-induced pre-contracted aortic rings. Repaglinide induced vasorelaxation in a concentration-dependent manner. The repaglinide-induced vasorelaxation was not affected by removal of endothelium. Pre-treatment with adenylyl cyclase inhibitor or the PKA inhibitor effectively reduced repaglinide-induced vasorelaxation. Also, pretreatment with guanylyl cyclase inhibitor or the PKG inhibitor effectively inhibited repaglinide-induced vasorelaxation. However, pretreatment with voltage-dependent K^+ channel inhibitor (4-AP), ATP-sensitive K^+ channel inhibitor (glibenclamide), big-conductance Ca^{2+}-activated K^+) channel inhibitor (paxilline), and the inwardly rectifying K^+ channel inhibitor (Ba^{2+}) did not affect the vasorelaxant effect of repaglinide. Furthermore, pretreatment with Ca^{2+} inhibitor (nifedipine) and SERCA inhibitor (thapsigargin) also did not affect the vasorelaxant effect of repaglinide. From these results, we concluded that repaglinide induced vasorelaxation by activation of adenylyl cyclase/PKA and guanylyl cyclase/PKG signaling pathway independently of endothelium, K^+ channels, Ca^{2+} channel and intracellular Ca^{2+} ($[Ca^{2+}]_i$).

Keywords: Repaglinide, Diabetes, Protein kinase A, Protein kinase G

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Changes of ATP-sensitive K^+ Channels Expression in Human Umbilical Smooth Muscle during Gestational Diabetes Mellitus

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We investigated the alterations of ATP-sensitive K^+ (K_{ATP}) channels in human umbilical arterial smooth muscle cells during gestational diabetes mellitus (GDM). The amplitude of the K_{ATP} current induced by application of the KATP channel opener pinacidil (10 μM) was reduced in the GDM group than in the control group. Pinacidil-induced vasorelaxation was also predominant in the normal group compared with the GDM group. Reverse transcription polymerase chain reaction and Western blot analysis suggested that the expression of K_{ATP} channel subunits such as Kir6.1, Kir6.2, and SUR2B, were decreased in the GDM group relative to the normal group. The application of forskolin and adenosine, which activate protein kinase A (PKA) and thereby K_{ATP} channels, elicited K_{ATP} current in both the normal and GDM groups. However, the current amplitudes were not different between the normal and GDM groups. In addition, the expression levels of PKA subunits were not altered between the two groups. These results suggest that the reduction of K_{ATP} current and K_{ATP} channel-induced vasorelaxation are due to the decreased expression of K_{ATP} channels, not to the impairment of K_{ATP}-related signaling pathways.

Keywords: ATP-sensitive K^+ channels, Umbilical artery, Gestational diabetes mellitus, Protein kinase A

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The Vasodilatory Effect of Nateglinide, a Meglitinide Class of Anti-diabetic Drug, via Activation of Voltage-gated K^+ Channels in Rabbit Aortic Smooth Muscle

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We investigated the vasorelaxant effect of nateglinide using phenylephrine-induced pre-contracted aortic rings. The application of nateglinide induced vasorelaxation in a concentration-dependent manner. Pretreatment with the BK_{Ca} channel inhibitor paxilline, Kir channel inhibitor Ba^{2+}, and K_{ATP} channel inhibitor glibenclamide, did not affect the vasorelaxant effect of nateglinide. However, pretreatment with the Kv channel inhibitor 4-AP, effectively reduced the vasorelaxant effect of nateglinide. Pretreatment with the Ca^{2+} inhibitor nifedipine and the SERCA inhibitor thapsigargin did not change the vasorelaxant effect of nateglinide. Additionally, the vasorelaxant effect of nateglinide was not altered in the presence of an adenylyl cyclase, a protein kinase A, a guanylyl cyclase, or a protein kinase G inhibitor. The vasorelaxant effect of nateglinide was not affected by the elimination of the endothelium. In addition, pretreatment with a nitric oxide synthase inhibitor, L-NAME, and a SK_{Ca} channel inhibitor, apamin did not change the vasorelaxant effect of nateglinide. From these results, we concluded that nateglinide induced vasorelaxation via the activation of the Kv channel independent of other K^+ channels, Ca^{2+} channels, intracellular Ca^{2+} ($[Ca^{2+}]_i$), and the endothelium.

Keywords: Nateglinide, Aortic smooth muscle, Voltage-dependent K^+ channel

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The Dipeptidyl Peptidase-4 Inhibitor Vildagliptin Induces Vasodilation via Activation of Kv Channel and SERCA Pump in Aortic Smooth Muscle

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This study investigated vildagliptin-induced vasodilation and its related mechanisms using phenylephrine induced precontracted rabbit aortic rings. Vildagliptin induced vasodilation in a concentration-dependent manner. Pretreatment with the large-conductance Ca^{2+}-activated K^+ channel blocker paxilline, ATP-sensitive K^+ channel blocker glibenclamide and inwardly rectifying K^+ channel blocker Ba2+ did not affect the vasodilatory effects of vildagliptin. However, application of the voltage-dependent K^+ (Kv) channel inhibitor 4-aminopyridine significantly reduced the vasodilatory effects of vildagliptin. In addition, application of either of two sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) inhibitors, thapsigargin or cyclopiazonic acid, effectively inhibited the vasodilatory effects of vildagliptin. These vasodilatory effects were not affected by pretreatment with adenylyl cyclase, protein kinase A (PKA), guanylyl cyclase, or protein kinase G (PKG) inhibitors, or by removal of the endothelium. From these results, we concluded that vildagliptin induced vasodilation via activation of Kv channels and the SERCA pump. However, other K^+ channels, PKA/PKG-related signaling cascades associated with vascular dilation, and the endothelium were not involved in vildagliptin-induced vasodilation.

Keywords: Vildagliptin, Voltage-dependent K^+ channel, SERCA pump, Aortic smooth muscle

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Role of JHDM in the Development of Non-alcoholic Fatty Liver Disease

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Non-alcoholic fatty liver disease (NAFLD) is caused by excessive fat accumulation in the hepatocytes. Mild steatosis may develop into aggressive forms of Hepatic fibrosis, cirrhosis and carcinoma. JHDM, a JmjC histone demethylase, is known as the demethylase of the Histone H3K9 while it binds to H3K4me3 with the PHD domain. JHDM is known to have associated with metabolism-related transcription factors. In this study, we identified the role of JHDM in the progression of hepatic steatosis.

For in vivo study, WT and JHDM overexpressed TG mice were fed normal diet or high fat diet for 8 weeks. And then, Liver steatosis and blood chemistry were analyzed. The expression level of protein and genes involved in liver lipid metabolism were measured. For in-vitro study, JHDM was stably silenced in HepG2, human liver cell line. Overexpression of JHDM attenuated lipid accumulation in liver and insulin tolerance in mice fed with high fat diet. The expression of lipogenic genes was decreased in TG mice liver. In *in vitro* study, increased levels of lipogenic genes were confirmed in JHDM knock-down stable cell. In addition, we found that JHDM directly interacts with SREBP1c through protein-protein interaction. These results suggest that JHDM plays a role as a repressor in the progression of hepatic steatosis through the association with SREBP1.

Keywords: JHDM, SREBP1c, NAFLD

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Role of SREBP 1c NEDDylation Pathway in Non Alcoholic Fatty Liver Disease and the Discovery of Therapeutic Agents

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Non-alcoholic fatty liver disease (NAFLD) represents a spectrum of liver disease that, can lead to simple steatosis, nonalcoholic steatohepatitis (NASH), fibrosis, cirrhosis and ultimately hepatocellular carcinoma. The development of NAFLD is intimately associated with obesity and diabetes. The most promising treatments for NAFLD are diet, exercise, weight loss, and surgery. Several drugs have been studied in the treatment of NAFLD. But there is no effective treatment for patients with NAFLD. Thus its prevention and therapy play an important role in hepatology. Sterol regulatory element-binding protein 1c (SREBP 1c) has crucial roles in lipogenesis and lipid accumulation within liver. Chronic activation of SREBP 1c with increased lipogenic activity contributes to the development and progression of several pathological conditions, such as fatty liver, obesity, and diabetes. Here, We demonstrate that the Neuronal precursor cell expressed, developmentally downregulated 8 (NEDD8) based post-translation modification (neddylation) of SREBP 1c is essential for lipogenesis. NEDD8 is robustly conjugates with SREBP 1c, leading to SREBP 1c stabilization by competition of ubiquitination. In addition mouse double minute 2 (MDM2) was found to be a specific E3 ligase of SREBP 1c. Based on these result, We tested whether a NEDD8-activting enzyme inhibitor, MLN4924, had an anti-fatty liver formation. The result showed that MLN4924 had therapeutic effect of fatty liver through by decreased lipid accumulation in HFD induced obesity mouse. In addition, the decrease in fat accumulation in liver is because MLN4924 reduced the expression of SREBP 1c. When the neddylation process was blocked by NEDD8-targeting siRNAs, transcriptional activity of SREBP 1c was substantially reduced in HepG2 cells. Based on these result, Our study demonstrates that neddylation of SREBP 1c is essential for fatty liver formation and provides a new strategy for the treatment of fatty liver through MLN4924.

Keywords: Neddylation, Obesity, NAFLD, Transcription factor, SREBP 1c

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Comparative Effects of Angiotensin A and Alamandine on Cardiac Functions and ANP Secretion in Rats

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Angiotensin (Ang) A was first identified in human plasma and it differs from Ang II in Ala(1) instead of Asp(1). The aim of this study is to investigate whether Angiotensin A (Ang A) has an effect on ischemia-reperfusion (I/R) injury in Langendorff hearts. After sacrificing Sprague-Dawley rats, the hearts were perfused with Krebs-Henseleit buffer for a 20 min pre-ischemic period with and without Ang A followed by 20 min global ischemia and 50 min reperfusion. Pretreatment with Ang A for 2 hr before ischemia showed deleterious effects on post-ischemic left ventricular end-diastolic pressure (LVEDP) and post-ischemic left ventricular developed pressure (LVDP) induced by reperfusion compared to untreated hearts. Ang A also increased infarct size and lactate dehydrogenase levels in effluent, and decreased coronary flow during reperfusion. In contrast, alamandine caused improvement of reperfusion-induced cardiac functions and infarct size via MrgD receptor and Ang II type 2 receptor (AT2R). Interestingly, both Ang A and Alamandine stimulated high stretch-induced ANP secretion from isolated perfused beating atria. The stimulatory effect of ANP secretion by alamandine was completely blocked by the pretreatment with MrgD receptor blocker and partially blocked by AT2R antagonist but not by AT1R antagonist or Mas receptor blocker. The stimulatory effect of Ang A was partially blocked by the pretreatment with AT1R and AT2R antagonists. Alamandine can be generated both from the "deleterious" Ang A as well as from the "protective" Ang-(1-7). This pathway modulates peripheral and central blood pressure regulation and cardiovascular remodeling. Further research will elucidate its interactions in cardiovascular pathophysiology and its possible therapeutic implications.

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Keywords: Alamandine, Angiotensin A, Ischemia, Reperfusion, Atrial natriuretic peptide, MrgD receptor

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Augmentation of Sodium Hydrosulfide-induced ANP Secretion During Hypoxia via K_{ATP} Channel Pathway

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Hypoxia is a common disorder which is induced by deficient oxygen supply or insufficient blood distribution. In hypoxic condition, ATP sensitive potassium (K_{ATP}) channel is overexpressed as compensatory effects. Recently, we reported that sodium hydrosulfide (NaHS) stimulated high stretch induced-atrial natriuretic peptide (ANP) secretion partially via K_{ATP} channel. However, whether H2S affects ANP secretion during hypoxia remains obscure. The purpose of the present study is to discover the impact of NaHS on ANP secretion in hypoxia and to unravel its signaling pathway. Isolated beating rat left atria were used for perfusion. After 80 min stabilization, atrial perfusate was collected for ANP measurement. 10 minutes later, 100% O_2 supply was changed to different condition (50% O_2 + 50% N_2, 21% O_2 + 78% N_2, and 100% N_2). The ANP secretion was increased from 19.57% to 17.07%, 54.27% and 588.26% in terms of increasing N_2 concentration. Exogenous application of 50 μM NaHS had no effects on ANP secretion in 100% O_2 condition whereas the ANP secretion was increased by 50 μM NaHS in hypoxia condition, especially in 21% O_2 + 78% N_2 (240.62 ± 30.01% vs 54.27 ± 6.46%). Therefore, this protocol was chosen for further researches. Pretreatment of K_{ATP} channel blocker (glibenclamide) blocked NaHS induced ANP secretion. Interestingly, K_{ATP} channel activator (pinacidil) enhanced NaHS induced ANP secretion during hypoxia. These results suggest that NaHS stimulated ANP secretion in hypoxic condition at least partly through K_{ATP} channel. The possible mechanisms are being investigated.

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Keywords: NaHS; atrial natriuretic peptide; hypoxia; K_{ATP} channel

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Isocitrate Dehydrogenase 2 Mediated Mitophagy by mtUPR in Endothelial Cells

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Aim: Mitochondrial dysfunction is a risk factor for vascular disease by overexpressing ROS caused by some stimuli in mitochondria which causes oxidative stress and enhances vascular inflammatory response. Isocitrate dehydrogenase 2 (IDH2) is $NADP^+$ dependent mitochondrial enzyme and an antioxidant enzyme that produces NADPH in the antioxidant system. Mitophagy and mitochondrial Unfolding Protein Response (mtUPR) are internal defense mechanism in mitochondria. In this study, we investigated whether IDH2 knockdown causes mitochondrial dysfunction then Mitophagy and mtUPR *in vitro* in HUVECs and *in vivo* in IDH2 knock out mice. **Results:** We showed that knockdown of IDH2 expression induced depolarization of mitochondrial membrane potential (MMP). Mitochondrial dynamics is mitochondrial fusion and fission. Knockdown of IDH2 increased Drp1 (fission protein) and mfn1 (fusion protein) compared with Tom20 (control). IDH2 deficiency increase Mitophagy related protein PINK-1 and Parkin expression and mRNA level (PINK-1, Parkin, BNIP3, NIX, FUNDC-1). Moreover, knockdown of IDH2 induced mtUPR mRNA level (USP30, Clpp) *in vitro*. In addition, IDH2 deficiency increases mtUPR mRNA level and decreases PINK-1 and Parkin protein expression *in vivo*. **Conclusion:** Our data show that IDH2 deficiency induces mitochondrial dysfunction and then Mitophagy and mtUPR expression in endothelial cells. These findings provide novel strategy for the development of therapeutic agents for restoring mitochondrial and endothelial function.

Keywords: IDH2, Mitochondria, Mitophagy, mtUPR, Endothelial cells

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The Role of RhoGDI2 in Cell Migration of CR6- Interacting Factor 1 Deficient HUVECs

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Aims: The Rho GDP-dissociation inhibitor (RhoGDI), a downregulator of Rho family GTPases is typified by its ability to prevent nucleotide exchange and membrane association. Although RhoGDI2 has been identified as a tumor suppressor gene for cellular migration and invasion, little is known about its role in endothelial cell migration. In this study, we examined the expression of RhoGDI2 in CR6-interacting factor 1 (CRIF1) deficient human umbilical vein endothelial cells (HUVECs) and its role in cell migration. **Results:** We found that the expression of RhoGDI2 was considerably increased and therefore, cell migration was decreased in CRIF1 deficient HUVECs. Furthermore, the phosphorylation of MAP Kinases ERK and JNK were found to be increased whereas; phosphorylation of Akt was decreased in CRIF1 deficient cells. To further investigate the molecular mechanism of RhoGDI2-induced cellular migration, HUVECs were transfected with RhoGDI2 small interfering RNA (siRNA). The results showed that depletion of RhoGDI2 significantly recovered cell motility and phosphorylation of Akt. We also examined the effect of CRIF1 downregulation on other major proteins involved in endothelial cell migration. **Conclusion:** The results in our study demonstrate for the first time that RhoGDI2 plays an important role in cell migration of CRIF1 deficient endothelial cells. We also uncovered the possible proteins and pathways involved in this process.

Keywords: RhoGDI2, CRIF1, cell migration, MAPK, Akt

▶▶▶ P-123

Nitric Oxide Modulates Stability of Lipocalin-2 Protein under Inflammatory Condition in RINm5F Beta Cells

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We previously reported that proinflammatory cytokines (interleukin-1β and interferon-γ) induced the expression of lipocalin-2 (LCN-2) together with inducible nitric oxide synthase (iNOS) in RINm5F beta-cells. Therefore, we examined the effect of nitric oxide (NO) on LCN-2 expression in cytokines-treated RINm5F beta-cells. Additionally, we observed the effect of LCN-2 on cell viability. First, we found the existence of LCN-2 receptor and the internalization of exogenous recombinant LCN-2 peptide in RINm5F and INS-1 beta-cells. Next, the effects of NO on LCN-2 expression were evaluated. Aminoguanidine, an iNOS inhibitor and iNOS gene silencing significantly inhibited cytokines-induced LCN-2 expression while sodium nitroprusside (SNP), an NO donor potentiated it. Luciferase reporter assay showed that transcription factor NF-κB was not involved in LCN-2 expression. Both LCN-2 mRNA and protein stability assays were conducted. SNP did not affect LCN-2 mRNA stability, however, it significantly reduced LCN-2 protein degradation. The LCN-2 protein degradation was significantly attenuated by MG132, a proteasome inhibitor. Finally, the effect of LCN-2 on cell viability was evaluated. LCN-2 peptide treatment and LCN-2 overexpression significantly reduced cell viability. FACS analysis showed that LCN-2 induced the apoptosis of the cells. Collectively, NO level affects LCN-2 expression via regulation of LCN-2 protein stability under inflammatory condition and LCN-2 may reduce beta-cell viability by promoting apoptosis.

Keywords: Lipocalin-2, Nitric Oxide, Interleukin-1β, Interferon-γ, RINm5F cells

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STIM2 and STIM1 Have Similarities and Differences, but Both Regulate Ca^{2+} Movement in Skeletal Muscle

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Stromal interaction molecule 1 (STIM1) along with Orai1 mediates extracellular Ca^{2+} entry into the cytosol through a store-operated Ca^{2+} entry (SOCE) mechanism in various tissues including skeletal muscle. However, the role(s) of STIM2, a homolog of STIM1, in skeletal muscle has not been well addressed. The present study, first, was focused on searching for STIM2-binding proteins from among proteins mediating skeletal muscle functions. This study used a binding assay, quadrupole time-of-flight mass spectrometry, and co-immunoprecipitation assay with bona-fide STIM2- and SERCA1a-expressing rabbit skeletal muscle. The region for amino acids from 453 to 729 of STIM2 binds to sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase 1a (SERCA1a). Next, oxalate-supported $^{45}Ca^{2+}$-uptake experiments and various single-myotube Ca^{2+} imaging experiments using STIM2-knockdown mouse primary skeletal myotubes have suggested that STIM2 attenuates SERCA1a activity during skeletal muscle contraction, which contributes to the intracellular Ca^{2+} distribution between the cytosol and the SR at rest. In addition, STIM2 regulates Ca^{2+} movement through RyR1 during skeletal muscle contraction as well as SOCE. Therefore, via regulation of SERCA1a activity, STIM2 regulates both intracellular Ca^{2+} distribution and Ca^{2+} movement in skeletal muscle, which makes it both similar to, yet different from, STIM1.

Keywords: STIM, SERCA1a, cytosolic Ca^{2+} level, SR, SOCE

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Regulation of Slow Delayed Rectifier K^+ Current by Protein Arginine Methyltransferase 1

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Arginine methylation is one of the most important post-translational modifications. It is mediated by protein arginine methyltransferases (PRMTs). In mammals, nine PRMTs have been characterized. PRMT1, originally identified as a histone H4 methyltransferases, methylates many non-histone proteins and it is implicated in diverse cellular processes. However, there is little information on the effects of PRMT1 on ion channel function and membrane excitability. In this study, we demonstrate that PRMT1 regulates the slow delayed rectifier K current (IKs) channel via PIP_2 affinity control. The IKs channel is mainly formed by KCNQ1, a pore-forming α-subunit and *KCNE1*, *an* auxiliary subunit. PRMT1 inhibition with furamidine, a PRMT1 specific inhibitor decreases KCNQ1/KCNE1 channel activity in HEK 293T cells. The decrease of KCNQ1/KCNE1 channel activities are recovered by exogenous PIP_2 addition. The mechanistic study suggests that KCNE1 might be a target for PRMT1 modulation.

Keywords: PRMT1, KCNQ1, KCNE1, PIP_2, methylation

▶▶▶ P-126

Effect of Carbon Monoxide on Ca^{2+}-activated K^+ currents of Human Cardiac Fibroblasts through the Protein Kinase Pathways

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Cardiac fibroblasts (CFs) are the major cell type that involved in regulating the extracellular matrix in the heart and play an important role in cardiac remodeling after myocardial infarction or in response to hemodynamic overload. Ca^{2+}-activated K^+ (K_{Ca}) channels play a role in the proliferation of the fibroblasts which may play a role in cardiac remodeling. Carbon Monoxide (CO) was shown to exert a variety of pharmacological effects including cardioprotective properties. However, its mechanisms of action are not completely understood. We investigated the effect of CO on K_{Ca} channels and the mechanism in human cardiac fibroblasts (HCFs). In whole-cell mode patch clamping, application CO delivery by carbon monoxide-releasing molecule 2 (CORM-2) increased the amplitude of K_{Ca} currents. Carbon monoxide-releasing molecule 3 (CORM-3) also stimulated the K_{Ca} currents. The CORM-2 or CORM-3 stimulating effect on K_{Ca} currents were blocked by pretreatment with KT5823 (a protein kinase G inhibitor) or 1 H-[1,-2, -4] oxadiazolo-[4,-3-a] quinoxalin-1-one (ODQ; a soluble guanylate cyclase inhibitor). Additionally, pretreatment with KT5720 (a protein kinase A inhibitor) and SQ22536 (an adenylyl cyclase inhibitor) blocked the CORM-2 or CORM-3 stimulating effect on the currents. These data suggest that CO enhances K_{Ca} currents in HCFs through the PKG and PKA pathways.

Keywords: Ca^{2+}-activated K^+ currents, Carbon Monoxide, Human Cardiac Fibroblast, PKA, PKG

▶▶▶ P-127

Effects of Nitric Oxide on L-Type Voltage-gated Ca^{2+} Currents of Human Cardiac Fibroblasts

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Human cardiac fibroblasts (HCFs) represent the most numerous cell type in heart and play an important role in cardiac function and diseases, including arrhythmogenesis. Nitric oxide (NO) has emerged as an important signaling molecule in the regulation of physiological and pathophysiological processes in heart. The purpose of the present study is to know the effects of NO on Voltage-gated Ca^{2+} channels and underlying signaling pathways in HCFs. We found various subtypes of the channels; L-type, N-type, R-type and T-type in the cells by RT-PCR. In whole cell mode patch-clamp recordings, nifedipine sensitive L-type Ca^{2+} currents ($I_{Ca,L}$) and mibefradil sensitive T-type Ca^{2+} currents ($I_{Ca,T}$) were recorded. S-nitroso-N-acetylpenicillamine (SNAP; an NO donor) inhibited the $I_{Ca,L}$ but not $I_{Ca,T}$. Pretreatment of 1H-[1,2,4]Oxadiazolo[4,3-a]quinoxalin-1-one (ODQ, a soluble guanylate cyclase blocker) or KT5823 (a PKG blocker) blocked the inhibitory effect of SNAP on $I_{Ca,L}$. 8-bromo-cGMP (a membrane-permeable cGMP analogue) also decreased the currents. However, pretreatment of N-ethylmaleimide (NEM; a thiol-alkylating reagent) could not block the SNAP effect on $I_{Ca,L}$. In addition, DL-dithiothreitol (DTT; a reducing agent) could not reverse the SNAP inhibition on $I_{Ca,L}$. The pretreatment of KT5720 (a PKA blocker) and SQ22536 (an adenylyl cyclase inhibitor) also inhibited the SNAP inhibiting effect on $I_{Ca,L}$. 8-Br-cAMP also decreased the $I_{Ca,L}$. Our data suggest that NO inhibited $I_{Ca,L}$ in HCFs through the PKG and PKA pathways but not S-nitrosylation.

Keywords: Human Cardiac Fibroblast, L-type Voltage-gated Ca^{2+} currents, Nitric Oxide

▶▶▶ P-128

Effects of Polychlorinated Biphenyl 77 on Kv1.3 Channel

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Polychlorinated biphenyls (PCBs) are a family of bicyclic chlorinated aromatic hydrocarbons. PCBs' unique chemical properties and the low cost of producing PCBs have contributed to their extensive industrial use. PCBs are detected in air, water, sediments, fish, and wild life and human adipose tissue, milk, and serum. Acute and long-term exposure to the compounds has been known to causes diseases such as developmental delays and motor dysfunction. The presence of PCBs in the environment presents various toxic effects in vivo and *in vitro*. But the mechanism is not yet fully understood. One immune-modulating mechanism is achieved by the Kv1.3 voltage-dependent potassium channel, which is expressed highly in lymphocytes including effector memory T lymphocytes. Here we studied the effect of 3,3′,4,4′-tetrachlorobiphenyl (PCB 77) on human Kv1.3 channels expressed in *Xenopus* oocytes. When we exposed the oocytes with PCB77 for 8 min, the peak current of Kv1.3 decreased by 12%. The 15-minute exposure to PCB77 also reduced the peak current by 15%. PCB77 inhibited the amplitude of the peak Kv1.3 channel current in a concentration-dependent manner. These results suggest the possibility that PCB77 could inhibit the immune mechanism by suppressing the current of the Kv1.3 channel.

Keywords: Polychlorinated biphenyls, PCBs, PCB77, Kv1.3

▶▶▶ P-129

Anoctamin1 Does Not Function as Ion Channel in Head and Neck Squamous Cell Carcinoma Due to Lack of Surface Expression

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Anoctamin1 (ANO1) gene (*TMEM16A*) encodes a calcium-activated chloride channel (CaCC) in various epithelial cells, and its role has also attracted attention in cancer research. In several tumors including head and neck squamous cell carcinoma (HNSCC), the expression of ANO1 is significantly amplified, and the ANO1 knock-down reduces cell migration and/or proliferation. However, the electrophysiological role of ANO1 in the tumor biology is still unclear. Here, we detected a highly over-expressed ANO1 in HNSCC patients and significant correlation between the expression level of ANO1 and prognosis by analyzing TCGA database. We further measure the current of ANO1 (I_{ANO1}) in three type of HNSCC, breast cancer (BCa), and prostate cancer (PCa) cell lines using whole-cell patch clamp. I_{ANO1} was detected in BCa and PCa, while not in any HNSCC cell line. Confocal imaging and immunoblot analysis of HNSCCs revealed no significant expression of ANO1 in the plasma membrane despite the high cytosol expression. In contrast, BCa and PCa cells show unequivocal membrane expression, consistent with the I_{ANO1} recordings. Moreover, in the present of ANO1-specific inhibitors, the migration and proliferation of cancer cell was reduced only in BCa and PCa cell lines with the surface expresses ANO1. Taken together, our results suggest that ANO1 does not function as ion channel in HNSCC due to the lack of surface expression. The surface expression of ANO1 is a prerequisite for the modulation of cancer cell proliferation and migration by the ANO1 channel inhibitor.

Keywords: ANO1, TMEM16A, Head and neck squamous cell carcinoma, Surface expression

▶▶▶ P-130

The Cellular Chloride Channels CLIC1 Inhibition Enhances Ca^{2+} and Reactive Oxygen Species Signaling in A549 Human Lung Cancer Cells

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Chloride channels are reported to be participated in tumor development and progression. Among the class of chloride ionic channels, intracellular chloride channels (CLICs) are related to the cancer development. Patients with CLIC1-positive tumors had worse overall survival than those with CLIC1-negative tumors. Furthermore, the treatment of pancreatic cancer cell lines with CLIC1-targeting siRNA oligonucleotides significantly reduced cell proliferation and diminished anchorage-independent growth on both soft agar and cell migration. It is known that CLIC1 is mainly existed in the cytosol but transiently expressed in the cell membrane during oxidative stress conditions. Given that the fluctuation in the cellular redox state could play a central role in regulating progression from G0/G1 to S to G2 and M cell cycle phases, CLIC1 might be hyperactivated in cancer cells which are in a highly proliferative state. Many ion channels at the cell surface and intracellular organelles are regulated by redox modifications. In turn, channel activation directly or indirectly changes Ca^{2+} signaling, which can influence the cellular generation of reactive oxygen species (ROS). Both Ca^{2+} and ROS are important mediators of cell death. However, the role of CLIC1 in Ca^{2+} and ROS signaling in cancer cells remain unclear. In this study, we investigated its function in Ca^{2+} and ROS signaling of A549 human lung cancer cells. The intracellular Ca^{2+} measurement revealed that basal Ca^{2+} level is significantly increased in CLIC1 knockdown A549 cells compared to control cells. CLIC1 knockdown also enhanced Ca^{2+} signaling in A549 cells in response to putative anticancer agent chelerythrine. In addition, CLIC1 knockdown greatly increased basal ROS level which is prevented by BAPTA-AM, the intracellular calcium chelator. These data suggest that CLIC1 might contribute to cancer cell survival via modulation intracellular Ca^{2+} and ROS signaling.

