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Hankok Medical Science Foundation (since 1971)

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2014
ANNUAL MEETING

KOREAN ASSOCIATION OF ANATOMISTS

제64회 대한해부학회 학술대회

순서 및 초록

2014. 10. 15 ~ 17

The-K 경주호텔

주관
대한해부학회

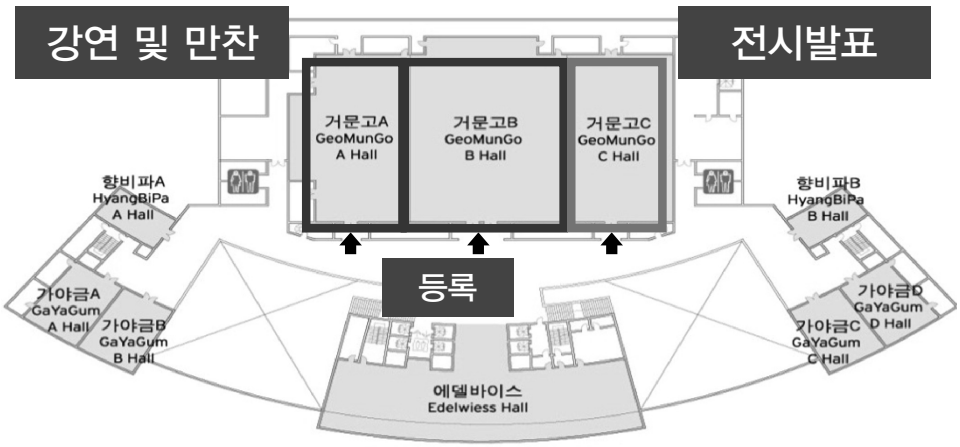
후원
한국과학기술인총연합회
한국의학학술지원재단

〈감사의 말씀〉
본 학술대회의 원활한 진행을 위해서 보이지 않는 곳에서 애써주신 분들께 심심한 감사를 표하는 바입니다.
본 학술대회 초록집은 2014년도 한국과학기술단체총연합회 학술활동 지원사업에 의해 인쇄 제작 되었으며, 본 행사는 한국의학학술지원재단의 일부 재정지원에 의하여 이루어졌습니다.

Contents

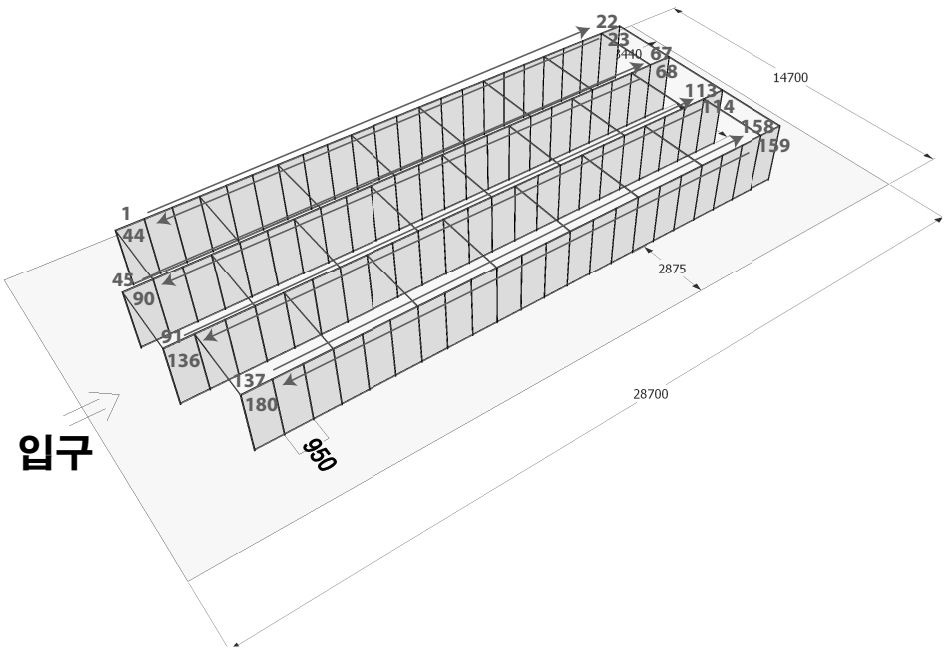
일시		발표 및 내용	
10. 15 수	14:00 ~ 15:00	등록	
	15:00 ~ 16:00	운영위원회별 활동	
	16:00 ~ 18:00	**패널토론(거문고 B홀)** "기초의학 학습성과와 해부학 교육" 1. 기초의학 학습성과(총론)의 평가 및 해부학교과 활용: 윤식 2. 기초의학 학습성과(각론)의 평가 및 해부학교과 활용: 황영일 3. 기초의학종합평가 문항분석 및 난이도 조정: 허영범 4. 해부학동영상의 수정 및 활용: 백두진	
10. 16 목	09:00 ~ 09:15	개회사 (거문고 B홀)	
	09:15 ~ 10:45	구연 발표 1 (거문고 A홀)	구연 발표 2 (거문고 B홀)
	11:00 ~ 12:00	**Plenary Lecture (거문고 B홀)** Functional Link between Circadian Timing System and DAergic Mood Regulation though Rev-erb alpha 발표자: 김경진(서울대)	
	12:00 ~ 13:10	사진 촬영 및 점심	
	13:10 ~ 16:00	**심포지엄 1 (거문고 A홀)** **자기공명영상과 해부학** 좌장: 정민석(아주대), 오창석(성균관대) Speaker: 정민석(아주대) 박진서(동국대) 유임주(고려대) 곽대순(가톨릭대) 서경진(동국대) 김남국(아산병원) 오창석(성균관대)	**심포지엄 2 (거문고 B홀)** **Perspectives for Human Disease Models** 좌장: 한기환(이화여대), 복진웅(연세대) Speaker: 이지연(서울대) 이지은(성균관대) 유영현(동아대) 고혁완(동국대) 김철훈(연세대)
	16:15 ~ 18:15	Poaster 발표 – 1 (1–83) (거문고 C홀)	
	18:30 ~	만찬 (거문고 A/B홀)	
10. 17 금	09:00 ~ 10:30	구연 발표 3 (거문고 A홀)	구연 발표 4 (거문고 B홀)
	10:40 ~ 12:10	**특별강연: Cutting Edge Tools for Anatomists (거문고 B홀)** Speaker: 권형배 (Max Planck, Florida) 이한웅 (연세대) 이경수 (삼성병원)	
	12:10 ~ 13:00	점심	
	13:00 ~ 14:00	Poaster 발표 – 2 (84–172) (거문고 C홀)	
	14:00 ~ 16:30	**심포지엄 3 (거문고 A홀)** **Plasticity and Mapping of Neural Circuits** 좌장: 이계주(뇌연구원), 선 웅(고려대) Speaker: 이계주(뇌연구원) 라종철(뇌연구원) 김진현(과기원) Rolf Sprengel (Max Planck)	**심포지엄 4 (거문고 B홀)** **Metabolism Mutifacedted** 좌장: 김현수(고려대), 이은영(충북대) Speaker: 최장현(UNIST) 이 완(동국대) 김성곤(종근당) 김현수(고려대)
	16:30 ~	제64회 정기총회 (거문고 B홀)	

학술대회장 배치도



전시발표 배치도 거문고 C홀

(전시시간: 2014년 10월 16일(목) 오전 7시 – 17일(금) 오후 4시)



Plenary Lecture

2014년 10월 16일(목) 11:00 – 12:00
거문고 B 홀

좌장 김 현
고려대학교 의과대학

PL **11:00-12:00**

Functional link between circadian timing system and DAergic mood regulation though Rev-erb alpha

Kyungjin Kim • 서울대학교 자연과학대학 생명과학부 뇌인지과학과

PL

Functional link between circadian timing system and DAergic mood regulation though Rev-erb alpha

Kyungjin Kim /서울대학교 자연과학대학 생명과학부 뇌인지과학과

Circadian rhythm is involved in the regulation of physiology and behavior in mammals. The mammalian circadian timing system is organized in a hierarchy: The central circadian pacemaker residing in the suprachiasmatic nucleus(SCN) of the anterior hypothalamus orchestrates numerous subsidiary local clocks in several regions of the brain and peripheral tissues. The molecular clock machinery has two interlocking feedback loops that drive the circadian oscillation in cell-autonomous and self-sustainable manner even at the single-cell level. It works through the transcription/translation and post-translational modifications that contribute to the fine regulation of molecular circadian clockwork. Following a brief overview of recent advance in chronobiology, I will discuss the novel functional link between the mood regulation by midbrain dopamine(DA) and circadian timing system through Rev-erba. Genetic abrogation of Rev-erba gene or pharmacological inhibition of Rev-erba activity in the ventral midbrain induced mania-like behaviors in association of hyperdopaminergic state. Rev-erba represses tyrosine hydroxylase(TH, a rate-limiting step of DA synthesis) gene transcription by competition with Nurr1(a crucial nuclear receptor for DA neuronal development and maintenance) and functions driving circadian expression of DA system.

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특별강연

2014년 10월 17일(금) 10:40 – 12:10
거문고 B 홀

Cutting Edge Tools for Anatomists

좌장 김 현
고려대학교 의과대학

특별강연-1 **10:40-11:10**
Neural circuit plasticity at synapses and neuronal ensemble
Hyungbae Kwon • Max Planck, Florida

특별강연-2 **11:10-11:40**
Genome engineering in mice by TALENs and RGENs
Hanwoong Lee • 연세대학교 생명시스템대학 생화학과 교수, 실험동물연구센터 센터장

특별강연-3 **11:40-12:10**
Cutting edge tools for anatomist: focused on radiologic imaging
Kyungsoo Lee • Department of Radiology, Samsung Medical Center, Sungkyunkwan University School of Medicine

특별강연-1

Neural circuit plasticity at synapses and neuronal ensemble

Hyungbae Kwon /Max Planck, Florida

An extraordinary feature of brain is its capacity to amend neuronal connectivity in response to ongoing experience or learning. Despite tremendous advances in our understanding of the plastic nature of neurons, how activity generated by sensory experience modifies neuronal wiring and ultimately alters an animal's behavior are still poorly understood. Recent development of new genetic and optical tools allows us to examine these processes on a fine scale. In this talk, I will discuss currently ongoing studies about how the architecture of neuronal connectivity in a mammalian brain is revised by the specific patterns of neuronal activity. This will be accomplished using a combination of genetic, electrophysiology, and imaging approaches to deliver highly-specific manipulations to selected neurons in vivo and subsequently determine the functional consequences for synapse, neuron, and circuit development. These studies will provide fundamental insights into the regulation of cortical circuit formation responding to demanding environments and may promote a better understanding of the pathophysiology underlying key brain disorders.

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특별강연-2

Genome engineering in mice by TALENs and RGENs

Hanwoong Lee /연세대학교 생명시스템대학 생화학과 교수, 실험동물연구센터 센터장

Phenotypic analysis of gene-specific knockout (KO) mice has revolutionized our understanding of in vivo gene functions. As the use of mouse embryonic stem (ES) cells is inevitable for conventional gene targeting, generation of knockout mice remains a very time-consuming and expensive process. To accelerate the large-scale production and phenotype analyses of KO mice, international efforts has organized global consortium such as the International Knockout Mouse Consortium (IKMC) and International Mouse Phenotype Consortium (IMPC), and they are persistently expanding the KO mouse catalogue that is publically available for the researches studying specific genes of interests in vivo. In addition, new technologies, adopting Transcription Activator-Like Effector (TALE) Nucleases (TALENs) and RNA-guided endonucleases (RGENs) to edit the mouse genome, are now emerging as valuable and effective shortcuts alternative for the conventional gene targeting using ES cells. Here I describe the establishment of gene-knockout mice by the injection of RGENs as Cas9 protein:guide RNA complexes or Cas9 mRNA plus guide RNA into one-cell stage embryos of both species. RGENs efficiently generated germ-line transmittable mutations in newborn mice with minimal toxicity. RGEN-induced mutations in the mouse Prkdc gene both in F0 and F1 mice. I propose that RGEN-mediated mutagenes is in animals will greatly expedite the creation of genetically-engineered model organisms, accelerating functional genomic research.

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특별강연-3

Cutting edge tools for anatomist: focused on radiologic imaging

Kyungsoo Lee[1,2] / [1]Department of Radiology, Samsung Medical Center, [2]Sungkyunkwan University School of Medicine

Digital tomosynthesis (DT) is a new technique that is reminiscent of old tomography. But, in this new technique, radiation dose as small as for chest radiography (CXR) is imposed to the patient while we can observe sectional images. Currently CT imaging is mainly focused on fast and low-dose technique. With the development of 324-slice CT (Toshiba) or dual-source dual-energy 128-slice CT (Siemens), you can image the whole brain or the heart within 10 second, or you can demonstrate dynamic whole brain CT for brain parenchymal or vascular study. For cardiac and lung imaging, submilli-Sievert (mSv) technique is devised and being used for coronary angiography and lung cancer screening, respectively. 3.0-T magnetic resonance imaging (MRI) has become popular for head and neck and even body imaging. 7.0-T MR imager is currently being launched for clinical study in several imaging centers worldwide. Except for pediatric imaging, the 7.0-T MR imager is expected to be more frequently used in the near future for adult brain imaging. Whole-body MR imaging (WB MRI) has become popular by developing rolling flat-form table. Thus, like WB CT, the WB MRI become popular for cancer imaging, vascular imaging, and for pediatric imaging. In this presentation, the speaker will show clinical utility of high-slice or submillSv CT imaging, 3.0-T imaging (including WB MRI), and 7.0-T MR imaging particularly for brain imaging.

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심포지엄-1

2014년 10월 16일(목) 13:10 – 16:00
거문고 A홀

자기공명영상과 해부학

좌장 정민석 아주의대 • 오창석 성균관의대

S1-1 **13:10-13:35**
자기공명영상을 익히는 데 도움 되는 절단면영상과 3차원영상
정민석 • 아주대학교 의과대학 해부학교실

S1-2 **13:35-13:55**
자기공명영상, 신경섬유영상, 절단면영상으로 연구하는 뇌의 회색질과 백색질
박진서 • 동국대학교 의과대학 해부학교실

S1-3 **13:55-14:15**
자기공명영상을 이용한 한국인 뇌 연구와 적용 예
유임주 • 고려대학교 의과대학 해부학교실

S1-4 **14:15-14:35**
자기공명영상, 컴퓨터단층촬영영상으로 연구하는 체질인류학과 임상해부학: 연구용 의료영상자료와 활용
곽대순 • 가톨릭대학교 의과대학 가톨릭응용해부연구소/해부학교실

S1-5 **14:50-15:10**
자기공명영상을 읽는 데 도움 되는 해부학 지식
서경진 • 동국대학교 의과대학 영상의학교실

S1-6 **15:10-15:30**
자기공명영상을 이용한 해부학적 영상 정보학(Anatomic imaging informatics using MRI)
Namkug Kim • Convergence Medicine, Radiology, Asan Medical Center University of Ulsan College of Medicine

S1-7 **15:30-16:00**
자기공명영상과 컴퓨터단층사진에 대해 학생들 눈 뜨게 만들기: 심봉사 프로젝트
오창석 • 성균관대학교 의과대학 해부학교실

S1-1 자기공명영상을 익히는 데 도움 되는 절단면영상과 3차원영상

정민석 /아주대학교 의과대학 해부학교실

저자는 지난 15년 동안 시신의 절단면영상과 3차원영상을 만들어 왔다. 이 절단면영상과 3차원영상이 환자의 자기공명영상을 익히는 데 도움 되는지 살펴 보았다. 먼저 남성 시신의 온몸을 대상으로 다음과 같은 연구를 하였다. 시신을 얼리기 전에 자기공명영상을 찍었고, 얼린 다음에 컴퓨터단층사진을 찍었다. 시신을 포매한 다음에 0.2 밀리미터 간격으로 연속절단하였고, 절단면이 나올 때마다 찍어서 절단면영상을 만들었다. 온몸의 절단면영상에서 구조물 하나하나의 테두리를 그려서 구역화영상을 만들었다. 서로 들어맞는 절단면영상, 자기공명영상, 컴퓨터단층사진, 구역화영상을 둘러보는 소프트웨어를 만들었다. 이 소프트웨어를 써서 절단해부학을 배우면, 나중에 자기공명영상을 익히는 데 도움 되었다. 구역화영상의 테두리를 쌓고 표면재구성해서 3차원영상을 만들었다. 3차원영상을 PDF 파일에 담아서 마음껏 둘러 보게 하였고, 이 3차원영상에 절단면영상을 꼽아 보게 하였다. 이처럼 3차원영상을 쓰면 절단해부학, 나아가 자기공명영상을 익히는 데 도움 되었다. 이어서 남성 시신의 머리를 대상으로 다음과 같은 연구를 하였다. 돌아가신 지 4시간 후에 7 테슬라 자기공명영상을 찍었다. 수평 방향의 자기공명영상과 절단면영상을 만들어서 서로 들어맞게 하였다. 시신의 절단면영상과 산 사람의 자기공명영상을 견주었고, 둘을 나란히 놓은 다음에 뇌 구조물의 이름을 붙여서 그림책을 만들기도 하였다. 이제까지 연구를 통해서 시신의 절단면영상과 3차원영상이 자기공명영상을 익히는 데 도움 되는 것을 알게 되었다.