Keywords: CLIC1, ROS, Calcium, Cell survival, A549 Human Lung Cancer Cells

▶▶▶ P-131

Effects of Alprenolol on Kv1.3 Channel

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Alprenolol is one of the adrenergic beta-antagonists used as an antihypertensive, anti-anginal, and anti-arrhythmic agent. Alprenolol non-selectively blocks beta-1 adrenergic receptors mainly in the heart, inhibiting the effects of epinephrine and norepinephrine resulting in a decrease in heart rate and blood pressure. The Kv1.3 voltage-dependent K^+ channel is highly expressed in lymphocytes and is involved in the immune response. However, it has not been known whether alprenolol has a rapid effect on the function of Kv1.3 channel. We examined the effect of alprenolol on the human Kv1.3 channel using a *Xenopus* oocyte expression system and a two-microelectrode voltage clamp technique. Alprenolol reduced or increased the amplitude of the Kv1.3 channel current according to the concentration of the drug. At 1 - 100 μM of alprenolol, relatively lower concentration, the drug increased the amplitude of the Kv1.3 channel current and decreased at 300 - 1000 μM, higher concentration. These results suggested that alprenolol changed Kv1.3 currents via a non-genomic mechanism. These effects might provide an electrophysiological mechanism for alprenolol' s immunosuppressive effects, probably by altering the properties of Kv1.3 channels.

Keywords: Alprenolol, Kv1.3 channel, non-genomic

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Effects of Paroxetine on Kv1.3 Channel

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Paroxetine is the most potent inhibitor of the reuptake of serotonin of all selective serotonin reuptake inhibitors. One immune-modulating mechanism is achieved by the Kv1.3 voltage-dependent potassium channel, which is expressed highly in lymphocytes including effector memory T lymphocytes. Here we studied the rapid effects of paroxetine on the human Kv1.3 channel expressed in *Xenopus* oocytes. Paroxetine reduced the amplitude of the Kv1.3 channel current in a concentration-dependent manner. Paroxetine rapidly and reversibly inhibited Kv1.3 currents, eliminating the possibility of genomic regulation. Inhibition rate was dependent on the degree of depolarization. Kinetically, paroxetine interacted with this channel in an open state. These results suggest that paroxetine inhibit Kv1.3 currents via a non-genomic mechanism, providing a mechanism for the immunosuppressive effects of paroxetine.

Keywords: Paroxetine, Kv1.3 channel, *Xenopus* oocytes

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Effects of Carteolol on hERG Current and Cardiac Action Potential

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Carteolol is a non-selective beta blocker used to treat glaucoma. We studied the effects of carteolol on a human K^+ channel, human *ether-a-go-go*-related gene (hERG), expressed in *Xenopus* oocytes and on action potential of guinea pig ventricular myocytes. The hERG encodes the pore-forming subunits of the rapidly-activating delayed rectifier K^+ channel in the heart. Mutations in hERG reduce I_{Kr} and cause type 2 long QT syndrome, a disorder that predisposes individuals to life-threatening arrhythmias. Carteolol increased hERG current amplitude at the end of the voltage steps and hERG tail currents in a concentration-dependent manner. Carteolol did not change the value of $V_{1/2}$ for activation curve of hERG tail current, indicating the drug did not affect activation gating. In guinea pig ventricular myocytes, carteolol did not change the action potential amplitude and the resting membrane potential, however, the drug increased the action potential duration (APD_{90}, APD_{50}, APD_{20}), showing that carteolol could cause arrhythmogenic effects in cardiac function.

Keywords: hERG channel; LQT; carteolol; action potential

▶▶▶ P-134

Effects of Pindolol on hERG Current and Cardiac Action Potential

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Pindolol is a beta blocker which is used in the treatment of hypertension and angina pectoris. We studied the effects of pindolol on a human K^+ channel, human *ether-a-go-go*-related gene (hERG), expressed in *Xenopus* oocytes and on action potential of guinea pig ventricular myocytes. The hERG encodes the pore-forming subunits of the rapidly-activating delayed rectifier K^+ channel, which has an important role in regulation of action potential duration of cardiac ventricle, resulting in changes in ECG wave. Pindolol decreased hERG current amplitude at the end of the voltage steps and hERG tail currents only at 1000 μM, the highest concentration we tested. Pindolol did not change the value of $V_{1/2}$ for activation curve of hERG tail current, indicating the drug did not affect activation gating. In guinea pig ventricular myocytes, pindolol did not change the resting membrane potential, however, the drug increased the action potential amplitude, action potential duration (APD_{90}, APD_{50}, APD_{20}), suggesting that pindolol could affect cardiac electrophysiology, particularly in overdose condition.

Keywords: hERG channel; LQT; pindolol; action potential

▶▶▶ P-135

Effects of Acebutolol on Action Potential in Guinea Pig Ventricular Myocytes and hERG K^+ Current

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K^+ channels are key components of the primary and secondary basolateral Cl^- pump systems, which are important for secretion from the salivary glands. Acebutolol is a cardioselective beta blocker with ISA (intrinsic sympathomimetic activity). We studied the effects of acebutolol on a human K^+ channel, human *ether-a-go-go*-related gene (hERG), expressed in *Xenopus* oocytes and on action potential of guinea pig ventricular myocytes. The hERG encodes the pore-forming subunits of the rapidly-activating delayed rectifier K^+ channel in the heart. Mutations in hERG reduce I_{Kr} and cause type 2 long QT syndrome, a disorder that predisposes individuals to life-threatening arrhythmias. Acebutolol decreased hERG current amplitude at the end of the voltage steps, however, the drug failed to induce a concentration-dependent changes hERG tail currents. Acebutolol did not change the value of $V_{1/2}$ for activation curve of hERG tail current, indicating the drug did not affect activation gating. In guinea pig ventricular myocytes, acebutolol did not change the resting membrane potential, however, the drug increased the action potential amplitude, action potential duration (APD_{90}, APD_{20}), showing that acebutolol could change cardiac electrophysiology function.

Keywords: hERG channel; LQT; acebutolol; action potential

▶▶▶ P-136

The role of CACC and ENaC in Epithelial Barrier Disruption During Bacterial Infection

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The Gram-negative bacterial lipopolysaccharide (LPS), increases the susceptibility of cells to pathogenic disease including inflammation and autoimmune disease. To date, LPS has been reported to perturb intracellular cell signaling related to epithelial barrier, calcium signals and ion transports. Meanwhile, Calcium activated chloride channel (CACC) and epithelial sodium channel (ENaC) play a key role in exocrine secretion. However, the pathogenic role of CACC and ENaC in LPS treated epithelial cells has not been fully examined. In this present study, we determined whether LPS evokes the activities of ion channels. We further investigated the effect of CACC and ENaC on LPS induced disruption of epithelial barrier function. The immortalized rat submandibular acinar cell lines, SMGC6, have been used. The activities of CACC and ENaC were monitored by short circuit current (Isc) in Ussing chamber. Epithelial membrane integrity was estimated via transepithelial electrical resistance (TER) and transwell permeability assay with FITC-dextran. Apical application of LPS increased a short circuit current, demonstrating transient inward current. The effect of LPS on Isc was nearly abolished by treatment of ENaC and CACC inhibitors, whereas basolateral administration of other inhibitors of NKCC and N+K+ATPase had no effect on the Isc. These results validated LPS alternatively increases activation of CACC and ENaC. LPS also impaired cellular barrier function; increased permeability; and downregulated Zo-1 due to depolarization induced tyrosine phosphorylation. Inhibitors of ENaC and CACC attenuated the effect of LPS on TER, permeability and Zo-1 expression suggesting that activation of ENaC and CACC is responsible for the epithelial barrier disruption. Furthermore, LAL endotoxin assay showed that the impairment of epithelial barriers by LPS increased susceptibility to secondary bacterial infections but was rescued in the presence of CACC and ENaC inhibitors. To conclude, CACC and ENaC regulate epithelial barrier function by bacterial infection.

Keywords: CACC, ENaC, LPS, Epithelial barrier, Zo-1

▶▶▶ P-137

High Glucose Increases Aβ, Production through Endosomal Traffic Jams in Neuronal Cells: Involvement of CHC/AP2A1/PICALM-and mTOR-Pathway

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Growing evidence supports that diabetes mellitus (DM) is the important risk factors for Alzheimer's disease (AD). Many researchers have demonstrated that the increment of residence time of Amyloid precursor protein (APP) at endosome is critical for Aβ production. However, detail mechanism how DM regulates Aβ processing is still unclear. Therefore, this study investigated the effect of high glucose on the Aβ producing endosome. Our results using STZ-induced diabetic mouse, showed that DM upregulated Aβ secretion and activation of endosome. In *In vitro* results with mouse hippocampal neuron and SK-N-MC, high glucose increased Aβ production and enlargement of endosome which were reversed by silencing Rab5a, early endosomal protein. High glucose increased clathrin mediated APP endocytosis which is crucial for endosomal enlargement proved by pretreatment of dynasore(endocytosis inhibitor) that reversing the effect of high glucose on endosome. In addition, high glucose increased endocytosis related proteins, Phosphatidylinositol binding clathrin assembly protein (PICALM) which recruits clathrin chain and AP-2. And, silencing of it inhibited APP endocytosis. In addition, high glucose decreased endosomal clearance through inhibition of fusion with autophagosome by mTORC1 activation. And, high glucose induced enlarged endosome and increased Aβ secretion were reversed by pretreatment of rapamycin, mTOR inhibitor. In conclusion, high glucose induces endosomal traffic jams through CHC/AP2A1/PICALM-induced endocytosis and mTOR-inhibited endosomal clearance, upregulating Aβ production.

Keywords: Diabetes mellitus, Amyloid beta, Endosomal traffic jams

▶▶▶ P-138

Best-1 Mediated GABA Release from Reactive Astrocytes Sustain Tonic Inhibition in Epileptic Hippocampus

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Bestrophin 1 (Best-1), a ca^{++} activated anion channel that displayed a significant permeability to GABA. GABA may release from astrocyte in brain but functional significance of astrocytic GABA release in not well demonstrated. Here we show that GABA released from reactive astrocyte via Best-1 anion channels generates tonic GABAA inhibition (I_{tonic}), thus established the neuronal circuit in epileptic hippocampus. 3 days after Kainic acid (KA) -induced epileptic model mice, engendered tonic GABA inhibition in CA1 pyramidal neurons that was sensitive to both NPPB (5-nitro-2(3-phenyl-propylamine benzoic acid), a Cl^- channel antagonist and BIC (Bicuculline): a $GABA_A$ receptors antagonist in wild type (WT) mice but not in Best-1 knockout (KO) mice. KA injection increased GABA in reactive astrocyte in both WT and Best-1 KO mice but did not affect $GABA_A$ receptors in CA1 neurons. In addition, GABA transporter (GAT) blocker potentiated I_{tonic} in normal hippocampus, which was facilitated by kA injection only in WT. In an agreement, KA significantly increased seizure activity and sensitivity to electrical stimuli in Best-1 KO mice compared WT. Furthermore, astrocyte specific best-1 rescue in KO mice efficiently restored enhanced I_{tonic} and supressed seizure susceptibility as well. Taken together our result showed that Best-1 channel-mediated astrocytic GABA release maintain tonic inhibition in epileptic hippocampus.

Keywords: hippocampus, bestrophin-1, reactive astrocytes, $GABA_A$ receptor, epilepsy

▶▶▶ P-139

Glucocorticoid-mediated Aβ, and SCG10 Upregulation Promotes Microtubule Destabilization and Memory Impairment: Involvement of ER-Mitochondria Interaction

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Microtubule dysfunction has been reported as the early pathological feature that culminates in memory deficits and Alzheimer's disease. Even though stress is a major risk factor of Alzheimer' disease, the mechanism of how stress triggers the Alzheimer's disease pathogenesis through altering microtubule networks still remains elusive. Therefore, we investigated that the glucocorticoid promoted microtubule instability and following cognitive impairment using 7-week-old male ICR mice (seventy two subjects) and human neuroblastoma SH-SY5Y cells to suggest a new therapeutic avenue of Alzheimer's disease. The mice group exposed to corticosteroid had reduced trafficking of AMPAR1/2 and mitochondria into the synapse due to microtubule destabilization, which finally impaired cognitive function. Furthermore, cortisol reduced microtubule stability through the mitochondria glucocorticoid receptor-dependent pathway in SH-SY5Y cells. Cortisol translocated the Hsp70-bound glucocorticoid receptor into mitochondria before stimulating ER-mitochondria interaction via increasing glucocorticoid receptor-Bcl-2 interaction and mfn2-PACS2 ligation. Subsequently, Aβ, which is attributed to microtubule destabilization, was produced since γ-secretase activity was upregulated by increased ER-mitochondria connectivity. Mitochondrial Ca^{2+} influx was also elevated due to IP3R-VDAC1 bridging which localizes in ER-mitochondria contact sites, resulting in AMPK dephosphorylation and subsequent activation of mTOR pathway. With upregulated mTOR phosphorylation, the autophagy inhibition failed to remove Aβ and led to its accumulation. Moreover, selective autophagy through ubiquitination of SCG10 to maintain the microtubule dynamics was also suppressed exerting SCG10 upregulation. We therefore showed that both elevated Aβ and SCG10 levels drive cells to fail trafficking AMPAR1/2 and mitochondria into the cell terminus, leading to cell apoptosis in both *in vitro* and *in vivo* models. Finally, mice exposed to pretreatment of paclitaxel showed restored translocation of AMPAR1/2 or mitochondria into synapses and improved memory function. In conclusion, glucocorticoid regulates ER-mitochondria coupling, which evokes Aβ accumulation and SCG10 upregulation. This eventually leads to microtubule destabilization and memory impairments.

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Extra-synaptic NMDA Receptors Antagonist Ameliorates Gait Deficits in MPTP-induced Parkinson's Model Mice

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Parkinson's disease (PD) is a major neurodegenerative disorder characterized by resting tremors, rigidity, slowness of movement and postural instability. Progressive loss of dopaminergic neurons in substantia nigra pars compacta (SNpc) hampered rhythmical walking in PD patients. It has been reported that gait readouts such as walking duration, step cycle, duty cycle, stance and cadence reflects PD behaviours and loss of dopaminergic neurons in SNpc. Here we confirmed MPTP mouse models mimic many aspects of PD by using computer-assisted CatWalk tests. In MPTP model mice we observed decreased stride lengths of limbs with increased run duration and cadence (step/s) was dropped significantly with compared to control. Also, swing speed of paws was decreased markedly whereas stance, duty cycles and step cycles of paw increased substantially suggesting MPTP model mice spend more time to change their paws during walking, results in slowness of movement. Furthermore we evaluate pain perception in MPTP model mice, we observed increased paw withdrawal frequency and also confirmed that increased pain is not a case for the slowness of movement. Numerous efforts had done to improve gait deficits in PD, we investigate the effect of extrasynaptic NMDA receptor's (eNMDAR) antagonist memantine on walking behaviours in MPTP induced PD model mice. Here, our result suggest that eNMDAR antagonist memantine ameliorates gait deficits in MPTP induced PD model mice.

Keywords: Catwalk, gait, MPTP, memantine, Parkinson's disease

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The Effect of Early Social Experience on Social Functions

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It has been well known that social experiences in early life cause lifelong permanent changes in cognitive functions. Previous studies showed that social isolation in the critical period (postnatal 21-35 day) alters social preference and medial prefrontal cortical (mPFC) functions of mice. However, it still remains unclear how other aspects of social functions or brain regions other than mPFC could be affected by early social experience. Here, we found that mice socially isolated in their early life show permanently the significant impairment in social recognition memory with normal object recognition memory. Our results support the hypothesis that early social experience can affect postnatal neuro-developments and normal social functions.

Keywords: Social experience, Sociability, Memory, Neuro-development

▶▶▶ P-142

Gonadotropin Releasing Hormone (GnRH) Neurons Experience less Glutamate Receptor-Mediated Excitation than Non-GnRH Neurons of Preoptic Area in Immature Mice

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The gonadotropin releasing hormone (GnRH) neurons found in the hypothalamic preoptic area (POA) are considered as the final output of the central nervous system that controls reproductive physiology and behavior in vertebrates. Many studies suggest that glutamate excites the GnRH neurons through glutamatergic innervation or regulatory neuronal subsets to stimulate the GnRH secretion required for the puberty. In addition, ionotropic glutamate receptors are found to be expressed on GnRH neurons to different extents. However, it has not been well studied the glutamate-mediated responses on immature GnRH neurons. In this study, we compared ionotropic glutamate receptor-mediated responses between GnRH neurons and non-GnRH neurons of POA in immature mice using brain slice patch clamp. Ionotropic glutamate receptor agonists including kainate, AMPA and NMDA were bath applied to both GnRH neurons and non-GnRH neurons and membrane current changes were compared between GnRH and non-GnRH neurons. All non-GnRH neurons tested were highly responded to bath application of kainate, NMDA and NMDA. All GnRH neurons tested were responded to kainate and NMDA but only 60% of GnRH neurons tested were responded to AMPA. The kainate-mediated inward currents on GnRH neurons were about half those of non-GnRH neurons. The responses to AMPA and NMDA on GnRH neurons were less than a tenth those of non-GnRH neurons. These result indicates that GnRH neurons are less affected by glutamate neurotransmission compared to surrounding non-GnRH neurons in POA in immature mice. This research was supported by Basic Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2016R1D1A3B03932241) and (2015R1C1A1A02036793).

Keywords: GnRH neurons, Patch clamp, Glutamate neurotransmission, immature mice

▶▶▶ P-143

Geraniol Activates GABA and/or Glycine Receptors on the Substantia Gelatinosa Neurons of the Trigeminal Subnucleus Caudalis in Mice

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The trigeminal subnucleus caudalis (Vc) is one of the principal relay sites for orofacial nociceptive information and the substantia gelatinosa (SG) neuron of the Vc receives Aδ- and C-primary afferent inputs and plays a key role in the processing and transmission of nociceptive information to the higher brain center. Geraniol is a monoterpenoid alcohol that is common constituent of several essential oils such as wild bergamot, palmarosa, citronella and geranium. In recent studies, geraniol showed neuroprotective, antinociceptive and antiinflammatory activities in animal models. However, the receptor types activated by geraniol and its precise action mechanisms on the SG neuron of the Vc have not been elucidated. So, in this study, we investigated the effects of geraniol on the SG neurons of the Vc using the whole cell patch clamp technique. Bath application of geraniol (1 mM) repeatedly induced inward currents without desensitization on all neurons tested in the condition of high chloride pipette solution. Further, geraniol-induced inward currents were sustained in the presence of tetrodotoxin (0.5 μM). In addition, geraniol-induced inward currents were significantly reduced in the presence of both picrotoxin (50 μM), a $GABA_A$ receptor antagonist and strychnine (2 μM), a glycine receptor antagonist but not affected by ionotropic glutamate receptor antagonists, CNQX (10 μM) and AP5 (20 μM). These results indicate that geraniol has inhibitory effects on the SG neurons of the Vc, which are due to the activation of $GABA_A$ and/or the glycine receptor and suggest that geraniol might be a potential therapeutic drug for orofacial pain modulation. This research was supported by Basic Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2016R1D1A3B03932241) and (2015R1C1A1A02036793).

Keywords: Geraniol, Substantia gelatinaosa, Whole cell patch clamp, GABA, Glycine

▶▶▶ P-144

Serotonin Increases Inhibitory Synaptic Transmission through Glycinergic and GABAergic Receptors in the Substantia Gelatinosa Geurons of Medullary Dorsal Horn

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The substantia gelatinosa (SG, lamina II) of the medullary dorsal horn (MDH) has been considered a critical region in the processing and modulation of orofacial nociceptive inputs conveyed to the higher brain centers. The serotonergic pathway originating from the rostroventral medulla plays a major role in the descending modulation of nociception in the MDH. 5-HT-containing axons are numerous in the superficial laminae, especially SG, and the 5-HT receptors are found at pre- or postsynaptic locus of SG neurons in the medullary or spinal dorsal horn. In the present study, we investigated the role of 5-HT on synaptic transmission in SG neurons of the MDH using whole-cell patch clamp technique in immature mice. Bath application of 5-HT (3 or 10 ㎛M) significantly increased the frequency, but not amplitude, of spontaneous postsynaptic currents (sPSCs). 5-HT-induced increase of sPSCs frequency was abolished by pretreatment of 2 ㎛M strychnine and 50 ㎛M picrotoxin, but not by pretreatment of 10 ㎛M CNQX and 20 ㎛M AP5. Significant increase in 5-HT-induced frequency of sPSCs was not observed in the presence of 2 ㎛M strychnine, 50 ?M picrotoxin, and 10 ㎛M gabazine, respectively. These results indicate that application of 5-HT significantly increased the frequency of inhibitory sPSCs through glycine and GABA release and suggest that inhibitory control by 5-HT is involved in the modulation of orofacial nociceptive processing in SG neurons of the MDH. This research was supported by the Basic Science Research program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2015R1D1A3A01018700).

Keywords: Serotonin, Inhibitory spontaneous postsynaptic current, Substantia gelatinosa, Glycinergic, GABAergic

▶▶▶ P-145

Trim69 E3 Ubiquitin Ligase Regulates Neuronal Excitability by SK Channels in Hippocampal Dentate Granule Cells

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Protein modification by ubiquitin has emerged as a key regulator of neuronal activity. However, many of the ion channels targeted and the underlying molecular mechanisms involved in this process have not yet been determined. Trim69, an E3 ubiquitin ligase, is structurally and evolutionarily conserved in zebrafish, mouse, rat, and human. Although Trim69 is implicated in zebrafish neurogenesis, its role in *mammalian brain* is unclear. In this study, we investigated its function in mouse hippocampal neurons by using mice lacking Trim69 function. The expression study revealed that Trim69 is highly enriched in the hippocampus. In addition, Trim69 deficient-dentate gyrus granule cells (GCs) exhibit neuronal hyperexcitability. Based on the electrophysiological analysis, Trim69 seems to regulate neuronal activity via modulation of SK channels. The mechanistic study suggests that Trim69 is required for the modulation of SK channel activity without altering their expression levels. Our finding provides a paradigm for investigating the fine tuning of ion channel activation by protein ubiquitination, particularly in preventing neuronal hyperexcitability and seizures.

Keywords: ubiquitination, potassium channel, SK channel, hippocampus

P-146

Effect of Electrical Stimulation on Reserpine-induced Pain-Depression Dyad in Mice

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This study was designed to investigate the effect of electrical stimulation on the reserpine-induced pain and depression in mice. In order to develop pain and depression-like behavior, reserpine (RSP, 1 mg/kg) was administered subcutaneously once a day for 3 consecutive days. Electrical stimulation (2 mA, 2 Hz, 30 min) was applied into the bilateral knee area once daily for 5 days. Von Frey filament test was performed to assess pain response and depression was evaluated by forced swimming and open field test. In order to investigate the neuronal mechanism, changes of hippocampal brain derived neurotrophic factor (BDNF) was examined by western blot analysis. Reserpine evoked tactile hypersensitivity, increased immobility time of forced swimming test, and reduced moving distance in open field test. Repeated electrical stimulation significantly attenuated reserpine-induced tactile allodynia and depression-related responses. In conclusion, results of this study suggest that the peripheral electrical stimulation may be a good candidate to treat patients who have both pain and depression.

Keywords: Electrical stimulation, Reserpine, Pain, Depression

P-147

Allopregnanolone Effects on Transmission in the Brain Stem Solitary Tract Nucleus (NTS)

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During pregnancy, the progesterone metabolite, allopregnanolone (ALLO), becomes elevated and has been associated with altered levels within the CNS and resulting changes in GABAA receptor function. Pregnant animals poorly compensate reflexes for a decrease in blood pressure during hemorrhage. Previous works suggested that ALLO decreases baroreflex responses by central actions, however, the underlying mechanisms are poorly understood. In this study, we tested ALLO actions on visceral afferent synaptic transmission at second-order neurons within medial portions of the nucleus tractus solitarius (NTS) using hindbrain slices from non-pregnant female rats. Solitary tract (ST) stimulation-evoked excitatory postsynaptic currents (ST-eEPSCs) in NTS neurons directly connected to vagal afferents within the ST. ST-eEPSCs were functionally identified as monosynaptic by the latency characteristics (low jitter = standard deviation of latency, $\leq$200 μs) to ST stimulation. Such second-order neurons all displayed spontaneous inhibitory postsynaptic currents (sIPSCs), and low micromolar concentrations of ALLO increased frequency and decay time. At submicromolar concentrations, ALLO induced a tonic, GABAergic inhibitory current and suppressed ST-eEPSCs' amplitude. While GABAA receptor antagonist, bicuculline, blocked all ALLO effects, gabazine only blocked sIPSC actions. In current-clamp mode, ALLO perfusion increased failure of ST stimulation to trigger action potentials in most neurons. Thus, our results indicate that ALLO acts to suppress visceral afferent ST synaptic transmission at first synapses by activating pharmacologically distinct GABAA subtypes at different concentration ranges. This ALLO-mediated attenuated visceral afferent signal integration in NTS may underlie reflex changes in blood pressure during gestation.

Keywords: Visceral afferent synaptic transmission, Solitary tract stimulation-evoked EPSC, Second-order neuron, Extrasynaptic GABA receptors

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▶▶▶ P-148

The E3 Ligase C-CBL Inhibits Cancer Cell Migration By Neddylating the Proto-oncogene c-Src

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Neddylation is a cellular process that covalently conjugates substrate proteins with the small ubiquitin-like molecule NEDD8. As neddylation is required for fast turnover of proteins in proliferating cancer cells, the neddylation process is currently regarded as a potential target for cancer therapy. However, little is known about the role of neddylation in cancer invasion and metastasis. Unexpectedly, we here found that the neddylation blockade stimulates migration of lung cancer and glioblastoma cells. Mechanistically, C-CBL acts as the E3 ligase for neddylation of the proto-oncogene c-Src. After neddylation, c-Src is poly-ubiquitinated and degraded through the proteasome, which inhibits the PI3K-AKT pathway responsible for cell migration. In human lung cancer tissues, the down-regulation of C-CBL was associated with c-Src/AKT, cancer metastasis, and poor survival in patients. Therefore, C-CBL is likely to play a tumor suppressive role by antagonizing a robust oncogenic signaling driven by c-Src. This study provides new insight about the role of neddylation in cancer metastasis. It also implies that the metastasis risk should be carefully evaluated before the clinical application of neddylation inhibitors as anticancer regimens.

Keywords: Neddylation, c-Src, C-CBL, Cell Migration, Metastasis

▶▶▶ P-149

Hydrogen Peroxide Inhibits the Growth of Lung Cancer Cells via the Induction of Cell Death and G1 Phase Arrest

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Hydrogen peroxide (H_2O_2) is frequently applied to the cultured cells to induce oxidative stress. The current study investigated the molecular and cellular effects of exogenous H_2O_2 on Calu-6 and A549 lung cancer cells. Based on MTT assays, H_2O_2 inhibited the growth of Calu-6 and A549 cells with IC_{50} values of approximately 50 μM and 100 μM at 24 h, respectively. Cells treated with H_2O_2 showed a considerable G1 phase arrest of the cell cycle. H_2O_2 dose-dependently augmented the numbers of dead (trypan blue-positive) and annexin V-FITC-stained cells in these cells, which was accompanied by the reduction of Bcl-2 and pro-caspase-3 levels, as well as the up-regulation of caspase-3 and -8 activities. In addition, H_2O_2 also triggered the failure of mitochondrial membrane potential (MMP; $\Delta\Psi$m). However, relatively higher doses of H_2O_2 did not raise the percentages of sub-G1 cells in these cell lines. All the tested caspase inhibitors (Z-VAD for pan-caspases, Z-DEVD for caspase-3, Z-IETD for caspase-8 and Z- Z-LEHD for caspase-9) decreased the percentages of sub-G1 and annexin V-FITC-stained cells in H_2O_2-treated Calu-6 and A549 cells. However, caspase inhibitors did not significantly prevent the loss of MMP ($\Delta\Psi$m) in H_2O_2-treated lung cancer cells. In conclusion, H_2O_2 inhibited the growth of Calu-6 and A549 lung cancer cells through cell death and G1 phase arrest. H_2O_2-induced cell death resulted from necrosis as well as caspase-dependent apoptosis.

Keywords: Lung Cancer Cells; H_2O_2; Caspase Inhibitors; Cell Growth; Cell Death

▶▶▶ P-150

Inhibition of Neddylation Facilitates Cell Migration through Enhanced Phosphorylation of Caveolin-1 in PC3 and U373MG Cells

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Protein neddylation is a post-translational modification by a covalent conjugation with the neural precursor cell expressed, developmentally downregulated 8 (NEDD8). Although this process has been reported to participate in diverse cellular signaling, little is known about its role in cancer cell migration. Given a recent proteomics report showing that NEDD8 is downregulated in prostate cancer tissues versus normal prostate tissues, we tested the possibility that neddylation plays a role in cancer evolution, and then tried to identify target proteins of the neddylation. The neddylation process was inhibited by transfecting cancer cells with NEDD8-targeting siRNAs or by treating the cells with a NAE1 inhibitor MLN4924. Cell migration was evaluated by an in vitro wound-healing assay and a Transwell migration assay. His/NEDD8-conjugated proteins were pulled down with nickel-affinity beads under a denaturing condition, and identified by Western blotting. Caveolin-1, which plays a critical role in cell migration, was identified to be conjugated with NEDD8. When the neddylation was inhibited, the phosphorylation of caveolin-1 at Tyr14 was augmented in PC3 and U373MG cells, thereby leading to increased cell migration. Such consequences by neddylation inhibition were abolished in the presence of a Src family kinase inhibitor PP2. NEDD8 seems to inhibit the Src-mediated phosphorylation of caveolin-1 by modifying the structure of caveolin-1 protein, which blocks the migration of cancer cells. Although the neddylation process is currently regarded as an emerging target for cancer therapy, our results suggest the possibility that the inhibition of neddylation could facilitate cancer invasion or metastasis at least in some types of cancers.

▶▶▶ P-151

HN1 Stimulates Tumorigenesis by Promoting Lipogenesis through SREBP Signaling in Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is the fifth most common cancer and is the third leading cause of cancer death. HCC is the most common type occurring in adults, and induces greater rate of death in people with cirrhosis. Although surgical resection of HCC provides the best chance for cure, the prognosis following surgery varies considerably among different patients, and recurrence is the major drawback of potentially curative treatment. Since the hematopoietic- and neurologic-expressed sequence1 (HN1) gene is detected a high expression level in various cancers, and is identified that associates with metastatic carcinoma progression, neural development, nerve and retina regeneration, its functional significance in HCC remains unclear. Thus, we investigated the regulation of HN1 in HCC using HepG2 and SNU449 cells. Silencing of HN1 significantly diminished the viability of HCC cells whereas overexpression of HN1 stimulated the viability of HCC cells. Silencing of HN1 increased apoptotic proteins and decreased the number and size of colonies. In addition, silencing of HN1 inhibited the invasion and metastasis of HCC cells whereas overexpression of HN1 promoted the invasion and metastasis of HCC cells. In gene expression profiling, we identified 130 upregulated genes and 379 downregulated genes after HN1 silencing in HCC cells. Putative gene networks revealed suppressed expression of proteins associated with lipogenic signaling pathway. Silencing of HN1 significantly inhibited the expression levels of SREBP1 and SREBP2 of HCC cells whereas overexpression of HN1 increased the expression levels of SREBP1 and SREBP2 of HCC cells. In addition, silencing of SREBP1 also diminished the expression levels of HN1 and suppressed the survival and metastasis of HCC cells. In cholesterol assay and triglyceride assay, silencing of HN1 inhibited the lipid formation of HCC cells whereas overexpression of HN1 promoted the lipid formation of HCC cells. Taken together, HN1 encourages the proliferation, invasion and metastasis of HCC cells in part through the activation of SREBP signaling pathway. Therefore, our results suggest that targeting HN1 may constitute a potential therapeutic strategy for HCC.

Keywords: HN1, hepatocellular carcinoma cells, cell proliferation, lipogenesis, microarray

P-152

Synergistic Effect of Ursolic Acid with Paclitaxel Inhibit Proliferation of Esophageal Cancer Cells

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Ursolic acid (UA) is a 3βhydroxy-12-urs-12ene-28-oic acid and is one of the pentacyclic triterpenoids present in different plants, herbs, and fruits. Extensive research has been conducted over the last few decades to clarify the role of UA in various cancers. Despite the fact that paclitaxel is widely used as chemotherapy agents against several types of cancer, their combined effects with natural compound on esophageal squamous cell carcinoma have never been fully elucidated. Therefore, we explored the effects of UA as well as its combination treatment with paclitaxel in ESCC cells by using TE-12 and TE-8 cell lines. UA plus paclitaxel treatment inhibited the proliferation of TE-12 cells and TE-8 cells in a dose-dependent manner when compared to treatment with UA or paclitaxel alone. In colony formation assay, UA potentiated the inhibition of colony formation by paclitaxel when compared to treatment with a single agent. Combination treatment substantially induced apoptosis as indicated by increased levels of cleaved polyADP-ribose polymerase (PARP) and cleaved caspase-9 protein. UA plus paclitaxel treatment significantly inhibited the invasion and metastasis of TE-12 and TE-8 cells. In addition, combination treatment increased the protein levels of p-Akt and decreased FOXM1 in ESCC cells. These results suggest that UA effectively potentiates the efficacy of chemotherapeutic agents such as paclitaxel via inhibition of proliferation and metastasis by inactivation of FOXM1 in ESCC cells. Taken together, UA enhances the therapeutic efficacy of paclitaxel in esophageal cancer and is a potential clinical anticancer agent for the prevention and/or treatment of esophageal cancer.

Keywords: ursolic acid, esophageal squamous cell carcinoma, apoptosis, FOXM1

P-153

Panobinostat Dimishes Metastasis and Invasion of Gastric Cancer Cells

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Panobinostat (LBH-589) is a hydroxamic acid, acts as a non-selective histone deacetylase inhibitor (HDAC inhibitor) and is an experimental drug developed by Novartis for the treatment of various cancers. Gastric cancer is the fourth most common cancer and the second leading cause of cancer-related deaths worldwide. Despite the significant progress made in gastric cancer chemotherapy, advanced disease remains largely incurable and novel efficacious chemotherapies are urgently needed. The purpose of this study was to identify genes in gastric cancer cells that are differentially regulated by panobinostat to provide the functional role of HDAC inhibition in gastric cancer. Pnobinostat significantly inhibited the proliferation of SNU484 cells in a dose-dependent manner and resulted in a significant inhibition of colony formation in SNU484 cells. Panobinostat significantly increased apoptosis as indicated by cleaved poly (ADP-ribose) polymerase (PARP) and cleaved caspase-9 and diminished caspase-3 protein levels in SNU484 cells. Statistical analyses of gene expression data from panobinostat treated cells revealed that 2814 genes were significantly upregulated, while 1788 genes were down-regulated in SNU484 cells. Putative canonical pathways showed that ATM signaling and G2/M DNA damage checkpoint genes were significantly altered by panobinostat treatment. Therefore, our present study shows that panobinostat inhibits proliferation of gastric cancer cells by induce cell apoptosis through G2/M cell cycle DNA damage regulation.

Keywords: Panobinostat, Gastric cancer cells, Apoptosis, Gene expression profiling, Cell cycle

P-154

Downregulation of HN1 Induced Alteration of Cell Growth and Autophagy in Colorectal Cancer

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Colorectal cancer has a high mortality rate among cancers worldwide and the incidence of colorectal cancer is increasing dramatically in Asian countries including South Korea. Previous studies demonstrated that the hematopoietic- and neurologic-expressed sequence 1 (HN1) is strongly associated with survival of cancer patients and its depletion leads to cell cycle arrest in several cancer cells. Although it has been reported that HN1 is overexpressed in various cancers, the specific functional significance of HN1 in colorectal cancer cells remains largely unknown. In our present study, we investigated the underlying molecular mechanisms by which HN1 regulates proliferation, metastasis and autophagy in colorectal cancer cells. In addition, knockdown of HN1 significantly decreased the viability of colorectal cancer cells. Knockdown of HN1 inhibited the invasion and metastasis of colorectal cancer cells. Moreover, downregulation of HN1 induced autophagy. Loss of HN1 decreased the expression of p62, whereas the LC3 II expression was increased. Therefore, our results suggest that HN1 regulates growth, metastasis, and autophagy of colorectal cancer cells and targeting HN1 may constitute a therapeutic strategy for colorectal cancer.

Keywords: Colorectal cancer, HN1, Proliferation, Metastasis, Autophagy

P-155

Valproic Acid Induces Caspase-dependent Apoptosis and GSH Depletion in Calu-6 Lung Cancer Cells

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Valproic acid (VPA) as a histone deacetylase (HDAC) inhibitor has various cellular effects such as differentiation and apoptosis. In the present study, we evaluated the effects of VPA on the growth and death of Calu-6 lung cancer cells. VPA inhibited the growth of Calu-6 cells with an IC_{50} of approximately 3 mM at 72 hours in a dose-dependent manner. DNA flow cytometric analysis indicated that VPA induced a G2/M phase arrest of the cell cycle. This agent also induced apoptosis, as evidenced by sub-G1 cells and annexin V-FITC staining cells. VPA-induced apoptosis was accompanied by the loss of mitochondrial membrane potential (MMP; $\Delta\Psi$m), PARP-1 cleavage, Bax increase, and the activation of caspase-3. All of the tested caspase inhibitors prevented Calu-6 cell death induced by VPA. VPA increased intracellular reactive oxygen species (ROS) levels and induced glutathione (GSH) depletion in Calu-6 cells. Generally, caspase inhibitors did not affect ROS levels in VPA-treated Calu-6 cells, but they significantly prevent GSH depletion in these cells. Furthermore, while the well-known antioxidant, N-acetyl cysteine (NAC) did not affect cell death, ROS level or GSH depletion, L-buthionine sulfoximine (BSO), a GSH synthesis inhibitor, enhanced cell death and GSH depletion in these cells. In conclusion, VPA inhibited the growth of Calu-6 lung cancer cells via caspase-dependent apoptosis, and the inhibition is dependent on GSH level changes.

Keywords: Valproic acid; Apoptosis; Calu-6; Caspase; Glutathione

▶▶▶ P-156

Combined Anti-cancer Effects of Arsenic trioxide and Valproic acid in Human Large Cell Lung Cancer Cells

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Valproic acid (VPA) is known for histone deacetylase inhibitor (HDACi). VPA shows anti-cancer effects on various cancer cells. Arsenic trioxide (ATO; As_2O_3) is a therapeutic drug clinically being used for relapsed or refractory acute promyelocytic leukemia (APL) patients. Recently, combinations of ATO and other anti-cancer drugs have been explored in various cancer types. However, little is known about the combined cellular effects of ATO and valproic acid (VPA) in lung cancer cells. Herein, we investigated the synergistic cell death effects of ATO and VPA in large cell lung cancer (LCLC) cell lines (NCI-H460 and NCI-H1299). ATO dose-dependently inhibited the growth of NCI-H460 and NCI-H1299 cells with an IC_{50} of 9 - 10 μM and 3 - 4 μM at 72 h, respectively. Based on MTT assays, combined treatment of ATO and VPA showed a synergistic effect on cell growth inhibition in NCI-H460 and NCI-H1299 cells at 72 h. VPA increased the percentages of sub-G1 cells and annexin V-FITC positive cells in ATO-treated NCI-H1299 cells, which were accompanied by the loss of mitochondrial membrane potential (MMP; $\Delta\Psi$m). The increase of intracellular ROS levels was detected when NCI-H460 cells were treated with ATO and VPA. In the nude mouse xenograft model, the combined treatment of ATO and VPA significantly reduced the tumor size of NCI-H460 xenograft mouse. In conclusion, co-treatment with ATO and VPA has a synergistic cell death effect in NCI-H460 and NCI-H1299 cells.

Keywords: Arsenic trioxide; Valproic acid; Large cell lung cancer; cell death

▶▶▶ P-157

Loss of CR6 Interacting Factor 1 Exerts Anticancer Effects by Inducing Mitochondrial Dysfunction and Inhibiting Pentose Phosphate Pathway in Breast Cancer

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Background: Mitochondria are the main organelles for energy production and metabolism, and mitochondria in cancer cells have a unique metabolic feature, which plays an important role in the regulation of cancer cell growth and proliferation. For these reasons, mitochondria can be exploited as a target for anti-cancer therapeutic intervention. Downregulation of CR6 interacting factor 1 (CRIF1), an essential mitoribosomal factor involved in the biogenesis of mitochondrial oxidative phosphorylation (OXPHOS) complexes, was previously shown to impair mitochondrial function in endothelial cells. **Aim:** In this study, we investigated whether CRIF1 deficiency had an effect on suppressing breast cancer growth and tumor development. **Results:** Our results showed that downregulation of CRIF1 suppressed cell proliferation and inhibited cell migration in both MCF-7 and BT-549 breast cancer cells. Moreover, the silence of CRIF1 decreased mitochondrial OXPHOS complex Ⅰ, Ⅱ assembly, induced production of reactive oxygen species, and hyperpolarized the mitochondrial membrane potential. TP53-induced glycolysis and apoptosis regulator (TIGAR) is an inhibitor of glycolysis and promoter of pentose phosphate pathway (PPP), which has a high expression in human breast cancers. To define the impact of CRIF1 silence on glycolysis and the PPP, we detected the expression of TP53 and TIGAR in breast cancers. CRIF1 downregulation regulated glycolytic activity via suppression of TP53 and TIGAR with reduced NADPH synthesis. Furthermore, the inhibition of CRIF1 reduced HIF-1α stabilization under hypoxia condition in breast cancer cells. **Conclusion:** Taken together, silenced CRIF1 suppressed breast cancer cells survival via destroying mitochondrial function and inhibiting TIGAR-regulated PPP metabolic pathway.

Keywords: CR6 interacting factor 1, Mitochondrial dysfunction, Breast cancer, TIGAR

▶▶▶ P-158

The Role of Sirt5 in Preventing TNF-α-induced Mesenchymal Stem Cell Senescence and Lipid Droplet Formation

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Umbilical cord blood derived mesenchymal stem cells (UCB-MSCs) have therapeutic potential for the treatment of immune-mediated adverse reactions. Despite the therapeutic effects of UCB-MSCs on inflammatory diseases, it has not been fully elucidated the direct effect of proinflammatory cytokines on free fatty acid synthesis and lipid accumulation resulting in UCB-MSC senescence. We investigated the involvement of sirtuins in balancing of lipid metabolism and rescuing senescence of UCB-MSCs in inflammatory environment. TNF-α, a major proinflammatory cytokine, reduced the expression of Sirt5, a mitochondrial sirtuin having demalonylase and desuccinylase activity, and knockdown of Sirt5 expression promoted TNF-α-induced UCB-MSC senescence. Moreover, UCB-MSCs exposed to TNF-α have shown that increased lipid droplet formation and up-regulated *SCD1*, *FAS* and *DGAT2* mRNA expression levels. Subsequently, TNF-α stimulated the nuclear translocation of SREBP1, a major transcriptional regulator of lipid metabolism. Inhibition of NF-?B signaling by Bay 11-7082 attenuated the TNF-α-mediated lipid droplet accumulation and UCB-MSC senescence, which was also prevented by fatostatin, a SREBP inactivator. Whereas TNF-α-reduced Sirt5 expression hindered both demalonylation of CPT1 and desuccinylation of CPT2 which is crucial step for the entry of long-chain fatty acyl CoA into the mitochondria. Furthermore, overexpression of Sirt5 prevented the TNF-α-induced lipid droplet accumulation and UCB-MSC senescence with increase of fatty acid oxidation. In conclusion, TNF-α-mediated senescence of UCB-MSCs is aggravated by lipid accumulation with reduction of fatty acid oxidation through NF-κB signaling pathway dependent DGAT2 expression and loss of Sirt5-induced demalonylation of CPT1 and desuccinylation of CPT2. These results indicate that therapeutic effects of UCB-MSCs can be improved by maintaining Sirt5 expression level in the stem cell therapy of immune-mediated inflammatory diseases.

Keywords: Umbilical cord blood derived mesenchymal stem cells, Sirt5, Inflammation, Senescence, Lipid droplet

▶▶▶ P-159

Novel Role of Bicaudal D Homolog 1 as a HIF1α Nuclear Transport Modulator in Human Mesenchymal Stem Cells under Hypoxia

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Hypoxia-inducible factor 1α (HIF1α) is a master regulator leading to hypoxia adaptation, an essential physiological process to maintain stemness and survival of stem cells. However, it has been poorly understood that how HIF1α translocate into nucleus in stem cells under hypoxia. Here, we investigated the role of a motor adaptor protein Bicaudal D homolog 1 (BICD1) in the dynein-mediated nuclear translocation of HIF1α, and determined the effect of BICD1 regulation on hypoxia reprogramming and therapeutic efficiency of hypoxia-pretreated human umbilical cord blood-derived mesenchymal stem cells (UCB-MSCs). We firstly showed that hypoxia-induced nuclear translocation of HIF1α was inhibited by microtubule destabilizer or cytosolic dynein inhibitor pretreatment. Transfection of *BICD1* siRNA but not *BICD2* siRNA abolished HIF1α nuclear translocation and activity. And, BICD1 overexpression further enhanced hypoxia-induced HIF1α nuclear translocation. Moreover, hypoxia stimulates direct bindings of HIF1α to *BICD1* and intermediate chain of dynein (Dynein IC), abolished by *BICD1* siRNA transfection. Akt inhibitor reduced the binding of HIF1α to *BICD1* and nuclear translocation of HIF1α. Conversely, Akt activator pretreatment or *GSK3β* siRNA transfection further enhanced hypoxia-induced nuclear translocation of HIF1α. Hypoxia increased mRNA expressions of HIF1α-targeted glycolysis enzymes, hexokinase activity, lactate production and intracellular alkalization, reversed by *BICD1* siRNA transfection. In the mouse skin wound healing model, transplanted cell survival and skin wound healing capacities of hypoxia-pretreated UCB-MSCs were reduced by *BICD1* siRNA transfection, and further increased by *GSK3β* siRNA transfection. In conclusion, BICD1-mediated HIF1α nuclear translocation enhances hypoxia adaptation and regenerative potential of UCB-MSCs.

Keywords: Bicaudal D homolog 1 (BICD1), Hypoxia, Hypoxia-inducible factor 1α (HIF-1α), Umbilical cord blood-derived human mesenchymal stem cells (UCB-hMSCs)

▶▶▶ P-160

Protective effect of 17β-Estradiol on High Glucose-induced Mitochondrial Reactive Oxygen Species through ERα-dependent Sirt3 and Nrf2 Expression in Human Umbilical Cord Blood-Derived Mesenchymal Stem Cells

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17β-estradiol (E2) has protective roles in mitochondrial dysfunction and damage during oxidative stress. Diabetes is closely related to oxidative stress and the risk of diabetes is high in postmenopausal women who are deficient in E2, but the exact mechanism is not clear. Therefore, the present study investigated the role of E2 in mitochondrial reactive oxygen species (mtROS)-induced autophagic cell death under high glucose conditions with regard to the tissue regeneration in postmenopausal diabetic mice. We found that high glucose (D-glucose, 25 mM) induces the autophagic cell death. High glucose-reduced cell viability was restored following transfection of siRNA against *Atg5*, autophagy-related gene to form autophagosome. On the other hand, E2 enhances autophagy-related proteins and cell viability under high glucose conditions. High glucose significantly elevated mtROS levels which was blocked by treatment with MitoTempo, a mitochondrial-targeted exogenous antioxidant. Subsequently, high glucose-induced mtROS production were reversed by E2 treatment with high glucose. We also found that MnSOD silencing was increased ROS production under high glucose conditions. Additionally, MnSOD acetylation was increased and Sirt3 was decreased by high glucose. Sirt3 silencing induces MnSOD acetylation, suggesting MnSOD activation is modulated by Sirt3. E2 facilitates estrogen receptor alpha (ERα) translocation to nuclear under high glucose conditions. ERα was in high abundance in the nuclear by E2-pretreated high glucose compared to control or high glucose only, but not as much as E2 alone. Sirt3 expression was induced via ERα and E2 increased Sirt3 expression and SOD activation, confirming the protective role of E2 on Sirt3-induced increased MnSOD activation through ERα in hUCB-MSCs. We also found that high glucose decreased nuclear Nrf2 while Keap1 was increased by high glucose. In contrast, nuclear Nrf2 was increased by E2 through ER α under high glucose conditions. Moreover, *Nrf2* siRNA-transfected cells were abolished Sirt3 expression. In postmenopausal diabetic mouse model, therapeutic effect of UCB-MSCs transplantation on skin-wound healing was significantly enhanced by E2 treatment. In addition, blood vessels were well developed in postmenopausal diabetic mice with hUCB-MSC engraftment. In conclusion, our results imply that E2 leads to the protective effect on mtROS production under high glucose conditions through ERα-dependent Sirt3 and Nrf2 expression in hUCB-MSCs.

Keywords: 17β-Estradiol; Estrogen receptor alpha; High glucose; Autophagic cell death; mtROS

▶▶▶ P-161

Effect of Histone Deacetylase Inhibitors on the Neurogenic Differentiation of Human Mesenchymal Stem Cells

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Histone deacetylase (HDAC) inhibitor has potential effects on cell homeostasis, cell cycle progression, and can act to promote self-renewal and enhance directed differentiation of several lineages of stem cells. However, the roles and mechanisms of HDAC inhibitors on neurogenic differentiation with a Wnt signaling have not yet been completely elucidated in stem cells. We hypothesized that the HDAC inhibitors including MS-275, sodium butyrate (NaB), trichostatin A (TSA), or valproic acid (VPA) regulate downstream Wnt signaling and control stem cell maintenance and neurogenic differentiation. We have investigated the effect of HDAC inhibitors on neurogenic differentiation of human mesenchymal stem cells (hMSCs), adipose tissue-derived stem cells and bone marrow-derived mesenchymal stem cells, using RT-PCR, western blot, and immunocytochemistry. Following neurogenic induction with basic fibroblast growth factor and forskolin hMSCs were differentiated into neuronal cells in vitro. The increase in the number of neurites and neural lineage specific markers was increased when MS-275, NaB, TSA, or VPA incorporated in the medium. The expression of neurofilament-L (NFL) and neurofilament-M (NFM) were highly increased in HDACi treatment compared control medium by RT-PCR. The expression of Wnt1, Wnt2, and LRP5/6, which are canonical Wnt and Wnt ligands, in hMSCs treated with VPA was significantly greater compared to that of control medium. However, the expression of Wnt5 and Fzd4 were increased with MS-275, NaB or TSA in the medium. There were no changes in the expression of b-catenin and GSK-3b. Furthermore, we found that the JNK expression was increased after NaB or TSA treatment. In conclusion, these findings indicated that HDACi could induce neurogenic differentiation of MSCs by activating canonical Wnt or non-canonical Wnt signaling pathway.

Keywords: Histone deacetylase inhibitor; Neurogenic differentiation; Mesenchymal stem cell; Wnt

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Effects of PCB77 and PCB126 on PKC Activation in Ventricular Myocytes

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Polychlorinated biphenyls (PCBs) have been known as serious persistent organic pollutants (POPs), causing developmental delays and motor dysfunction. PCBs have 208 possible congeners and we investigated the effects of two congeners, 3,3′,4,4′-tetrachlorobiphenyl (PCB 77) and 3,3′,4,4′,5-pentachlorobiphenyl (PCB 126). We observed the phosphorylation of protein kinase C (PKC) with signal transduction, cell growth, gene expression, and tumor promoter function by western blotting. We treated ventricular myocytes from guinea pig with 0.1 ~ 100 μM of PCB77 and PCB126 for 15 ~ 60 min. The phosphorylation of PKC $\alpha\beta$II decreased significantly by 40% at 0.1 μM of PCB77 and decreased by 20% at 1 μM of PCB126. As for PKC γ, PCB 77 increased the phosphorylation of the PKC subtype by 20% at 1 ~ 100 μM, however, PCB 126 decreased the phosphorylation. In addition, phosphorylation of PKC ε decreased by 15% at 0.1 μM PCB77 and by 40% at 10 μM PCB 77. However, PCB126 did not change the phosphorylation of PKC ε at all concentrations of we tested. Phosphorylation of PKC ζ decreased by 40% by 0.1 μM PCB 77. The present data indicate that PCBs, the environmental toxicants, can acutely affect activation of PKC, resulting in toxic effects on the cardiac function in view of the possible accumulation of the PCBs in human body.

Keywords: Polychlorinated biphenyls, PCBs, Protein kinase C, PKC

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The Inhibitory Effects of Pulsed Radiofrequency (RF) Stimulation on Acute Knee Joint Pain in Rats

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Osteoarthritic pain has been managed with invasive treatment such as pharmacological drugs and surgery. Radiofrequency (RF) can be an alternative non-invasive treatment for attenuating pain. We investigated whether pulsed RF application was effective in relieving acute knee joint pain. Under 1 to 2% isofluorane anesthesia, we injected carrageenan (1%, 50 μl/200 g) into the knee joint space to induce arthritis in 7 weeks male SD rats, and then applied 4.4 MHz RF (HIPER-500, JS-ON company, South Korea) on the left knee joint by placing the electrode perpendicularly to the shaved left knee joint. We used a pulsed time cycle of 3 sec (on)/ 3 sec (off) for 20 min. On 4 h after the induction of arthritis, we stimulated RF and measured consecutively dynamic weight load of left limb before and 4, 6, 7, 8, and 24 h after carrageenan injection. In addition, we performed western blotting of COX2 and IL1β 4, 6, and 8 h after carrageenan injection. We found that pulse radiofrequency stimulation significantly reversed the reduction of dynamic weight load, or relieve the pain, 6, 7 and 8 h after carrageen injection, and for western blot this stimulation significantly decreased COX2 and IL1β 6 and 8 h after carrageen injection. Our results indicate that pulsed RF stimulation applied to inflamed knee joint is effective to decrease inflammatory cytokines and pain.

Keywords: pulsed radiofrequency stimulation, non-invasive, acute arthritis, cytokine, weight load

▶▶▶ P-164

In Vitro and *in Vivo* Anti-inflammatory Action of Anthocyanin-Rich Extract from Red Chinese Cabbage

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Anthocyanins are an important subfamily of flavonoids, which are abundant in flowers, fruits, seeds and plant leaves. Anthocyanins have a broad spectrum of biomedical functions, including improving immune responses and reducing risk for chronic diseases. In this study, the anti-inflammatory activities of anthocyanin-rich extract from red Chinese cabbage (ArCC) (18% cyanidin) were demonstrated based on inhibitory effects on cultured endothelial cells and on hyperlipidemic apolipoprotein E-deficient ($ApoE^{-/-}$) mice. ArCC treatment suppressed the expression and transcription of adhesion molecules in tumor necrosis factor-α-stimulated endothelial cells. ArCC significantly inhibited aortic inflammation in hyperlipidemic $ApoE^{-/-}$ mice. The aortas from these mice exhibited markedly lower leukocyte infiltration, lower concentrations of blood inflammatory cytokines, and reduced plaque formation than those from control mice did. We demonstrate for the first time that ArCC suppresses aortic vascular inflammation, using *in vivo* imaging, most likely by inhibiting expression of adhesion molecules and inflammatory cytokines. These data may contribute to the development of a promising natural approach in chronic inflammatory diseases management.

Keywords: Anthocyanin-rich red Chinese cabbage; Apolipoprotein E-deficient mice; In vivo imaging; Vascular cellular adhesion molecule; Vascular inflammation

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Crif1 Deficiency Inhibits the Invasive Growth of Keloid Fibroblasts via TGF/SMAD Signaling Pathway

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A keloid is an abnormal proliferation tissue in excessive response to damaged skin tissue, which appears in the wound healing process. Keloid fibroblasts(KF) are the main cells that induce keloid disease. The migration of KF may play an important role in infiltrating abnormal tissue and forming keloid tissue, but the mechanism has not been elucidated. In this study, we investigated whether CR6-interacting factor 1(CRIF1) deficiency-induced mitochondrial dysfunction had an effect on cell migration, proliferation and extra cellular matrix synthesis in human primary KF. Our results revealed that downregulation of CRIF1 reduced cell migration, cell proliferation and extracellular matrix synthesis in KF compared with SiControl cells. TGF/SMAD pathway-related proteins play the main role in synthesizing extracellular matrix. Western blot data showed that CRIF1 deficiency downregulated SMAD2 and SMAD3 by increasing the inhibitory SMAD protein(SMAD7 andSMURF2) in KF compared with SiControl cells. Our results proved that crif1 knockdown-induced mitochondrial dysfunction decreased cell migration, cell proliferation, extracellular matrix synthesis, which that CRIF1 may be used as a therapeutic target protein in the treatment of keloid diseased.

Keywords: Keloid, Keloid Fibroblast, CRIF1, SMAD

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Activation of $P2Y_2R$ by Extracellular ATP Induces OxLDL-mediated Mitochondrial Damage and Inflammasome Activation in Endothelial Cells

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Inflamm-aging is suggested as a persistent, chronic and low-grade inflammation-related aging process and closely associated with many diseases including atherosclerosis. Recently, it has been reported that mitochondrial damage, inflammasome activation and the resultant secreted IL-1β are directly involved in the development of atherogenesis. In addition, we previously reported that endothelial cells (ECs) exposed to oxLDL released ATP and activated $P2Y_2R$, resulting in the expression of RAGE and adhesion molecules which are involved in pathogenesis of atherosclerosis. Therefore, it is expected that $P2Y_2R$ activation by ATP released in the inflammatory condition may be linked to the inflammasome-mediated pathogenesis in atherosclerosis. However, it is not well known yet. Thus, in this study, we investigated the role of $P2Y_2R$ in the oxLDL-mediated inflammasome activation and the related atherosclerotic pathogenesis in ECs. Oxidized LDL-treated ECs increased intracellular ATP level as well as secretion of ATP into extracellular medium. In addition, caspase-1 activity and IL-1β secretion were increased in ECs stimulated with oxLDL or ATP. Moreover, oxLDL or ATP treatment induced mitochondrial damage as measured by mtDNA expression and release in ECs. Oxidized LDL- or ATP-induced mtDNA expression and release were inhibited by apyrase, caspase-1 inhibitor and knock-down of $P2Y_2R$, suggesting that ATP released from oxLDL-treated ECs is involved in activation of inflammasome and the resulting in mitochondrial damage through $P2Y_2R$ activation. Furthermore, oxLDL or ATP-mediated mtDNA release activated toll-like receptor 9-NF-κB pathway, which was partially linked to IL-1β secretion. Finally, oxLDL or ATP-mediated IL-1β secretion was downregulated by mtDNA and caspase-1 inhibition as well as $P2Y_2R$ siRNA. Taken together, our results suggest that $P2Y_2R$ activation by ATP is involved in the oxLDL-mediated mitochondrial damage in endothelial cells through inflammasome activation.