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S1-2 자기공명영상, 신경섬유영상, 절단면영상으로 연구하는 뇌의 회색질과 백색질

박진서 /동국대학교 의과대학 해부학교실

사람 뇌는 회색질과 백색질로 이루어져 있다. 자기공명영상으로 회색질을 낱낱이 볼 수 있고, 신경섬유영상(diffuse tensor image)으로 백색질을 낱낱이 볼 수 있다. 절단면영상으로는 자기공명영상에서 안 보이는 몇몇 회색질을 포함한 대부분의 회색질과 그 외 뇌 주변 구조물을 고해상도, 실제빛깔로 볼 수 있다. 이 연구의 목적은 고해상도 7 Telsa 자기공명영상, 신경섬유영상, 절단면영상으로 뇌의 회색질과 백색질을 낱낱이 볼 수 있다는 것을 알리고, 이 영상들로 할 수 있는 연구에 대해서 소개하는 것이다. 이를 위해서 생체 뇌의 7 Telsa 자기공명영상을 만들고(화적소 크기 0.4 mm), 이 자기공명영상을 컴퓨터에서 가공하여 신경섬유영상(화적소크기 0.4 mm)을 만들었다. 시신의 뇌를 연속절단하고 절단면을 사진 찍어서 절단면영상(화적소크기 0.1 mm)을 만들었다. 자기공명영상에서 뇌의 각 이랑과 고랑을 나누고, 회색질의 각 핵을 찾고 표시하였다. 신경섬유영상에서 백색질을 연합섬유, 교차섬유, 투사섬유로 나누고, 각각의 신경로를 찾고 표시하였다. 절단면영상에 지금까지 찾은 구조물과 그 밖에 구조물을 찾고 표시하였다. 이렇게 작업한 결과를 뇌 회색질 그림책과 백색질 그림책으로 출판하였다. 더불어 절단면영상으로 뇌 구조물의 3차원영상도 만들었다. 7 Telsa 자기공명영상, 신경섬유영상, 절단면영상은 상호보완관계이다. 어느 한 영상에서 보이지 않는 구조물이 있다면 다른 영상에서 볼 수 있기 때문이다. 따라서 세 영상을 함께 보면 교과서에서 이론으로만 듣던 구조물까지 낱낱이 볼 수 있어서 뇌 공부와 연구에 큰 도움이 된다. 사사: 이 연구는 2012년도 정부(교육과학기술부)의 재원으로 한국연구재단의 기초연구사업 지원을 받아 수행된 것임(2012-0006885).

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S1-3 자기공명영상을 이용한 한국인 뇌 연구와 적용 예

유임주 /고려대학교 의과대학 해부학교실

뇌는 우리 몸무게의 불과 2%를 차지하고 있는 작은 기관이지만, 인간이 갖는 신비로운 능력의 많은 부분을 책임지고 있다. 이에 뇌에 대한 많은 연구가 거대형태에서부터 유전자 수준까지의 광범위한 연구가 진행되고 있다. 최근 자기공명영상(MRI) 덕분에 사람의 두경부를 포함한 뇌영상을 비침습적으로 관찰이 가능해서 기초연구와 임상연구에 많은 활용이 되고 있다. 뇌 자기공명영상을 이용하여 얻은 연구내용을 소개하고자한다. 첫번째로 해부학자로서 한국인의 뇌 크기에 대하여 분석하였다. 기존의 연구에서는 사망 후 적출한 뇌의 무게를 중심으로 기술하였지만, 살아 있는 사람을 대상으로 정상 한국인의 뇌의 부피에 관한 분석을 진행하여 머리뼈안의 크기, 뇌의 크기, 소뇌, 바닥핵, 뇌줄기, 뇌실 등의 부피를 남녀, 노소에 따라 분석하여 흥미로운 보고를 하였다. 두번째로 신경과학자로서 신경가소성에 대한 연구를 진행하였다. 지속적으로 훈련을 받아온 엘리트 농구선수의 소뇌와 기저핵을 분석하여 농구선수가 일반인들에 비해 더 발달되었다는 사실을 알게 되었고, 얼음판 위에서 정교하게 균형을 잡으면서 한쪽 방향으로 경기를 진행하는 쇼트트랙 선수들의 소뇌는 좌우가 비대칭성을 보이는 현상을 관찰하였다. 꾸준한 패턴의 운동이 뇌의 구조적 가소성을 유도할 수 있음을 알게 되었고, 이는 임상적으로 적용되고 있는 재활훈련 치료의 과학적 기초를 제공한다. 이상에서는 주로 살아 있는 사람을 대상으로 MRI 영상의 구조적 분석을 통하여 한국의 뇌의 특성을 보고하고, 노화 및 운동 활동에 따른 뇌의 구조적 변화에 대한 흥미로운 연구를 소개하였다. 최근 MRI의 다양한 촬영 프로토콜과 분석기법들이 개발되면서 사람의 신비로운 뇌를 좀 더 이해 할 수 있는 토대가 마련되어 가고 있다. MRI는 사람 뇌 연구의 중요한 도구로 지속적으로 자리매김 할 것으로 보인다.

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S1-4 자기공명영상, 컴퓨터단층촬영영상으로 연구하는 체질인류학과 임상해부학: 연구용 의료영상자료와 활용

곽대순 /가톨릭대학교 의과대학 가톨릭응용해부연구소/해부학교실

과학기술의 발전은 우리에게 많은 것의 변화를 가져오고 있다. 특히 영상의학 기술의 발전은 직접 해부를 하지 않고도 몸속을 볼 수 있는 방법을 제공하고 있다. 현대의학에 있어 의료영상은 대부분의 질병을 진단하는 기본 방법으로 자리매김하고 있으며, 몸속 구조물을 원하는 시야에서 관찰할 수 있는 장점이 있어 연구용 자료로도 넓게 활용되고 있다. 영상을 생성하기 위해 사용하는 에너지원(X-선, 초음파, 자기력 등)의 종류에 따라 관찰할 수있는 영상의 한계가 존재했으나, 기술의 발전에 따라 점차 경계가 모호해지고 있다. 해부학 연구에 적합한 의료영상자료는 진단을 위한 자료와 차이를 보일 수 있다. 병의원에는 방대한 분량의 영상자료를 보유하고 있지만 진단을 위한 영상은 인체 구조물의 형태를 연구하기에 부적합한 점이 존재할 수 있다. 진단을 위한 영상은 병변이 있는 부분을 강조해서 나타내지만, 해부학 연구를 위한 자료는 구조물을 세밀하게 관찰 할 수 있게 제작되어야 한다. 가톨릭응용해부연구소에서는 국가 지식 정보 DB 구축 사업의 일부분으로 연구용 한국인 인체영상정보(Digital Korean)를 구축하여, 한국과학기술정보연구원에서 연구자에게 서비스 되고 있다. 이 자료에서는 한국인 106 표본의 기증시신을 1mm 간격으로 전신 컴퓨터단층촬영(CT, Computerized Tomography)한 영상과 3차원 재구성 뼈대 모델을 제공하고 있다. 뇌 자기공명영상(MRI, Magnetic Resonance Image)과 3차원 모델 20 표본, 고령자 척추 CT 영상 73 표본, 중국인 하지 CT 영상 50 표본을 함께 제공하고 있다. 특히 중국인 영상은 무릎관절과 발 부분의 MRI 영상을 함께 제공하여 활용범위를 넓히고 있다(http://dk.kisti.re.kr). 가톨릭응용해부연구소에서는 다년간의 연구용 의료영상자료 제작 경험을 바탕으로 가톨릭디지털휴먼자료(CDHL, Catholic Digital Human Library)를 구축하고 있다. 현재 기증시신 CT 영상 197 표본(전신 및 부분 정밀 촬영), 연구용 척추 영상 90표본, 환자로부터 얻어진 머리뼈/위쪽 목뼈 영상 684표본(연령대별 30 표본 이상)이 구축되어 있으며, 지속적으로 추가되고 있다. 이 연제에서는 해부학 연구에 활용할 수 있는 공개 영상자료와 가톨릭응용해부연구소의 영상자료를 소개하고 이를 활용한 대표적 연구결과물을 소개한다. 해부학 연구 수행에서 적절한 영상자료의 선택 또는 제작, 계측학적 연구에서 주의할 사항, 3차원 재구성 모델을 이용한 연구 방법 등을 소개하고, 가톨릭응용해부연구소에서 수행한 각종 한국형 의료제품의 형상 결정을 위한 연구, 한국인의 법/체질인류학 연구, 수술적 접근법 등 임상해부학 연구 사례 등을 소개한다.

곽대순 | 가톨릭대학교 의과대학 가톨릭응용해부연구소/해부학교실 • Tel 02-2258-7434 • daisoon@catholic.ac.kr

S1-5

자기공명영상을 읽는 데 도움 되는 해부학 지식

서경진 /동국대학교 의과대학 영상의학교실

해부학 지식은 영상의학과 의사가 환자를 검사하고 영상들을 해석하는 데 제일 중요한 기본임은 누구나가 알고 있는 사실이다. 영상검사는 먼저 해부학 지식을 바탕으로 해부 구조물과 병변을 잘 볼 수 있도록 영상을 만든 것이 중요하다. 그 다음 구조와 병변을 분석하고 해석하여 정확한 진단으로 치료 방침을 결정하는 데 도움을 준다. 근골격계 영상검사는 여러 가지 영상검사방법을 사용하고 있지만 자기공명영상이 많은 장점을 가지고 있기 때문에 가장 중요한 검사인 환자들이 많다. 자기공명영상은 여러 방향의 단면을 볼 수 있고 조직 간의 대조도가 높으며, 다른 영상검사에서 발견할 수 없는 구조물들을 볼 수 있어, 특히 근골격질환의 검사에 아주 적합한 영상검사이다. 근골격계의 자기공명영상검사는 대부분의 근골격 질환에 이용되고 있으며 종양, 염증성 질환, 골수질환, 외상 등에 필수 검사이다. 가장 빈도가 높은 매일 접하는 근골격계 환자는 외상으로 자기공명영상검사로 치료 방침을 결정하는 경우가 많다. 특히 관절이 다친 경우는 진찰 소견이나 다른 영상검사로 판정이 어려워 대부분의 환자에서 자기공명영상검사를 시행한다. 우리 몸은 각각의 관절에 따라 아주 다른 해부구조를 가지고 있어 자기공명영상의 판독을 위해서는 거시적인 해부지식 뿐만 아니라 미세주조물에 대한 지식이 필수적이다. 요즈음 자기공명영상기기의 발달로 추측만 하던 미세 구조물들 실제 영상에서 판독할 수 있어 해부학자들의 업적을 확인하고 치료에 결정적인 정보를 제공한다. 관절 자기공명영상의 판독은 각각의 관절마다 구조물이 다르고 분석과 해석을 다르게 해야 하기 때문에 영상의학과 의사들이 어려워하는 분야 중 하나이다. 관절 자기공명영상검사는 척추와 무릎관절이 가장 많고, 어깨관절과 발목관절의 검사가 증가하고 있는 추세이다. 그러나 환자가 흔하지는 않지만 턱관절, 팔꿈치관절, 손목관절, 손가락관절, 엉덩관절, 발가락관절 등 모든 관절을 검사한다. 요즈음 환자검사가 증가 추세에 있는 팔꿈치관절의 근육, 인대 그리고 신경을 중심으로 해부학 모식도와 자기공명영상을 중심으로 〈자기공명영상을 읽는 데 도움 되는 해부학 지식〉을 설명한다.

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S1-6

자기공명영상을 이용한 해부학적 영상 정보학 (Anatomic imaging informatics using MRI)

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Nowadays, most of medical images can be digitalized and used for various purposes. In addition, the rapid development of recent medical imaging equipment, especially MRI which produces a very accurate medical image data, could be used for MRI imaging informatics. In general, imaging Informatics, also known as Radiology informatics or medical imaging informatics, is a subspecialty of biomedical informatics that aims to improve the efficiency, accuracy, usability and reliability of medical imaging services within the healthcare enterprise. As radiology is an inherently data-intensive and technology-driven specialty of medicine, radiologists could become leaders in Imaging Informatics. However, with the proliferation of digitalized images across the practice of medicine to include fields such as anatomy, cardiology, ophthalmology, dermatology, surgery, gastroenterology, obstetrics, gynecology and pathology, the advances in Imaging Informatics are also being used in other areas of medicine. Various industry players and vendors involved with medical imaging, along with IT experts and other biomedical informatics professionals, are contributing in this field. In this abstract, my research experiences including medical image processing, image segmentation & registration, image analysis & understanding, applications including the table, image-enabled EMR, imaging vocabularies and ontologies, imaging big data for imaging informatics will be presented. Based on these experiences, I'll cover various topics related with MRI based anatomic imaging informatics.

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S1-7

자기공명영상과 컴퓨터단층사진에 대해 학생들 눈 뜨게 만들기: 심봉사 프로젝트

오창석 /성균관대학교 의과대학 해부학교실

해부학을 배우는 동안, 기본적인 자기공명영상(MRI) 과 컴퓨터단층(CT) 사진에 대해 학생들의 눈이 뜨이도록 하기 위해 몇 가지 방법을 사용했다. (1) Clay modeling (Anat Sci Edu, 2009): 색점토를 재료로, 심장과 뇌의 모형을 만들고 절단한 후, 이들 모형의 절단면을 통해 심장의 4 칸과 뇌의 바닥핵, 시상 및 셋째뇌실의 단면해부학(cross-sectional anatomy)을 익혔다. (2) Digit anatomy (Anat Sci Edu, 2011): 손가락의 다양한 표현력과 motor memory를 이용하여 우리 몸의 여러 구조들을 입체적으로 익혀, CT와 MR 영상에 접근하였다. Digit anatomy로 익힌 구조에는 다음이 포함된다. ① 대동맥활(aortic arch), 빗장밑동맥(subclavian artery)과 겨드랑동맥(axillary artery) 및 이들의 가지. ② 심장의 4 칸과 큰 혈관. ③ 문맥세동이(portal triad), 복강동맥(celiac trunk), 지라동맥(splenic artery), 이자(pancreas) 뒤에서 간문맥(hepatic portal vein)의 형성, 위창자간막동맥(superior mesenteric artery)의 가지. (3) Digital report (Surg Radiol Anat, 2014): 해부학 실습 보고를 디지털화(실습과제를 PowerPoint형식으로 on-line제출)하고, 매 시간 조별 단위의 실습평가를 함으로써, 학생들의 보다 적극적인 실습참여를 유도했다. 각 학년의 Digital report를 데이터베이스화하여, 이전 학생들의 실습경험을 활용할 수 있도록 했다. 더욱 철저한 실습은, CT와 MR 영상을 이해하기 위한 튼튼한 해부학적 바탕이 되었다. (4) CT and MR movies: 연속적인 영상으로 구성된 movie를 통해, 영상 속 구조들의 변화를 시작부터 끝까지 추적할 수 있도록 했다. (5) Exams: (신경)해부학 과정의 마지막에 CT, MR 시험을 치렀다. 이상의 방법들을 사용한 결과, 학생들의 81%와 87%가 몸통 CT와 뇌 MR의 기본영상에 눈을 떴다고 하였다.