Keywords: Inflamm-aging, Mitochondrial damage, $P2Y_2$ Receptor, Inflammasome, Atherosclerosis

▶▶▶ P-167

Cysteine Export Triggers Copper-dependent Cell Death

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It has been known that high concentration of cysteine in culture medium induces cell death, in which hydrogen peroxide generated from metal-catalyzed cysteine oxidation is involved. Meanwhile, numerous recent reports showed that a proportion of intracellular cysteine, obtained mainly through uptake of cystine, the oxidized form of cysteine, is exported out of the cell. This phenomenon is often termed the "cysteine-cystine cycle". We observed, in cultured H9c2 cardiac myoblast cells, that incubation in Krebs-Henseleit physiologic solution (KH) containing 0.2 mM cystine induced profound cell death within 24 hours. Parallel cells incubated in cystine-free KH showed no significant cell death. During incubation in cystine-containing KH, the thiol concentration in the medium increased to reach a plateau in 4 hours and decreased gradually thereafter. As expected, inhibition of cystine uptake or cysteine release attenuated cell death. Addition of bathocuproine sulfonate, a copper-specific chelator, prevented cell death while deferoxamine, an iron chelator, was not effective. Comparing parallel cells incubated in full DMEM medium and investigating the effects of medium components, we found that glutamine efficiently prevented cell damage triggered by cysteine export. However, pre-incubation in glutamine-containing medium was not protective against the cell damage during subsequent exposure to glutamine-free cystine-containing KH, implying the extracellular action of glutamine. We speculated that one of the physiological functions of extracellular glutamine, the concentration of which is the highest among plasma amino acids and maintained by export from muscle tissues, might be the prevention of the damage associated with copper-catalyzed cysteine oxidation.

Keywords: Cysteine Export, Cysteine Oxidation, Copper, Glutamine, Cell Death

▶▶▶ P-168

Plant Lignan A from Natural Product Could Sensitize TRAIL Resistance in TRAIL-Resistant Glioblastoma Cells

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Tumor Necrosis Factor related apoptosis-inducing ligand (TRAIL) has been considered as a promising anti-cancer agent due to its advantage in selective cytotoxicity in cancer cells, but not in normal cells. However, the occurrence of resistance to TRAIL is the current main obstacle of TRAIL therapy. Therefore, the discovery of a therapeutic approach module that would eradicate the tumor cell without the restoration of resistance is an important challenge in the field of oncology. To identify a substance that would overcome the resistance to TRAIL-induced apoptosis, the single constituents of natural product were screened, and it was found that the plant lignan A could induce cell death upon TRAIL treatment in several TRAIL-resistant glioblastoma cells. Pretreatment with the lignan A drastically enhanced LN428 cells to TRAIL-mediated apoptosis in a caspase-dependent manner. Such TRAIL sensitization of lignan A was found to be achieved through the downregulated expression, but not mRNA levels, of the anti-apoptotic proteins, c-FLIP and survivin. Especially, downregulation of c-FLIP levels accelerates Death Inducing Signaling Complex (DISC) formation in LN428 cells. Consistently, when c-FLIP overexpressing cells were treated with lignan A followed by TRAIL, the percentage of cell death was significantly reduced than cells transfected with mock vector. In addition, *in vitro* translation analysis showed that the lignan A was able to suppress the protein synthesis with mammalian cell extracts in a dose-dependent manner in the same with cycloheximide. These data suggest that the down-regulation of c-FLIP by the lignan A is closely associated with its inhibitory effect on the protein synthesis machinery, and thus enhancing death receptor-mediated apoptosis in certain types of TRAIL-resistant cancer cells.

Keywords: TRAIL Sensitization, Natural Product, c-FLIP, Protein Synthesis

▶▶▶ P-169

Cyclic Hexapeptides from Rubiaceae Prevents Inflammatory Responses in Rheumatoid Fibroblast-like Synoviocytes

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Background: Rheumatoid arthritis (RA) is a chronic inflammatory disease by autoimmune disorder that primarily affects joints. Various anti-TNF-α therapy should be lead to substantial functional improvement in RA patients. **Objectives:** We studied the isolated two polypeptides (Rp53, Rp54) from *Rubia philippinensis*, about anti-inflammation effects in fibroblast-like synoviocytes (FLS) derived from patients with RA. **Methods:** The effects of polypeptides on anti-inflammation were measured by cytokine assay kits (TNFα, IL-6, IL-8). The underlying for NF-κB signaling pathway was examined by western blot and NF-kB reporter activity. We examined the effect of Rp53 on the formation of the TNFR1 signaling complex, recruitment of TRADD, RIP in response to TNF by immunoprecipitation experiments. To determine whether Rp53 induced TNF receptor 1 shedding were exposed to these compounds for 1 h, and then culture media and cell lysates were analyzed by Western blotting. **Results:** Pretreatment with Rp53 resulted in a remarkable decrease of the secretion of TNF-induced proinflammatory cytokines TNFα, IL-8 and IL-6 in RA -FLS. Rp53 strongly inhibited the nuclear factor kB (NF-κB) signaling pathway induced by TNFα. Analysis of the upstream signaling events affected by Rp53 revealed that it strikingly inhibited the TNF-induced recruitment of TNFR1-associated death domain protein (TRADD) and receptor-interacting protein (RIP) to TNFR1. Rp53 reduced the interaction with TNFR1 to TNF cytokines and enhanced the activation of the p38 mitogen-activated protein (MAP) kinase. Rp53, the polypeptides induced the proteolytic cleavage of TNF-R1 and its release into the culture medium by shedding of TNF receptor 1 ectodomain by TNF-α-converting enzyme (TACE). Along with the TACE inhibitor TAPI-2, the p38 kinase inhibitor SB203580 suppressed the ectodomain shedding of TNF receptor 1 induced by Rp53. **Conclusions:** Rp53 induces the TACE-dependent ectodomain shedding of TNF receptor 1 through the activation of p38 MAP kinase, and thereby inhibits the TNFα induced NF-κB signaling pathway in RA-FLS cells.

Keywords: Polypeptides, Anti-inflammation, TNFR1 shedding, P38, RA-FLS

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The Significance of Non-Drug Factors Involved in Drug Responses

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The main foundation of drug therapy is to observe the change of drug responses by drug-related factors such as the pharmacokinetic/pharmacodynamic (PKPD) principles. Pharmacotherapeutic approaches using the PKPD principles, which are scientific and biomedical models, have many advantages such as quantification, prediction, or control of variable drug responses. Non-drug factors, which have not been sufficiently dealt with, are also involved with the variability of drug responses. This study aims therefore to manifest non-drug factors to aid better fine tuning of pharmacotherapy. Currently proposed types of non-drug factors are 1) drug treating process element (medication errors, compliance issues, etc.), 2) individual human element (mental factors like experiences, memory, etc.), 3) societal or cultural element, 4) environmental element, 5) measurement or analysis factor, etc. These non-drug factors are so far poorly investigated and characterized, rendering it more difficult to predict or control the efficacy and safety effectively. Mutual influences between drug-related PKPD factors and non-drug factors affect variously therapeutic responses, adverse drug responses, toxicities, resistances, sensitivities, cost-effectiveness, and etc. In addition to placebo or nocebo effect as one of important psychological factors, proposed mental factors of patients, medical personnel, and societies are expectation, satisfaction, misconception, fear, and etc. The scientific model like PKPD principles has its limit in full explanation for various drug responses. Optimal drug therapy involved with several types of non-drug factors is a complex process of various combinations of drugs, humans, environments, and etc. It is therefore suggested that comprehensive or integrative approaches including philosophical reflection are requested for more optimized and improved drug treatment.

Keywords: Non-drug factors, Variable drug responses

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Coumarins from *Paramignyatrimera* Prevents Inflammatory Responses in Raw264.7 Macrophages

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Paramignyatrimera is well known as a medicinal plant used to treat a various disease in Vietman. Pharmacological studies have identified that *P. trimera* has antioxidant activity and cytotoxic effects to several cancer cell lines. This study investigated chemical constituents of the *P. trimera* stems and roots about anti-inflammatory effects. We identified 10 compounds from *P. trimera* and screened for the capability to block the NF-kB activity in Raw264.7 macrophage cell lines. PT-9 and PT-10 dramatically have the effects of inhibition in NO secretion to stimulation of LPS in Raw264.7 cell lines and efficiently inhibited LPS-induced expression of proinflammatory mediators including iNOS and COX-2. Inhibitory effects of compounds (20 μM) on iNOS and COX-2 protein expression were evaluated by RT-PCR and Western blot analysis. The present study provides that the PT-9 and PT-10 might have potential therapeutic effects and should be considered for further development as new anti-inflammatory agents.

Keywords: Coumarins, Anti-inflammation, Macrophage

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Association of MicroRNA 72a with Colon Cancer in a Korea Population

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MicroRNA (miRNA) regulate the gene expression via binding to the 3'-untranslated region (3'UTR) of target mRNAs after maturation. Genetic mutations in miRNA has been known to influence the pathogenesis of various diseases including cancers. Colon cancer is the second most cancer in Korean. Previous studies have shown that polymorphisms in miRNA contributed to a risk of colon cancer. In this study, we investigated the association between polymorphisms in microRNA and colon cancer in a Korea population. For a pilot study, twenty single nucleotide polymorphisms (SNPs) that located on seed region of miRNA or shown significant association with various cancers in previous studies were selected for this study (the minor allele frequencies ≥ 0.05 in Asian populations). SNPs were genotyped using Fluidigm Dynamic Array in 96 control (64 ± 2.78 years, male/female = 48/48) and 96 case (66.22 ± 10.49, male/female = 53/43). Among 20 SNPs, we found a significant association between rs895819 of miRNA-27a and colon cancer (p = 0.021). Thus, we further studied the association of rs895819 in increased sample size [356 control (59.99 ± 14.02, male/female = 164/192) and 250 case (65.90 ± 10.93, male/female = 76/124)], genotyping using direct sequencing. Further analysis also showed the significant association of rs895819 with colon cancer [odds ratio (OR) OR = 1.89, 95% confidential interval (CI) = 1.26-2.85, p = 0.0069 in codominant, OR = 1.75, 95%CI = 1.18-2.61, p = 0.0048 in dominant, OR = 1.77, 95%CI = 1.22-2.55, p = 0.0022 in overdominant]. In particular, the T allele of rs895819 was associated with an increased risk of colon cancer (OR = 1.89, 95%CI = 1.26-2.85, p = 0.0069). These results suggest that rs895819 of miRNA-27a contributed to the development of colon cancer in a Korea population.

Keywords: MicroRNA-27a, Single Nucleotide Polymorphism, Colon Cancer

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Action of Fluvoxamine, a Selective Serotonin Reuptake Inhibitor, on the Potassium Channel

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The action of fluvoxamine, a selective serotonin reuptake inhibitor, on the cloned neuronal rat Kv3.1 channels stably expressed in Chinese hamster ovary cells was investigated using the whole-cell patch-clamp technique. Fluvoxamine reduced Kv3.1 whole-cell currents in a reversible concentration-dependent manner, with an IC_{50} value and a Hill coefficient of 8.59 μM and 1.14, respectively. Fluvoxamine accelerated the decay rate of inactivation of Kv3.1 currents without modifying the kinetics of current activation. The inhibition increased steeply between 0 and +30 mV, which corresponded with the voltage range for channel opening. In the voltage range positive to +30 mV, inhibition displayed a weak voltage dependence, consistent with an electrical distance δ of 0.35. The binding (k_{+1}) and unbinding (k_{-1}) rate constants for fluvoxamine-induced block of Kv3.1 were 4.5 $\mu M^{-1}s^{-1}$ and 111.7 s^{-1}, respectively. The theoretical K_D value derived by k_{-1}/k_{+1} yielded 24.7 μM. Fluvoxamine did not affect the ion selectivity of Kv3.1. Fluvoxamine slowed the deactivation time course, resulting in a tail crossover phenomenon when the tail currents, recorded in the presence and absence of fluvoxamine, were superimposed. Inhibition of Kv3.1 by fluvoxamine was use-dependent. The present results suggest that fluvoxamine acts on Kv3.1 currents as an open-channel blocker.

Keywords: Fluvoxamine, Selective serotonin reuptake inhibitor, Kv3.1

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Effects of Acidic pH on Hyperpolarization-Activated and Cyclic Nucleotide-Modulated Cation Channels in Dural Afferent Neurons

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Effects of acidic pH on hyperpolarization-activated and cyclic nucleotide-modulated cation (HCN) channels were examined in enzymatically isolated rat dural afferent neurons using a whole-cell patch clamp technique. Medium sized dural afferent neurons were identified by retrograde labeling of these neurons using the fluorescent dye DiI. The hyperpolarization-induced membrane currents, which were substantially blocked by specific HCN channel blocker Cs^+ (5 mM) or ZD7288 (30 μM), were found in most medium-sized DiI-positive neurons. In a voltage-clamp condition, acidic pH decreased the hyperpolarization-induced currents in a pH-dependent manner. Acidic pH did not affect the voltage-dependency of HCN channel activation. In the current-clamp condition, the membrane potentials of medium-sized DiI-positive neurons were recorded using the whole-cell patch-clamp technique. Under these conditions, acidic pH (pH 6.0) significantly decreased the number of action potentials induced by depolarizing current injection. Acidic pH (pH 6.0) also increased the rheobase currents, consistent with an increase in the threshold value for the generation of action potentials. Taken together, the acidic pH was able to inhibit HCN channels in medium-sized dural afferent neurons, but further study would be needed to evaluate that the acid inhibition of HCN channels directly affects the excitability of dural afferent neurons.

Keywords: migrane, acidic pH, trigeminal ganglion, HCN channels, dural afferent neurons

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Mosapride, Gastrokinetic Agent, Inhibits 5-Hydroxytryptamine 3 Receptor Function in NCB-20 Neuroblastoma Cells

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Mosapride accelerates gastric emptying through acting on a 5-hydroxytryptamine (5-HT) 4 receptor and is used for the treatment of gastritis, gastroesophageal reflux diseases, and irritable bowel syndrome. But its mechanism is still unclear, therefore we tested the effect of mosapride on 5-HT_3 receptor currents, because the 5-HT_3 receptors are known to be expressed in the gastrointestinal system and have an important role for the regulation of bowel movement. Using whole cell voltage clamp method, we compared the currents of 5-HT_3 receptor when 5-HT was applied alone and co-applied with mosapride in cultured NCB-20 cells known to express the 5-HT_3 receptors. The 5-HT_3 receptor current amplitudes were inhibited by mosapride in a concentration dependent manner. Mosapride blocked the peak currents in a competitive manner, because the EC50 was shifted to the right without the change of maximal effect evoked by the 5-HT application. The 5-HT_3 receptor current rise slopes were decreased by the mosapride. It accelerated the desensitization of 5-HT_3 receptor, but did not affect the receptor deactivation. There were no voltage-, and use-dependency in its blocking effects. Mosapride also did not change the recovery process from the receptor desensitization. These results suggest that mosapride inhibits the 5-HT_3 receptor through a competitive blocking mechanism. From this study, we could expand our understanding the pharmacological and therapeutic mechanisms of mosapride to improve gastrointestinal motility and to treat several gastrointestinal disorders.

Keywords: 5-Hydroxytryptamine 3 Receptor, Mosapride, Gastrokinetic, Patch-clamp

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Anesthesia and Cognition: Memory Formation During General Anesthesia and Development of Preclinical Model for the Prevention of Postoperative Cognitive Decline (POCD)

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Dysfunction of cognitive function especially in memory and executive functions after surgery is called POCD(postoperative cognitive decline). The causes of POCD is not well understood yet, but young and old age, highly stressful environment, repeated anesthesia and inflammatory responses during surgery are known risk factors for the development of POCD. The occurrence of POCD and the resulting reluctance of surgery are serious problems, especially in children and the elderly. POCD can have more influence on intelligence, because childhood is the developing period and old age is the declining period of intelligence. However, due to congential anomalies in the childhood and tumors or chronic diseases in elders, major surgery is more necessary than in young adults. Therefore, the development of precautionary measures against POCD is urgent. We tried to test the hypothesis that the cause of POCD is 1) excessive anxiety about surgery and 2)) brain inflammation due to microembolism and BBB destruction. This hypothesis was tested in 3 weeks, 8 weeks, and 30 months old mice with behavioral test measuring cognitive functions. After repeated exposure to isoflurane induced general anesthesia, behavioral tests were performed using Y-maze, Novel object test, and Passive avoidance test. Y-maze and Novel object test of mice at 3 weeks and 30 months old showed that the repeated anesthesia group had reduced cognitive function compared to the non-treated group, but not at 8 weeks old mice. Passive avoidance test showed no significant change in cognitive function due to repeated anesthesia in mice of all ages. We obtained the brain of mice that participated in the experiment through perfusion surgery, and performed GFAP immunostaining to confirm the activity of astrocytes. As a result, it was observed that the number of active astrocytes in the 3 weeks and 30 months old mice was higher than that in the non-treated group, but not at 8 weeks old mice. Thus, we confirmed that the activity of astrocytes is related to the impairment of cognitive function due to repeated anesthesia. According to these results, 1) the role of inflammatory astrocytes on cognition 2) why young and old aged brain are more susceptible to astrocytic inflammation compared to mature brain and 3) whether anti-inflammatory substances can prevent deterioration of cognitive function by anesthesia will be tested.

Keyword : POCD, Anesthesia, Isoflurane

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P2Y2R-mediated Inflammasome Activation Regulates Tumor Progression in Breast Cancer Cells and Radiotherapy-resistant Breast Cancer Cells

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Based on many reports, extracellular nucleotides are released and accumulated in the tumor microenvironment and can activate the $P2Y_2$ receptor ($P2Y_2R$), which mediates various responses in tumor cells, resulting in tumor progression and metastasis. In addition, the inflammasome has been reported to be associated with tumor progression. However, the role of $P2Y_2R$ in inflammasome activation in breast cancer cells remains unclear. Thus, in this study, we investigated the role of $P2Y_2R$ in inflammasome-mediated tumor progression in breast cancer cells and radiotherapy-resistant(RT-R) breast cancer cells. We established RT-R-breast cancer cells (RT-R-MDA-MB-231, RT-R-MCF-7, and RT-R-T47D cells) by fractionated irradiation (2 Gy each, total 50 Gy) and found that RT-R-breast cancer cells, especially RT-R-MDA-MB-231 cells, release higher levels of ATP than their parental breast cancer cells, which was potentiated by stimulation with TNF-α. TNF-α and ATP induced inflammasome activation as measured by caspase-1 activity and IL-1β secretion in MDA-MB-231 cells, which was enhanced in RT-R-MDA-MB-231 cells. Meanwhile, the inflammasome activation induced by TNF-α or ATP was notably decreased by $P2Y_2R$ knock-down or hydrolyzing ATP in both MDA-MB-231 and RT-R-MDA-MB-231 cells, suggesting the involvement of ATP-activated $P2Y_2R$ in inflammasome activation. Moreover, TNF-α or ATP increased the invasion, colony formation and MMP-9 activity of MDA-MB-231 and RT-R-MDA-MB-231 cells, and these effects were modulated by caspase-1, in a $P2Y_2R$-dependent manner. Lastly, athymic nude mice injected with RT-R-MDA-MB-231-EV cells showed increased tumor growth, MMP-9 expression level in tumor and IL-1β secretion in serum compared with the mice injected with RT-R-MDA-MB-231-$P2Y_2R$ shRNA. These results suggest that extracellular ATP enhances tumor progression in RT-R-breast cancer cells and breast cancer cells by regulating invasion and associated molecules via the $P2Y_2R$-inflammasome activation pathway.

Keywords: ATP, IL-1β, inflammasome, $P2Y_2$ Receptor, Radiotherapy-resistant Breast Cancer Cells, Tumor Progression

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Oleandrin and Odososide A Exhibit Anti-cancer Effects via Suppressing the p-STAT3 Signaling Pathway

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Recently, cardiac glycosides oleandrin and odoroside A, the polyphenolic monomer compounds extracted from Nerium oleander, are known to have an antitumor effect on various tumor cells including breast cancer, lung cancer as well as leukemia at low doses. However, the mechanisms of oleandrin and odoroside A-induced anti-cancer effects are not well known. Therefore, in this study, we aimed to investigate the anti-cancer effects of oleandrin and odoroside A and their associated mechanisms in highly metastatic breast cancer cells MDA-MB-231 and radio-resistant MDA-MB-231 cells. Our results showed that oleandrin and odoroside A significantly decreased the colony formation of both cell lines in a dose-dependent manner. Oleandrin and odoroside A significantly reduced the expression of adhesion molecules such as ICAM-1 and VCAM-1, resulting in the inhibition of the adhesion of MDA-MB-231 and radio-resistant MDA-MB-231 cells to ECs. Moreover, oleandrin and odoroside A significantly inhibited the invasion of MDA-MB-231 and radio-resistant MDA-MB-231cells through EC-matrigel?coated transwell membranes. Then, expression of β-catenin and secretion of MMP-9 were significantly down-regulated by oleandrin and odoroside A from 50 nM and 100 nM, respectively. Moreover, we investigated whether oleandrin and odoroside A regulate breast cancer stem cells markers CD24/CD44 or Oct3/4. Oleandrin and odoroside A reduced CD44 and Oct3/4 levels but reduced CD24 level, suggesting that oleandrin and odoroside A may reduce cancer stem cell population. Finally, we found that phospho-STAT3 level was increased in RT-R-MDA-MB-231 compared to MDA-MB-231, which was significantly decreased by oleandrin and odoroside A. In addition, inhibition of phospho-STAT3 significantly reduced the expression of adhesion molecules and the activity of MMP-9. These results suggest that the anti-cancer effects of oleandrin and odoroside A might be due to the suppression of the p-STAT3-mediated pathways which are involved in the regulation of invasion-related molecules such as adhesion molecules and EMT-related proteins.

Keywords: Breast cancer cell, Invasion, Oleadrin, Odoroside A, STAT3

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Incidence of Dementia in Patients with Type 2 Diabetes Mellitus by the Nationwide Population-Based Cohort Study

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Objective: The antidiabetic medication in type 2 diabetic mellitus patients and its association with dementia has been studied previously, but remains controversial. We aimed to investigate the relationship between diabetic medication and incidence of dementia using a nationwide population-based dataset. **Methods:** This is a retrospective population-based cohort study using the Korean National Health Insurance Service - Elderly sample cohort. We identified 116,674 patients with age of 60 or more who were newly diagnosed with type2 diabetes mellitus and compared diabetic medication group and non-medication group for the follow up period of 11 years, 2003 to 2012 .The endpoint of the study was the occurrence of administrative claims with dementia in Alzheimer's disease(F00), vascular disease(F01), others dementia including dementia in other diseases classified elsewhere (F02), unspecified dementia (F03), Alzheimer's disease (G30). **Results:** Incidence of dementia was investigated with diabetic monotherapy and combination therapy. In monotherapy, the risk ratio was statistically significant in sulfonylurea and biguanide. The risk of dementia in sulfonylurea monotherapy was 1.21 times higher (95% CI 1.12-1.31) and biguanide monotherapy group showed 0.78times lower risk of dementia (95% CI, 0.74-.0.86). In combination therapy, α-glucosidase inhibitor, biguanide, thiazolidinedione, DPP4 inhibitor were statistically significant when compared to non-medication group. The combined use of meglitinide showed an increase in the risk of dementia of 1.17 (95% CI, 1.09-1.25) and decreased risk in biguanude and DPP4 inhibitor (cHR= 0.72 and 0.86, 95% CI 0.64,-0.82 and 0.81-.0.90, respectively). The incidence and rate of dementia according to the duration of diabetes mellitus showed a gradual increase regardless of diabetic medication use and peaked at 6 to 8 years(26.79%, non-medication group: 27.12 % and medication group: 25.93 %). **Conclusion:** The incidence of dementia in diabetes medication group was lower especially in metformin treated patients when compared to non-medication group.

Keywords: Type 2 Diabetes Mellitus, Dementia, National Health Insurance Data

대한예방의학회

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Association between Oxidative Stress and PRMTs Levels on Childhood Asthma

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Protein arginine methyltransferases (PRMTs) that catalyze methylation of specific arginine residues is a possible therapeutic target in asthma studies, and the expression of PRMTs were reported to be increased in asthma airway smooth muscle cells. However, the expression of PRMTs has been not surveyed in childhood asthma. This study evaluated the expression PRMT1 and PRMT4 in asthmatic children with oxidative stress and inflammatory response molecules. PRMT1 and PRMT4 were increased in asthma patients compared with control subjects. Furthermore, malondialdehyde (MDA), a marker of lipid peroxidation, and intercellular adhesion molecules 1(ICAM-1), one of inflammatory response molecules, were significantly increased in asthma patients than control subjects. Also ICAM-1 showed significant positive correlation with PRMT 4 in all study subjects. This study showed increased level of PRMT1 and PRMT4 in asthma patients and suggested that increase of PRMTs were related with inflammatory response in childhood asthma. Acknowledgements: This work was supported by the National Research Foundation of Korea(NRF) grant funded by the Korea government (2016R1D1A1A02937060). Also this study was funded by the Korea Ministry of Environment (MOE) as “The Environmental Health Action Program (2016001360007)” and “Basic Science Research Program through the National Research Foundation of Korea(NRF) funded by the Ministry of Education (2016R1A6A3A11930602).

Keywords: Asthma, Protein arginine methyltransferases (PRMTs), Oxidative Stress, Intercellular Adhesion Molecule-1, Malondialdehyde-low density lipoprotein

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Cost-Minimization Analysis of Rotavirus Vaccination in South Korea

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Value of rotavirus (RV) vaccination has been demonstrated for Korea through a cost-effectiveness analysis. Although the analysis assessed human-bovine reassortant RV vaccine (HBRV) only, human RV vaccine (HRV) and HBRV have globally demonstrated comparable effectiveness against homotypic and heterotypic RV strains. As per existing evidence, this study conducts a cost-minimization analysis between the two-dose HRV and three-dose HBRV. The analysis evaluates a single Korean birth cohort from a societal perspective over 1 year, considering vaccine acquisition and administration costs (direct medical), transportation cost (direct non-medical) and productivity loss incurred due to RV vaccination (indirect). In the base-case, per-course parity is assumed between HRV and HBRV for vaccine acquisition cost based on their private market prices, as well as for vaccine administration cost based on their comparable effectiveness. Assuming a complete coverage of either RV vaccine, HRV would induce cost savings of ₩9,390 million (M) compared to HBRV. However, in Korea, several vaccines against the same disease can be simultaneously included and reimbursed in the National Immunization Programme (NIP). Given this characteristic, when market share is considered and assumed at 50:50, total societal costs associated with RV vaccination would amount to ₩125,291 M (HRV: ₩60,298 M; HBRV: ₩64,993 M) in the base-case. Several factors may influence the decision of the vaccinator to choose one vaccine over the other. One such factor could be difference in vaccine administration costs per course. These factors may potentially change the market dynamics and depending on the reimbursement scenarios tested, the societal costs associated with RV vaccination may be impacted. Given the Korean NIP characteristics and subsequent market dynamics, appropriate administration reimbursement scheme should be determined for RV vaccines with differing dosing requirements to minimize overall societal costs.

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Conflict of interest: KEK, GLB and CL are employees of the GSK group of companies. GLB holds shares in the GSK group of companies. HJ was an employee of the GSK group of companies at the time of the study and reports personal fees from Gang-Won National University, outside the submitted work.

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Estimating the Cost-Effectiveness of Inactivated Quadrivalent Influenza Vaccination in the Prevention of Influenza and Related Complications in South Korean Individuals with Co-Morbid Conditions

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Individuals with chronic medical conditions (including asthma, heart diseases and weakened immune systems) are at a high risk of serious complications following influenza infection, and are recommended by the World Health Organization for annual influenza vaccination. Evidence on the cost-effectiveness of influenza vaccination (particularly with the inactivated quadrivalent influenza vaccine [IIV4]) in this at-risk group is lacking. This study attempted to estimate the cost-effectiveness of IIV4 in South Korean children and adolescents 5-19 years of age and adults 20-64 years of age with chronic medical conditions identified by a set of international classification of diseases (ICD)-10 codes. A static 1-year population model was populated with data on incidence, costs and outcomes estimated using the Korean National Health Insurance System database. Two definitions of influenza were constructed: a narrow 'confirmed' -influenza (CI) and a broad influenza-like illness (ILI) definition. At-risk individuals were sub-divided into those with or without immune-compromised conditions. Due to the limited robust vaccine effectiveness (VE) data available for various at-risk groups, a high-low VE scenario analysis was used to estimate a plausible range of cost-effectiveness of IIV4 compared to no vaccination in an aggregated risk group comprising the major groups. In adults, under the CI definition, IIV4 was estimated to be cost-effective (compared to willingness to pay threshold of 32,038,000 South Korean Won) or cost-saving irrespective of the VE scenario used; and cost-saving under the ILI definition. IIV4 was estimated to be not cost-effective in children and adolescents using the CI definition but was cost-saving using the ILI definition. IIV4 is largely expected to be cost-effective in preventing the significant burden of influenza in at-risk age groups, however, robust effectiveness studies are required to better estimate value of IIV4 in this sub-population.

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Keywords: Influenza, Inactivated Quadrivalent Influenza Vaccination, Cost-Effectiveness, Co-Morbid Conditions

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Prediction of Metabolic Syndrome Severity According to Body Fat Mass

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Body composition such as body fat mass index may different effects on the metabolic syndrome risk associated with obesity. However, measurement of body fat mass was difficult without specific methods using bioelectrical impedance analysis (BIA). Therefore, the purpose of this study is to predict body fat mass (kg) based on easily measurable physical description, and find optimal cut-off of body fat for the prediction of metabolic syndrome severity. A total of 7,040 participants aged 40 to 69 enrolled in Ansan and Ansung baseline study from the Korean Genome and Epidemiology Study (KOGES) with body fat measurements and without any diagnosis of cardiovascular diseases and cancer were included in this study. To develop the body fat prediction model, Elastic net regression with 10-fold cross validation were performed based on height, weight, waist, and hip size. To predict the metabolic syndrome with body fat mass (kg) and find optimal cut point, we performed Area under curve (AUC) analyses and Youden's index from receiver operating characteristics curve (ROC). Adjusted R-square between body fat and predicted body fat reached 0.872. Prevalence rate of metabolic syndrome for men (23.2%) was lower than women (33.1%). AUC of prediction model according to predicted body fat was 0.810 in men and 0.811 in women, respectively. In men, the optimal cut-off value of predicted fat for metabolic syndrome was 16.6kg provided a sensitivity of 71.7%, a specificity of 78.2%. In women, 18.4kg provided a sensitivity of 74.6%, a specificity of 61.5%. For disease severity, the cut-off point value of 3 components were 16.6kg, 17.0kg for 4 components, and 17.6kg for five components in men. In women, 18.4kg for 3 components, 19.1kg for 4 components, and 20.0kg for 5 components. In conclusion, predicted body fat index had a moderate power to identify the severity of metabolic syndrome.

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Keywords: Prediction model, metabolic syndrome, body composition, body fat mass

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어린이에서 뇨중 프탈레이트 노출수준과 갑상선 호르몬과의 연관성 연구

박보현, 한혜진, 박보미, 박혜숙
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프탈레이트의 인체 유해성이 많은 연구들에서 보고되었으나 아직까지 프탈레이트는 플라스틱 등 생활용품에 광범위하게 사용되고 있는 실정이다. 갑상선 호르몬은 인체 내에서 다양한 대사에 관여하며 특히 어린이에서 성장, 발달에 중요한 역할을 한다. 상대적으로 환경물질 노출 감수성이 취약한 아동기 시기의 프탈레이트 노출은 성인에서의 노출보다 더 큰 건강 영향을 줄 있다. 따라서 본 연구에서는 우리나라 아동에서 프탈레이트 노출 수준과 갑상선 호르몬과의 연관성을 살펴보고자 하였다. 이화여자대학교 목동병원 영아성장 출생코호트(Ewha Birth & Growth Cohort)에 등록된 아동을 대상으로 하였으며 만 3-5세, 만 7-9세 추적관찰에 모두 참여하여 뇨중 프탈레이트 측정이 완료된 아동 중 만 10-12세 추적관찰 조사를 완료한 128명을 최종 연구대상자로 선정하였다. 9종류의 뇨중 프탈레이트 대사산물(MBzP, MEHP, MEHHP, MEOHP, MECPP, MEP, MiBP, MnBP, MiNP)을 LC-MS/MS(The Liquid Chromatograph Triple Quadrupole Mass Spectrometer) 방법으로 측정하였고, 혈청시료를 사용하여 TSH(thyroid-stimulating hormone), Free T3, Free T4 수준을 분석하였다. 만 3-5세 시기의 프탈레이트 노출 수준이 만 10-12세 사춘기 이후 갑상선 호르몬 수준에 미치는 영향을 분석하였을 때, 남아에서 MEHHP 제1삼분위군보다 제2분위군과 3분위군에서 TSH 농도가 현재 시기의 혈당, 중성지방, 체질량 지수 보정 후 유의하게 높았다. MEP 또한 비슷한 양상으로 경계성 유의수준의 관련성을 보였다. Free T3의 경우, 남아에서 MECPP 수준이 증가할수록 유의하게 감소하였고, 여아에서는 MEP 수준과 유의한 연관성을 보였다. 만 7-9세 시기에 측정된 뇨중 프탈레이트 대사체와 사춘기 이후 시기의 혈청 내 TSH 농도와는 유의한 연관성을 보이지 않았으나, 남아에서 MiNP 노출이 증가된 군에서 혈청 내 Free T4 농도가 유의하게 감소하였으며, MECPP와 MEHP 대사체 노출 수준이 높은 군에서 free T3 농도가 낮은 것으로 분석되었다. 여아에서는 프탈레이트와 갑상선 호르몬 수준과의 유의한 연관성은 관찰되지 않았다. 본 연구에서는 사춘기 이전 시기의 일부 프탈레이트 대사체의 노출수준이 증가할수록 사춘기 이후 시기의 혈중 TSH 농도는 증가하고, free T3와 free T4 농도는 감소하는 연관성을 보였다. 프탈레이트와 갑상선 호르몬간의 보다 명확한 인과관계 규명을 위해 향후 연구들이 수행되어야 할 것으로 생각된다.

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Keywords: 프탈레이트, 갑상선 호르몬, 아동, 출생코호트

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5세에서 12세까지의 한국 소아 코호트에서 K-CBCL을 통한 행동 발달 장애 추적

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행동 발달장애는 뇌, 신경계의 기능 이상과 관련이 있으며, 소아에서의 행동 발달장애에 포함되는 주의력 결핍 과잉 행동 장애와 자폐 스펙트럼 장애는 지난 30년간 증가 추세를 보여왔다. 행동 발달 장애는 어린 나이에 시작하여 성인이 될 때까지 생애에 걸쳐 지속되므로 이로 인한 경제적 부담의 크기는 크다. 이번 연구에서는 유아, 아동 및 청소년의 정서, 행동 장애의 문제를 진단하고 평가할 수 있는 표준화된 아동 행동 평가 척도인 K-CBCL (Child Behavior Checklist) 을 사용하여 5세에서 12세까지의 소아에서의 문제 행동을 추적하였다. 2000년부터 2005년까지 이대목동병원 산부인과에 내원한 임신 중기의 산모의 자녀를 대상으로 구축된 이화 영아 성장 코호트의 참여자가 5, 7, 9, 11, 12세 추적 관찰에 참여하여 시행받은 K-CBCL 검사 결과의 T 점수를 이용하여 상관분석과 궤도분석을 시행하였다. 총 355명의 대상자가 5세에서 12세 사이에 적어도 한 번의 K-CBCL 검사를 받았으며, 전임상단계 (T점수 60이상; 백분위 84이상)나 임상단계 (T점수 64이상; 백분위 92이상)의 유병률은 총문제행동 점수 기준으로는 3.8~8.4%, 내재화 문제 점수 기준으로는 3.8%~15.2%, 외현화 문제 점수 기준으로는 5.0%~9.0%으로 나타났다. 내재화 문제 점수의 7년간 추적 상관 계수는 기준 연령 (5, 7, 9, 11세)과 추적 기간 (1년~7년)에 따라 0.20~0.55 사이로 나타났으며, 외현화 문제 점수는 0.27~0.55, 총문제행동점수는 0.33~0.63으로 확인되었다. 궤도분석 결과, 기준연령인 5세 시기에 총문제행동 T점수가 상대적으로 높았던 그룹은 이후 시기 지속적으로 높은 점수를 유지하며 총점이 계속해서 상승하는 것을 확인하였고, 5세 시기에 총문제행동 T점수가 상대적으로 낮았던 그룹은 지속적으로 낮은 점수를 유지하여 연령이 높아질수록 두 그룹간의 점수 차이가 커지는 것을 확인하였다. 이 연구를 통하여 소아 시기 K-CBCL 점수의 연령간 상관계수가 크며, 어린 시기 점수가 높은 경우 이후 시기까지 높은 점수가 지속되는 것을 확인하였다. 이 결과는 이른 시기의 신경 행동 발달 장애 위험의 발견 및 중재가 중요할 수 있음을 시사한다.

Keywords: 신경 행동 발달 장애, K-CBCL, 소아, 추적상관계수, 궤도분석

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Analysis of Co-morbidities between Various Types of Cancers and Ovarian Cancer Using National Health Insurance Database in Korea

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Purpose: Recently NCCN(National comprehensive Cancer Network) published newest version of guidelines that include indications for further genetic risk evaluation including BRCA mutation assessment. According to this guideline, people with past history of various cancers are recommended with further evaluation. Therefore, we decided to analyze co-morbidities between various types of cancers and ovarian cancer. **Method:** We used National Helath Insuracne Services database containing total of about 1,000,000 subjects and in these subjects, we excluded men, people aged less than 20 years old, and people who were diagnosed with any type of cancer within 2 years. We ended up with 379,715 subjects. In order to find incident cases of different types of cancers, we included subject with diagnosis of a certain cancer at least once between 2004-2013. To rule out reversal causality, we excluded any cases where ovarian cancer developed before incidence of a certain cancer. After that, in order to assess hazard ratio between different types of cancers with ovarian cancers, we used Cox proportional hazard model with 95% confidence interval. **Result:** Subjects with Breast cancer history had 1.42 times more risk than subjects without Breast cancer history in association with ovarian cancer [HR 1.42 CI (0.53-3.79)]. In endometrial cancer, it had 15.6 times more risk [HR 15.6 CI (8.60-28.47)], for endometriosis it had 2.15 times more risk [HR 2.15 CI (1.31-3.55)], for colon cancer it had 2.25 times more risk [HR 2.25 CI (1.12-4.55)], and for bladder cancer it had 7.47 times more risk [HR 7.47 CI (2.39-23.30)] **Conclusion:** It was found that subjects with past history of certain cancer type such as endometrial cancer, colon cancer, and bladder cancer increased significantly the risk of ovarian cancer mortalities. Further study are needed to find clear association between various types of cancers and ovarian cancer.

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위암환자의 10년 생존율과 관련 예후인자 및 역학적 특성

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최근 위암 발생자 수는 감소 추세이나 위암은 암종 별 발생순위 1위로 여전히 가장 많이 발생하는 암이다. 위암 생존율은 지속적으로 증가하고 있는 추세로, 2011-2015년의 위암 5년 상대생존율은 75.4%이었다. 암 환자의 5년 이상 생존은 암의 완치를 판정하는 통상적인 지표라고 인식되어 왔으나, 5년이 경과한 환자라도 암이 재발할 수 있으므로 지속적으로 관찰 및 관리가 필요하다. 이러한 생존율은 임상병리학적 특성과 역학적 요인에 따라서도 예후가 달라진다. 이에 본 연구에서는 위암환자를 10년 이상 추적하여 다양한 임상병리학적 및 역학적 특성에 따라 생존율 차이가 있는지 살펴보고자 하였다. 2002-2006년까지 충남대학교병원과 한양대학교구리병원에서 위암을 처음 진단받은 739명의 위암 환자 코호트를 구축하여 역학자료를 수집하였으며, 이 중 *Helicobactor pylori(H. pylori)* 감염 검사를 실시한 490명을 최종 분석대상자로 선별하였다. 의무기록조사를 통해 추적조사를 실시했으며, 2016년 12월 31일를 종료시점으로 하여 위암 사망, 다른 질병 사망, 재발, 추적실패, 생존으로 구분 조사하였다. 위암환자의 평균 생존 기간은 79.5±59.1개월이었으며, 관찰 종료 시점까지의 생존율은 61.8%였다. 5년과 10년 관찰 생존율(이하 생존율)은 각각 62.7%, 59.3%였으며, 여자(5년 생존율 59.3%, 10년 생존율 57.7%)에 비해 남자(5년 생존율 66.1%, 10년 생존율 60.8%)에서 5년에서 10년 사이의 생존율 차이가 더 컸으나 통계적 유의성은 없었다(p=0.353). 연령에 따라서는 60세 미만까지 비슷한 수준의 생존율을 보이다, 60대 이상부터 현격히 생존율이 떨어지는 것으로 나타났다(p<0.001). 진단 전 흡연상태에 따라서는 비흡연자의 5년과 10년 생존율은 62.0%, 59.5%, 현재와 과거 흡연자는 각 65.1%, 60.0%로 비슷한 수준이었으며(p=0.825), 위암의 가족력이 없는 경우 각 62.4%, 57.3%, 가족력이 있는 경우 각 69.6%, 68.5%로 가족력이 없는 경우에 생존율이 더 낮게 나타났다(p=0.039). 임상병리학적 특성에 따라서는, 병리학적 병기 1기의 환자는 각 90.1%, 87.5%였으며, 4기 환자는 각 11.4%, 8.6%로 관찰되었다. 로렌의 조직학적 분류로 보면 장형이 각 77.5%, 69.3%, 미만형은 61.1%와 59.6%로 나타나 장형의 생존율이 유의하게 컸다(p=0.016). 성과 연령을 보정한 비례위험도(Hazard ratio, 이하 HR)를 분석한 결과, 위암 가족력이 있는 경우 사망위험이 낮은 경향이었으나 통계적 유의성은 없었다(HR=0.71, 95% confidence interval (95% CI)=0.49-1.04). 조직학적 병기가 증가할수록 급격하게 사망위험이 높아졌으며, 4기 환자는 1기에 비해 사망위험이 26.4배 증가했다(95% CI =16.6-42.1). 장형 위암에 비해 미만형 위암은 사망위험이 1.72배 증가했으며(95% CI =1.16-2.54), *H. pylori* 감염에 따라서는 비감염자와 감염자의 사망위험 차이가 없었다(HR=1.01, 95% CI =0.71-1.43). 결론적으로, 위암 발생 후 생존률은 여자, 60세 이상, 조직학적 병기가 높고 미만형 위암인 경우 낮았으며, 가족력, 흡연, *H. pylori* 감염 유무에 따라서는 차이가 없는 것으로 나타났다.

Keywords: 위암, 생존율, 예후, 추적관찰

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도시규모 및 주택유형에 따른 알레르기 비염 진단 경험률과 영향요인에 관한 연구

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호흡기 알레르기면역질환(알레르기성 비염, 천식 등)의 유병률 증가는 전세계적으로 나타나는 결과로, 국내의 경우 산업화 이전시기와 비교하여 1990~2000년대로 들어서면서 호흡기 알레르기 면역질환이 크게 증가한 것으로 보고되고 있다. 이러한 역학적 결과는 도시화, 산업화와 같이 서구화되는 환경인자가 질병의 병인과 밀접한 관련이 있는 것으로 이해되고 있다. 우리나라는 급격하게 진행된 산업화에 따라 도시규모에 따른 환경이 크게 다르고 가옥구조 또한 아파트와 단독주택 등 다양하게 존재하고 있다. 국내외에서 환경과 알레르기 질환과 관련된 연구는 많이 진행되었지만, 도시 규모와 가옥 구조를 세분화하여 심층적으로 분석하려는 시도는 드물었다. 따라서 이번 연구에서는 도시 규모 및 가옥 구조에 따른 알레르기성 비염 질환 경험률과 알레르기성 비염에 미치는 영향요인을 분석해보았다. 설문지는 전문가들의 자문 및 문헌검색을 통하여 문항을 개발하였고, 알레르기 질환 관련 설문 항목은 한국판 ISAAC 표준 설문지를 참고하여 미성년자, 성인 각각에 맞게 변환하였다. 도시규모는 지방자치법 내 대도시 분류 기준에 따라 도시지역(인구 50만명 이상) 및 농촌지역(군 지역)으로 분류한 후 포항시(대도시)와 영덕군(농촌지역)을 연구대상지역으로 선정하였으며, 각 지역별로 거주 주택유형에 따라 아파트 및 주택으로 각각 25가구 씩 총 100가구를 선정하여 2017년 11월부터 2018년 1월까지 방문면접을 통한 설문조사를 진행하였다. 연구대상자는 포항시 132명(남 61명, 여 71명)과 영덕군 170명(남 88명, 여 82명)이며, 통계분석은 SPSS 22.0 for Windows 프로그램을 활용하였다. 대상자들의 알레르기성 비염 질환 진단여부를 종속변수로 하고 일반적 특성 및 환경 요인을 독립변수로 하여 각각 chi-square test, Fisher' s exact test, chi-square for trend test 등을 활용하여 단변량 분석을 실시하였다. 단변량 분석에서 알레르기성 비염 질환 진단 경험에 유의한 차이가 있었던 범주화된 변수들을 서로 보정하여 이분형 로지스틱 회귀분석을 실시하여 각각의 유의성을 파악하였다. p값은 0.05 미만인 경우를 유의하다고 판단하였다. 연구 결과 도시 규모에 따른 알레르기성 비염 진단경험률은 포항시 38.6%, 영덕군 15.3%로 포항시가 유의하게 높았으며, 주거 가옥 형태에 따른 알레르기성 비염 진단경험률은 유의한 차이가 없는 것으로 나타났다. 직계가족 알레르기 질환 가족력에 따른 알레르기성 비염 진단경험률은 가족력이 있는 경우 47.5%로 없는 경우 11.0%에 비해 유의하게 높았다. 모유 수유 여부에 따른 알레르기 비염 진단경험률도 모유 수유를 하지 않은 경우가 50.0%로 모유 수유를 한 경우 23.2%에 비해 유의하게 높은 것으로 나타났다. 단변량 분석을 통하여 알레르기성 비염 진단경험률에 유의하게 영향을 주는 것으로 파악된 독립변수는 성별, 성인여부, 지역, 가족력, 모유수유 경험 등이었다. 이들 변수를 서로 보정한 후에 이분형 로지스틱 회귀분석을 시행하였다. 그 결과 모유수유만이 통계적 유의성에서 제외되었고, 그 외에 남성이 여성에 비해서 알레르기성 비염 진단경험률이 유의하게 높았고(OR=2.339, p=0.009), 조사 시점에서 미성년자들이 성인에 비해 알레르기성 비염 진단경험률이 여전히 유의하게 높았고(OR=4.401, p<0.001). 포항시가 영덕군에 비하여 알레르기성 비염 진단경험률이 유의하게 높았으며(OR=2.844, p=0.001) 알레르기 질환 가족력이 있는 경우가 없는 경우에 비해서 알레르기성 비염 진단경험률이 유의하게 높았다(OR=6.703, p<0.001). 환경성 질환으로서 관심이 높아지고 있는 알레르기 질환을 다양한 관점에 접근하여 도출된 이번 연구결과는 기후 변화, 주거 환경에 따른 특정 allergen과의 연관성 파악 등으로 확대하여 연구를 진행할 수 있는 기반이 될 것이다.

Keywords: 알레르기 비염, 도시규모, 주택유형, 영향요인

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북한이탈 가정내 아동 및 청소년 성장

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2012년 국제기구 식량지원 프로그램 효과검증을 목적으로 북한당국과 유니세프(UNICEF), 세계식량계획(WFP), 유럽연합(EU)가 공동으로 북한 내 아동들을 대상으로 전국규모의 영양 조사를 실시한 결과, 60개월 미만의 아동 중 만성영양결핍 35.1%, 급성영양결핍 4.6%, 저체중아 15.2%로 나타났고, 여전히 많은 아동들이 영양장애가 있었다. 현재 국내에 거주하는 북한이탈주민의 수는 2016년 9월말 기준 29,830명이며, 이들 중 19세 이하 북한이탈청소년은 4,700명으로 15.8%를 차지한다. 북한이탈주민이 증가함에 따라 이들을 대상으로 다양한 건강연구들이 진행되었지만, 신체적 건강보다는 대부분 심리적, 정신적 건강에 대한 연구가 많았고, 특히 북한이탈가정 내 아동 및 청소년들의 성장에 대한 연구는 거의 없었다. 본 연구는 부모 중 한명이라도 북한이탈주민인 아동 95명, 청소년 106명, 총 201명을 면접조사하였고 신체계측을 측정하였다. 또한 측정한 신체계측자료를 질병관리본부와 대한소아과학회가 공동 연구한 2017 성장도표를 이용하여 북한이탈 가정의 아동 및 청소년들의 성장발달 상태를 평가하였다. 본 연구 결과 만선영양장애 (Length/height-for-age <-2Z)가 아동에서 8명 (8.4%), 청소년에서 10명 (9.4%) 이었고, 체중미달 (Weight-for-age < -2Z)이 아동에서 7명 (7.4%), 청소년에서 13명 (12.3%)이었다. 또한 급성영양장애(Weight-for-length/height < -2Z)인 경우도 아동이 3명 (3.2%), 청소년이 9명 (8.5%) 이었다. 이러한 결과는 남한 출생 아동 및 청소년들과 비교할 때 북한이탈 가정의 아동 및 청소년들의 성장이 매우 낮고, 이들의 영양과 성장발달을 돕기 위한 보건학적 개입이 시급하게 필요함을 나타낸다.

Keywords: 북한이탈주민, 어린이, 청소년, 성장

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소비자 암 정보 요구도 체계적 문헌고찰

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소비자들의 암 정보에 관한 관심이 높아짐에 따라, 여러 채널에서 정보를 탐색하고 이용하고 있다. 소비자들이 확인할 수 있는 암 관련 정보는 많이 있지만, 전문 의료인이 제공하는 정보 이외의 많은 정보들은 신뢰성이 낮고 맞춤형 정보가 아닌 한계를 보이고 있다. 그러므로 근거가 불충분한 암 관련 정보로 인한 혼란으로부터 소비자들을 보호하고 개개인이 필요로 하는 암 정보에 대한 양질의 정보를 제공하기 위한 방안으로 실제 소비자들이 알고 싶어 하는 암 정보 주제가 무엇인지 파악하여 소비자의 요구에 부합하는 정보를 제공하는 것은 필요하다. 많은 연구들에서 암 환자의 정보요구와 탐색채널에 대한 연구는 진행하였지만, 주로 암 환자에게 집중되어 있었으며 환자의 가족과 일반인을 대상으로 진행된 연구는 적었다. 따라서 본 연구는 최근 10년간 수행된 암 정보에 대한 소비자들의 요구도 및 탐색채널을 파악하기 위해 체계적 문헌 고찰 방법을 이용하여 확인하였다. 본 연구는 2008년부터 2017년까지 국내·외 암 관련 건강정보탐색 및 요구도 논문을 대상으로 하였다. 문헌고찰을 위해 COSI MODEL을 사용하여 검색하였다. 검색에 사용한 데이터베이스는 Medline, Embase, Cochran library, PsycINFO, CINAHL(nursing and allied health professionals), Pubmed, DBPia, KoreaMed, 학술데이터베이스(KISS), 한국교육학술정보원(RISS), 한국의학논문데이터베이스, 보건사회연구원(발간자료실), 보건복지부(연구조사자료실), 질병관리본부(연구결과보고서), PRISM 그리고 국립암센터 자료실 이다. 문헌은 지난 10년간의 연구로 한정하였으며(2007.01-2017.07) 문헌 제목과 초록에서 암, 건강, 정보, 탐색(또는 추구)가 한 번에 나올 수 있도록 검색하였다. 국외 문헌 검색 시, 'cancer' and 'health' and 'information (or 그와 비슷한 단어)' , and 'searching (or 그와 비슷한 단어)' 로 검색식을 구성하여 검색하였다. 초기 검색결과, 전체 data base에서의 검색결과 총 4,532개의 논문이 검색되었다. 검색된 논문 중, 먼저 제목과 저자를 기준으로 중복된 논문을 제거하였다(n=1,757 제거). 2,775개 논문 중, 제목과 초록을 확인하여 1차 배제 작업을 거쳤다. 연구의 배제기준은 다음과 같다: (1) 7대암(2014년 가장 많이 발생한 암종으로 갑상선암, 위암, 대장암, 폐암, 유방암, 간암, 전립선암) 이외의 암종에 대한 연구, (2) 정보검색기술의 연구, (3) 정보웹사이트 평가연구, (4) Genome 연구, (5) 조사도구에 대한 타당성 연구, (6) 원문이 제공되지 않은 연구(초록, editorial), (7) 질적 연구, (8) 영어와 한글 이외의 언어로 작성된 연구. 문헌 선정과정에서는 연구자 3인이 적절한 문헌을 선택하기 위해 독립적으로 선정하는 과정을 거쳤다. 진행과정에서, 연구자간의 불일치가 있는 경우, 연구자 간의 토의를 통해 불일치를 해소하였다. 문헌 선택과정을 통해 최종 선정된 논문은 117개이다. 해당 문헌을 대상으로 자료를 추출하여 정리하였다. 연구결과 소비자들은 전문의료인과 인터넷을 통해 암 관련 정보를 주로 탐색함을 확인할 수 있었다. 특히 일반인의 경우에는 인터넷과 의사 그리고 미디어만이 주된 정보원이었으며, 환자의 경우에는 의사, 인터넷, 미디어와 더불어 지인, 간호사, 다른 암환자 등 여러 정보원을 통해 암 관련 건강정보를 확인하는 것으로 파악하였다. 암 정보 요구도에 대해서는 전체적으로 '치료' , '암의 예후' , '암의 일반정도' , '심리적 지원' 에 대한 정보요구가 높게 나타났다. 환자의 경우 '예후' 와 '치료' 의 정보에서 가장 높은 정보요구도가 있는 반면, 일반인에서는 '암의 일반정보' , '예방' , '검사' 에서 가장 높은 정보요구도를 나타났다. 또한 caregiver의 '치료' , '예후' 그리고 '심리적 지원' 에 대한 정보를 요구하는 것으로 나타났다. 암 환자들의 경우 일반인들보다 의료진을 통해 암 정보를 제공받는 경우가 높게 나타났다. 환자의 경우 의료진에 대한 의존도와 신뢰도가 높고 순응도가 높으므로 의료진들에게 환자에게 제공할 양질의 암 정보를 교육자료, 상담자료 형태로 개발하여 이를 제공할 필요가 있다. 또한 환자의 가족, care giver들의 정보 요구도가 높음을 알 수 있었다. 환자를 돌보는 가족과 돌봄자들이 실제 진단, 치료 및 치료 후 과정에서 단계별로 환자의 정서적 불안을 지지하고 의학적, 비의학적 측면에서 돌봄에 필요한 정보들을 요구하게 된다. 그러므로 보호자 관점에서 이해를 도울 수 있는 맞춤형 정보를 제공할 필요가 있다고 사료된다.

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Keywords: 온라인, 암 정보, 탐색채널, 요구도

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The Association between Handgrip Strength and Cardiometabolic Risk in Korean Adults: Findings from the Korea National Health and Nutrition Examination Survey (KNHANES) VI (2014, 2015) VII (2016)

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There were few studies to examine the association between handgrip strength and metabolic syndrome and cardiovascular disease risk by separating sex. This study aimed to assessing the association of handgrip strength with cardiometabolic risk factor in the general population in Korea. Data were derived from an ongoing cross-sectional survey of the Korean National Health and Nutrition Examination Survey (KNHANES), 2014-16, which involved 12,831 participants aged 19 years and older (male: 5,670, female: 7,161). In multivariate linear regression analysis showed the significant inverse association between relative hand grip strength and cardiometabolic risk factors including blood pressure, fasting glucose level, triglyceride, low level of high density cholesterol, waist circumstance in both male and female. The odds ratio (OR) of the metabolic syndrome was significantly higher in men and women with the lowest quartile of handgrip strength than in those with the highest quartile. In both men and women, hand grip strength was inversely associated with Framingham risk score and high-sensitivity C-reactive protein.

Conclusion: Using a large national sample, our results suggest that increased hand grip may decrease metabolic syndrome and cardiovascular risk. Longitudinal studies are needed to examine the relationship between muscle strength and cardiometabolic risk.

Keywords: Handgrip strength, Cardiovascular disease, Metabolic syndrome

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The Association between Handgrip Strength and Type 2 Diabetes Mellitus in Korean Adults: Results from the Korea National Health and Nutrition Examination Survey (KNHANES) VI

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Diabetes mellitus (DM) is a significant chronic disease, and health burden from DM is increasing. Recently, studies on the relationship between handgrip strength, which is a measuring tool for muscle strength, and type 2 DM were published. However, the results have been conflicting. In addition, few studies that used data from adults in Korea have been conducted. Thus, this study aimed to identify the association between handgrip strength as well as type 2 DM and insulin resistance in adults using data from the Korea National Health and Nutrition Examination Survey (KNHANES) 2014-2015. Inflammation is a condition affecting the muscle strength of individuals with type 2 DM; therefore, its mediating effects were also examined. We included 8,208 participants aged between 19 and 80 years who had undergone a handgrip test and had received information about type 2 DM. General linear and binary logistic regression models were used to examine the association between handgrip strength and type 2 DM variables. In addition, mediation analysis was conducted to estimate the role of inflammation in the relationship between handgrip strength and type 2 DM. After adjusting for age, sex, education, alcohol consumption, lifetime smoking, obesity, and aerobic physical activity, handgrip strength was inversely associated with fasting glucose, HbA1c, and fasting insulin levels as well as the homeostasis model assessment of insulin resistance (HOMA-IR) score. Multivariable logistic regression analyses showed that handgrip strength was significantly inversely associated with type 2 DM and insulin resistance. The high-sensitivity C-reactive protein (hs-CRP), an inflammation-related biomarker, mediated approximately 10% of the association between handgrip strength and type 2 DM. Using large, well-defined, nationally representative cross-sectional data on adults in Korea, we found that handgrip strength, which is an indicator of muscle strength, was associated with type 2 DM.