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심포지엄-2

2014년 10월 16일(목) 13:10 – 16:00
거문고 B홀

Perspectives for Human Disease Models

좌장 한기환 이화의대 • 복진웅 연세의대

S2-1 **13:10-13:45**
Secondary neurulation in error: Pathoembryogenesis of terminal myelocystocele based on morphological analysis
이지연 • 서울대학교 의과대학 해부학교실

S2-2 **13:45-14:15**
Molecular genomic approaches to the study of human disorders: Disease modeling using zebrafish
이지은 • 성균관대학교 삼성융합의과학원

S2-3 **14:15-14:45**
Alleviation by STAMP2 of free fatty induced lipid accumulation and insulin resistance: A study employing in vitro and in vivo nonalcoholic fatty liver disease (NAFLD) disease models
유영현 • 동아대학교 의과대학 해부학교실

S2-4 **15:00-15:30**
Genetic model system for human ECO syndrome reveals evolutionary conserved role for Intestinal Cell Kinase in ciliogenesis and Hedgehog signaling
고혁완 • 동국대학교 약학대학

S2-5 **15:30-16:00**
mGluR5 and stress resilience
김철훈 • 연세대학교 의과대학 약리학교실

S2-1

Secondary neurulation in error: Pathoembryogenesis of terminal myelocystocele based on morphological analysis

Ji Yeoun Lee[1], Saet Pyoul Kim[2], Sung-Hye Park[3], Kyu-Chang Wang[2]

[1]Department of Anatomy, Seoul National University College of Medicine
[2]Division of Pediatric Neurosurgery, Seoul National University Children's Hospital, Seoul National University College of Medicine
[3]Department of Pathology, Seoul National University Hospital, Seoul National University College of Medicine

Purpose: Terminal myelocystocele (TMC) is thought to be caused by a misstep during secondary neurulation. However, due to the paucity of data on secondary neurulation and the rarity of TMC, proofs of this pathogenetic mechanism are unavailable. Based on a previous observation that TMC resembles a step of secondary neurulation in chick, a closer look was taken at secondary neurulation of chick embryos focusing on the cerebrospinal fluid-filled distal neural tube (terminal balloon). **Methods:** Chick embryos at Hamburger and Hamilton (H-H) stages of 28, 30, 33, 35, 37, and 40 were harvested. Hematoxylin-eosin staining, additional immunohistochemistry (laminin, cytokeratin, nestin), and scanning electron microscopy were performed. **Results:** In H-H stages 28 to 30, after merging of the lumina of the primary and secondary neural tubes, the caudal end of the confluent tube dilates into a balloon-like structure (terminal balloon). As the proximal tube progressively becomes narrower, the terminal balloon dilates even further and its wall fuses with the surface ectoderm (H-H stage 33). Later in H-H stages 35 to 40, the terminal balloon shrinks and becomes detached from the surface ectoderm and ultimately disappears as the proximal lumen of the secondary neural tube continues to collapse.

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S2-2

Molecular genomic approaches to the study of human disorders: Disease modeling using zebrafish

Ji Eun Lee /Samsung Advanced Institute of Health Science & Technology (SAIHST), Sungkyunkwan University

Tubulin glutamylation is a post-translational modification (PTM) occurring predominantly on ciliary axonemal tubulin and has been suggested to be important for ciliary function. However, its relationship to disorders of the primary cilium, termed 'ciliopathies', has not been explored. Here, in Joubert syndrome (JBTS), we identify the JBTS15 locus and the responsible gene as TSGA14, encoding a centrosomal protein of 41 KDa (CEP41). We show that CEP41 is localized to the basal body/primary cilium, and regulates the ciliary entry of TTLL6, an evolutionarily conserved polyglutamylase enzyme. Depletion of TSGA14 causes ciliopathy-related phenotypes in zebrafish and mouse, and induces cilia axonemal glutamylation defects. Our data identify loss of TSGA14 as a cause of JBTS ciliopathy and highlight involvement of tubulin PTM in pathogenesis of the ciliopathy spectrum.

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S2-3

Alleviation by STAMP2 of free fatty induced lipid ac cumulation and insulin resistance: A study employing in vitro and in vivo nonalcoholic fatty liver disease (NAFLD) disease models

Hye Young Kim, Young Hyun Yoo /Department of Anatomy, Dong-A University College of Medicine, Busan

Six transmembrane protein of prostate 2 (STAMP2; also called STEAP4/TIARP) is a protein that has been studied due to its association with prostate cancer. Recent studies show that STAMP2 plays a role in preventing insulin resistance in the presence of inflammation and obesity. Even so, the molecular mechanism of STAMP2 activity and its downstream effectors are still largely unknown. Non-alcoholic fatty liver disease (NAFLD) is considered to be among the most common liver diseases world-wide, and has emerged as a major public health concern. NAFLD has the potential to progress through the inflammatory phase of nonalcoholic steatohepatitis (NASH) to fibrosis, cirrhosis, and in some cases to liver failure or hepatocellular carcinoma (HCC). Despite the increasing prevalence of NAFLD, the exact molecular/cellular mechanisms remain obscure and effective therapeutic strategies are still limited. Recently, NAFLD is increasingly regarded as a hepatic manifestation of metabolic syndrome. NAFLD is caused by imbalance between the delivery of fat in the liver and its subsequent secretion or metabolism. Fat accumulates in the liver for various reasons, in particular because of excessive intake of dietary free fatty acids (FFAs), de novo hepatic lipogenesis, and great liver FFA influx caused by insulin resistance. One of them, insulin resistance represents its pathophysiological hallmark. Since STAMP2 plays a role in preventing insulin resistance, we have been investigating whether STAMP2 modulates insulin resistance in free fatty acid-induced NAFLD. For this study, in vitro and in vivo nonalcoholic fatty liver disease (NAFLD) models were employed. We will first present data obtained from oleic acid (OA)-induced in vitro NAFLD model. Our data indicates that hepatic overexpression of stamp2 improves insulin resistance and abnormal lipid accumulation and that STAMP2 prevents degradation of IRS1 protein, which mediates hepatic insulin signaling, as well as restored insulin-mediated inhibition of gluconeogenic enzyme expression from OA-induced insulin resistance. We will further present data supporting that STAMP2 suppresses lipid accumulation through down-regulation of the lipogenic and adipogenic genes. These results suggest that increased hepatic STAMP2 plays a protective role in maintaining hepatic insulin signaling and lipid homeostasis in OA-induced NAFLD. We will further present in vivo data reinforcing our in vitro data. We will show immunohistochemical findings supporting that expression of STAMP2 was markedly decreased in needle biopsied hepatocyte from NAFLD patients. In addtion, we will present data obtained from high-fat diet induced NAFLD mouse.

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S2-4

Genetic model system for human ECO syndrome reveals evolutionary conserved role for Intestinal Cell Kinase in ciliogenesis and Hedgehog signaling

Hyuk Wan Ko /College of Pharmacy, Dongguk University, Goyang, 410-820, South Korea

The Hedgehog (Hh) signaling pathway regulates many aspects of cellular process such as cell growth, survival, and fate determination. Disruption of Hh signaling in early development causes developmental disorders. Aberrant activation in Hh pathway by somatic mutations has been linked to multiple forms of cancers in human. Many components involved in Hh signal transduction in Drosophila have been identified and characterized. They have been considered as having conserved role in mammalian Hh signaling. However, there are now accumulating evidences that divergent aspects of Hh signaling between Drosophila and mammals exist. Intriguingly, more recent findings indicate that mammalian Hh signaling occurs within primary cilia and misregulation of ciliogenesis affect metabolism of Hh signaling components. Endocrine-cerebro-osteodysplasia (ECO) syndrome, a human genetic disorder affecting multiple organs, is caused by a mutation in the intestinal cell kinase (Ick) gene. In algae and invertebrates, ICK homologues are known to be associated with ciliary formation. However, it is unclear whether this role of ICK is conserved in mammals and clinical symptoms of ECO syndrome are caused by ciliary defects. Using in vivo and in vitro approaches, we found that abnormal Ick function indeed resulted in defective cilia, leading to abnormal Hedgehog signaling. Our results suggest that the role of ICK in ciliogenesis maybe highly conserved throughout evolution and that ECO syndrome maybe categorized as a ciliopathy, an increasingly recognized class of human genetic disorders.

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S2-5

mGluR5 and stress resilience

Chul Hoon Kim / Yonsei University College of Medicine

The resilience plays a central role in determining whether stress-induced depression develops or not. The metabotropic glutamate receptor5 (mGluR5) has been implicated in the pathophysiology of depression; however, possible links between mGluR5 function and resilience are not clear. Here, we found that mGluR5-/-mice showed depressive-like behavior, including enhanced helplessness, social withdrawal and decreased sucrose preference after stressful events. Using viral-mediated gene transfer, 'rescue' of mGluR5 prevented defeat-induced social aversion of mGluR5-/-mice. Our study identifies mGluR5 as an essential molecule for promoting resilience, which is a previously unknown role of mGluR5 indepression. The molecular mechanism of mGluR5-dependent modulation of resilience will be discussed.

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심포지엄-3

2014년 10월 17일(금) 14:00 – 16:30
거문고 A홀

Plasticity and Mapping of Neural Circuits

좌장 이계주 뇌연구원 • 선 웅 고려의대

S3-1 **14:00-14:35**
Activity-dependent homeostatic plasticity at mossy fiber-CA3 synapses of mature hippocampal neurons
이계주 • 한국 뇌연구원

S3-2 **14:35-15:05**
Thalamocortical input onto layer 5 pyramidal neurons measured using quantitative large-scale array tomography
라종철 • 한국 뇌연구원

S3-3 **15:20-15:50**
mGRASP for mapping mammalian synaptic circuit at multiple scales
김진현 • 한국과학기술연구원

S3-4 **15:50-16:30**
Improved fluorescent protein stabilization in non-aqueous clearing for high resolution imaging in uncut mouse brain
Rolf Sprengel • Max Planck

S3-1

Activity-dependent homeostatic plasticity at mossy fiber-CA3 synapses of mature hippocampal neurons

Keajoo Lee / Lab of Synaptic Plasticity & Circuit Mapping Research Division Korea Brain Research Institute

Network activity homeostatically alters synaptic efficacy to constrain neuronal output. However, it is unclear how such compensatory adaptations coexist with synaptic information storage, especially in established networks. Here, we report that in mature hippocampal neurons in vitro, network activity preferentially regulated excitatory synapses within the proximal dendrites of CA3 neurons. These homeostatic synapses exhibited morphological, functional, and molecular signatures of the specialized contacts between mossy fibers of dentate granule cells and thorny excrescences (TEs) of CA3 pyramidal neurons. In vivo TEs were also selectively and bidirectionally altered by chronic activity changes. TE formation required presynaptic synaptoporin and was suppressed by the activity-inducible kinase, Plk2. These results implicate the mossy fiber-TE synapse as an independently tunable gain control locus that permits efficacious homeostatic adjustment of mossy fiber-CA3 synapses, while preserving synaptic weights that may encode information elsewhere within the mature hippocampal circuit.
· Mature hippocampal neurons have spatially segregated homeostatic plasticity in vitro.
· Adaptation modulates mossy fiber synapses onto CA3 neuron thorny excrescences (TEs).
· Mossy fiber synaptoporin is necessary and sufficient for homeostatic plasticity.
· Network activity and Plk2 selectively regulate TE structural plasticity in vivo.

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S3-2

Thalamocortical input onto layer 5 pyramidal neurons measured using quantitative large-scale array tomography

Jongcheol Rah / Principal Investigator, Korea Brain Research Institute

The subcellular locations of synapses on pyramidal neurons strongly influences dendritic integration and synaptic plasticity. Despite this, there is little quantitative data on spatial distributions of specific types of synaptic input. Here we use array tomography (AT), a high-resolution optical microscopy method, to examine thalamocortical (TC) input onto layer 5 pyramidal neurons. We first verified the ability of AT to identify synapses using parallel electron microscopic analysis of TC synapses in layer 4. We then use large-scale array tomography (LSAT) to measure TC synapse distribution on L5 pyramidal neurons in a $1.00 \times 0.83 \times 0.21\ mm^3$ volume of mouse somatosensory cortex. We found that TC synapses primarily target basal dendrites in layer 5, but also make a considerable input to proximal apical dendrites in L4, consistent with previous work. Our analysis further suggests that TC inputs are biased toward certain branches and, within branches, synapses show significant clustering with an excess of TC synapse nearest neighbors within 5–15μm compared to a random distribution. Thus, we show that AT is a sensitive and quantitative method to map specific types of synaptic input on the dendrites of entire neurons. We anticipate that this technique will be of wide utility for mapping functionally-relevant anatomical connectivity in neural circuits.

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S3-3 mGRASP for mapping mammalian synaptic circuit at multiple scales

Jinhyun Kim / Center for functional connectomics Korea institute of science and technology

Mapping mammalian synaptic connectivity has long been an important goal of neuroscientists since it is considered crucial for explaining human perception and behavior. Our new genetically controlled method to resolve synapses at the level of LM, termed mammalian GFP reconstitution across synaptic partners (mGRASP), is synapse-specific labeling with two complementary GFP components. mGRASP is based on two non-fluorescent split-GFP fragments (called spGFP1-10 and spGFP11) tethered to synaptic membranes in each of two neuronal populations. When two neurons, each expressing one of the fragments, are tightly opposed across a synaptic cleft, fluorescent GFP is reconstituted. mGRASP can relatively quickly reveal the precise locations and numbers of synapses along postsynaptic dendrites, sites responsible for determining many important characteristics of signal processing. Thus, mGRASP technology is suitable for mapping large-scale connectivity patterns at multiple scales: micro-scale for synapse-by-synapse or neuron-by-neuron analysis; and meso-scale for revealing local circuits. We performed a comprehensive fine-scale circuit mapping of hippocampal regions using the mGRASP. This mapping revealed spatially non-uniform and clustered synaptic connectivity patterns. Furthermore, synaptic clustering was enhanced between groups of neurons that shared a similar developmental/migration time window, suggesting a mechanism for establishing the spatial structure of synaptic connectivity. Such connectivity patterns are thought to effectively engage active dendritic processing and storage mechanisms, thereby potentially enhancing neuronal feature selectivity. Based on these prime connectivity characteristics, our study recently focuses on understanding synaptic connectivity profiles associated with neurological disorders using mGRASP.

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S3-4 Improved fluorescent protein stabilization in non-aqueous clearing for high resolution imaging in uncut mouse brain

Rolf Sprengel / Max Planck Institute for Medical Research

To detect and quantify long-range neuronal connections in the intact mouse brain by light microscopy the brain needs to be cleared, which means light scattering has to be suppressed by largely eliminating refractive-index variations. Here we describe a method (FluoClearBABB) that uses a non-aqueous index-matching medium (BABB), and that clears the tissue very well while also preserving the signal from proteinaceous fluorophores (XFPs). We show that high-resolution fluorescence imaging of entire, structurally intact juvenile and adult mouse brains is possible at subcellular resolution, even many months after clearing the brain. Crucial is the use of C3 or C4 alcohols (1-propanol or tert-butanol), during dehydration, and a basic pH during clearing. We show that axonal long-range projections EGFP-labelled by modified rabies virus (mRABV) can be imaged throughout the brain using a purpose-built light sheet fluorescence microscope. As example, we mapped in detail the monosynaptic projections onto a target cell population in the lateral entorhinal cortex. Thus we could demonstrate that FluoClearBABB permits the quantification of whole-brain connectivity patterns at the subcellular level.

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심포지엄-4

2014년 10월 17일(금) 14:00 – 16:30
거문고 B홀

Metabolism Mutifacedted

좌장 김현수 고려의대 • 이은영 충북의대

S4-1 **14:00-14:35**
PPARg phosphorylation and the anti-diabetic PPARg ligands
최장현 • 울산과학기술대학교 나노생명화학공학부

S4-2 **14:35-15:05**
Implication of microRNAs in mitochondrial dysfunction-induced insulin resistance
이 완 • 동국대학교 의과대학 생화학교실

S4-3 **15:20-15:50**
Theoretically convincing but unproven story: HDL
김성곤 • 종근당 효종 연구소

S4-4 **15:50-16:30**
Decoding multifacet of AMPK; implications on diabetes and cancer
김현수 • 고려대학교 해부학교실

S4-1

PPARg phosphorylation and the anti-diabetic PPARg ligands

Jang Hyun Choi / School of Nano-Bioscience & Chemical Engineering (NBC) Ulsan National Institute of Science and Technology (UNIST)

Obesity is a major risk factor of Metabolic Syndromes such as type 2 diabetes, dyslipidemia and cardiovascular disease. In addition, it is now clear that increasing rates of obesity are contributing to increases in the incidence and mortality of certain cancers. Therefore, understanding the molecular pathways that link adipose tissue biology to this staggering array of pathologies is scientifically and clinically crucial. The nuclear receptor PPARg is a master regulator of adipose cell differentiation and development. It is also the functioning receptor for the thiozolidinedione (TZD) class of anti-diabetic drugs such as rosiglitazone or pioglitazone. Recently, we showed that obesity induced in mice by high-fat feeding activates the protein kinase Cdk5, and this results in phosphorylation of PPARg at Ser273 in adipose tissues. This modification of PPARg does not alter its adipogenic capacity, but leads to dysregulation of a large number of genes whose expression is altered in obesity, including a reduction in the expression of the insulin-sensitizing adipokine, adiponectin. Unexpectedly, the phosphorylation of PPARg by Cdk5 is blocked by anti-diabetic PPARg ligands, such as rosiglitazone and MRL24. This inhibition works both in vivo and in vitro, and surprisingly, is completely independent of classical receptor transcriptional agonism. Similarly, inhibition of PPARg phosphorylation in obese patients by rosiglitazone is very tightly associated with the anti-diabetic effects of this drug. Here, I'll present how we can approach to develop novel anti-diabetic drugs which can block using chemical screening.

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S4-2

Implication of microRNAs in mitochondrial dysfunction-induced insulin resistance

Wan Lee / Endocrine Channelopathy, Channelopathy Research Center, and Department of Biochemistry, Dongguk University College of Medicine, Gyeongju 780-714, Korea

Mitochondria are indispensable for normal cell function and survival, and dysfunction of the OXPHOS system can lead to various metabolic diseases, such as diabetes, hypertension, and dyslipidemia, etc. Insulin resistance is a major hallmark of type 2 diabetes mellitus (T2DM) and obesity that is characterized by impaired insulin-mediated glucose transport and glycogen synthesis and by increased intramyocellular content of lipid metabolites. Over the past decade, several studies have provided evidence for mitochondrial dysfunction in skeletal muscle and liver of type 2 diabetic and prediabetic subjects, primarily due to a lower content of mitochondria (mitochondrial biogenesis) and possibly to a reduced functional capacity per mitochondrion. These observations have led to the theory that compromised mitochondrial oxidative function, particularly in skeletal muscle, causes excess lipid deposition and the development of insulin resistance. However, the precise mechanisms how mitochondria dysfunction lead to insulin resistance have not been elucidated fully, but there is a strong association between cellular reduction of oxidative capacity and inappropriate lipid accumulation under mitochondrial dysfunction. In this presentation, I will introduce the latest findings regarding the link between mitochondrial metabolism and insulin action and, in particular, highlight several recent studies that small non-coding microRNAs associated with mitochondrial dysfunction is casually linked to the pathogenesis of insulin resistance and T2DM.

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S4-3

Theoretically convincing but unproven story: HDL

Su Yeal Bae, Seung Kon Kim / 종근당 효종 연구소

There is an inverse association between the concentration of high-density lipoprotein (HDL-c) and the risk of coronary heart disease. Many investigators are interested in HDL-c as a therapeutic target. Cholesteryl ester transfer protein (CETP) is a plasma protein that mediates the transfer of cholesteryl ester from HDL to apolipoprotein B containing lipoprotein in exchange for triglyceride. Inhibition of CETP is expected to reduce cardiovascular risk due to increased level of HDL-c.
Our discovery program identified a potent and orally available CETP inhibitor, CKD-519, which is structurally novel and currently in the clinical development stage. CKD-519 demonstrated its strong inhibitory activity against CETP in vitro. When orally administrated in 2 week studies, CKD-519 significantly elevated HDL-c level in a panel of in vivo models. Given the undesirable cardiovascular safety issues seen with torcetrapib, the effects of CKD-519 on blood pressure were measured in normal SD rats that do not express CETP. In contrast to torcetrapib, CKD-519 did not alter the blood pressure or the plasma aldosterone and corticosterone levels following the administrations of CETP inhibitors. These findings indicate that CKD-519 is a highly potent CETP inhibitor and significantly increase the HDL-c level in pre-clinical animal models with little effect on blood pressure.

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S4-4

Decoding multifacet of AMPK; implications on diabetes and cancer

Hyeonsoo Kim / Department of Anatomy, College of medicine, Korea University

AMP-activated protein kinase (AMPK) is an enzyme that plays an important role in cellular energy homeostasis. AMPK, a heterotrimeric complex consisting of a catalytic subunit and two regulatory subunits, is activated upon depletion of cellular energy stores by allosteric binding of AMP or through phosphorylation at Thr172 of the catalytic subunit by AMPK kinase. Activation leads to an acceleration of ATP-generating catabolic pathways, including glycolysis and fatty acid oxidation, and a simultaneous reduction in ATP-consuming anabolic pathways, such as the synthesis of cholesterol, fatty acids, and triacylglycerol. Activation of AMPK can potently suppress cellular growth via inhibiting the mTOR pathway which is hyperactive in many types of cancer. On the other hand, downregulation of AMPK activity is associated with the type II diabetes, diet-induced obesity, insulin resistance and the development of other metabolic disorders. Therefore, now, AMPK becomes a promising research target for diabetes and cancer and regarded as an excellent therapeutic target. However, many things still remain unanswered due to its mutifacet. My research interest is to understand molecular mechanisms of AMPK, especially disease-specificity of AMPK in diabetes and cancer. My hypothesis is that activity regulator, interacting protein, and substrate may decode AMPK's mutifacetroles. To prove this hypothesis, I tried to identify AMPK's (1) activator (2) interacting protein (3) novel substrate, and now characterizing its hypoglycemic or antitumor functions. In this talk, I will introduce about these results and discuss of its functional implications.

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구연발표

2014년 10월 16일(목) 09:15 – 10:45
구연발표 1 (O1–1~8) 거문고 A 홀
구연발표 2 (O2–1~8) 거문고 B 홀

2014년 10월 17일(금) 09:00 – 10:30
구연발표 3 (O3–1~8) 거문고 A 홀
구연발표 4 (O4–1~8) 거문고 B 홀

01-1~8 신경 및 발생
좌장 노구섭
경상의대

02-1~8 조직 및 기타 내용
좌장 강태천
한림의대

03-1~8 Gross Anatomy
좌장 김인범
가톨릭의대

04-1~8 영어 세션
좌장 정호성
연세의대

구연발표 1 신경 및 발생 (O1–1∼8)

2014년 10월 16일(목) 09:15–10:45, 거문고 A홀

좌장: 노구섭 (경상의대)

01-1 ---------- 31

TonEBP inhibition attenuates NF-kB-mediated neuroinflammation in kainic acid-induced seizures

Hyun Joo Shin[1], Hwajin Kim[1], Chin-ok Yi[1], Rok Won Heo[1], Kyung Eun Kim[1], Dong Hoon Lee[1], Hyun Joon Kim[1], Sang Soo Kang[1], Gyeong Jae Cho[1], Wan Sung Choi[1], Hyuk Moo Kwon[2], Gu Seob Roh[1,*]

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01-2 ---------- 31

ER stress induces autophagy impairment in the spinal dorsal horn in a model of neuropathic pain

Enji Zhang, Min-Hee Yi, Nara Shin, HyunJung Baek, SeNa Kim, YongChul Bae, O-Yu Kwon, YoungHo Lee, DongWoon Kim*

Department of Anatomy, Brain Research Institute Chungnam National University School of Medicine

01-3 ---------- 31

Quantitative analysis of afferents expressing substance P, calcitonin gene-related peptide, isolectin B4, neurofilament 200, and Peripherin in the sensory root of the rat trigeminal ganglion

Jin Young Bae, Yi Sul Cho, Soo Hyun Bae, Hoi Jin Oh, Yong Chul Bae*

Department of Anatomy and Neurobiology, School of Dentistry, Kyungpook National University, Daegu 700-412

01-4 ---------- 32

Effects of abnormal neurotransmissions in the hippocampus following Febrile Seizure (FS)

Yeon Hee Yu, Ji-Heon Jeong, Su-Jeong Jeon, Eun-Myeong Kang, Dae-Kyoon Park, Kyung-Ho Park, Jeong-Sik Ko, Duk-Soo Kim*

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01-5 ---------- 32

Sonic hedgehog signaling confers regional identity along the tonotopic axis of the cochlea

Ji-Hyun Ma[1], Eun-Jin Son[2], Harinarayana Ankamreddy[1], Jeong-Oh Shin[1], Jae-Young Choi[2], Doris K. Wu[3], Jinwoong Bok[1,2,*]

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01-6 ---------- 33

Alterations of Phospholipase C (PLC) beta1 in the rat hippocampus following pilocarpine-induced status epilepticus

Ji-Heon Jeong, Su-Jeong Jeon, Yeon Hee Yu, Jeong-Se Noh, Dae-Kyoon Park, Kyung-Ho Park, Jeong-Sik Ko, Duk-Soo Kim*

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01-7 ---------- 34

Ethyl pyruvate ameliorates 3-nitropropionic acid-induced striatal toxicity through anti-neuronal cell death and anti-inflammatory mechanisms

Minhee Jang, MinJung Lee, Jonghee Choi, Eun-Jeong Kim, Ik-Hyun Cho*

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01-8 ---------- 34

Role of epigenetic CCCTC-binding factor in the inner ear development

Jeong-Oh Shin[1], Youn-Wook Chung[2], Hyoung-Pyo Kim[2], Jinwoong Bok[1,*]

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구연발표 2 조직 및 기타 내용 (O2–1∼8)

2014년 10월 16일(목) 09:15–10:45, 거문고 B홀

좌장: 강태천 (한림의대)

02-1 ---------- 35

Inhibition of c-FLIP expression by miR-708 increases the sensitivity to anticancer drug in renal cancer cells

Eun-Ae Kim, Ji-Hoon Jang, Eon-Gi Sung, In-Hwan Song, Joo-Young Kim, Tae-Jin Lee*

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02-2 ---------- 35

AQP2–cre;Atg7$^{f/f}$ 모델에서 자가포식작용에 의한 AQP2의 조절 기전

김완영[1], 남선아[1], 김유미[1], 최아름[1], 김용균[1,2], 김 진[1,*]
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02-3 ---------- 36

WHI-131 promotes osteoblast differentiation and prevents osteoclast formation and resorption

Yoon-Hee Cheon[1,2], Ju-Young Kim[3], Jaemin Oh[1,2,3,4,*]
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02-4 ---------- 36

Expression of cyclin-dependent kinases (CDKs) and CDK inhibitors in fumonisin B1-treated mouse kidney and liver

Sae-Jin Lee[1], Suk-Young Yang[1], Sei-Kwan Oh[2], Ki-Hwan Han[1,*]
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02-5 ---------- 37

C/EBP homologous protein (CHOP)-gene deficiency attenuates renal ischemia/reperfusion injury in mice

MiRa Noh[1], JeeIn Kim[2], Jincheol Seo[1], Hee-Jung Cho[1], Kwon Moo Park[1,*]
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02-6 ---------- 37

A MITF antagonist peptide (SE207C) inhibits melanogenesis by suppression of MITF activity in B16F1 melanoma cells and human epidermal malanocytes

Dongyoung Lim, KyoungJin Lee, KyeongHan Park, JungHyun Park, Dae Joong Kim, Jang-Hee Hahn*
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02-7 ---------- 38

BDNF expression of macrophages and angiogenesis after myocardial infarction

Jun-Hee Hong [1], Hyoung-Min Park[1] , Kyung-Hee Byun[1,2], Bong-Hee Lee[1,2], Woong-Chol Kang[3], Goo-Bo Jeong[1,*]
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02-8 ---------- 38

Bioactive fish collagen/polycaprolactone composite nanofibrous scaffolds fabricated by electrospinning for 3D cell culture

Da Jeong Choi[1,5], Seung Mi Choi[1,5], Hae Yeong Kang[1,5], Hye-Jin Min[1,5], Rira Lee[1,5], Sun-Yong Baek[1], Song Wan Jin[2,5], Young Hun Jeong[3,5], Jong-Young Kwak[4,5], Sik Yoon[1,5,*]
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구연발표 3 Gross Anatomy (03–1∼8)

2014년 10월 17일(금) 09:00–10:30, 거문고 A홀

좌장: 김인범 (가톨릭의대)

03-1 ---------- 39

한국인이 선호하는 눈썹의 형태(Brow archetype preferred by Korean women)

Geon Hwang*
인하대학교 의과대학 성형외과학교실

03-2 ---------- 39

Stable isotope analysis of Joseon people skeletons from the cemeteries of old Seoul city, the capital of Joseon dynasty

Jeong-A Yu[1], Chang Seok Oh[1], Jong Ha Hong[1], So Ri Min[2], Seung Whan Oh[3], Yi-Suk Kim[2], Dong Hoon Shin[1,*]
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03-3 ---------- 40

3D-reconstruction and anatomical analysis of the mental canal using MicroCT

Sun-Kyoung Yu, Myoung-Hwa Lee, Heung-Joong Kim*
Department of Anatomy and Orofacial Development, School of Dentistry, Chosun University, Korea

03-4 ---------- 40

Effect of caffeine intake on the reproductive system in the immature male rat

Minji Park, Yuri Choi, Hyeonhae Choi, Jaesook Roh*
Laboratory of Reproductive Endocrinology, Dept. of Anatomy & Cell Biology, College of Medicine, Hanyang University, Seoul 133-791

03-5 ---------- 41
Gantzer's muscle and its association with neurovascular structures
Gi-Uk Yang, Seung-Won Park, Hyunsu Lee, Hyo-Seok Park, Jae-Ho Lee, In-Jang Choi*
Department of Anatomy, School of Medicine, Keimyung University, Daegu, Republic of Korea

03-6 ---------- 41
사시수술을 위한 transverse superior fascial expansion의 해부학적 연구
남용석[1], 신선영[2], 김인범[1,*]
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03-7 ---------- 42
Histomorphometric evaluation of mechanoreceptors in Bassett's ligament: cadaveric study
Dasom Kim[1], ChangSub Uhm[1], YoungKoo Lee[2], EuiDong Yeo[2], ImJoo Rhyu[1,*]
[1]Department of Anatomy, College of Medicine, Korea University, [2]Department of Orthopedic Surgery, Soonchunhyang University, Bucheon Hospital

03-8 ---------- 42
한국인 머리뼈의 노화 과정에 대한 형태학적 분석
전안나[1], 김동민[1], 이우영[2], 김경용[1], 이원복[1], 한승호[1,*]
[1]중앙대학교 의과대학 해부학교실, [2]가톨릭대학교 의과대학 해부학교실, 가톨릭응용해부연구소

구연발표 4 영어 세션 (O4-1~8)
2014년 10월 17일(금) 09:00-10:30, 거문고 B홀

좌장: 정호성 (연세의대)

04-1 ---------- 43
Activated T cells secrete an soluble common γ-chain that inhibits cytokine signaling and exacerbates inflammation
Changwan Hong*
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04-2 ---------- 43
Temporal requirement of TGF-beta and hedgehog signaling during middle ear ossicle formation
Harinarayana Ankamreddy[1], Xiao Yang[2], Eui-Sic Cho[3], Jinwoong Bok[1,*]
[1]Department of Anatomy, Yonsei University College of Medicine, [2]Genetic Laboratory of Development and Diseases, Beijing Institute of Biotechnology, [3]Laboratory of Craniofacial Biology, Chonbuk National University School of Dentistry

04-3 ---------- 44
Ultrastructural investigation of microcalcification and the role of oxygen–glucose deprivation in cultured rat hippocampal slices
Tae-Ryong Riew[1], Hong Lim Kim[2], Yoo-Jin Shin[1], Joo-Hee Park[1], Ha-Jin Pak[1], Mun-Yong Lee[1,*]
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04-4 ---------- 45
AGE-albumin from activated macrophage is critical in human BD-MSC survival and post-ischemic reperfusion injury
Myeongjoo Son[1,2], Seyeon Oh[2], Jaesuk Lee[2], Hye-Jeong Park[2], Goo-Bo Jeong[1], YongMan Kim[3], TaeHoon Ahn[4], WoongChol Kang[4], Kyunghee Byun[1,2,*], Bonghee Lee[1,2,*]
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04-5 ---------- 45
Spontaneous specification of secondary neural tube-derived embryonic neural stem cells in vitro
Mohammed R.Shaker, JooYeon Kim, Huyn Kim, Woong Sun*
Department of Anatomy and Division of Brain Korea 21 Biomedical Science, Korea University College of Medicine, Seoul, 136-705, Korea

04-6 ---------- 46
Immunoreactivity of neurogenic factor in the guinea pig brain after prenatal hypoxia
Yong Hyun Jun, Jong Joong Kim, Yoon Young Chung*
Department of anatomy, School of Medicine, Chosun University

04-7 ---------- 46

Neural stem/progenitor cells containing human arginine decarboxylase promotes neural differentiation after ischemic damage

JaeYoung Kim[1,2], Eunjin Kim[1,2], Hosung Jung[1,2,3], WonTaek Lee[1], KyungAh Park[1], JongEun Lee[1,2,3,*]

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04-8 ---------- 47

Functional analysis of Apcdd1 in mice molar development

Sanjiv Neupane, Wern-Joo Sohn, Gi-Jeong Gwon, Young kyun Lee, Jae-Young Kim*

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01-1

TonEBP inhibition attenuates NF-kB-mediated neuroinflammation in kainic acid-induced seizures

Hyun Joo Shin[1], Hwajin Kim[1], Chin-ok Yi[1], Rok Won Heo[1], Kyung Eun Kim[1], Dong Hoon Lee[1], Hyun Joon Kim[1], Sang Soo Kang[1], Gyeong Jae Cho[1], Wan Sung Choi[1], Hyuk Moo Kwon[2], Gu Seob Roh[1,*]

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Kainic acid (KA)-induced seizures followed by neuronal death are associated with neuroinflammation and blood-brain barrier (BBB) leakage. Tonicity-responsive binding protein (TonBEP) plays an important role in osmoprotection, inflammation, and apoptosis. TonEBP is known as a transcriptional factor activating osmoprotective genes and, in brain, it is expressed in neuronal nuclei. Thus dysregulation of TonEBP may involve in the pathology of KA-induced seizures. Here, we used TonEBP heterozygote (+/-) mice to study the roles of TonEBP. Electroencephalographic study showed that TonEBP (+/-) mice reduced seizure frequency and severity compared to wild-type during KA-induced status epilepticus. Immunohistochemistry and Western blotting analysis showed that KA-induced neuroinflammation and BBB leakage were dramatically reduced in TonEBP (+/-) mice. TonEBP haplodeficiency prevented KA-induced nuclear translocation of NF-kB p65 and attenuated inflammation. Our findings identify TonEBP as a critical regulator of neuroinflammation and BBB leakage in KA-induced seizures, which suggests TonEBP as a good therapeutic target.