Keywords: Handgrip strength, Diabetes mellitus, Insulin

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The Association between Handgrip Strength and Depression in Korean Adults: Results from the Korea National Health and Nutrition Examination Survey (KNHANES) VI

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There was little study examined the association between muscle strength and mental health, such as depressive symptoms and stress in Korea adults. And there was no study of the rate of explaining medicating pathways among influences of handgrip strength on mental health. We investigate the relationship between handgrip strength and depression and stress in general population and the rate of explaining mediated pathway by quality of life. A cross-sectional study using 4,252 subjects from individuals aged 19-80 years in Korea adults, based on the sixth Korea National Health and Nutrition Examination Survey (KNHANES VI) of 2014. We investigated the adjusted association between handgrip strength and depression, which was measured by the Patient Health Questionnaire 9 (PHQ-9). We also conducted mediation analysis for quality of life, which was measured by the EuroQol Five-Dimension Questionnaire (EQ5D). After adjusting for age, sex, education, alcohol consumption, lifetime smoking, body mass index, and aerobic physical activity, handgrip strength was inversely associated with PHQ-9 score. The odds ratios (OR) of depression symptom and stress perception were statistically significant in the first and second quartile of handgrip strength compared to those with the highest quartile. There were about 40% mediation effect of EQ5D in the relationship between handgrip strength and depression and stress perception. Using large nationally sample, our results found that lower hand grip strength is increased the risk of depression and stress. These finding suggest that increases in handgrip strength may be a protective factor for depression and stress in Korean adults.

Keywords: Handgrip strength, Depression, Mental health, Quality of life

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Association between Body Mass Index and Gastric Cancer Risk: A Pooled Analysis of Over 400,000 Asians in the Asia Cohort Consortium

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Impact of body mass index (BMI) on gastric cancer (GC), especially non-cardia GC, risk is controversial so far. Hence, this study was conducted to evaluate the association between BMI and GC risk in Asian population. More than four million participants (N=488,923) from thirteen cohorts in Asia cohort consortium (ACC) were included in this study. A total of 9,711 GC cases were newly diagnosed during a median follow-up period of 13.2 years. BMI was classified by following categories: ≤18.5, 18.5-22.9, 23.0-24.9 (reference), 25.0-27.4, 27.5-29.9, 30.0-34.9, ≥35.0 kg/m^2. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) to assess impact of BMI on GC risk were calculated using the Cox proportional hazard regression model. Stratified analyses by smoking and alcohol drinking status were conducted to investigate effect modification by these factors on the relationship between BMI and GC risk. Low BMI (<23.0 kg/m^2) was associated with significantly increased GC risk compared to the reference BMI. (HR=1.17, 95% CI=1.08-1.27 for BMI <18.5kg/m^2; HR=1.08, 95% CI=1.03-1.14 for BMI of 18.5-22.9kg/m^2). When we considered 2-year wash out period, elevated GC risks in groups with low BMI were persistent. In non-smokers, both low BMI (<23.0 kg/m^2) and high BMI (25.0-29.9 kg/m^2) were associated with higher GC risk compared to the reference BMI. Whereas, only BMI of 18.5-22.9 kg/m2 was related with increased GC risk in smokers. In the same manner, U-shaped association between BMI and GC risk were only found in non-drinkers. This study suggests U-shaped relationship between BMI and GC risk, especially in non-smokers and alcohol non-drinkers whose baseline hazard is not higher than smokers and alcohol drinkers.

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Keywords: Stomach Neoplasms, Body mass index, Incidence rate, Cohort, Asian

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Auto-reporting System for Notifiable Infectious Diseases in Korea: IT-based System Capable of Reporting in Real Time

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Early recognition of infectious disease (ID) outbreaks is a prerequisite for prompt response to and preventing the spread of ID. Notification of healthcare providers is the first requirement. Hence, medical institutions should report ID to National Notifiable Infectious Disease Surveillance System as soon as possible. This project aimed to develop and operate the infectious disease auto-reporting system (IDARS) to facilitate reporting of ID. IDARS supports healthcare providers' reporting of ID by automatically filling out required information based on electronic medical record. The present project was conducted in four steps: 1) Definition and redesign of the criteria for IDs, 2) Survey and analysis of current status, 3) Developing a support strategy, and 4) Verification and Evaluation. The research/activities performed at each step are as follows; We designed this system based on '1) Definition of data standards for data linkage, Verification of usability of standard healthcare terminology, Redesigning the process of ID reporting of medical institutions, Development of the amendment of ID notification form', and '2) Analysis of case for the linkage strategy of medical institution, Survey and analysis of utilization level of an ID monitoring system at medical institutions'. Next, we installed the system through '3) Support the development of guideline for linking procedures and standard application, Operation of homepage to spread the system, Development of education contents and curriculum for user of IDARS'. After installing the system, we have been performing '4) Verification of data consistency for data reliability, Monitoring the usage of auto-reporting system'. IDARS is a good practice using ICTs to promote health. It improved the process of ID reporting: quickly, conveniently and accurately. So far, more than 2,000 medical institutions are participating in IDARS at the end of 2017. Expansion of IDARS is necessary to prevent delay or unreported cases of ID and to recognize the occurrence of ID in real time.

Keywords: Auto-reporting System, Infectious Disease, Korea, ICTs, Real Time

대한의사학회

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후지나미 아키라의 학술적 궤적 — 의사학적 활동을 중심으로

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후지나미 아키라(藤浪鑑, 1871~1934)는 근대병리학의 창시자 피르호(Rudolf Virchow, 1821 ~ 1902)를 사사하고 교토제국대학 병리학교실의 초대 교수로 부임하여 일본의 근대적 기초의학의 토대를 구축한 인물이다. 일본주혈흡충증의 박멸 및 후지나미육종(Fujinami sarcoma)의 발견이라는 세계적인 업적으로 잘 알려져 있지만, 대만, 만주, 브라질 등지를 답사하며 지리병리학적 연구를 진행하고 사회의학 관련 저술을 남기는 한편, 의사학의 계몽활동에도 진력했다. 특히 1907년 교토의학회 총회에서 대규모의 의학사 전시회를 기획했고, 1909년에는 일본의사학계의 태두 후지카와 유(富士川游, 1865~1940)의 교토제대 의사학 강의를 실현시켰으며, 1927년 일본의사학회 발족 때 발기인 및 평의원으로 참여하기도 했다. 하지만 당시 의학계에서는 의학사 전시회를 "보람 없는 헛수고"라 폄하하거나 의사학자 후지카와의 의학박사 학위 수여를 못마땅하게 여기는 등 의사학에 대한 불만 내지는 몰이해가 팽배했다. 이에 대해 후지나미는 다수의 지상 발표를 통해 철저한 모방의학인 일본의학의 현상을 엄중하게 지적하고 역사인식의 재고를 통해 일본의학을 확립해야 한다고 역설했다. 의사학이란 의학의 한 분야로서 현재의 의학적 지식을 충실하게 만들 뿐만 아니라 미래 진보의 방침까지 가르쳐주며, 의학이 전문화될수록 그것을 종합하고 총괄하는 의사학의 존재 의의가 커진다는 것이다. 또 직접 병리학과 각기병 등의 사적 연구를 실천하고, 인간문화사로서의 의학사라는 인식을 바탕으로 인간과 사회에 대해 탐구했다. 이처럼 그는 근대의학의 수용 및 발전을 촉진하면서도 전통의학을 포함한 과거의 성과를 이해하고 소화함으로써 서양의학의 아류에서 벗어날 일본의학의 장래를 구상했다. 그리고 당대 문화계의 인사들과 교류하며 동서고금을 망라하는 다원적인 사색을 펼쳤다. 그의 학술적 궤적은 온후한 성격 및 확고한 교육철학과 어우러져 후학들에게 큰 영향을 주었는데, 그 중에는 한국인 최초의 병리학자이자 대한의사학회 초대 이사장인 윤일선도 포함되어 있었다.

Keywords: 후지나미 아키라, 교토제국대학, 근대의학사, 일본의학사, 윤일선

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4차 산업혁명을 계기로 맞은 한국의 의료일원화

김재식, 박언휘, 서영익, 정승필, 김인겸, 김대현, 여상희, 김학균, 김건엽
경북대학교 의과대학 경북대동서의학연구회

세계가 4차산업혁명의 계기를 맞아 의학도 불가사의하게 변하고 있다. 특히 임상의학에 있어서 불가사의한 혁명을 초래하여 상상을 초월하는 첨단과학의 초현대의학을 이루고 있어서 인간의 평균수명은 100세 이상으로 늘어 날 전망이다. 현상학적으로 상상을 초월하는 가능한 인간복제 시대를 만들었다. 분자유전자의학에 이어 외과적수술방법에 있어서 로봇수술이 등장했는가 싶었는데 에이아이인공지능왓슨 암치료센터에서 기계가 악성종양인 암을 진단하고 치료한다. 지금까지 한국의학은 후진성의 의료이원화제도를 아직도 고집하고 있는 모순된 의료제도 깨문에 비과학적인 고대원시의학 즉 한의학(漢醫學)이 정책적으로 병용되고 있는 실정이다. 가까운 이웃 선진국 일본은 한의사제도를 지금으로부터 123년전인 1895년 결사반대에도 국회에서 폐지하여 오늘날까지 의료일원화를 하여 한의사(漢醫師)가 없다. 결과적으로 피해는 국민에게 돌아간다. 특히 초를 다투는 심장마비나 노출혈같은 응급환자의 경우 시기를 놓지는 경우가 허다하다. 생명을 다루는 의학은 과학적 근거중심의 친료를 해야한다. 그래서 생명을 다루는 의학은 객관적이고 정확하고 가장 안전한 근거중심의 의학이 되어야 한다. 치료의 원리에서 현대서양의학은 기본적으로 청진기, 체온계, 혈압계와 초음파, 심전도, 임상병리검사등을 중심으로 초고도의 임상검사를 총동원하여 진단하고 오늘 날의 로봇수술과 심지어 인공지능암치료 등등 까지 초과학적방법을 이용하여 완벽한 치료까지 하는 시대인데 반하여 한방에서 시행하는 손으로 하는 진맥(診脈)과 음양오행설의 경락을 이용한 치료를 한다는 것은 이제 뒤를 돌아 보아야 한다. 이렇듯 현대의학과 한의학은 천지의 차이이다. 중국의 장궁야오(張功耀)교수의 십여년전의 초청강연에서 한방의 무용론강의는 아직도 세계에 경종을 울리고 있다

Keywords: 4차산업혁명, 의료이원화제도, 현대의학과 한의학, 로봇수술, 인공지능암치료, 장궁야오(張功耀)

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한국과 일본의 기생(寄生) 혐오 담론과 기생충 박멸운동

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1798년 독일의 시인이자 소설가 노발리스는 암(癌)을 "완전히 다 자라난 기생충"이라 정의했다. 당대 사람들이 인식한 기생충의 존재는 암이 주는 해악에 비견할 만한 것으로, 기생하는 존재에 대한 감정은 혐오 이상이었을 것이다. 한국에서 기생충은 거위, 회 등으로 불리며 사람과 더불어 사는 생물이었다. "거위가 없으면 말을 못한다", "거위가 없으면 밥맛이 없고 거위가 하나도 없으면 죽는다"라며 오히려 사람의 몸에 기생충이 없으면 해를 입는다고 생각했다. 일본 또한 한국과 마찬가지로 기생충 감염이 만연해 있었고 역시 기생충에 대한 속담과 관용구가 민간에 전해 내려왔다. 화가 가라앉지 않는다는 의미로「腹の虫がおさまらない」, 기분이 나쁘다는 의미로「(腹の) 虫の居所が悪い」라는 관용적인 표현들이 사용되었다. 이처럼 신체 내에 기생하는 벌레의 감정을 숙주와 동일시한 것을 보면 기생충을 숙주와 매우 친밀한 존재로 여겼음을 짐작할 수 있다. 하지만 '거위'를 '기생충'이라 명명하고 그 생활사를 알게 되면서 생존에 필수적이고 자신과 감정을 공유한다고 여겼던 '거위'를 대하는 대중의 인식이 바뀌게 된다. 한국과 일본 모두 무위도식하며 다른 사람이 이룬 것을 취하는 존재들을 그 지위 고하를 막론하고 기생충에 빗대어 비난했다. 한국에서는 일제 강점기 조국의 어려운 상황을 외면하고 본인들의 영달만 추구하는 부류를 기생충에 비유하며 지탄하는 경우가 많았고, 일본에서는 노동하지 않는 빈민이나 투자자본가 등 각 계층의 '눈엣가시'들을 기생충이라 부르며 비하했다. 이와 같은 기생하는 존재에 대한 혐오의 담론은 더불어 살던 기생충을 박멸의 대상으로 바꾸는 데 정당성을 부여했다. 성경의 미가서에도 "밭이 탐나면 밭을 빼앗고 집이 탐나면 집을 빼앗는" 존재들에 대한 언급이 있다. 기생하는 존재는 인류 사회에 늘 있어왔고 혐오의 대상이 되었으며 그들에 대한 혐오감이 기생충이라 불리게 된 뱃속 벌레들에게 전이되었다. 20세기 중·후반에 기생충의 감염률이 급격히 감소하게 된 데는 위생환경 개선, 대규모 구충사업 등이 기여했지만, 무엇보다 일반 대중이 기생충을 박멸의 대상으로 취급하는 것에 동의하고 전 국가적인 기생충 박멸운동에 호의적으로 참여했기 때문에 가능했을 것이다. 요컨대 한국의 '기생충 박멸운동', 일본의 '회충제로작전' 등 기생충 퇴치 사업은 사람의 몸에 사는 벌레를 뜻하는 미시기생(微視寄生)뿐만 아니라 사람을 포함한 기생하는 모든 존재를 뜻하는 거시기생(巨視寄生)에 대한 대중의 혐오를 바탕으로 성공적으로 시행될 수 있었다.

Keywords: 기생충, 거시기생, 기생충 박멸운동, 회충제로작전, 혐오

▶▶▶ P-201

윌리엄슨 대 리 옵티컬 사건을 통하여 분석한 현대 미국의 안경 관련 업무 영역 분쟁

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본 연구는 미국과 우리나라의 안과 관련 의료 전문가 집단의 구성과 구성원의 업무 범위를 비교하여, 그들이 지니고 있는 직무 속에서 발생한 직무 영역 분쟁의 역사를 탐구하고, 그러한 영역 분쟁이 지니는 역사적 의의를 연구하였다. 1955년 미국에서 검안사와 안경사의 영역에 관한 소송이 일어난다. 이 사건은 광학적인 기술에 측면을 가지고 있는 안경사와 의료적 성격을 가지고 있는 검안사 간의 직무 영역 분쟁이라는 측면과, 같은 보건의료인 간의 직무 영역 분쟁이라는 양 측면을 모두 가지고 있다. 본 연구는 그 가운데 특히 동일한 안경 관련 보건 전문가 집단 사이의 직무 영역 갈등이라는 측면에 초점을 맞추어 소송 사건의 전개과정을 분석하였다.

Keywords: 안경사, 검안사, 직무 영역 분쟁

대한해부학회

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Puerariae Radix Extract Stimulates Cell Proliferation via Phosphorylation of ERK and Akt in Human Dermal Papilla Cells

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In animal studies, *Puerariae Radix* extract was proven to have antidepressant, antioxidation, osteonecrosis prevention, hypolipidemic, elevating the apoptosis rates of NB4 cells. We investigated the effect of ethanol extracts of *Puerariae Radix* (EPR) on cell proliferation, and analyzed the molecular mechanism in human hair dermal papilla cells (HHDPCs). After exposure to EPR in HHDPCs, cell proliferation was increased compared with minoxidil-treated cells. Treatment with EPR led to phosphorylation of extracellular signal-related kinase (ERK) and Akt. Moreover, EPR-mediated increase of cell proliferation was attenuated by PD98059, ERK inhibitor, and LY294002, Akt inhibitor. These results suggest that EPR induced cell proliferation in HHDPCs by the activation of ERK and Akt.

Keywords: *Puerariae Radix*, HHDPCs, Cell Proliferation, ERK, Akt

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응집-유도 형광방출 분자의 분해에 기반한 금 이온 검출 프로브 개발 및 생체영상화 연구

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금 (Au)은 기술 혁신의 초기 단계에서부터 가치 있는 소재로서 전세계에 널리 사용되고 있다. 최근에는 금과 금이온의 고유한 화학적, 광 물리적 성질이 기초의학 및 첨단 시스템 전반에 걸쳐 다양한 용도로 사용되고 있다. 특히 금의 높은 생체 적합성은 약물 및 유전자 전달 시스템, 바이오 센서, 바이오 영상화 소재, 항암제, 항생제 및 정수 시스템을 포함한 생물학, 의학분야에 널리 응용되고 있다. 일반적으로, 금속성 금 [Au(0)]은 안정하지만, 특정 조건 (활성산소종 등) 하에서는 금 이온 [Au(III)] 형태로 산화된다. 금 이온은 반응성이 높아 촉매반응 등에 사용되어지고 있으나, 이러한 높은 반응성은 잠재적인 생물학적 독성을 보일 수 있다는 문제점을 가진다. 현재까지, 금 이온을 분석하기 위한 다양한 종류의 분석 방법 (분광법, 전기 화학적 분석법 등)이 개발되었지만, 이러한 분석 방법은 생물학적 및 의학적 시료분석으로 큰 제한점을 보였다. 최근 큰 주목을 받고 있는 형광 기반 프로브 물질은 이러한 문제점을 극복할 수 있는 대안으로 제시되고 있다. 형광 기반 프로브는, 간단하고 편리하며 비용 효율적이고, 고감도 및 높은 선택성이 있고, 높은 생체 적합성을 가진다. 본 연구에서는 응집-유도 형광방출 분자의 분해를 기반으로 한 금 이온 검출 목적의 새로운 형광 프로브가 개발하였고, 이를 이용한 생체 영상화 연구를 수행하였다. 개발된 프로브는 응집-유도 특성으로 인하여 형광을 발현하고 있으나, 금이온을 만나 선택적으로 분해되어 형광이 소멸되는 특징을 보였다. 프로브는 소량의 금 이온을 검출할 수 있는 높은 감도를 보였으며, 빠른 반응 시간, 다른 금속에 비해 높은 선택성, 높은 생체 적합성 등의 우수한 성능을 보였다. 본 연구를 통해 개발된 금 이온 검출 프로브는, 금 이온이 생체에 미치는 영향에 대한 분석이나, 금 이온 입자의 생체 축적 검증 등의 목적으로 의학, 생물학, 등 다양한 분야로 활용이 가능할 것이라 기대된다.

Keywords: 금, 금 이온, 형광 탐침, 응집-유도방출, 생체영상화

▶▶▶ P-204

다공성 실리콘 나노입자와 이광자 현미경을 이용한 암 특이적 생체영상화 연구

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형광을 기반으로 한 생체 영상화는 고해상도로 원하는 부위만을 선택적으로 관찰할 수 있고 비교적 조작이 간단하며, 비용이 저렴하고 비침습적으로 특정 기질만은 신속하게 시각화한다는 장점이 있다. 공초점 형광 현미경 (confocal microscopy)은 이러한 생체 영상화 연구에 많이 활용되고 있지만, 조직을 관찰하는 데 있어 생체 내의 다양한 종류의 물질들 영향 (빛의 산란, 자가 형광 간섭, 등)으로 인해 샘플의 표면 (수십 마이크로미터)만을 관찰할 수 있다는 한계를 가진다. 이러한 문제점을 극복하기 위하여 개발된 이광자 현미경 (two-photon microscopy)은, 공초점 형광 현미경보다 긴 여기 파장(650-1000nm)을 사용할 수 있으며, 이로 인해 조직의 자가 형광 및 산란의 감소로 인해 침투 깊이가 증가하고, 향상된 공간 해상도를 보인다는 장점이 있다. 본 실험에서는 상대적으로 높은 광 흡수량과 큰 양자 수율을 가지고 광학적으로 안정하며 근적외선 영역(near-infrared)에서 광 발광할 수 있는 다공성 실리콘 나노입자를 합성하고, 입자 표면에 암 표적화 작용기를 기능화하여, 이를 암을 이식한 살아있는 동물 모델에서의 생체 영상화 연구를 수행하였다. 다공성 실리콘 나노 입자는 일반적인 유기 형광체와 비교하여 광 안정성이 좋고, 생체 내에서 자연적으로 존재하는 실리콘의 형태인 $Si(OH)_4$ 형태로 분해되는 장점이 있다. 연구 결과, 질병 표적 작용기를 부착한 다공성 실리콘 나노입자는 암 부위에 선택적으로 응집되어 생체 영상화가 효과적으로 구현되었으며, 이는 암뿐만 아니라 표적 작용기의 종류에 따라 다양한 종류의 질병을 쉽고 빠르며 정확하게 영상화하는 연구로 응용 가능함을 제시하였다.

Keywords: 나노입자, 생체영상화, 나노의학, 이광자 현미경

▶▶▶ P-205

파장대 조절이 가능한 신규 분자 프로브의 개발 및 이를 이용한 생체내 세포막 영상화 연구

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생체내의 다양한 세포와 세포소기관들, 그리고 그 내부에 존재하는 소포체들은 막으로 둘러싸인 구조로 막 외부의 환경과 독립적으로 내부의 고유한 환경을 유지하고 있다. 세포의 현상들을 조절하는 여러 단백질 또한 막에 존재하며, 나아가 세포의 성장, 사멸, 분화 혹은 이동과 같은 생명현상들이 막 지질의 조성과 막 구조의 변화로부터 동반된다. 이렇듯 생체막은 세포질로부터 구분지어지는 경계이자 여러가지 생리현상을 조절하는 역할 또한 수행하기 때문에 기초의학에서 생물학적 기전 연구 및 막과 관련된 다양한 질병의 연구에 있어서 중요한 연구분야 중 하나로 자리잡고 있다. 분자 프로브를 이용한 생체내 물질의 영상화는 세포 및 분자수준 혹은 그 이상의 생물학적 과정에 대한 연구 수행에 있다는 점을 바탕으로 생물학적, 의학적 연구분야에서 활발하게 활용되어 왔다. 형광 프로브는 이러한 생체막과 관련하여 물리적인 특성에 대한 정보를 제공해주고, 생체막의 시각화를 가능하게 한다. 특히 살아있는 세포의 실시간 이미징을 할 수 있다는 점에서 생체와 관련된 연구에서의 형광 프로브는 강력한 도구로 알려져 있다. 본 연구에서는 분자 프로브 중에서도 형광을 기반으로 하고, 세포막에 특이적인 새로운 구조의 신규 형광 분자 프로브를 개발하였고, 이를 이용한 생체내의 세포막 영상화 연구를 수행하였다. 공초점 현미경 (confocal microscopy)과 이광자 현미경(two-photon microscopy)을 이용한 생체영상화 연구를 통해 개발된 프로브가 생물학적인 환경에서 성공적으로 세포막을 선택적으로 표지화 함을 보였다. 프로브는 간단한 구조적 변화를 통해 생체막을 원하는 파장대의 색상으로 염색할 수 있게 해준다. 안정적이고, 민감하여 세포막을 파괴하지 않으며 막에 결합할 수 있기 때문에 기존의 세포막 염색법들과 차별적으로 전처리 과정이 간단하다는 장점을 가지고 있다. 더 나아가 생체 내에 존재하는 여러 물질 및 소기관들을 목표할 수 있는 표적화 작용기를 추가로 도입할 수 있다는 점에서 다양한 연구분야로의 확장 연구가 가능하다는 장점을 가진다. 생체내 세포막의 시각화를 통해 살아있는 세포의 동적인 과정을 측정하고, 그 역학을 이해할 수 있는 기능적인 형광 프로브의 개발은 생물학적 기초연구와 기초의학의 질병 기전 및 응용 연구에 있어 토대가 될 것으로 전망된다.

Keywords: 분자 프로브, 형광 영상화, 세포막 영상화

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EnGel™-Based 3D Cell Culture System as an *in Vitro* Prostate Cancer Model

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Conventional 2D prostate cancer cell culture models do not reflect the true biological activities of prostate cancer cells in vivo, and thus drug screening and testing in 3D prostate cancer cell culture models are more effective than conventional 2D monolayer culture system. In the present study, we established a hydrogel-based 3D prostate cancer culture system using various human prostate cancer cell lines (LNCaP, DU145 and PC3). It was found that cells cultured in the hydrogels grow as tumor-like clusters in 3D formation when compared to cells cultured in 2D monolayer culture. Histological examination of all the three types of prostate cancer cells demonstrated the formation of spheroids, whereas none of the cell types in 2D formed any spheroids. RT-PCR, Western blot, drug resistance and immunofluorescence staining analyses revealed that the expression of various genes related with prostate cancer malignancy was significantly up-regulated in all the three types of cells in 3D cell culture when compared to 2D cell culture. Furthermore, increased migration and invasion in all three types of the human prostate cancer cells were observed in cells cultured in 3D compared to those in 2D. Therefore, this study provides a novel hydrogel-based 3D culture technique for human prostate cancer cells that closely mimicked in vivo cancer progression. Furthermore, our data may provide a useful platform technology to develop functional, biocompatible, three-dimensional scaffolds for 3D culture of various cancer cells.

Keywords: EnGel Hydrogel, 3D Culture, Tumor Spheroid, Postate Cncer

▶▶▶ P-207

In Vitro 3D Culture Model of Thymic Epithelial Cells on Bioactive Electrospun Nanofibrous Scaffolds

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Bioactive electrospun nanofibrous scaffolds have been gaining increasing attention as a promising strategy for 3D cell culture and for tissue engineering applications. We constructed a novel composite marine collagen-based (MC/PCL) nanofibrous scaffold by electrospinning method to develop scaffolding materials with outstanding biocompatibility and favorable mechanical strength for 3D culture of thymic epithelial cells (TECs). Nanofibrous scaffolds were characterized using a scanning electron microscope (SEM), and it was revealed that the nanofiber diameters decreased with increasing MC content in the MC/PCL composite nanofibers. The cytocompatibility of the MC/PCL scaffolds was evaluated by SEM, WST-1 assay, confocal microscopy, western blot, and RT-PCR. It was found that the scaffolds not only facilitated the adhesion, spreading, protrusions, and proliferation of TECs but also effectively stimulated the expression of genes and proteins involved in cell adhesion and T cell development. Therefore, these results suggest that the composite MC/PCL nanofibrous scaffolds will be a useful model of 3D cell culture for TECs, and may have wide applicability in the future for 3D cell culture of various cell types and for tissue engineering.

Keywords: Nanofiber, electrospinning, 3D cell culture, thymic epithelial cells

▶▶▶ P-208

Regulation of Necroptotic Factors in Gastric Cancer Cells through miR-93-5p and EBV-miR-BART 18-3p

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Epstein-Barr virus (EBV), as well as Helicobacter pylori, has recently been admitted as an infective agent causing gastric carcinoma(GC). EBV encodes multiple non-coding RNAs during all types of latency, 44 mature miRNAs have been identified. EBV-encoded microRNAs showed that these small molecules function as post-transcriptional gene regulators and may play a role in the carcinogenesis process. MiR-BARTs produced by EBV can regulate cellular genes for preventing apoptosis and escaping the host immune system. We examined interactions of microRNAs with necroptosis factors in EBV positive/negative gastric cancer cells. RIPKs(receptor-interacting serine/threonine-protein kinase) were little expressed in EBV positive cells. Incubation of EBV negative gastric cells with EBV particles or exosome purified from EBV positive cells revealed that MLKL as a regulator of necroptosis were decreased. We investigated expression profiles for viral and cellular miRNAs in EBV positive/negative gastric cancer cells. To identify possible miRNAs targeting necrotic factors, we searched miRNA candidates that could bind to sequence in the 3'UTR of necrosis factors using an online miRNA database. We found the putative target binding sites of EBV-miR-BART18-3p (BART18-3p) within MLKL 3UTR and miR-93-5p within RIPK3 3'UTR. Expectedly, we observed that EBV negative KATOIII transfected with mimics for BART18-3p diminished expression of p-MLKL, inhibitor for BART18-3p increased p-MLKL in EBV positive SNU719. However, mimics for miR-93-5p decreased RIPK1 rather than RIPK3 in EBV negative KATOIII. Taken together, we suggested that EBV might regulate necroptosis in gastric cancer cells through miRNAs including BART18-3p and miR-93-5p.

Keywords: EBV, gastric cancer, necoptosis, miRNA

▶▶▶ P-209

Role of KLF4 in Controlling Proliferation and Survival of Periovulatory Granulosa Cell

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In the ovary, LH surge suppresses proliferation and induces luteinization of preovulatory granulosa cells (GCs), which is crucial for the survival of terminally differentiated GCs. KLF4 has known to play a role in regulating cell cycle and apoptosis in various cell types. In addition, rapid induction of KLF4 expression by LH surge was found in preovulatory GCs. To evaluate whether KLF4 affects GC proliferation and survival, primary rat GCs were isolated from PMSG-primed rat ovary and transfected with KLF4 expression vector or KLF4-specific siRNA, followed by determination of cellular proliferation or transcript levels of Bcl-2 and Bax, which are involved in GC apoptosis. Cell viability and proliferation were analyzed by CCK-8 and BrdU incorporation. The results showed that KLF4 overexpression caused significant decreases in cell viability and proliferation rate, accompanied with decreases in Bcl-2 expression or Bcl-2/Bax ratio. On the other hand, KLF4 knockdown increased endogenous mRNA expression of Bcl-2, whereas Bax expression was not changed. In conclusion, KLF4 may affect the fate of preovulatory GCs possibly by directly inhibiting proliferation and anti-apoptotic gene expression. Therefore, KLF4 may represent an endogenous key factor in determining the rate of GCs apoptosis until GCs could attain enough resistance to apoptosis in response to LH surge.