01-2

ER stress induces autophagy impairment in the spinal dorsal horn in a model of neuropathic pain

Enji Zhang, Min-Hee Yi, Nara Shin, HyunJung Baek, SeNa Kim, YongChul Bae, O-Yu Kwon, YoungHo Lee, DongWoon Kim*

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Endoplasmic reticulum (ER) stress has been implicated in neurodegenerative disease but its role in neuropathic pain remains unclear. In this study, we examined the association of ER stress and the unfolded protein response (UPR) with autophagic activity in a L5 spinal nerve ligation (SNL)-induced neuropathic pain rat model. SNL-induced neuropathic pain was assessed behaviorally, using a CatWalk system, and histologically, by quantifying microglial activation in the dorsal spinal horn. Among UPR sensor proteins, expression of BIP and ATF6 were increased in spinal dorsal horn neurons. Spliced XBP1 was also significantly elevated in the ipsilateral spinal dorsal horn. The PERK-eIF2 pathway was activated in astrocytes of the SNL model spinal dorsal horn. LPS-treated microglia conditioned medium induced ER stress and autophagic activity in cultured neurons through the ATF6 and IRE1-XBP1 pathways, but not the PERK-eIF2 pathway. Electron microscopy revealed swollen cisternae and autophagosomes in the dorsal spinal cord after SNL. Inhibition of the ATF6 pathway by intrathecal treatment with ATF6 siRNA reduced pain behavior and autophagic activity. This suggests that an accumulation of autophagic markers in response to immune-mediated ER stress might be involved in the induction and maintenance of neuropathic pain. Furthermore, a disturbance of autophagic signaling may render spinal neurons vulnerable to peripheral nerve injury or neuropathic pain stimuli.

Keywords: ER stress, Autophagy, Neuropathic pain, Microglia, Spinal nerve ligation

01-3

Quantitative analysis of afferents expressing substance P, calcitonin gene-related peptide, isolectin B4, neurofilament 200, and Peripherin in the sensory root of the rat trigeminal ganglion

Jin Young Bae, Yi Sul Cho, Soo Hyun Bae, Hoi Jin Oh, Yong Chul Bae*

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Substance P (SP), calcitonin gene-related peptide (CGRP), and

isolectin B4 (IB4) are widely used as markers for peripheral neurons with unmyelinated fibers, whereas neurofilament 200 (NF200), and Peripherin are used as markers for neurons with myelinated fibers, and with unmyelinated or small-caliber fibers, respectively. To study the selectivity of these markers for specific neuronal types, we analyzed their expression in neurons in the rat trigeminal ganglion by light- and electron-microscopic immunocytochemistry. Most SP-immunopositive (+), CGRP+, and IB4+ fibers were unmyelinated, but a small fraction (~5%) were small myelinated fibers (<20 μm^2 in cross-sectional area, equivalent to <5 μm in diameter, AΩ fiber). Similarly, whereas the majority of NF200+ fibers were myelinated, a large fraction (23.9%) were unmyelinated, and whereas the majority of Peripherin+ fibers were unmyelinated and small myelinated, a significant fraction (15.5%) were large myelinated (>20 μm^2 in cross-sectional area, equivalent to >5 μm in diameter, AΩ fiber). Our findings confirm that SP, CGRP, and IB4 can be used as reliable markers for neurons with unmyelinated fibers, and question the suitability of NF200 as a marker for neurons with myelinated fibers, and of Peripherin as a marker for neurons with unmyelinated, or fine-caliber fibers.

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01-4

Effects of abnormal neurotransmissions in the hippocampus following Febrile Seizure (FS)

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Febrile seizure (FS) induced by fever is most frequent seizure type in the infant and young child, it is impacted in developmental abnormality of hippocampal neuronal circuitry and thus contributed toward the development of temporal lobe epilepsy (TLE). Many previous investigators demonstrated that an imbalance of excitatory and inhibitory neurotransmissions was involved to wide spreading of seizure attack in the brain. Therefore, we in the present study investigated whether the expressional changes and the functional alterations of hippocampal interneuons involved to epileptogenesis following FS. In the present results, EEG and Timm's staining was shown differentially alterations depend on time courses after FS in the hippocampus. In addition, GABAA-α1 and calretinin (CR) expressions in the hippocampal interneurons were significantly altered during recurrent seizure period after FS. Briefly, GABAA-α1 immunoreactivity was markedly enhanced for a period of 11 - 12 weeks following FS and significantly down-regulated as compared to control groups after 13 week following FS. On the other hand, CR expression were significantly enhanced in the hippocampal interneurons of 7 - 8 weeks after FS, after that it was down-regulated more than control group in 13 week after FS. Indeed, in order to examined regarding the main cause of GABAA-α1 changes in recurrent seizures after FS, we investigated the 5-bromo-2-deoxyuridine (BrdU), vesicular GABA transpoter (VGAT) and GABA transporter 1 (GAT1) expressions. At the recurrent seizure stage following FS, BrdU expression was migrated from subgranular zone to hilus of dentate gyrus (DG) and enhanced its expression, while VGAT positive GABAergic interneurons were significantly increased at DG. Moreover, GAT1 expression at the same time was elevated and an abnormality of excitatory postsynaptic potential (EPSP) also observed in the recurrent seizure period after FS. Therefore, these results in the present study revealed that time-dependent alterations of hippocampal neuronal circuit by the abnormality of interneruonal activities may involved to the imbalance of excitatory and inhibitory neurotransmission in the hippocampus following FS. Thus, it may lead to the epileptogenesis and the spreading of seizure activity in the hippocampal neuronal circuit of brain.

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01-5

Sonic hedgehog signaling confers regional identity along the tonotopic axis of the cochlea

Ji-Hyun Ma[1], Eun-Jin Son[2], Harinarayana Ankamreddy[1], Jeong-Oh Shin[1], Jae-Young Choi[2], Doris K. Wu[3], Jinwoong Bok[1,2,*]
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Sound frequency discrimination is crucial for verbal communication and survival throughout animal kingdoms. This is possible because the vertebrate auditory organ, the cochlea, is tonotopically organized, such that sensory hair cells in the base respond to high frequency sound, and hair cells in the apex respond to low frequencies. Although anatomical and physiological features that contribute to the frequency discrimination have been extensively studied, it is unclear how and when the tonotopic axis is established during cochlear development. Previous studies have been shown that sonic hedgehog gradient provides distinct positional information in the neural tube and limb. Since developing cochlear duct receives graded levels of Shh signaling, we hypothesized that Shh gradient may confer regional identity to the developing cochlea, which is later manifested by the tonotopic axis. To test this hypothesis, we disrupted Shh gradient by implanting Shh-soacked beads into the chicken otocyst in ovo or expressing constitutively active Smo mutant protein in the mouse cochlea using Cre/loxp system (*Pax2*^{cre}*;Smo*$^{M2/+}$). When Shh-beads are implanted in otocysts, the basal hair cells displayed characteristics of apical hair cells. Moreover, apical specific genes such as *Bmp7* and *IRK1* were ectopically upregulated in middle region of basilar papilla, while base specific gene such as *Calbindin* was downregulated. Similarly, the cochlea of *Pax2*^{cre}*;Smo*$^{M2/+}$ mutants acquired the apical identity at the expense of the basal identity in the entire cochlear duct. In summary, conserved shh gradient signaling provides positional identity to the developing cochlea, which prefigures the tonotopic axis of the mature cochlea both in chicken and mouse.

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01-6

Alterations of Phospholipase C (PLC) beta1 in the rat hippocampus following pilocarpine-induced status epilepticus

Ji-Heon Jeong, Su-Jeong Jeon, Yeon Hee Yu, Jeong-Se Noh, Dae-Kyoon Park, Kyung-Ho Park, Jeong-Sik Ko, Duk-Soo Kim*
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Status epilepsy (SE) is characterized by without recovery and telogen of seizures and induces neuronal disorder. Pilocarpine was muscarin acetylcholin agonist, widely used as experiment for SE Phospholipase C (PLC) beta was a component of cell membrane lipids to produce a pair of second messengers, activates IP3 receptors to gather Ca^{2+} from the smoothendoplasmicreticulum(sER) For these reasons, PLC beta is important components of signal transduction processes in the brain Thus, activation of the PLC beta pathway produces important effects on cellular function, differentiation and activity Because recent studies have suggested that PLC beta1 and PLC beta4 may be associated with many kinds of seizures, we investigated whether the distributional alterations of PLC beta1 immunoreactivities in the hippocampus following pilocarpine-induced SE PLC beta1 immunoreactivities were decreased depending on time course following SE. At 5 days after SE, PLC beta1 immuoreactivity was markedly decreased in hippocampus We were confirmed NeuN and PLC beta1 double immunofluorescence for the PLC beta1 is to make sure that the normal operation after SE NeuN immunoreactivity was colocalized within PLC beta1 positive neurons and decreased as similar to PLC beta1 expression following SE We study correlation between GABAergic interneuron and PLC beta1. Parvalbumin (PV) positive neuron, one of the GABAergic interneuron, was diminished following SE At 2week after SE, PV immunoreactivity was almost disappeared in the hippocampus We study electrophysiology for confirm comparison of the neuronal function in normal state and SE state So we were recording electroencephalogram (EEG), excitatory post synaptic potential (EPSP) The electrophysiology result was dissimilar to each other situation. Therefore, these results in the present study revealed that PLC beta may change following SE and induce an abnormal neuronal function Thus we considered that PLC beta1 abnormal condition was relation SE and this situation trigger the disorder of neuronal function.

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01-7

Ethyl pyruvate ameliorates 3-nitropropionic acid-induced striatal toxicity through anti-neuronal cell death and anti-inflammatory mechanisms

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The potential neuroprotective value of ethyl pyruvate (EP) for the treatment of the striatal toxicity is largely unknown. We investigated whether EP promotes the survival of striatal neurons in a 3-nitropropionic acid (3-NP)-induced mouse model of Huntington's disease (HD). EP (5, 10, 20, and 40 mg/kg/day, i.p.) was daily injected from 30min before 3-NP intoxication (pretreatment) and from onset/progression/peak point of neurological impairment by 3-NP intoxication. EP produced a neuroprotective effect in dose- and time-dependant manners. EP pretreatment of 40 mg/kg/day produced the best neuroprotective effect among other conditions. Pretreatment of EP significantly attenuated neurological impairment and lethality and prevented formation of lesion area and neuronal loss in the striatum after 3-NP intoxication. This neuroprotection afforded by EP was associated with the suppression of succinate dehydrogenase activity, apoptosis, and microglial activation. The suppressive effect of EP corresponded to the down-regulation of mitogen-activated protein kinases (MAPKs) and nuclear factor-kappa B (NF-κB) signal pathways, and mRNA expression of inflammatory mediators including tumor necrosis factor-alpha, interleukin (IL)-1β, IL-6, inducible nitric oxide synthase, and cyclooxygenase-2 in the striatum after 3-NP intoxication. Interestingly, the intrathecal introduction of inhibitors MAPKs and NF-κB into control mice decreased the lethality after 3-NP intoxication. Our findings indicate that EP may effectively alleviate 3-NP-induced striatal toxicity by inhibition of the MAPKs and NF-κB pathways in the striatum, and that EP has a wide therapeutic window, suggesting that EP may have therapeutic value in the treatment of aspects of HD's disease related to inflammation.

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Keywords: Ethyl pyruvate, 3-Nitropropionic acid, Huntington's disease, Microglia, Mitogen-activated protein

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01-8

Role of epigenetic CCCTC-binding factor in the inner ear development

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The inner ear is comprised of diverse cell types specialized to convert sound waves into electrical stimuli and convey the signals to the brain. Organization of the inner ear requires proper genetic harmonization between regional specification and cell fate. Structural and functional features has been rigorously investigated during the past decades. Recent advancements of epigenetics, however, demonstrated that in addition to the classical views of "genetic" regulations (i.e. a signaling molecule activates specific transcription factors, which in turn regulate expressions of specific genes), "non-genetic" regulations such as a conformational change of chromatin structures induced by modifications in the histone proteins or modifications in the DNA molecules are also important for cellular differentiation and development. CCCTC-binding factor (CTCF) is an essential nuclear zinc finger protein that is implicated in transcriptional activation/repression, insulation, imprinting, and X chromosome inactivation. As an effort to understand how the epigenetic regulation contributes to inner ear development, we conditionally deleted CTCF using Cre/loxP system in mice. Our analyses of the inner ears from the CTCF conditional knockout (cKO) mice showed that inner ear morphogenesis was severely disrupted, such that anterior and lateral semicircular canals and cristae were absent and the cochlear duct was shortened and malformed. Gene expression analysis indicated that neurogenesis was suppressed while hair cell differentiation occurs relatively normally in the malformed cochlear duct. We also observed massive cell death in the CTCF cKO otocysts, suggesting that abnormal chromatin architecture caused by the absence of CTCF may lead to non-specific global cell death pathways. Taken together, our results suggest that CTCF plays important roles in morphogenesis and neurogenesis in mammalian inner ear via regulating apoptosis and neuronal determination gene. We are investigating whether epigenetic regulation by CTCF controls the organization

of chromatin architecture in the transcriptional-regulating region of Neurogenin1.

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02-1

Inhibition of c-FLIP expression by miR-708 increases the sensitivity to anticancer drug in renal cancer cells

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Dysregulation of the antiapoptotic protein cellular FLICE-like inhibitory protein (c-FLIP) has been proven to be associated with tumorigenesis and chemoresistance in various types of human cancers. Therefore, c-FLIP is an excellent target for therapeutic intervention. MicroRNAs (miRNAs) are small non-coding RNAs that are involved in tumorigenesis, tumour suppression, and resistance or sensitivity to anticancer drugs. It remains unclear whether miRNAs can regulate the expression of c-FLIP. The goal of this study was to identify miRNAs that could inhibit the growth and induce cell death of renal cancer by targeting cFLIP expression. We show that c-FLIP and miR-708 expressions are inversely correlated, that is, c-FLIP is upregulated and miRNA-708 is rarely expressed in renal cancer cells. Luciferase report assay demonstrated miR-708 negatively regulated c-FLIP expression via a conserved miRNA-binding site in 3' untranslated region (3'UTR) of c-FLIP. We also show that ectopic expression of miRNA-708 increases the accumulation of sub-G1 as well as the cleavage of procaspase-3 and PARP, which were prevented by pretreatment with the pan-caspase inhibitor, Z-VAD. Furthermore, ectopic expression of miRNA-708 increases the sensitivities to various apoptotic stimuli such as tumor necrosis factor–related apoptosis-inducing ligand (TRAIL), doxorubicin, brefeldin A (BFA), sylibin in Caki cells. In contrast, inhibition of endogenous miR-708 by use of antago-miR results in increase of c-FLIP protein expression and resistance to TRAIL, BFA, and sylibin treatment. We found that miRNA-708 expression was reduced in renal cell carcinoma (RCC) tissues. Inversely, cFLIP expression was upregulated in RCC tissues compared with normal renal tissues. In conclusion, these findings suggest that miR-708 should be considered as a tumor suppressor because it negatively regulates the antiapoptotic protein c-FLIP and regulates sensitivities to various apoptotic stimuli.

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02-2

AQP2-cre;Atg7$^{f/f}$ 모델에서 자가포식작용에 의한 AQP2의 조절 기전

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콩팥 집합관의 주세포에서 수분 조절에 중요한 역할을 담당하고 있는 수분통로 2(aquaporin 2, AQP2)의 조절기전과 자가포식작용과의 연관성에 대한 연구는 거의 없는 실정이다. 이에 본 연구는 AQP2의 분해과정에 대한 자가포식작용의 역할에 대해 알아보고자 자가포식소포가 현저히 증가하는 것으로 알려진 저칼륨혈증 모델을 대상으로 PI3K (phosphatidylinositol-3 kinase) 저해제인 3-methyladenine (3-MA)를 투여한 군과 콩팥의 주세포에서만 선택적으로 DNA-cre recombinase가 발현되는 *AQP2-cre* mice와 *Atg7$^{f/f}$*을 교배하여 제작한 *AQP2-cre;Atg7$^{f/f}$*를 대상으로 한 저칼륨혈증군을 제작하였다. 정상동물의 주세포에서 total AQP2는 자유면세포막과 세포질에, s256이 인산화된 AQP2만을 표지하는 s256-AQP2, 즉 활성화된 AQP2는 주로 자유면세포막에, s261이 인산화된 AQP2만을 표지하는 s261-AQP2, 즉 비활성화된 AQP2는 주로 세포질에서 관찰되었다. 그러나 저칼륨식이군에서 자유면세포막의 s256-AQP2는 현저히 감소하였고, s261-AQP2는 주로 자가포식소포에 위치하고 있었다. 이러한 소견은 저칼륨혈증때 나타나는 다뇨증이 활성화된 s256-AQP2의 감소와 s261-AQP2의 자가포식작용에 의한 제거에 의해 나타나는 현상임을 의미한다. 한편 3-MA 투여군과 *AQP2-cre;Atg7$^{f/f}$* 저칼륨혈증군에서는 두 군 사이에 정도의 차이는 있으나 p62가 증가하고 LC3-양성 자가포식소포가 감소한 것으로 보아 이 두 군 모두에서 자가포식작용이 차단되었음을 확인할 수 있었다. 자가포식작용이 저하된 3-MA 투여군과 *AQP2-cre;Atg7$^{f/f}$* 저칼륨혈증군 모두에서 저칼륨식이에 의해 나타나는 자가포식소포가 완전히 감소하지는 않았으며, 흥미롭게도 남아있는 자가포식소포에 이 두 군 모두에서 s261-AQP2가 표지되

지 않았고 세포질에 퍼져 있어 s261–AQP2가 자가포식소포에 의해서 제거되는 길이 차단되었음을 알 수 있었다. 이와 같은 연구결과로 보아, 체내 수분 조절에 중추적 역할을 담당하는 AQP2의 분해과정에 LC3/Atg7–의존성 자가포식작용이 관여함을 알 수 있었다.

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02-3

WHI-131 promotes osteoblast differentiation and prevents osteoclast formation and resorption

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WHI-131/JANEX-1 (4-(4′Hydroxyphenyl)-amino-6,7-dimethoxyquinazoline), quinazoline-type small molecule compound is well known a kinase inhibitor that demonstrated as potent therapeutic agent about anti-inflammatory, anti-cancer and anti-leukemia in several animal models. However, has not been fully investigated for regulatory effects on osteoblast and osteoclast activity by WHI-131. Therefore, in this study, we examined the effects of WHI-131 in bone remodeling between bone formation and resorption. IL-1 and IL-6 are multi-functional cytokine, they induce RANKL expression on the surface of osteoblasts. RANKL is an important factor on differentiation and activation of osteoclasts. WHI-131 inhibited osteoclast formation in the co-culture system with primary osteoblast (pOB) and mouse bone marrow cells in the presence of IL-1 or IL-6/IL-6R. Also, WHI-131 decreased RANKL-induced osteoclast differentiation on the bone marrow derived marcrophages cultures and reduced the resorbing activity of mature osteoclasts. WHI-131 suppressed the protein expression and mRNA level of c-Fos and NFATc1, and down-regulated mRNA level of *TRAP*, *OSCAR*, *DC-STAMP*, *OC-STAMP*, *ATP6v0d2* and *CathepsinK*, these are osteoclast differentiation and function related gene which are importnant for osteoclast differentiation and function. WHI-131 diminished phosphorylation of Akt, and NFk-B activation, PLCg2 and Ca2+oscillation. Moreover, WHI-131 promote differentiation of osteoblast that is reveal increasing level of a alkalinephosphate, alizarinredstain activity related with osteoblast differentiation in pOB. WHI-131 increased the mRNA level of *Runx2* related with osteoblastic differentiation and induced the phosphorylation of Akt, p38 and smad 1/5/8. Interestingly, WHI-131 (10 mg/kg) had great anti-resobing effects in LPS-induced calvaria bone loss model and also enhanced bone formation along with the outer bone surface of calvaria *in vivo*. Thus, WHI-131 has dual effect through inhibition of osteoclast differentiation and promotion of osteoblast differentiation. This suggests that WHI-131 may be useful phamacologic agent as a safe and effective dual-action therapeutic against osteoporosis that promotes robust bone growth while inhibiting resorption.

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02-4

Expression of cyclin-dependent kinases (CDKs) and CDK inhibitors in fumonisin B1-treated mouse kidney and liver

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Fumonisin B1 (FB1) is an environmental toxin produced by Fusarium molds. Experimental animal studies have indicated that FB1 induces tissue damage and compensatory cell proliferation in the kidney and liver. Cyclin-dependent kinases (CDKs) and CDK inhibitors play an important role in the regulation of cell proliferation. The purpose of this study was to examine the expression of CDKs and CDK inhibitors in FB1-treated kidney and liver. C57BL/6 mice were divided into 3 groups and received FB1 (0, 5, and 20mg/kg/day, i.p) for 5 days. Kidney and liver tissues were processed for immunohistochemistry and immunoblot analysis. Low-dose FB1 (5 mg/kg) did not affect serum AST, BUN, and creatinine levels. However, high-dose FB1 (20 mg/kg) significantly increased AST serum levels and caused extensive liver necrosis. Some histological change (e.g. vacuole formation) appeared in the kidney, but creatinine levels did not rise. Both low-dose and high-dose FB1 significantly induced cell proliferation. Immunohistochemical detection of PCNA and

quantification revealed that cell proliferation increased by 4.69-fold (5 mg/kg) and 4.86-fold (20 mg/kg), respectively, in the liver. Cell proliferation increased by 15.9-fold (5 mg/kg) and 16.4-fold (20 mg/kg) in the kidney. Expression of CDK2, CDK4, and CDK6 significantly increased in both low-dose and high-dose FB1 groups. Also, expression of CDK associated cyclins (D1 and D3) increased in both FB1 groups. Confocal microscopy showed that expression CDK2 was co-localized with PCNA in the nucleus of many hepatocytes and renal tubular cells. In contrast, expressi! on of P18INK4C and P27KIP1 significantly decreased in both low-dose and high-dose FB1 groups. Interestingly, double immunohistochemistry using tubular marker proteins demonstrated that expression of P27KIP1 specifically decreased in the proximal tubule in the kidney with FB1 treatment. These results suggest that expression and cellular localization of CDKs and CDK inhibitors may play an important role in FB1-induced cell proliferation in the kidney and liver.

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02-5

C/EBP homologous protein (CHOP)-gene deficiency attenuates renal ischemia/reperfusion injury in mice

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Background: Endoplasmic reticulum (ER) is involved in the pathology of renal ischemia/reperfusion (I/R) injury. C/EBPα homologous protein (CHOP) plays an important role for ER stress-induced cell and organ injury. Here, we investigated the role of CHOP in I/R-induced kidney injury using CHOP-knockout ($CHOP^{-/-}$) and their wild-type ($CHOP^{+/+}$) mice. **Method:** Mice were subjected to either 30 minutes of bilateral renal ischemia or sham-operation in CHOP-knockout ($CHOP^{-/-}$) and their wild-type ($CHOP^{+/+}$) mice. Renal functional and histological changes were evaluated by concentrations of plasma creatinine (PCr) and blood urea nitrogen (BUN), and the periodic acid Schiff (PAS) staining, respectively. TUNEL assay was performed to determine apoptotic cells. **Results:** Twenty-four hours after ischemia, the increases of PCr and BUN concentrations were less in $CHOP^{-/-}$ than in $CHOP^{+/+}$ mice. Disruption and congestion in tubules appeared in the outer medulla in PAS-stained kidney sections of both $CHOP^{-/-}$ and $CHOP^{+/+}$ mice 24 hours after ischemia. The damage scores of kidneys after ischemia were lower in $CHOP^{-/-}$ mice than $CHOP^{+/+}$ mice. Apoptosis was evaluated with Terminal deoxynucleotidyl transfer-mediated dUTP nick end-labeling (TUNEL) assay. The number of TUNEL-positive cells were less in $CHOP^{-/-}$ mice than in $CHOP^{+/+}$ mice. The activation of caspase3 and pro-apoptotic Bax was less in $CHOP^{-/-}$ mice than in $CHOP^{+/+}$ mice. In contrast, the activation of anti-apoptotic Bcl-2 and Bcl-xL was greater in $CHOP^{-/-}$ mice than in $CHOP^{+/+}$ mice validated TUNEL results. **Conclusion:** CHOP-deficiency attenuates kidney injury by inhibition of necrosis and apoptosis in tubular epithelial cells, suggesting that CHOP is a potential therapeutic target protein in I/R injury.

Keywords: C/EBP homologous protein, CHOP, ER stress, ischemia, apoptosis

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02-6

A MITF antagonist peptide (SE207C) inhibits melanogenesis by suppression of MITF activity in B16F1 melanoma cells and human epidermal malanocytes

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Melanin is synthesized in melanosomes present in melanocytes by the action of a variety of stimulators, α-melanocyte stimulating hormone (α-MSH) and cyclic AMP (cAMP)-elevating agents or by absorbing ultraviolet light. These external stimulators activate ad-

enylyl cyclase and upregulate intracellular cyclic AMP level, which subsequently activates microphthalmia-associated transcription factor (MITF) that is a transcription factor for melanocyte-specific enzymes, including tyrosinase (TYR), tyrosinase-related protein-1 (TRP-1), and tyrosinase-related protein-2 (TRP-2). In this study, we investigated anti-melanogenic activities of a MITF-derived antagonist peptide (SE207C) and its underling mechanism in B16F1 melanoma cells and primary human epidermal melanocytes (HEMs). Treatment of melanocytes with SE207C inhibited α-MSH-induced melanin production, TYR activity and proliferation. Furthermore, SE207C reduced the expression of melanin-related genes at both mRNA and protein levels in a dose-dependent manner. On the other hand, the mRNA and protein expression of MITF were not changed by treatment with SE207C. The upstream signaling pathways including cAMP response element-binding protein (CREB), glycogen synthase kinase-3β (GSK-3β), and Akt for activation were also not affected by SE207C. Interestingly, we found that the SE207C inhibited MITF from binding to the promoter region of tyrosinase gene. Moreover, SE207C decreased the formation of MITF-β-catenin and MITF-CREB a complex, which led to a decrease in melanin synthesis. Collectively, these results suggest that SE207C might be a promising candidate for the treatment of MITF-associated disorders.

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02-7

BDNF expression of macrophages and angiogenesis after myocardial infarction

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After myocardial infarction (MI), the heart produces new blood vessels in the infarct area, and the macrophages recruited to infarct sites are known to play a significant role in this process. Furthermore, recent studies indicate that blood levels of brain-derived neurotrophic factor (BDNF) are markedly elevated after MI. However, the source of BDNF was not determined in MI heart. In this study, the authors adopted immunohistochemical and immunocytochemical approaches, flow cytometry and PCR analysis to assess the relationship between BDNF expression and macrophage activation during angiogenesis after coronary artery ligation in a murine model. BDNF expression was elevated in cardiomyocytes at day 1 post-ligation and then diminished in MI hearts. On the other hand, macrophages expressed BDNF progressively in peri-infarct and infarct areas. Interestingly, BDNF expression in macrophages was strong at 5 and 7 days (active angiogenesis period) post-ligation in MI hearts. To identify the macrophage subtype responsible for strong BDNF expression, double immunofluorescence staining, flow cytometry and RT-PCR analysis were conducted for comparison of BDNF expression level in M0, M1 and M2 macrophages. It was found that both M1 and M2 macrophages displayed strong BDNF expression in both mRNA and protein levels. Furthermore, activated macrophages were found to be located around new blood vessels during angiogenesis. BDNF stimulated endothelial tube sprouting directly in CAM on plant assay. These findings suggest that both M1 and M2 macrophages are sources of BDNF in MI heart, and the BDNF secreted from activated macrophages are associated with angiogenesis in MI heart.

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02-8

Bioactive fish collagen/ polycaprolactone composite nanofibrous scaffolds fabricated by electrospinning for 3D cell culture

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One of the most challenging objectives of 3D cell culture is the development of scaffolding materials with outstanding biocompatibility and favorable mechanical strength. In this study, we fabricated a novel nanofibrous scaffold composed of fish collagen (FC) and polycaprolactone (PCL) blends by using the electrospinning method. Nanofibrous scaffolds were characterized using a scanning electron microscope (SEM), and it was revealed that the diameter of nanofibers decreased as FC content was increased in the FC/PCL composite nanofibers. The cytocompatibility of the FC/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 thymic epithelial cells (TECs) but also stimulated the expression of genes and proteins involved in cell adhesion and T cell development. Thus, these results suggest that the FC/PCL composite nanofibrous scaffolds will be a useful model of 3D cell culture for various cell types including TECs, and may have wide applicability in the future for engineering tissues or organs.

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03-1

한국인이 선호하는 눈썹의 형태(Brow archetype preferred by Korean women)

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본 연구의 목적은 한국인이 선호하는 눈썹의 형태를 알아보는데 있다. 문헌조사를 통하여 도안이 상세히 기술되어졌으며 재현가능한 눈썹의 형태들을 5개 선택하였다. (웨스트모어 Westmore, 라마스 Lamas, 아나스타시아 Anastasia, 쉬라이버 Schreiber, 황 Hwang). 300명의 한국여성에게 설문조사를 실시하여 이상적인 눈썹을 그리는 방법이 있다고 생각한 이들에게 위 다섯 가지의 눈썹형태 중에 가장 이상적인 것을 선택하도록 하였다. 300명 중 232명 (77.3%)은 이상적인 눈썹을 그리는 방법이 있을 것이라고 답하였고, 68명 (22.7%)는 없을 것이라고 하였다. 다섯 가지 눈썹형태에 대한 선호도는 각각 달랐다 (p=0.0001, [Chi-square]). 그 중 아나스타시아가 가장 선호되었으며 (44.8%, 콧구멍의 중심을 지나는 수직선에서 눈썹이 시작하며, 코의 중심과 동공중심을 잇는 선에 눈썹산이 있고, 콧방울의 가쪽선과 가쪽눈구석을 잇는 선에서 눈썹이 끝나는 형태), 라마즈가 두 번째로 선호되었다 (22.0%). 이 연구 결과는 얼굴회춘수술이나 눈썹문신을 시행할 때 이용될 수 있을 것이다.

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03-2

Stable isotope analysis of Joseon people skeletons from the cemeteries of old Seoul city, the capital of Joseon dynasty

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Stable carbon and nitrogen isotope analysis reflect the diets of different human populations in history. In this study, we performed stable isotope analysis on the human skeletons from Joseon period cemeteries discovered around Old Seoul City. Our data clearly showed that Joseon peoples consumed more C_3-based foods as main staple than C4-based foods; and they should have ingested proteins mainly of terrestrial origin than of marine origin. In our study, the values of stable isotope exhibited unique patterns in each subgroup. While δ13C value did not show any statistical differences between subgroups, significantly higher values of δ15N were found in males than in females, which might be caused by the dietary differences in each sex group. More studies should be done in the future, on the Joseon samples from archaeological sites of this country, to comprehend the dietary pattern of Korean people's ancestors before industrialization in 20th century.

Keywords: Stable isotope analysis, human bones, nitrogen, carbon, Joseon Dynasty, South Korea

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03-3

3D-reconstruction and anatomical analysis of the mental canal using MicroCT

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The mandibular canal containing the inferior alveolar neurovascular bundle is divided into the mental and incisive canals at the premolar region. The aims of this study were to 1) identify and classify the divergent shape of the mental canal using 3D-reconstruction, 2) elucidate the general anatomical structure via the morphological measurement, and 3) analyze the histologic composition in the region where the mandibular canal diverges into two canals. Thirty-four hemimandibles from 19 cadavers were used (16 males, 3 females, mean death age 54.4 years). The specimens scanned by MicroCT (microscopic computerized tomography) were reconstructed and classified into three types according to the divergent shape of the mental canal posterior-superiorly. Nine measurement items were measured from bony landmarks using digital calipers. After tissue processing of the neurovascular bundles, these histologic sections were stained with hematoxylin-eosin and observed on the light microscope. The most common divergent shape of the mental canal was posterior-superiorly at an angle of approximately 50° (type 2 = 30~60°) from the mandibular canal by 53% (n=13). The anterior loop of the mental canal was located 3.05±1.15 mm anteriorly from the anterior margin of the mental foramen and 2.72±1.41 mm inferiorly from the superior margin of the mental foramen, and had a length of 4.34±1.46 mm. The mandibular, mental, and incisive canals had a diameter of 2.80±0.49, 2.63±0.64, and 2.22±0.59 mm, respectively. The inferior alveolar neurovascular bundle divided into mental branch and dental branch, and the mental branch run inside the mental canal and the dental branch continued anteriorly in the incisive canal. The mental canal which made the anterior loop at the point of 3.1 mm anterior and 2.7 mm inferior from the mental foramen curved posterior-superiorly at an angle of approximately 50° from the mandibular canal to the mental foramen. Such detailed morphological features of the mental canal would suggest a practical anatomical knowledge in mandibular premolar and incisive region.