Keywords: KLF4, Granulosa Cells, LH surge, Apoptosis, Proliferation

▶▶▶ P-210

사람 다형성아교모세포종 세포주인 U87-MG와 T98G에서 할미꽃 추출 사포닌 D의 항암효과에 관한 연구

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다형성아교모세포종(glioblastoma multiforme; GBM)은 진단 후 1~2년 내에 사망할 정도로 생존율이 낮고 치료하기 어려운 뇌종양이다. GBM에 대한 표준 치료 방법은 수술적 제거를 원칙으로 하면서, 동시에 방사선 치료와 항암제 치료를 병행하는 것이다. 이때 항암제로 널리 사용되는 것이 구강 복용용 알킬화약물(alkylating agent)인 temozolomide (TMZ)인데, 이에 대한 내성과 부작용이 문제가 되고 있다. 부작용을 줄이고 내성을 극복하기 위한 전략으로 여러 종류의 약제를 병행하여 사용하는 것이 시도되고 있다. 대표적으로 autophagic flux 억제제들이 TMZ와 함께 사용되어 효과를 나타내지만, 이 또한 부작용이 있다. 할미꽃 뿌리에서 추출한 사포닌 D (SB365)는 *in vitro*와 *in vivo* 실험에서 다양한 암세포의 세포사멸를 유도하고, autophagic flux를 억제하는 것으로 보고되었다. 하지만 GBM에서의 항암효과에 대해서는 연구된 바가 없다. 본 연구에서는 SB365가 GBM에 항암효과를 나타내는지를 확인하고자 하였다. 동시에, autophagic flux 억제제로서 TMZ와 동시 투여 시 상승작용을 나타내는지 확인하고자 하였다. *In vitro* 실험 결과 SB365는 GBM 세포주인 U87-MG 세포와 T98G 세포에서 용량-의존적으로 세포성장 억제와 세포사멸을 유도하였고, autophagic flux를 억제하였다. 또한 TMZ와 동시 투여 시 이들 암세포주의 세포사멸을 부가적으로 증가시켰다. 생쥐에 U87-MG 세포를 접종 후 실시한 in vivo 실험에서 SB365와 TMZ의 combination은 종양 성장을 각각의 약물을 단독으로 투여했을 때 보다 현저히 억제하였다. 정리하자면, SB365는 GBM 세포주인 U87-MG와 T98G에서 항암효과를 나타내었으며, TMZ와 동시 투여 시 부가적 효과를 나타내었다. 이러한 결과는 SB365가 GBM에 대한 새로운 치료제나 TMZ에 대한 보조치료제로서의 가능성을 시사하는 것으로 사료된다.

키워드: 할미꽃 사포닌 D, 다형성아교모세포종, U87-MG, T98G, Temozolomide

▶▶▶ P-211

The Effects of High Peripubertal Caffeine Exposure on the Adrenal Gland in Immature Male and Female Rats

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The consumption of high levels of dietary caffeine has increased in children and adolescents. Human and animal studies have shown that chronic intake of high doses of caffeine affects serum glucocorticoid levels. Given that glucocorticoids play a role in peri-pubertal organ growth and development, chronic high doses of caffeine during puberty might impair maturation of the adrenal glands. To evaluate any effects of caffeine exposure on growing adrenal glands, 22-day-old male and female SD rats were divided into 3 groups; group 1 received tap water (control) and groups 2 and 3 receivedwater containing 120 and 180mg/kg/day caffeine via gavage for 4 weeks. At the end of experiment, adrenal glands were weighed and processed for histological analysis. Relative adrenal weights increased in both caffeine-fed males and females, whereas increases in absolute weights were only noted in the females. Adrenal cortical area increased and appeared as irregularly arranged cords in the female caffeine-fed groups, whereas no sucheffects were found in the male rats. Serum corticosterone levels decreased in the caffeine-fed males and females. Our results indicate that peri-pubertal caffeine exposure disturbsthe gross and microscopic maturation of the adrenal glands as well as the coordinated regulation of the hypothalamo-pituitary-adrenal axis, and its impact is more profound in female than in male rats.

Keywords: Adrenal gland, Caffeine,Corticosterone, Puberty, Rat

▶▶▶ P-212

Prognostic Value of TZAP Expression in Various Cancers: TCGA Data Analysis

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The zinc finger protein ZBTB48 is a telomere-associated factor and renamed it as telomeric zinc finger-associated protein (TZAP). It binds preferentially to long telomeres competing with TRF1 and TRF2. However, its expression in cancers has not been performed. Methods: In the present study, we analyzed the prognosis of TZAP expression in 22 kinds of cancers by using TCGA data analysis. TZAP expression had a prognostic value in cervical, colon, and pancreatic cancers. When sorting the patients differently, it got the significance in bladder, breast, kidney, brain, and lung cancers. TZAP expression was associated with better prognosis in bladder, breast, cervical, lung, and pancreatic cancers. However, it showed poorer survival results in colon, kidney, and brain cancers. This result suggested that TZAP expression appears to be a possible prognosis marker in various cancers.

Keywords: TZAP, Telomere, ZBTB48, TCGA

▶▶▶ P-213

Age Estimation of Children Using Tomography-based Volumetric Quantification of the Ossification Centers

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Background: Estimation of age is used for the assessment of growth disorder, bioarchaelogic research, forensic science and criminal proceeding. However, classical scoring system of secondary ossification centres for age estimation requires the involvement highly-expertised person but lacks the precise results. This study aimed to get the equations between age and the volume of various ossification centres in the body. **Methods:** Two hundred CT image sets of the patients between the age zero and 26 were used for this study. The volumetric information was taken from the ossification centres in femoral head, iliac crest, humeral head and manubrium. It was determined at which stages of ossification the volume and age had an association with each other. The equations for the age estimation by the volume of the ossification centres during those stages were calcutated. **Results:** The volume of secondary ossification centre in the femoral head and the volume of the secondary ossification centres in the iliac crest had a great correlation with the age before the complete fusion. The volume of the secondary ossification centres in the proximal part of the humerus had a great correlation with the age before the beginning of any fusion with the diaphysis. The volume of the manubrial ossification centre had a great coefficient before the beginning of any fusion between the ossification centres in the sternal body. In the male, the equations for the age estimation by the volume of the femoral head, iliac crest, proximal humerus and sternum were age(year)=1.89×volume(cm^3)$^{0.64}$, age=(-0.009)×volume^2+0.47×volume+14.01, age=1.21×volume$^{0.75}$, and age=(-0.043)×volume^2+1.58×volume-1.3, respectively. In female, they were age=(-0.0094)×volume^2+0.79×volume+1.74, age= 15.04×volume0.075, age=(-0.021)×volume2+0.95×volume+0.60, and age= 1.08×volumeV. The accuracy of the equation was best with the iliac crest in male (standard error of estimates=0.92 years) and with the humerus in female (0.64). **Clinical Relevance:** By the volumetry of the ossification centres in series of the body parts depending on the development stage, the age of children can be estimated with a minimal error.

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한국인의 얼굴비례계측 및 개인의 미적만족도 간의 상관관계

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현대시대에서 얼굴이 형태와 미에 대한 기준과 기대치가 높아져가고 있다. 이에 한국인의 얼굴구조 및 비례를 계측해보고 그 결과와 개인의 미적만족도와의 상관관계에 대해서 알아보고자 한다. 계명대학교 의과대학 재학생 44명(남 29명, 여 15명)을 대상으로 자체개발한 설문조사를 시행하였다. 설문조사는 한국의 대학생들의 얼굴의 가로비율, 세로비율, 눈의 크기, 코의 높이 등을 포함한 항목에 대한 신체 계측과 개인의 미적만족도와 관련된 총 10개의 문항을 포함한다. 얼굴계측을 통해 얻은 데이터를 가공하여 각종 비율을 얻었고, 이 비율과 각 평가 문항에 대한 응답과의 상관관계를 SPSS를 사용하여 분석하였다. 계측결과 얼굴의 세로높이와 가로넓이의 평균은 1:1:1의 비율을 보였다. 평균적인 눈의 크기는 가로는 3.32cm, 높이는 1.25cm으로 나타났다. 코의 평균높이는 2.43cm이였다. 보조개는 12명(28.6%)에서 나타났으며, 피부톤은 보통(n=30)이 대부분이고, 나쁘다와 좋다(n=7)가 똑같이 나왔다. 미적만족도는 50점 만점에 평균 29.9점이였으며, 이 결과는 이마의 넓이(r=-0.379, p = 0.016)와 반비례 하였고, 코의 넓이(r=0.379, p =0.018)와 피부톤(r=0.346, p = 0.026)은 양의 상관관계를 보였다. 본 연구를 통해서 얻은 한국인 얼굴의 형태와 비례에 대한 기본 자료로써 다양하게 이용될 수 있으며, 이를 개인의 미적만족도와 비교해봄으로써, 개인의 미적 기준에 따른 잘못된 인식과 스트레스를 줄일 수 있을 것으로 생각된다.

Keywords: 얼굴비례, 미적만족도, 황금비율

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Variations in Branching Pattern of the Anterior Circumflex Humeral Artery

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Anatomic variations in the branching pattern of the axillary artery are common and have been studied by many authors. The origin of the anterior circumflex humeral artery is also various and its association with other variations has been focused recently. This study identified the origin of the anterior circumflex humeral artery, the communication between the musculocutaneous and median nerves, and the third head of the biceps brachii muscle, and then their associations were examined. Axillae of 75 cadavers were dissected and these variations were collected. The anterior circumflex humeral artery arose directly from the third parts of the axillary artery in 82.0% of upper limbs. It also arose as common stem for both humeral arteries in 7.3% of the third part of the axillary artery and in 5.3% of the subscapular artery, respectively. The anterior circumflex humeral artery was absent in 2.7% and two anterior circumflex humeral artery was found in 1.3% of limbs. The communication between the musculocutaneous and median nerves and the third head of the biceps brachii muscle were found in 32.0% and 16.0% of upper limbs, respectively. These variations were not statistically associated with each other. These results may provide deep knowledge about the anatomy of the anterior circumflex humeral artery and contribute to explain its clinical implications.

Keywords: Anterior circumflex humeral artery, Axillary artery, Cadaver, Variation

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Quantification of Intraepidermal Nerve Fiber Density Using Three-dimensional Microscopy

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Three-dimensional microscopy provides more extended depth of penetration compared with conventional light microscopy and is known to be useful in clinical evaluation of thick biological specimens. Skin nerve biopsy together with the quantification of intraepidermal nerve fibers in multiple thick sections has been widely adopted for evaluating peripheral neuropathies. The aim of the present study was to evaluate the effectivity of three-dimensional microscopy in reducing the required time and inter-rater discrepancies, especially in the case of personnel not familiar with the quantification methods. A total of six cryo-sectioned specimens were analyzed for the study and the skin samples were collected from one patient with post-herpetic neuralgia who voluntarily participated in the study. Two investigators, a physician and non-physician assessed the intraepidermal nerve fiber densities and required analysis time using three different methods including direct visualization of tissue slides, and analysis with two- and three-dimensional images. Three-dimensional microscopy could produce images that enabled reliable evaluation of intraepidermal nerve fibers; the accuracy of analysis was statistically comparable between the physician and non-physician (p> 0.05). Three-dimensional microscopy also enabled the non-physician to proceed meaningfully faster evaluation compared with the direct visualization method (p= 0.03). Three-dimensional microscopy could be one of the useful methods to improve accuracy and convenience of the analysis of intraepidermal nerve fibers especially appropriate for unaccustomed physician or non-physician.

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The Pathogenic Role of Interleukin-22 and its Receptor during UVB-induced Skin Inflammation

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Recent studies show that IL-22, a cytokine produced by activated $CD4^+$ T cells and NK cells, plays a pathogenic role in acute and chronic skin diseases. While IL-22 is produced by immune cells, the expression of IL-22Rα, the functional subunit of IL-22R, is mostly restricted to non-hematopoietic cells in organs such as the skin and pancreas. Although it is well known that ultraviolet B (UVB) radiation induces skin inflammation, there have been no reports regarding the effect of UVB on the expression of IL-22Rα. This study investigated IL-22Rα expression and IL-22-mediated proliferation and pro-inflammatory cytokine production by UVB-irradiated keratinocytes. IL-22Rα was increased in HaCaT and primary human keratinocytes after UVB irradiation through the translocation of IL-22Rα from the cytosol to the membrane. This increase in the expression of IL-22Rα was mediated by the PI3K/Akt pathway. Moreover, the suppression of keratinocyte proliferation by UVB irradiation was inhibited by treatment with IL-22. At the same time, IL-22 increased the production of IL-1α, IL-6, and IL-18 in UVB-irradiated HaCaT cells and primary human keratinocytes. Finally, IL-22Rα expression was increased in UVB-irradiated human and mouse skin by immune- histochemistry. The increased expression of IL-22Rα therefore promotes keratinocyte proliferation and pro-inflammatory cytokine production during UVB-induced skin inflammation, suggesting that UVB facilitates skin inflammation by increasing the responsiveness of keratinocytes to IL-22. This study provides a new insight into UVB-induced skin inflammation and the regulation of related inflammatory skin diseases.

Keywords: Interleukin-22, Interleukin-22R, UVB

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Alloferon Alleviates Dextran Sulfate Sodium-induced Colitis

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Dysfunction of gut immune regulation is involved in mucosal damage in inflammatory bowel disease (IBD). However, there is still no efficacious immune-regulator for the treatment of IBD. Alloferon is a novel immune-modulatory peptide that was originally isolated from infected insects. It shows anti-inflammatory effects by the regulation of cytokine production by immune cells and their activities. Therefore, we investigated the effect of alloferon in a mouse model of colitis using dextran sulfate sodium (DSS). Colitis was induced by administration of DSS in drinking water for 7 consecutive days. It was confirmed by the presence of weight loss, diarrhea, hematochezia, and colon contraction. Alloferon was injected 4 days after DSS administration. We found that alloferon improved the pathogenesis of IBD based on the reduced disease activity index (DAI) and colon contraction. Edema, epithelial erosion, and immune cell infiltration were found in mice administered DSS, but the phenomena were reduced following alloferon treatment. The plasma level of IL-6, a classical pro-inflammatory cytokine in colitis, was also decreased by alloferon. Moreover, alloferon inhibited the TNF-α-induced degradation and phosphorylation of IκB in Colo205 colon cancer cells. Taken together, these results show that alloferon has anti-inflammatory effects and attenuates DSS-induced colitis.

Keywords: Alloferon; Anti-inflammation; DSS-induced colitis; Inflammatory bowel disease (IBD)

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Anti-inflammatory Effect of Alloferon on Ovalbumin-induced Asthma

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Asthma is a well-known inflammatory lung disease; however, the specific underlying mechanism is largely unknown. We previously demonstrated that alloferon effectively downregulates pulmonary inflammation. In this study, we examined whether alloferon has a therapeutic effect on asthma. Alloferon remarkably decreased the number of eosinophils, macrophages, and neutrophils in the bronchoalveolar lavage fluid (BALF) from ovalbumin (OVA)-induced asthma mice. It was synergistically decreased with 2.5 mg/kg prednisolone (PDA). Inflammatory cell infiltration around the bronchioles and in the alveolus of OVA-induced asthma mice was effectively prevented by alloferon alone and combined treatment with alloferon and PDS. The production of IL-5 and IL-17 was decreased by alloferon alone and combined treatment with alloferon and PDS. There was no change the level of total immunoglobulin (Ig) following alloferon administration; however, total Ig was decreased by PDS. IgG2a levels were not changed by either alloferon alone or alloferon in combination with PDS. However, the levels of OVA-specific IgG1 and IgE were decreased by alloferon and PDS. In conclusion, our results suggest that a combination of alloferon and prednisolone is effective for the treatment of asthma, as it prevents inflammatory cell infiltration via the downregulation of IL-5 and IL-17 production and decreases IgG1 and IgE production via the suppression of T helper type 2 immune response.

Keywords: Alloferon; Asthma; Interleukin-17

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Efficacy of a pan-NADPH Oxidase Inhibitor on Streptozotocin-induced Rat Models

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Objective: Dye eye syndrome (DE) was common ocular disorders of diabetic patients. The symptoms of DE include decreased tear volume, itchy eye, aching sensations, and dryness sensation. We recently reported that a pan-NADPH oxidase inhibitor may have an effect on EBV-infected retina epithelial cells, but it' s role in DE has not been determined. Therefore, we investigated whether the pan-NADPH oxidase inhibitor effected on diabetic rat models with dry eye in this study. **Method:** Diabetic rat models was induced in male Sprague Dawley rats by intraperitoneal injection of streptozotocin, and then we treated eyeballs of diabetic rats with eye drop solution contained the pan-NADPH oxidase inhibitor or control solution. Tear secretion was measured with phenol red thread tear test. Morphology of eyeball and lacrimal gland tissues was stained with H&E. In addition, the localization of NADPH oxidase 2 (NOX2), NADPH oxidase 4 (NOX4) and VEGF in the Eyeball and lacrimal gland tissues were detected for immunohistochemistry. The mRNA expression level and protein expression level for NADPH oxidase 2 (NOX2), NADPH oxidase 4 (NOX4), and VEGF were measured by real-time PCR and western blot. **Results:** The pan-NADPH oxidase inhibitor treatment was no effect on body weight, blood glucose level and sizes of the eyeballs and lacrimal glands. However, morphological changes were found on a component ratio of serous cells and mucous cell in lacrimal glands of diabetic rat and diabetic rat with the pan-NADPH oxidase inhibitor. In immunohistochemistry, NOX2 expression level and VEGF expression level were decreased in diabetic rat with the pan-NADPH oxidase inhibitor, whereas the outcome of mRNA expression level and protein expression level made no odds. **Conclusion:** The pan-NADPH oxidase inhibitor improved the tear secretion and demonstrated positive effects from histological changes, but could not draw molecular changes. These findings suggest that the pan-NADPH oxidase inhibitor indicate a potential therapeutic role for DE.

Keywords: Diabetes Mellitus, Dry eye syndrome, NOX2, VEGF

▶▶▶ P-221

mTOR Mediates Neuronal Death Following Transient Global Cerebral Ischemia in the Striatum of the Chronic High-fat diet-induced Obese Gerbils

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Recent studies have shown that obesity and its related metabolic dysfunction exacerbate outcomes of ischemic brain injuries in some brain areas, such as hippocampus and cerebral cortex when subjected to transient global cerebral ischemia (tGCI). However, the impact of obesity in the striatum after tGCI has not yet been addressed. The objective of this study was to investigate the effects of obesity on tGCI-induced neuronal damage and inflammation in the striatum and to examine the role of mTOR which is involved in the pathogenesis of metabolic and neurological diseases. Gerbils were fed with a normal diet (ND) or high-fat diet (HFD) for 12 weeks and then subjected to 5 min of tGCI. HFD-fed gerbils showed significant increase in body weight, levels of blood glucose, serum triglycerides, total cholesterol and low-density lipoprotein cholesterol without affecting food intake. In the HFD-fed gerbils, neuronal loss was occurred in the dorsolateral striatum 2 days after tGCI and increased neuronal loss was observed 5 days after tGCI; however, no neuronal loss was observed in the striatum of the ND-fed gerbils after tGCI, as a assessed by neuronal nuclear antigen immunohistochemistry and Fluoro-Jade B histofluorescence staining. HFD-fed gerbils also showed severe activated microglia and further increased immunoreactivities and protein levels of tumor necrosis factor-alpha, interukin-1beta, mammalian target of rapamycin (mTOR) and phosphorylated-mTOR in the striatum during pre- and post-ischemic conditions compared with the ND-fed gerbils. These findings reveal that chronic HFD-induced obesity results in severe neuroinflammation and significant increase of mTOR activation, which would contribute to neuronal death in the stratum following tGCI. Especially, abnormal mTOR activation would play a key role in mediating the obesity-induced severe ischemic brain damage.

Keywords: Obesity; Transient global cerebral ischemia; Neuroinflammation; mTOR; Neuronal death

▶▶▶ P-222

Pretreated Fucoidan Confers Neuroprotection against Trainset Global Cerebral Ischemic Injury in the Hippocampal CA1 Area via Reducing Glial Cells Activation and Oxidative Stress

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Fucoidan is a sulfated polysaccharide derived from brown algae and possesses various beneficial activities, such as anti-inflammatory and antioxidant properties. Previous studies have shown that fucoidan displays protective effect against ischemia-reperfusion injury in some organs. However, few studies are reported regarding the protective effect of fucoidan against cerebral ischemic injury and its related mechanisms. Therefore, in this study, we examined the neuroprotective effect of fucoidan against cerebral ischemic injury, as well as underlying mechanisms using a gerbil model of transient global cerebral ischemia (tGCI) which shows loss of pyramidal neurons in the hippocampal cornu ammonis 1 (CA1) area. Fucoidan (25 and 50 mg/kg) were intraperitoneally administered once daily for 3 days before tGCI. Pretreatment with 50 mg/kg of fucoidan, not 25 mg/kg fucoidan, attenuated tGCI-induced hyperactivity and protected CA1 pyramidal neurons from ischemic injury following tGCI. In addition, pretreatment with 50 mg/kg of fucoidan inhibited activations of resident astrocytes and microglia in the ischemic CA1 area. Furthermore, pretreatment with 50 mg/kg of fucoidan significantly reduced the increased 4-hydroxy-2-noneal and superoxide anion radical production in the ischemic CA1 area after tGCI and significantly increased the expressions of superoxide dismutase 1 (SOD1) and SOD2 in the CA1 pyramidal neurons compared with the vehicle-treated-group. In brief, these results indicate that fucoidan can effectively protect neurons from tGCI-induced ischemic injury through attenuation of activated resident glial cells and reduction of oxidative stress following increasing SODs. Thus, we strongly suggest that fucoidan can be used as a useful preventive agent in cerebral ischemia.

Keywords: Fucoidan; Transient global cerebral ischemia; Neuroprotection; Resident glial cell; Superoxide dismutase

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Optimizing Tissue Clearing Method for Human Brain Tissue: Preparing Methods, Clearing Efficiency, Staining Methods, and Imaging Strategy

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Currently, the tissue clearing method is actively used in neuroscience research. Recent advances in tissue clearing method allow visualization of neural networks inside of unsectioned whole brain tissues. However, a protocol applicable for human brain tissue has not yet been optimized because of difficulty to gain fresh human samples. We aimed to optimize human brain clearing and imaging methods using fresh human samples. Fresh human brain samples obtained at autopsy and cadavers donated for medical school practice were used. The cadaver sample was fixed for more than one year, and the autopsy sample was fixed for about one week. We applied active electrophoretic clearing for human brain tissue. Every hour after clearing, we quantified the degree of transparency using Image J. DAPI(Nucleus) and GFAP(Astrocyte) was stained for 4 days and 11 days. Confocal microscope was used to investigated staining depth. Fresh human brain samples showed higher clearing efficiency compared with cadaver samples (20% transparent; 4hr vs. 40hr). Fresh human brain samples showed less autofluorescence compared with cadaver sample. DAPI was stained to over 150μm depth for fresh human brain samples. However, there was no DAPI staining in cadaver sample. GFAP staining was vivid until the staining depth of 20-50μm for 4 days incubation, on the other hand, in 11 days incubation, GFAP stained over 200μm depth. For GFAP staining, fresh human brain samples were stained denser than cadaver samples. For NeuN, no staining was shown. We have shown successful human brain 3D imaging results using fresh human samples. Fresher samples have better clearing efficiency, fewer autofluorescence, high number of stained antigen. Fresh human brain samples are prerequisite for 3D visualization of human brain.

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Chemogenetic Activation/Inhibiton of Dorsal Vagal Complex (DVC) Regulates Feeding and Energy Homeostasis

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Neural circuits are known to regulate food intake and energy expenditure, in the brainstem (NTS;DMV) and hypothalamic (LH,PVH,ARC) nuclei. The dorsal vagal complex (DVC) encompasses the nucleus tractussolitarii (NTS), the dorsal motor nucleus of the vagus nerve (DMX) modulate autonomic nervous system. Which regulates fuel availability, feeding behavior, energy storage and glucose metabolism in liver, adipose tissue, pancreas and other organs. However, the direct role of DVC on appetite and energy metabolism has been poorly understood. In the present study, we investigated the role of DVC in regulation of feeding behavior and energy metabolism by chemogenetic methods using DREADDs (designer receptors exclusively activated by designer drugs). The stimulatory hM3Dq and inhibitory hM4Di DREADD receptors were selectively expressed on a population of neurons in dorsal motor nucleus of the vagus (DMV) and NTS by stereotaxic surgery infusion of cre-recombinase-dependent adeno-associated virus vectors into the DVC of Phox2b-Cre and ChAT-IRES-Cre mice. Acute activation of DVC by intraperitoneal i.p injection of the M3-muscarnic receptor ligand clozapine-N-oxide (CNO) (1mg/kg), significantly suppressed food intake. During intraperitoneal glucose tolerance test, DVC activation via hM3Dq significantly decreased blood glucose, whereas DVC inhibition via hM4Di significantly increased blood glucose. Stimulation of DVC complex via i.p injection of CNO(1mg/kg) increased oxygen consumption and energy expenditure by Comprehensive Laboratory Animal Monitoring System (CLAMS). These results suggest that direct activation of DVC decreases food intake and improve glucose tolerance. These findings indicate that dysfunction of the DVC could predispose type 2 diabetes mellitus, and modulating DVC could be a therapeutic target for obesity and type 2 diabetes mellitus.

Keywords: Chemogenetics , DREADD,.CNO, Obesity, Autonomic nervous system

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Early Exposure to High Fat Diet Affects Feeding Related Behavior

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The prevalence of obesity has increased and it is well known that obesity can cause many health problems. Moreover, the consumption of the palatable foods like high-fat diet (HFD) can cause obesity. Also, exposure to over nutrition environment leads to not only alter the metabolism but also the mental state. Previous studies has reported that the maternal HFD can increase the risk of being obesity in offspring. However, the effect of eating HFD during childhood and adolescent is not well studied in the perspective of the behavior. We hypothesized that early exposure to the palatable foods after weaning state may cause obesity and modulate neuronal developmental process to increase feeding behavior. We measured the food-reward behavior by three tests : operant conditioning test (motivation level for appetitive pellet), conditioned place preference test (CPP) using palatable food, and three chamber test using social cue and food cue. Locomotive function and anxiety was tested using open field test. Memory function was tested using novel object recognition test. Locomotive function and anxiety was not significantly different between control diet group and HFD group. HFD mice showed significantly decreased motivation level for appetitive pellet compared with control group. HFD mice significantly drank less sucrose water compared with control group. When both control group and HFD group was combined, motivation level for appetitive pellet was in inverse correlation with bodyweight. These results suggest that early exposure to high fat diet may affect neural circuits and feeding related behavior.

Keywords: DIO, HFD, Behavior

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Neuroanatomical Change of Colon Enteric Nervous System in Inflammatory Bowel Disease Mouse

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Background & Aims: Enteric Nervous System (ENS) is part of autonomic nervous system especially innervate in the GI tract. However, the full 3 dimensional structure of ENS is not yet well known, especially in humans. Inflammatory Bowel Disease(IBD) is increasing steadily in Korea as well as in the world, and the life quality is severely affected by abdominal pain, diarrhea. The causes of the disease and innovative treatments are not clearly known. Among the various induced IBD models, DSS induced Colitis is similar and easy to mimic human UC diseases. So we observed from a neuroanatomicalcomparing animal models with normal mice. We wanted to compare the structure of ENS to obtain results that could help with future treatments. **Methods:** 8~12-week old C57BL/6 Male mice were administered 1.5~3% DSS with water for 7~10days to induce IBD. All mice were checked daily for loss of body weight and the presence of gross bleeding. More than 20% weight loss was observed, stop DSS treatment and mice were sacrificed. The colon samples were frozen in liquid nitrogen to frozen section or fixed in 4% PFA to clearing. Immunohistochemistry and H&E staining were performed for histology and disease scoring. 12-week old C57Bl/6 Male ChAT-Cre-dTomato Mice which is known as the cholinergic neuron marker tagged with red fluorescence was used to clearing and observed through confocal microscope and light sheet fluorescence microscopy **Result:** The 3 dimensional fluorescence image showed that ENS is a net form network surrounding colon lumen. Macro- and Micro-structure of ENS in human and mouse colon are shown. We compared Colon ENS structure between normal and IBD mouse.There was no significant difference in phenotypes between 1.5, 2%, 2.5%, 3% DSS treatment groups. However, lower percent DSS treatment group mice lived longer than higher percent group. All group observed body weight loss, gross rectal bleeding and shorten colon length compared with normal mouse. The ENS of IBD mice were significantly different from control mice. The ENS of IBD human patients were different from control subject. **Conclusion:** This is the first study to demonstrate 3 dimensional structure of colon ENS by large scale imaging. ENS structure was altered in IBD mice and patient.