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03-4

Effect of caffeine intake on the reproductive system in the immature male rat

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Objectives: Today, high caffeinated energy drinks sales have grown by more than 50% since 2005 and represent the fastest growing segment of the beverage industry. Caffeine is the most widely used CNS stimulant in the world and numerous studies have examined the effects of caffeine intake on male fertility. Previously, caffeine has been reported to have deleterious effects on the testicles in the study using adult animals. Also, our previous result demonstrated that chronic caffeine intake altered normal testis growth and serum levels of testosterone in peri-pubertal rats. However, it is not clear the critical point of time in developmental stage and minimum dose of caffeine which can affect the reproductive efficiency of male rat. **Material & Method:** Thus, to investigate the impact of caffeine on the testicular growth by time and dosage dependent manner, a total 72 immature male SD rats (45~50gm) were used. The rats were assigned to 4 groups and each group received tap water (control, CT) or water containing caffeine 20(CF20) or 60(CF60) or 120 mg/kg/day (CF120) via gastric tube. After weaning on day 21 of age to post datum 30(PD30) or 40(PD40) or 50(PD50) or 60(PD60), each rat received water or caffeine contained water (n=18/group). Body weight, daily food intake were monitored throughout the experiment and body composition was also analyzed with DEXA at the end of experiment. In addition, final testes weight and other accessory reproductive organs were measured. **Results:** Caffeine significantly decreased body weight gain throughout the experiment period (CT=361.33 ± 30.8g, CF20=326.60 ± 10.8g, CF60=284.00 ± 28.5g, CF120=236.40 ± 32.0g, $p<0.001$ compared to the CT). Decrease in food intake was accompanied by decrease in body weight dose dependently (CT=282.33± 24.7g, CF20=258.50 ± 21.2g, CF60=234.30 ± 24.2g, CF120=195.80 ± 16.5g; $p<0.05$, CTvsCF180). Amount of total body fat was significantly decreased in CF120 group in different stages of postnatal development from PD40 (CT=34.90 ± 5.4 g, CF120= 20.38 ± 2.0g) ($p <0.01$), PD50 (CT=67.90 ± 7.6 g, CF120= 32.98 ± 3.6g) ($p <0.001$), PD60 (CT=93.03 ± 13.1 g, CF120= 43.06 ± 11.5g) ($p <0.01$). Also, CF60 group showed significant decrease at PD50 (CF60=43.04 ± 7.7g) ($p <0.05$) and PD60 (CF60= 53.08 ± 3.7g) ($p <0.01$). Interestingly, CF20 group showed significant decrease

in PD60 (CF20=65.26 ± 2.7g) ($p < 0.01$). Proportion of fat to the total body mass was significantly decreased at PD60 in all caffeine group (CT=18.98 ± 2.0%, CF20=18.98 ± 1.1%, CF60=18.10 ± 1.0%, CF120=16.64 ± 2.5%) ($p<0.05$). In CF120 group PD40 (CT=16.17 ± 2.0%, CF120=12.32 ± 1.7%) ($p<0.05$) and PD50 (CT=22.57 ± 1.4%, CF120=17.06 ± 2.5%) ($p<0.05$) showed significant decrease. Caffeine also caused a decrease in weight of testis and accessory sex organs in high-dose groups. But there was no statistically significant difference between groups. **Conclusion:** Our result demonstrated that intake of caffeine (even the lowest concentration) significantly decreased body weight and food intake at all groups of postnatal development. At different ages of postnatal development, total body fat mass and body weight showed decrease tendency dose dependently. Given that intake of large amount of caffeine (more than 30mg/kg/day) during pregnancy led to a subsequent decrease of plasma testosterone concentrations in male offspring, it is conceivable that mean testis weight and total body fat mass significantly decreased in CF120 groups. However, not only high dose group but also CF20 group showed significant decrease of total body fat mass at PD60 and this mean even the lowest caffeine intake can be harmful if one chronically intake caffeine. So further study will be needed to investigate the cellular/molecular mechanism by which caffeine can affect male reproductive system using in vivo/vitro experimental models.

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03-5

Gantzer's muscle and its association with neurovascular structures

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Gantzer's muscle is an additional muscle in the forearm as the accessory head of the flexor pollicis longus and the accessory head of the flexor digitorum profundus. In the present study, we studied the incidence and the morphology of Gantzer's muscle and its relation with neurovascular structures. In 26 upper limbs, the correlation between the presence of Gantzer's muscle and topographic measurements of neurovascular structures was analyzed. Gantzer's muscle was found in 38.46% (10/26). They originated from the medial epicondyle and inserted to the flexor pollicis longus (80%) or the flexor digitorum profundus (20%). Its insertion point (the relative length of Gantzer's muscle) was located at 48.77 percentile of the distance of the reference line connecting from the medial epicondyle to the pisiform bone. Gantzer's muscle passed over the anterior interosseous nerve and artery at 31.47 percentile and 29.66 percentile of the distance of the reference line, respectively. The branching point of the anterior interosseous nerve was not statistically different whether Gantzer's muscle exists or not. However, the branching point of the anterior interosseous artery was located more distally in the cases with Gantzer's muscle than in the cases without it. Moreover, the length of Gantzer's muscle was correlated with the branching point of the anterior interosseous artery ($r = 0.674$, $p = 0.033$). Our results suggest that the presence of Gantzer's muscle might be relation to the topography of the anterior interosseous artery.

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03-6

사시수술을 위한 transverse superior fascial expansion의 해부학적 연구

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위곧은근과 눈꺼풀올림근에 연결된 transverse superior fascial expansion (TSFE)은 사시수술인 위곧은근의 뒤옮김수술 또는 절제수술 시 눈꺼풀올림근에 영향을 주는 중요한 구조물이다. 따라서 이 연구의 목적은 TSFE와 위곧은근, 눈꺼풀올림근과의 해부학적 관계를 밝히는데 있다. 고정하지 않은 한국인 시신 23구 45쪽 (평균 73.2±13.4 세)의 눈확을 대상으로 하였으며, 눈확위벽을 제거하여 위곧은근을 기준으로 TSFE의 해부학적 위치, 길이, 너비, 두께, 인장강도를 계측하였다. 위곧은근의 길이는 46.15±4.77 mm이며, 위곧은근의 신경은 이는곳에서 16.50 ±2.30 mm (위곧은근 이는곳의 1/3지점) 지점에 위치하고 있었다. TSFE는 위곧은근과 눈꺼풀올림근 사이에 단단하게 연결되어 있었다. 위곧은근에서 시작한 TSFE는 안쪽으로는 도르래를 지난

위빗근힘줄을 싸고 가쪽으로는 눈물샘을 싸고 있으며, 눈꺼풀올림근 위쪽의 Whitnall's ligament와 연결되어 있었다. TSFE는 위곧은근의 닿는곳에서 13.58±1.85 mm 떨어진 지점 (위곧은근 닿는곳의 1/3지점)에서 시작하여 앞쪽 8.01±5.48 mm 떨어진 지점에 눈꺼풀올림근과 연결되어 있었다. TSFE의 너비는 위곧은근에서 6.70±0.19 mm, 눈꺼풀올림근에서 11.42±6.70 mm로 넓게 퍼진 사다리꼴 모양으로 부착하였다. TSFE의 두께는 안쪽(1.53±0.47 mm)이 가쪽(1.19±0.19 mm)보다 두꺼웠다. TSFE의 뒤쪽에는 위곧은근의 안쪽모서리에서 눈꺼풀올림근로 연결하는 느슨한 근육사이막이 있으며, 근육사이막이 끝나는 부위에 눈꺼풀올림근으로 들어가는 신경을 확인할 수 있었다. 눈꺼풀올림근의 신경은 위곧은근의 닿는곳에서 19.49±1.84 mm (위곧은근의 1/2지점) 지점에 위치하였다. TSFE의 인장강도는 9.74 ± 4.53 N으로 근육사이근막(3.02 ± 1.85 N)보다 큰 차이를 보였다 (P = 0.001). 이러한 결과를 토대로 위곧은근의 절제술 또는 뒤옮김수술 시, 눈꺼풀올림근에 영향을 주지 않는 수술 방법을 제시할 수 있을 것으로 사료된다.

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03-7

Histomorphometric evaluation of mechanoreceptors in Bassett's ligament: cadaveric study

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Bassett's ligament is the distal part of the anterior inferior tibiofibular ligament(ATFL), and one of the factor of soft tissue impingement of the ankle joint. Because frequently removed for treatment. Currently, there has been no report about mechanoreceptors of Bassett's ligament for functional instability of ankle. In this study, we evaluated the distribution and three types of mechanoreceptors in ankle ligaments and adjacent synovial membrane to understand the role of the Bassett's ligament as functional stability of ankle. Tissue samples from Basset's ligament, AIFL and synovium were obtained from 10 cadavers donated to Korea University (mean age 62 years: ranged from 34 to 92 years). Histologically mechanoreceptors (Golgi-Mazzoni, Ruffini, Vater-Pacinian) and Free nerve ending were identified, and classified by gold chloride staining method. And evaluation of the density of the mechanoreceptor was performed 30um sections under a light microscopy counting each receptor and compare density on three tissues. Mechanoreceptors and free nerve ending were investigated in each tissues were identified depending on Freeman and Wyke. Type I (Ruffini) dendritic structure resembles a tree, with a trunk, branches, and leaves ; type II (Vater-Pacini) mechanoreceptors were spherical or cylindrical with lamellated internal structure; type III (Golgi-Mazzoni) largest receptor with a helical or coil-like shape; and type IV (free nerve endings) axons did not terminate in any specific shape. When the densities of the mechanoreceptors in three tissues (Bassett's ligament, ATFL and synovium) were compared, the difference was not statistically significant. In this study, mechanorecetors of the type previously discovered in other joints are also present in this three tissues. Based on results, Bassett's ligament, like the ATFL and the synovium, because we think Bassett's ligament has correlation with functional instability of ankle joint. Remove the Basset's ligament because it balks against the talus, and causes pain at the ankle. Additionally, when surgery of the lateral ligament, it is difficult to position a suture anchor on the ATFL insertion site of the fibular tip if Bassett's ligament has not been removed. Clinically recommend removing Bassett's ligament during ankle arthroscopy for soft tissue impingement, should be determined only on the situation can not be avoided.

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03-8

한국인 머리뼈의 노화 과정에 대한 형태학적 분석

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사람의 뼈는 성장이 멈춘 후 뼈의 생성보다 흡수가 많아지는 노화현상이 발생한다. 머리뼈에서도 노화에 따른 뼈의 흡수가 일어나는데, 머리뼈의 노화 과정을 형태학적으로 연구한 것은 서양인을 대상으로 한 것에 국한되어 있고, 한국인을 포함한 동양인을 대상으로 한 연구는 미비한 것이 현재의 실정이다. 이 연구는 한

국인 얼굴의 CT DATA를 이용하여 노화에 따른 머리뼈의 변화를 여러 항목을 계측하여 비교 분석하였다.0.65mm 간격으로 촬영된 한국인 머리뼈 CT 영상을 컴퓨터 프로그램(Mimics, Materialise NV, Belgium)을 이용해 3차원으로 재구성하였다. 재구성된 파일 중, 남녀를 20대와 60대 두 연령그룹으로 나누어 각각 10개씩 총 40개를 대상으로 계측하였다. 눈확의 크기 변화를 관찰하기 위하여 가쪽모서리의 이마광대봉합과 안쪽모서리의 맞닿은 부분에 계측점을 찍어 x축으로 설정하고, 이에 수직하게 10등분 한 y축의 높이를 측정하여 눈확의 위쪽가장자리와 아래쪽가장자리의 변화를 계측하였다. 그리고 머리뼈바닥의 뇌하수체오목 중앙점과 코뿌리점을 이은선(Sella–Nasion)을 기준선으로 하여, 나이에 따른 미간, 눈확, 위턱, 뼈콧구멍의 4군데 각도 변화를 측정하였다.한국인 머리뼈에서 눈확 위쪽 가장자리의 나이에 따른 변화는 남녀 모두 통계적으로 유의할 만한 변화가 없었으며, 남자의 아래쪽 가장자리의 높이는 평균 1.8 ± 0.2 mm로 증가하여 뼈의 흡수가 일어난 것으로 나타났다. 여자의 경우는 나이에 따라 아래가쪽 가장자리의 높이가 증가하였으나 미미한 차이였다. 눈확 및 미간 각도는 나이에 따른 변화가 남녀 모두에서 통계적으로 의미있는 차이가 없었다. 하지만 남자의 위턱각도는 20대 그룹에서 45.6 ± 3.6°, 60대 그룹에서 40.7 ± 3.7°로 약 5° 가량 감소하여(P–value = 0.00685) 통계적으로 의미있는 차이를 보였으며, 여자의 경우도 각각 44.0 ± 5.5°, 41.4 ± 3.4°로 약 2.5° 감소하였다. 뼈콧구멍 각도는 남자 20대와 60대 그룹에서 각각 평균 53.6 ± 6.2°, 48.4 ± 4.2°로 연령 그룹 간에 5°의 감소를 보였다(P–value = 0.04770). 그러나 여자의 경우는 53.4 ± 2.5°, 53.2 ± 7.1°로 나이에 따른 뼈의 흡수가 많지 않은 것으로 나타났다. 이러한 한국인 머리뼈의 노화에 따른 변화는 서양 인구집단을 대상으로 한 연구 결과와 차이를 보였다.

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04-1

Activated T cells secrete an soluble common γ-chain that inhibits cytokine signaling and exacerbates inflammation

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The common γ-chain (γc) plays a central role in signaling by IL-2 and other γc-dependent cytokines. Here we report that activated T cells produce an alternatively spliced form of γc mRNA that results in protein expression and secretion of the γc extracellular domain. The soluble form of γc (sγc) is present in serum and directly binds to IL-2Rβ and IL-7Rα proteins on T cells to inhibit cytokine signaling and promote inflammation. sγc suppressed IL-7 signaling to impair naive T cell survival during homeostasis and exacerbated Th17-cell-mediated inflammation by inhibiting IL-2 signaling upon T cell activation. Reciprocally, the severity of Th17-cell-mediated inflammatory diseases was markedly diminished in mice lacking sγc. Thus, sγc expression is a naturally occurring immunomodulator that regulates γc cytokine signaling and controls T cell activation and differentiation.

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04-2

Temporal requirement of TGF-beta and hedgehog signaling during middle ear ossicle formation

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The vertebrate auditory system consists of outer, middle, and inner ears. Although most of hearing loss observed in humans is originated from the inner ears, malformation of the middle ear ossicles can also cause hearing loss. The middle ear ossicles consist of malleus, incus and stapes. These ossicles are derived from neural crest cells (NCCs), but stapedial footplate is derived from mesenchymal cells. NCCs from rhombomeres 1 and 2, which migrate to branchial arch (BA1), will later form malleus and incus, whereas NCCs from rhombomere 4 migrating to BA2 will form stapes. However, it is currently unclear how NCCs migrate to the correct location, where they condense and differentiate into bony ossicles. In order to elucidate the molecular mechanisms regulating the initial condensation and differentiation of NCCs into middle ear ossicles, we manipulate signaling pathways specifically in NCCs using Cre/lox system. In

particular, we focused on Hedgehog (Hh) and TGF-β signaling, which are known to be involved in NCC development. When Hh signaling was inactivated in the NCCs using *Wnt1*^{Cre};*Smo*$^{lox/lox}$mutants, initial condensation in both BA1 and BA2 were severely reduced due to cell death. On the other hand, ectopic activation of Hh signaling in the NCCs using *Wnt1*^{Cre}; *Smo*$^{M2/+}$ mutants led to enlarged condensation of the NCCs in both BA regions atE11.5, resulting infused middle ear ossicles dislocated from the inner ear at E15.5. Although reduced, there was mesenchymal condensation in the prospective middle ears in the absence of Hh signaling, indicating that there should be another signal regulating initial condensation of migrating NCCs. We found that expression of Sox9, a marker for mesenchymal condensation, was closely associated with Bmp4 expression in the pharyngeal endoderm in BA2. When TGF-β signaling was inactivated in NCCs using *Wnt1*^{Cre}; *Smad4*$^{lox/lox}$ mutants, NCCs failed to migrate to the prospective stapes region in BA2, while their migration to BA1 was unaffected, suggesting that Bmp4 secreted from pharyngeal endoderm dictates the migration and initial condensation of NCCs in BA2, but not in BA1. Together, our results suggest that Bmp4 signaling from the endoderm guides the NCCs to condense in the prospective stapes region, and Hh signaling is subsequently require for normal development in to middle ear ossicles.