Keywords: Enteric Nervous System, Colon, IBD

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Activation of Leptin Receptor-expressing Neuronsin Lateral Hypothalamus Enhances Food-seeking without Altering Food Intake in Mice

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The symptom of eating disorders that is difficult to treat is a dissociation between food-seeking behavior and metabolic needs. The lateral hypothalamus (LHA) regulates various motivated behaviors including food intake, and among many neuronal populations inside, LHA GABAergic neurons are known to be involved in modulation of food reward and consumption. Previous studies showed that activation of LHA GABAergic neurons enhance food intake and compulsive behaviors in mice. However, specified behavioral phenotypes and functions of the subset of LHA GABAergic neurons are unclear. Thus, our research aimed to identify the food-related behavioral phenotypes that are regulated by leptin receptor-expressing neurons in LHA. We performed food-seeking test, operant chamber test, overall chow/sucrose/saccharin consumption, preference test and marble burying test.Interestingly, through behavior assays, we found that chemogenetic activation of LHA leptin receptor neurons only increased 'food-seeking' behavior without altering food intake. However, activation of LHA GABAergic neurons increased both food intake and compulsive behaviors without affecting food-seeking. These results suggest that food-seeking is independent from food intake, and LHA leptin receptor neurons are specifically involved in food-seeking behavior that can be targeted to treat eating disorders.

Keywords: Food-seeking, Lateral Hypothalamus, Leptin receptor-expressing neurons,?GABAergic neurons,?Eating disorders

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The Relationship between Circulating Adiponectin and Arterial Stiffness is Associated with *ADIPOQ* 276G>T Polymorphisms

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Low adiponectin levels are associated with insulin resistance (IR), and arterial stiffness in hypertensive patients, but higher adiponectin levels were also found in heart failure patients. The discrepancy has not been fully elucidated, but it may be related to adiponectin gene (*ADIPOQ*) regulating adiponectin production. We aimed to investigate if the relationship between adiponectin and arterial stiffness is associated with *ADIPOQ* 276G>T in non-diabetic Korean men. In nondiabetic men without disease (n=301), anthropometric parameters, lipid profiles, IR, circulating adiponectin, oxidative stress/inflammation, and brachial pulse wave velocity (baPVW) indicating arterial stiffness were measured. *ADIPOQ* 276G>T was also analyzed. Circulating adiponectin levels were negatively correlated with baPWV and HOMA-IR in 276T allele carriers (n=167), but which was not observed in the GG subjects (n=134). On the other hand, positive correlation between IR and baPWV was observed in the GG subjects, but not in the T carriers. These patterns were still maintained after the adjustment. A stepwise linear regression analysis revealed that circulating adiponectin and systolic blood pressure (BP) were main influencing factors on baPWV levels in the 276T allele carriers, but systolic BP, IR and age were main contributors to increased baPWV levels in the GG subjects. The present study demonstrates that the relationship between circulating adiponectin and arterial stiffness is associated with 276G>T polymorphism, and suggests that 276T allele might be more susceptible to the influence of adiponectin on arterial stiffness. It may provide the useful information for personal-based early prevention and management of atherosclerotic risk.

Keywords: adiponectin; insulin resistance; brachial-ankle pulse wave velocity; *ADIPOQ* 276G>T

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Secretory Protein PRELP Mediates Mitotic Clonal Expansion During Adipogenesis

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Proline arginine-rich end leucine-rich repeat protein, called PRELP, is a secretory glycoprotein with the length of 382 amino acids and molecular weight of 55kDa. PRELP is a member of small leucine-rich proteoglycan superfamily of extracellular matrix molecules. It has been discovered as a secretory protein in a human genome-wide secretome as well as a molecule which shows higher mRNA expression level in mature adipocytes than in preadipocytes according to the microarray data. It has a characteristic mRNA expression pattern in preadipocytes as they enter differentiation program; the level of PRELP mRNA expression drops with MDI treatment and increases again in the later stage of differentiation. To explore the function of PRELP, its expression was silenced with siRNA transfection; as a result, PRELP-silenced group showed greater amount of lipid accumulation in oil-red-o staining and higher expression level of differentiation markers such as PPARγ. Also, in a gain-of-function test, PRELP-overexpressed group showed much less differentiation, which indicates that PRELP should not exist for preadipocytes to enter differentiation program. Thus, proline arginine-rich end leucine-rich repeat protein inhibits adipogenesis.

Keywords: Adipogenesis, Differentiation, Obesity, Secretory Protein

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Up-regulated Expression of Quinolinate Phosphoribosyltransferase (QPRTase) was Revealed in Colorectal Adenocarcinoma Tissues

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Colorectal cancer (CRC) is the third most prevalent cancer worldwide and has poor prognosis. Recent improvement in methods for proteome analysis has offered the possibility of identifying disease-associated protein markers to assist in diagnosis or prognosis, and for selecting potential targets for specific drug therapy. In current study, the proteome of colorectal adenocarcinoma and the corresponding normal tissues was visualized and analyzed a number of proteins to isolate and identify tumor-specific proteins for CRC. Ten proteins were dominantly expressed and five proteins were largely repressed in CRC by the analysis of 2-DE and MALDI-TOF/mass spectrometry. Quinolinate phosphoribosyltransferase (nicotinate nucleotide pyrophosphorylase) was focused to be increased in CRC tissues compared with normal colorectal tissues. The elevated expression of quinolinate phosphoribosyltransferase in CRC was confirmed by Western blot analysis and real time PCR. Immunohistochemistry also verified largely up-regulation of quinolinate phosphoribosyltransferase in 85 CRC patients. These findings suggest that quinolinate phosphoribosyltransferase could be possible tumor biomarker candidates in CRC tissues.

Keywords: Colorectal Adenocarcinoma, Neoplasm, Proteomics, Quinolinate phosphoribosyltransferase

▶▶▶ P-231

Calpain-dependent Beclin1 Cleavage Stimulates Senescence-associated Cell Death in HT22 Hippocampal Cells under the Oxidative Stress Conditions

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Oxidative damage in neurons including glutamate excitotoxicity has been linked to increasing numbers of neuropathological conditions. Under conditions of excessive oxidative stress, cells trigger several different cellular responses such as autophagy, apoptosis, necrosis and senescence. However, the connection between these responses is not well understood. In this study, we found that the 60-kDa BECN1 was specifically degraded to a 40-kDa BECN1 fragment in hippocampal HT22 cells treated with 5 mM glutamate. Increased BECN1 cleavage was specifically associated with a decrease in cell viability under conditions of oxidative stress. Interestingly, this BECN1 cleavage was specifically inhibited in the presence of the calpain inhibitor ALLN but was not affected by other protease inhibitors, including the pan caspase inhibitor zVAD. Also, the BECN1 cleavage was not detected in calpain-4-deficient cell lines, suggesting that BECN1 proteins are degraded in a calpain-specific manner. Furthermore, calpain likely cleaved BECN1 at a specific site between the coiled-coil domain and Bcl2 homology 3 domain, which is associated with the anti-apoptotic protein Bcl-2. Moreover, some cellular senescence markers, including β-galactosidase, p21, and p6INK4a, increased proportionally to those of BECN1 cleaved fragments. These results suggest that calpain-mediated BECN1 cleavage under oxidative conditions is specifically associated with cell death induced by apoptosis independent cellular senescence, thus implying a molecular and functional linkage between autophagy and cellular senescence.

Keywords: BECN1, senescence, calpain, glutamate excitotoxicity, oxidative stress

▶▶▶ P-232

Serotonin Regulates β-cell Proliferation During Perinatal Period

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Determination of β-cell mass largely depends on β-cell neogenesis during embryonic period and replication during perinatal period. After endocrine differentiation is completed, β-cells proliferate rapidly and comprise the major portion of pancreatic islet. Interestingly, serotonin production is increased in β-cells during perinatal period as well as pregnancy, two physiological conditions that β-cells proliferate actively. Although serotonin is known to regulate β-cell proliferation during pregnancy, its role in perinatal β-cell expansion has not been elucidated. Here, we have generated β-cell specific Tph1 knock-out (Tph1 βKO) mice to block serotonin production and show how serotonin defines β-cell mass during perinatal period. Robust serotonin production was observed by immunostaining in β-cells at postnatal day 0 (P0). Serotonin faded out gradually and was not detectable at postnatal day 14. Accordingly, both Tph1 and Tph2 expressions are elevated in pancreas at P0. However, serotonin was not detected by immunostaining in Tph1 βKO at P0, suggesting the major role of Tph1 in serotonin production in β-cells. Normal endocrine differentiation was observed in the pancreas of Tph1 βKO mouse. At P0, β-cell mass and β-cell proliferation were substantially decreased in Tph1 βKO. Decreased β-cell mass in Tph1 βKO was maintained up to 9 weeks of age, which resulted in impaired glucose tolerance at adulthood.

To investigate the downstream pathway of serotonin in regulating β-cell proliferation, expressions of serotonin receptors were assessed in embryonic pancreas before and after perinatal period. Amongst, Htr2b expression was upregulated at embryonic day 18.5 and downregulated in adulthood. We then evaluated β-cell specific Htr2b (Htr2b βKO, Gq) mouse. In accordance with Tph1 βKO, Htr2b βKO had smaller β-cell mass at birth despite β-cell differentiation looked normal. In conclusion, serotonin plays a critical role in the determination of β-cell mass by regulating β-cell proliferation through Htr2b receptor during perinatal period.

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Proteasome Inhibition Attenuated Diet-induced Gallstone Formation by Modulating Cholesterol and Bile Acid Homeostasis

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Gallstone disease is one of the most prevalent and costly gastrointestinal disorders worldwide. In this study, we examined the effects of proteasome inhibition on gallstoneformation using the proteasome inhibitors bortezomib or carfilzomib. C57BL/6J mice were fed a lithogenic diet to generate gallstones with injection of bortezomib and carfilzomib for 12 weeks. After 12 weeks of the lithogenic diet, 8 of 10 mice in the control group showed gallstones, whereas none of the mice who received proteasome inhibitors had gallstones. Interestingly, the expression of genes related to cholesterol synthesis (SREBP-2, HMGCR), cholesterol secretion (ABCG5, ABCG8), and bile acid synthesis (Cyp7a1, Cyp7b1, Cyp27a1, Cyp8b1) were reduced in the livers of mice with bortezomib or carfilzomib injection. In particular, Cyp7a1 encodes cholesterol 7-alpha-hydroxylase, the rate-limiting enzyme in the synthesis of bile acid from cholesterol. We measured the expression levels of transcription factors that are known to inhibit Cyp7a1 expression - farnesoid X receptor (FXR), pregnane X receptor (PXR), and small heterodimer partner (SHP). Although we expected FXR, PXR, and SHP expression to elevate in the presence of proteasome inhibitors, their expression levels were decreased upon treatment of proteasome inhibitors; thus, we concluded that they are not involved in the proteasome inhibition-induced regulation of Cyp7a1. Further exploration of the MAP kinase (MAPK) and protein kinase-A (PKA) signaling pathways in human hepatoma cells revealed that proteasome inhibition-induced c-Jun N-terminal kinase (JNK) phosphorylation reduced CYP7A1 and CYP27A1 expression. In addition, reduced PKA phosphorylation as a result of proteasome inhibition regulated ABCG5 and ABCG8 expression. In conclusion, our findings suggest that proteasome inhibition regulates cholesterol and biliary metabolism via the JNK and PKA pathways and is a promising therapeutic strategy to prevent gallstone disease

Keywords: Gallstone, CYP7a1, Cholesterol metabolism, Bile acid metabolism

▶▶▶ P-234

Ceramide Synthases Modulate Hepatic Triglycerides by Regulating Endoplasmic Reticulum Stress-induced SREBP-1 Activation

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The endoplasmic reticulum (ER) is not only important for protein synthesis and folding, but also crucial for lipid synthesis and metabolism. The contribution of ER stress in nonalcoholic fatty liver disease (NAFLD) has been nominated, and the present study demonstrated an important role of ceramide synthases (CerS) in ER stress and NAFLD progression. Ceramide is located in the center of sphingolipid metabolism, and its acyl chain length is determined by a family of six CerS in mammals. CerS2 generates C22-C24 ceramides, and CerS5 or CerS6 produces C16 ceramide. To gain an insight of CerS role in NAFLD, we used high fat diet (HFD) induced NAFLD mouse model. Interestingly, the decrease of CerS2 and the increase of CerS5/6 were observed in steatotic liver during HFD. In vitro experiments with Hep3B cells indicated the protective role of CerS2 and the aggravating role of CerS5/6 in ER stress response induced by palmitate treatment. Especially, CerS6 overexpression increased sterol regulatory element binding protein-1 (SREBP-1) cleavage with Insig-1 decrease, leading to increased lipogenesis. Blocking ER stress abrogated the aggravating effects of CerS6 in palmitate-induced SREBP-1 cleavage. In accordance with the protective role of CerS2 in palmitate-induced ER stress response, CerS2 knockdown aggravated ER stress and SREBP-1 cleavage, and CerS2 heterozygote liver exhibits higher ER stress response and triglyceride levels upon HFD. Finally, low dose bortezomib (BT) treatment increased hepatic CerS2 expression specifically, and protected the development NAFLD upon HFD. These results indicate that CerS and its derivatives impact hepatic ER stress and lipogenesis distinctly, and may be applied as therapeutic targets for NAFLD.

Keywords: sterol regulatory element binding protein-1, ER stress, nonalcoholic fatty liver disease, sphingolipid acyl chain length

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Wilms Tumor 1 (WT1) Inhibits the p53-induced Transcription of *p21WAF1* via Recruitment of TLE1-HDAC1 Complex

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WT1 functions as a transcription factor and a co-regulator as well that regulate the transcription of multiple genes associated with growth, development, and apoptosis. WT1 has been reported to bind to p53, inhibiting the apoptosis induced by p53, but it is not clarified, yet, how WT1 modulates the p53-induced gene expression. We observed that WT1 prevented the p53-induced *p21WAF1* expression at the level of transcription. To clarify the mechanism involved in WT1-mediated inhibition of p53-induced *p21WAF1* transcription, we performed chromatin immunoprecipitation (ChIP) assay, co-immuniprecipitation (Co-IP) assay, immunofluorescence staining (IF) and proximity ligation assay (PLA). In ChIP assay, WT1 did not alter the p53 binding activity at the p21WAF1 promoter, implying WT1' s role as a transcriptional co-regulator. Interestingly, WT1 suppressed p53-induced H3K14 acetylation (H3K14ac) and H3K4 tri-methylation (H3K4me3). To identify whether WT1 is able to recruit co-repressors for transcriptional inhibition of p21WAF1, we identified candidate co-repressors which are associated with histone modification. The depletion of HDAC1 (Histone deacetyl trasferases 1) and TLE1 (Transducin-like enhancer of split1) showed a rescue effect on p21WAF1 expression. Results of Co-IP, IF and PLA demonstrated that WT1 is physically binds to TLE1 and HDAC1. Moreover, in the absence of TLE1 expression, binding between WT1 and HDAC1 was remarkably reduced in CO-IP assay. Consistently, confocal findings revealed that the overlapped images of WT1 and HDAC1 were decreased in TLE1 knocked-down cells, indicating that WT1 recruites HDAC1 via interaction with TLE1. Therefore, collectively, it can be suggested that WT1 inhibits p53-induced *p21WAF1* transcription via recruitment of TLE1-HDAC1 complex.

Keywords: WT1, p53, Histone acetylation, Corepressor, Groucho/TLE1

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Aberrant Hypometnylation of *sortilin1* is Associated with Moyamoya Disease

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Moyamoya disease (MMD) pathogenesis remains poorly understood and no reliable molecular biomarkers for MMD have been identified to date. In this study, we sought to identify epigenetic biomarkers for diagnosing MMD. We performed integrated analysis on gene expression profiles and DNA methylation profiles of endothelial colony forming cells (ECFCs) from three MMD patients and two healthy individuals. Candidate gene mRNA expression and DNA methylation status were further validated using reverse transcription-quantitative polymerase chain reaction (RT-qPCR) and pyrosequencing analysis in an expanded ECFC sample set from nine MMD patients and ten controls. We evaluated the diagnostic accuracy of the potential biomarkers using receiver operating characteristic curve analysis. We measured major angiogenic factor expression levels using tube formation assay and RT-qPCR to investigate the angiogenic roles of the candidate genes. Five candidate genes were selected via integrated analysis; all five selected genes were upregulated by hypomethylation of specific promoter CpG sites. After further validation in the expanded sample set, we identified a candidate gene, s*ortilin 1* (*SORT1*); DNA methylation status at the specific promoter CpG site on *SORT1* in ECFCs readily distinguished MMD patients from normal controls with high accuracy (area under the curve = 0.94, sensitivity = 87.5%, specificity = 100%). Furthermore, *SORT1* overexpression suppressed endothelial cell tube formation and modulated major angiogenic factor and matrix metalloproteinase-9 expression, implying *SORT1* involvement in MMD pathogenesis. Our findings suggest DNA methylation status at the *SORT1* promoter CpG site is a potential biomarker for diagnosing MMD.

Keywords: Moyamoya disease, DNA methylation, Biomarkers, Diagnosis, *Sortilin 1*

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Passiflora incarnata L. has Potential Effects on Anti-Alzheimer's Disease

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Recently, Passion flower (Passiflora incarnata L.; PF) has been attracted attention due to its sleep inducing effects for people who are experiencing insomnia. In addition, this plant has sedative, anxiolytic, anti-inflammatory, and anti-convulsant effects on the central nervous system (CNS). These positive effects are normally associated with neuronal environmental maintenances in the CNS and anti-inflammation effects. We hypothesized that this plant might have pharmacological effects by enhancing neurogenesis in the hippocampal dentate gyrus in animal models. In this study, we used experimental animal models(mice and rats) and investigated whether short-term(<12 days) oral administration of PF extracts could enhance neurogenesis in hereditary-caused sleep disordered DBA/2 mice, and Sprague-Dawley rats via immunohistochemistry and Western blot. We confirmed by HPLC that the main component of the extract is vitexin, and the leaves and fruits were extracted with ethanol solvent. We performed the MTT assay from ICR mice bone marrow cells and measured *C.elegans* survival rate to confirmed the safety of Passion flower extracts. Additionally, we evaluated body weight changes and real-time food bouts and intakes with BioDAQ® system. We also determined animal feeding behavior, mobility, respiration amount of O_2 and CO_2, water consumption, and body compositions (fat, body fluid and lean tissue) were precisely measured using Phenomaster® and Mini-spec LF 50. And we evaluated pTau/Tau protein expressions in the hippocampus of SD rats. We found repeated administration of PF extracts for a short period have a excellent effect for the prevention of Alzheimer's disease as shown in the experimental results. Taken together, these results may be more important to people than the PF's sleep inducing effect.

Keywords: Passion flower, Hippocampus, Neurogenesis, Alzheimer' s disease, Insomnia

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Passiflora incarnata L. has Potential Effects against Insomnia

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Sufficient and high quality sleep is essential for comfortable life for humans. In modern society, people are constantly faced with various stress situations, while sleeping time is decreasing, and even patients who are suffering from insomnia tend to increase. It has been already proven by many researchers that if people can not get enough sleep, they have a gradual negative impact on cognitive function in the brain. Accumulation of stress due to long-term insufficient sleep is one of the many causes of dementia patients increasing in the elderly population in recent years. In this situation, we have been investigating with *Passiflora incarnata L.* (Passion flower, PF) that natural substances. Recently, Passion flower has been attracted attention due to its sleep inducing effects for people who are experiencing insomnia. In addition, this plant has sedative, anxiolytic, anti-inflammatory, and anti-convulsant effects on the central nervous system(CNS). Therefore, we hypothesized that the PF extracts had a sleep-inducing effect. In this study, we used experimental animal models(mice) and investigated the sleep-inducing effect of oral administration at high-concentrated(500mg/10ml/kg, 1000mg/10ml/kg) PF extracts. We confirmed by Immunohistochemistry(c-fos) that the activation site in the brain of the PF extracts. We performed another animal experiments and recorded and analyzed for verifying sleep-inducing effect in ICR mice after oral administration of high-concentrated of PF extracts. Additionally, we examined the protein expression in the brain by PF extracts through Proteomics. We also determined animal feeding behavior, mobility, respiration amount of O_2 and CO_2, water consumption were measured using Phenomaster®. In conclusion, we found that the administration of short-term, high concentration of PF extracts has a potential sleep-inducing effect. And we confirmed that the activation site of the PF extracts in the brain is Mammillary body.

Keywords: Passion flower, Insomnia, Sleep, sleep-inducing effect, Mammillary body

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Protective Mechanism of Vitamin C in Neuronal Cell Death by Streptozotocin

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Alzheimer's disease(AD), a neurodegenerative disease, is unclear in its cause and mechanism. In this study, we investigated the mechanism by which vitamin C protects SH-SY5Y cells from streptozotocin(STZ)-induced neuronal death. The vitamin C (100ug) was pre-treated for 30 minutes, and the STZ (2.5mM) was treated for 24 hours. The CCK-8 test found that the cell survival rate was measured with a 15 % increase in vitamin C pretreatment than the STZ alone. We conducted a Western blot experiment to find out about the protective mechanism of Vitamin C from apoptosis. Compared to the STZ alone treatment group, the expression of p-ERK and Bcl-2 in vitamin C pretreatment groups increased, and the expression of p-JNK and Bax decreased. In the oxidative stress induced by STZ, the expression of SOD-1, an antioxidant enzyme, was increased by more than 30% when vitamin C was pretreated. This study suggests that vitamin C inhibits apoptosis and helps prevent AD.

Keywords: Alzheimer's Disease, Streptozotocin, Reactiveoxygen Species, Vitamin C

P-240

Aberrant Hypermetnylation of *α-N-acetylgalactosaminidase* Enhances Cisplatin Resistance in Ovarian Cancer

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Although cisplatin is one of the most effective antitumor drugs for ovarian cancer, the emergence of chemoresistance to cisplatin in over 80% of initially responsive patients is a major barrier to successful therapy. The precise mechanisms underlying the development of cisplatin resistance are not fully understood, but alteration of DNA methylation associated with aberrant gene silencing may play a role. To identify epigenetically regulated genes directly associated with ovarian cancer cisplatin resistance, we compared the expression and methylation profiles of cisplatin-sensitive and -resistant human ovarian cancer cell lines. We identified *α-N-acetylgalactosaminidase (NAGA)* as one of the key candidate genes for cisplatin drug response. Interestingly, in cisplatin-resistant cell lines, *NAGA* was significantly down-regulated and hypermethylated at a promoter CpG site at position +251 relative to the transcriptional start site. Low *NAGA* expression in cisplatin-resistant cell lines was restored by treatment with a DNA demethylation agent, indicating transcriptional silencing by hyper-DNA methylation. Furthermore, overexpression of *NAGA* in cisplatin-resistant lines induced cytotoxicity in response to cisplatin, whereas depletion of *NAGA* expression increased cisplatin chemoresistance, suggesting an essential role of *NAGA* in sensitizing ovarian cells to cisplatin. These findings indicate that *NAGA* acts as a cisplatin sensitizer and its gene silencing by hypermethylation confers resistance to cisplatin in ovarian cancer. Therefore, we suggest *NAGA* may be a promising potential therapeutic target for improvement of sensitivity to cisplatin in ovarian cancer

Keywords: Ovarian cancer, Cisplatin resistance, *α-N-acetylgalactosaminidase*, DNA methylation

▶▶▶ P-241

Autophagy-dependent SNAI1 Degradation Regulates the Epithelial to Mesenchymal Transition and Metastasis in Cancer Cells

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Autophagy, an intracellular degrading system, is essential for maintaining cell homeostasis by removing damaged organelles and proteins under various stress conditions. In cancer cells, it has been suggested that autophagy has a double-edged function. Autophagy play a key role in maintaining the genomic stability by removing the damaged organelles, generating genotoxic components and subsequently leading to cancerous transformation. On contrast, autophagy promotes cancer survival through the continuous supply of nutrients from the self-digestion under metabolic stresses. However, the molecular mechanism underlying regulation of the epithelial to mesenchymal transition (EMT) and metastasis by autophagy is still elusive. Here we showed that starvation-induced autophagy promoted SNAI1 degradation and prevented EMT and metastasis in cancer cells. Interestingly, we found that SNAI proteins were physically associated with LC3 and p62. Furthermore, inhibition of autophagy by ATG7 knockdown rescued SNAI1 degradation. These findings suggest that SNAI1 proteins are specifically degraded by autophagy to regulate the EMT and cancer metastasis during tumorigenesis.

Keywords: autophagy, cancer metastasis, EMT, LC3, SNAI1

▶▶▶ P-242

Efficient Production of Enhanced Functions of Hepatocytes Derived from Human Pluripotent Stem Cells Using Size-controlled 3D Culture System

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Hepatocyte-like cells (HLCs) derived from human pluripotent stem cells have received extensive attention in the development of drug screening and toxicity testing. However, it has been reported that stem cell-derived HLCs showed hepatic functions that were too limited to be of use in drug screening and toxicity testing, possibly due to the lack of sufficient intercellular communication under conventional two-dimensional (2D) culture conditions. Therefore, a 3D differentiation system may overcome the in vitro limitation of 2D culture to produce stem cell-derived hepatocytes with mature metabolic functions. In this study, the feasibility of using a silicone-based spherofilm, specifically designed to produce spherical cell clusters, to generate uniformly sized 3D hepatic spheroids from hESCs was investigated. Hepatic spheroids generated on the spherofilm showed more homogenous size and shape than those generated in conventional low-attachment suspension culture dishes. The 3D culture system is suitable for hepatic maturation and that our size-controlled 3D culture conditions might accelerate hepatic function.

Keywords: Hepatocyte, 3D culture, Stem cell

▶▶▶ P-243

Purification of Hepatocytes Derived from Multiple Human Pluripotent Stem Cell Lines using Chemically Modified Compound

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Hepatocytes and hepatic progenitors derived from human ES cells are useful sources for therapeutical as well as pharmaceutical application. Therefore, identification and purification of these cell types would be following important issues after hepatic differentiation. There are very few candidate surface markers that can be used to identify and purify hepatocyte-like cells by using MACS or FACS sorting. In the present study, we tested chemically modified compound for FACS-mediated sorting of hepatocytes after differentiation of human pluripotent stem cells. After the final differentiation, differentiated cells and primary hepatocytes (control group) were incubated with a chemically modified compound and were sorted by FACS. Importantly, the chemically modified compound selectively stained cells that expressed albumin. Furthermore, FACS analysis data showed that the purity of hepatocytes that expressed albumin was significantly increased after the purification of chemically modified compound-positive cells. Therefore this compound can be used as a valuable tool to identify and purify stem cell-derived hepatocytes for both *in vitro* drug screening and *in vivo* transplantation studies.

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Keywords: Hepatocytes, Purification, Pluripotent Stem Cells, FACS, Chemically Modified Compound

▶▶▶ P-244

VISTA-dependent Role of Kidney-resident Macrophages is Essential for Maintenance of Kidney Homeostasis

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V-domain Ig suppressor of T cell activation (VISTA), expressed primarily on antigen-presenting cells, has been known to participate in the progression of cancer through an immune checkpoint. Nevertheless, both the expression pattern and role of VISTA in non-cancerous states remain unresolved. The present study is the first to address that the functioning of kidney-resident macrophages (rMΦ) in homeostasis is attributable to VISTA. Kidney myeloid cells were categorized based on the expression of CD11b and F4/80 as follows: kidney rMΦ (CD11bint F4/80high), bone marrow-derived MΦ (CD11bhigh F4/80int Ly6G-), and neutrophils (CD11bhigh F4/80low Ly6G+). Kidney rMΦ expressed CD11c, MHC II, CD86, and CX3CR1 together, but did not express CD80, Ly6C, Ly6G, or CD115. Among several immune checkpoints, all rMΦ expressed VISTA, but not CD273, CD274, or galectin-9. The VISTA expression of rMΦ differed between organs: high expression was found in the kidneys and peritoneum; moderate to high expression in the bone marrow and spleen; low expression in the liver and brain; and none in the lungs and skin. The high VISTA expression in kidney rMΦ was retained after IRI, but the expression was reduced if the injured kidney became fibrotic. In the VISTA overexpression experiments, using bone marrow-derived MΦ, VISTA increased the efferocytotic efficacy against apoptotic cells, indicating that the VISTAhigh kidney rMΦ participated in apoptotic cell surveillance even in a homeostatic kidney environment. It has been known that the kidney rMΦ is scarcely replaced by the bone marrow-derived cells in adulthood. We explored this issue in the post-inflammatory environment: unilateral IRI was induced in the parabiosis mouse model, and parabionts were harvested after 1 month. When compared with 50% exchange of peripheral blood between parabionts, 5% of kidney rMΦ originated from paired parabionts and 95% were derived from self-parabionts. Their VISTA expression levels were dependent on whether or not the kidney recovered, similar to the above results. This data indicates that VISTA, distinctively shown in kidney rMΦ, functions via phagocytosis. The very low replacement of rMΦ suggests that the VISTA-dependent activity of kidney rMΦ may be essential to maintaining kidney homeostasis.

Keywords: Kidney Resident Macrophage, Kidney homeostasis, VISTA

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