This work was supported by the Brain Korea21 PLUS Project for Medical Science, Yonsei University.

Keywords: Middle ear, initial condensation, hedgehog and TGF-β signaling, pharyngeal endoderm

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04-3

Ultrastructural investigation of microcalcification and the role of oxygen–glucose deprivation in cultured rat hippocampal slices

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Intracellular calcium accumulation is associated with cell death in several neuropathological disorders including brain ischemia, but the exact mechanisms of calcification need to be clarified. We used organotypic hippocampal slice culture cultures subjected to oxygen–glucose deprivation (OGD) mimicking the in vivo situation to investigate the events underlying ectopic calcification. Alizarin red staining indicating calcium deposition was observed in the cornu ammonis (CA)1 and dentate gyrus regions in control hippocampal slices despite no specific labeling for cell death markers. Electron microscopy using the osmium/potassium dichromate method revealed scattered degenerated cells throughout the normally appearing CA1 region. They contained electron-dense precipitates within mitochondria, and electron probe microanalysis confirmed that they were calcifying mitochondria. Selective calcium deposition was noted within, but not beyond, mitochondria in these mineralized cells. They showed ultrastructural features of non-necrotic, non-apoptotic cell death and retained their compact ultrastructure, even after the majority of mitochondria were calcified. Unexpectedly, no intracellular calcification was not edinnecrotic CA1 pyramidal cells after OGD, and there was no progression of calcification in OGD-lesioned slices. In addition, mineralized cells in both control and OGD-lesioned slices were closely associated with or completely engulfed by astrocytes but not microglia. These astrocytes were laden with heterogeneous cytoplasmic inclusions that appeared to be related with their phagocytic activity. These data demonstrate that micro calcification specifically associated with mitochondria might lead to a novel type of cell death and suggest that astrocytes may be involved in the phagocytosis of the semineralized cells and possibly in the regulation of ectopic calcification.

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04-4

AGE-albumin from activated macrophage is critical in human BD-MSC survival and post-ischemic reperfusion injury

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Post-ischemic reperfusion injury (PIRI) triggers an intense inflammatory response which is essential for repair but also implicated in pathogenesis of postischemic remodeling in several organs in human. Recently stem cell therapy emerged as one of the promising way for PIRI in human, however, the satisfactory results did not report in the PIRI including acute myocardial infarction, stroke or critical limb ischemia (CLI). For PIRI, CLI and reperfusion were generated by tie and reperfusion of femoral artery in Balb/c mouse. We evaluated the recovery of PIRI-CLI by injection of hBD-MSC with or without sRAGE, the AGE-albumin inhibitor. Our results revealed that activated M1 macrophages synthesize and secrete AGE-albumin and MAPK pathway, and this was critical in skeletal muscle cell death in PIRI-CLI model through RAGE increase. AGE-albumin also induced hBD-MSC death by RAGE increase. Combined injection of sRAGE and hBD-MSC enhanced the survival of hBD-MSC in PIRI-CLI mouse model and angiogenesis. Our data revealed that AGE-albumin from activated macrophages is critical for skeletal muscle cell death and hBD-MSC death in PIRI-CLI. Taken together, it suggested that AGE-albumin from activated macrophages induced the skeletal muscle cells and hBD-MSCs death through RAGE increase. Inhibition of AGE-albumin with sRAGE protected the apoptosis of both skeletal muscle cells and hBD-MSCs, so the PIRI-CLI protected dramatically with improved angiogenesis. Therefore, regulation of RAGE or AGE-albumin with stem cells could be one of the successful therapeutic strategies for treatment of PIRI including CLI, acute myocardial infarction, etc.

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04-5

Spontaneous specification of secondary neural tube-derived embryonic neural stem cells in vitro

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Secondary neurulation is an embryonic progress which gives rise to secondary neural tube, a precursor of lower spinal cord region. Secondary neural tube is derived from aggregated Sox2+ neural cells at the dorsal region of the tail bud, which eventually form rosette or tube-like structures. We addressed the question whether tail bud contains neural stem cells, namely secondary NSCs (sNSCs), with self-renewal and multi-potent potentials invitro. Using in vitro neurosphere assays, neurospheres were readily formed at the rosette and neural tube level, but much less at tail bud level. Further, we identified that sNSCs-generated neurospheres were significantly smaller in size when compared to cortical neurospheres. Interestingly, RT-PCR, BrdU labelling and cell cyclean alysis showed that this difference was not due to the reduction in proliferation, but rather because of sNSCs prone to neuronal commitment, as we observed that sNSCs-derived neurospheres contained more committed neuronal progenitor cells even in the presence of appropriate growth factors, EGF and bFGF. These results suggest that higher tendency to spontaneous specification of sNSCs into progenitor cells may explain the limited expansion of secondary neural tube during the embryonic development.

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04-6

Immunoreactivity of neurogenic factor in the guinea pig brain after prenatal hypoxia

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Chronic prenatal hypoxia is considered to cause perinatal brain injury. It can result in neurological disorder such as cerebral palsy, learning disability. These neurological problems are related to chronic placental insufficiency (CPI), which leads to chronic hypoxemia and hypoglycemia. The effects of hypoxia on neurogenesis have been controversial during development. We therefore investigated the effect of chronic prenatal hypoxia in the brain of fetal guinea pig the using the guinea pig CPI model. Chronic placental insufficiency was induced by unilateral uterine artery ligation at 30~32 days of gestation (dg: with term defined as ~67dg). At 50 and 60 dg, fetuses were sacrificed and assigned to either the growth-restricted (GR) or control (no ligation) group. Immunohistochemistry was performed with HIF-1α, PCNA, NeuN and BDNF antibody in the cerebral cortex and dentate gyrus. The number of NeuN-IR and BDNF-IR cells was lesser in GR fetuses than in controls in the cerebral cortex and dentate gyrus at 60 dg ($p<0.05$). The growth of the developing brain is dependent upon the availability of growth factors such as BDNF. The reduction in the number of neuronal cells observed in our GR group was associated with the observed reduction in BDNF protein found at 60 dg. There was no significant difference between control and GR fetuses in the densities of PCNA-IR cells in the subventricular zone and subgranular zone at 50 and 60 dg. These findings suggest that the survival of neurons in the cerebral cortex is decreased by chronic prenatal hypoxia at 60 dg.

Keywords: Chronic placental insufficiency (CPI), prenatal hypoxia, guinea pig, neurogenesis

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04-7

Neural stem/progenitor cells containing human arginine decarboxylase promotes neural differentiation after ischemic damage

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Neural stem cell therapy is a promising therapeutic strategy for various CNS diseases. However, transplanted stem cells have several limitations for clinical approach. Our previous studies demonstrated that L-arginine decarboxylase gene containing neural stem/progenitor cells (ADC-mNSPCs) which can synthesize agmatine effectively conferred cytoprotection following oxidative stress. In continuation of our previous studies, this present investigation intended to demonstrate whether ADC genes could regulate neural differentiation after ischemic damage *in vitro*. The experimental groups were divided into 3 conditions: Normal control (NC), mock vector infection, and ADC gene infection following our previous study. After infection, mNSPCs were subjected to oxygen-glucose depravation (OGD) performed at 37 °C for 2 hours. The potency of neural differentiation was evaluates by detecting STAT through interacting with P38 MAPK, CREB after OGD. Our results showed that the ADC-mNSPCs group had significant increase of pSTAT1 expression which is known to be regulated by pP38 MAPK and pCREB in the nucleus and the expressions of DCX and Olig2 were increased in ADC-mNSPCs suggesting the cell fate toward neuronal differentiation. However, the GFAP expression was significantly decreased in ADC-mNSPCs. Our overall data suggest that ADC gene transfection promote neurogenesis in mNSPCs via STAT1 phosphorylation and this specificity maybe make ADC gene valuable in engineered stem cells therapy for various CNS diseases.

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Keywords: human arginine decarboxylase (ADC), neural stem/progenitor cells (mNSPCs), neurogenesis, neuronal differentiation, Oxygen-glucose depravation (OGD)

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04-8

Functional analysis of Apcdd1 in mice molar development

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After the genome wide screening, a molar tooth forming gene, Apcdd1 (Adenomatosis polyposis coli down-regulated 1), was selected and evaluated expression pattern in mice tooth development using RT-qPCR and in situ hybridizations. At E13.5 distinctive expression pattern of Apcdd1 was detected in condensed mesenchyme and at E14.5, Apcdd1 was observed in the enamel knot (EK). In vitro organ cultivation using Apcdd1 antisense oliodeoxynucleotides (AS-ODN) was employed at E13 for 2 days to define the developmental function of Apcdd1. After knocking down of Apcdd1, histogenesis and cellular events such as cell adhesion, proliferation and apoptosis, were examined. These results showed the altered morphogenesis of tooth germ with lower cell proliferation and changed localization patterns of cell adhesion molecules after the Apcdd1 knocking down. Epithelial rearrangement was also affected by Apcdd1 knocking down. Further, we evaluated altered expression patterns of signaling molecules, related with EK, using RT-qPCR to understand the precise signaling regulations of Apcdd1. In addition, renal transplantation was employed to understand the detailed developmental function of Apcdd1 at cap stage in tooth crown formation. Overall, we suggest that Apcdd1 would play crucial roles at cap stage in tooth development.

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Poster

전시발표-1 (P1-P83)
2014년 10월 16일(목) 16:15 – 18:15 거문고 C홀
■ Gross anatomy: P1~P15
■ 신경 및 발생: P16~P48
■ 조직 및 기타 내용: P48~P83

전시발표-2 (P84-P172)
2014년 10월 17일(금) 13:00 – 14:00 거문고 C홀
■ Gross anatomy: P84~P98
■ 신경 및 발생: P99~P132
■ 조직 및 기타 내용: P133~P172

P1

초등학생을 위한 인체탐험캠프가 건강증진에 미치는 교육적 효과

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아동 및 청소년을 위한 전문적이고 체계적인 건강증진 교육은 올바른 생활습관을 확립하고 건강관리의 방법을 익히는 데 매우 중요하며, 평생건강의 초석이 된다. 우리나라 학교보건교육은 체계와 전문성이 결여되어 있다. 또한 보건교육의 교육과정과 실시 여부에 따른 효과분석은 진행되어 왔으나 효과적인 교육방법에 대한 연구는 미비하다. 이에 본 연구는 강원대학교 의학전문대학원 교수와 학생들이 중심이 되어 청소년을 위한 인체탐험캠프를 개최하였고, 참가학생들의 건강지식 이해도와 건강증진 태도의 변화를 설문조사 후 분석하였다. 캠프에 참가한 초등학생 61명을 대상으로 사전 동의를 얻어 사전, 사후, 추후(3개월) 총 3회 설문조사를 실시하였고, 자료를 통계처리 하였다. 건강지식 이해도는 사전과 사후, 사전과 추후를 각각 비교한 결과 모두 유의하게 증가하였다($p<0.01$). 건강증진 태도의 변화에서도 사전과 사후($p<0.01$), 사전과 추후($p<0.05$) 모두 긍정적인 변화를 나타내었다. 캠프 프로그램 만족도와 태도변화를 살펴보면, 만족도가 높을수록 태도 변화가 큰 것으로 나타났다($p<0.01$). 그러나 만족도와 지식이해도는 서로 상관관계가 없는 것으로 나타났다($p=0.307$). 결론적으로 기존의 전통적인 건강증진교육 형태를 벗어나 주제별 실습 중심의 교육콘텐츠를 숙박형 캠프로 진행한 결과, 학생들의 건강지식 이해도 및 건강증진 태도의 변화가 뚜렷하였고, 그 효과도 지속되는 것으로 나타났다. 따라서 인체탐험캠프는 건강증진교육에 있어 새로운 패러다임을 제시할 수 있는 대안이 될 것으로 사료된다.

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P2

Differential expression of CCR5 by orthodontic biophysical force application

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Tooth movement by orthodontic biophysical force reflects the role of soluble factors released from the periodontal ligament (PDL) which is primary to maintain homeostasis of periodontal tissues. Thus far, many molecules have been reported to be involved in tooth movement, but key molecules and their mechanism of action responsible for the movement are still enigmatic. In this study, to detect the key molecules, rat upper 1stmolars were mesially moved by a 50cN force. Differential display-PCR and Westernblot revealed that CC motif chemokine receptor type5 (CCR5) was differentially increased at day 1 after the movement. Also, mRNA levels of CCR5 ligands, CCL3 and -5 showed a similar change as seen in CCR5. Strong immunoreactivity against CCR5 was found in the PDL undergoing the force application. Either in vitro compression or tension force on primary human PDL cells increased the expression of CCR5 and its ligands. CCR5 siRNA and its ligands application revealed that several factors for bone remodeling including ALP, OCN, RUNX and RANKL etc. were regulated through CCR5. These result ssuggest that CCR5-itsligands axis in PDL cells may play a regulatory role in the remodeling of periodontal tissue and be a target for controlling orthodontic tooth movement.

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P3

Topographic anatomy of superior labial artery for dermal filler injection

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The superior labial artery (SLA), which is a branch of the facial artery (FA), supplies the upper lip area. Despite the importance of having detailed knowledge of SLA topography for dermal filler injection to the upper-lip area, very few studies have been performed. The aim of this study was thus to determine the distribution pattern of the SLA and provide precise topographic information of SLA for dermal filler injection. Sixty hemi-faces from 18 Korean and 18 Thai cadavers were used for this present study. The various distribution patterns of the SLA were classified according to its relationship with the FA. The course of SLA was classified into four types: type I type I (56.7%), in which the SLA and the alar branch both arise directly and independently from the FA; type II (21.7%), in which the SLA branches off from the FA and then gives off an alar branch; type III (15.0%), in which the SLA is the terminal branch of the FA; and type IV (6.7%), in which the SLA is absent. The origin of the SLA was located 12.1±3.1 mm (mean±SD) lateral and at variable angle of 42.8±26.9° relative to the mouth corner. The SLA proceeded from the origin of SLA located within a 1.5-cm-sided square superolateral to the mouth corner as running along the vermilion border of the upper lip to the facial sagittal midline in depth of 3mm. Thus, clinicians should be careful when injecting dermal filler in this area.

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P4

The relationships between masticatory performance and maloc clusion (skeletal type) using the FEA

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It is not fully understood whether masticatory performance is compromised in individuals with the skeletal malocclusion relationships. The aim of this study is to establish the relationships between masticatory performance and malocclusion (skeletal type) using the finite element analysis (FEA) method. Three representative human cone beam computed tomography (CBCT) images of three skeletal malocclusions were obtained at the department of orthodontics, Yonsei University Dental Hospital, Seoul, Korea. FEA analysis was performed to obtain the three-dimensionional deformation of the mandibles when 100, 150, 200 and 225 Kg was loaded. The results showed that the distortion in all three skeletal malocclusion was comparable among groups. It was shown that the greater the force is that the distortion is increased as shown in the FEA. Further studies are warranted to fully evaluate the impact of skeletal malocclusion on the masticatory performance using the information of the muscle attachment and three dimensional temporomandibular joint movement.

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P5

The development of a novel bone healing mouse model by a frontal bone defect

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Among the previously existing bone healing models, the most commonly used one is cranial defect model. While it has the advantages of producing uniform defect areas among specimens and enabling quantitative assessment, its limitations are complex surgical procedure and risk for cerebral damage, since the surgery is performed on the parietal bone. Thus, this study was conducted to develop a new bone healing model that overcomes drawbacks of the existing models. 8-weeks-old ICR male mouse was used. After Mice was breathing anesthetized to isofurorane, we disinfected the treatment site using 70% ethanol, and incised middle of the forehead using 5 mm scissors along the sagittal line. Then we opened up the treatment site and checked the sites of inferior cerebral vein and sagittal suture. Then we made 2 symmetrical holes at sites located 3 mm beneath

the inferior cerebral vein and 2 mm next to sagittal suture using 21 gauage needle. It was possible to obtain an image by using the Micro-CT, and confirm that significant difference of bone healing existed by means of quantitative analysis. Also, the level of mRNA of osteoblast marker genes, such as osteoclain, collagen type I, bone sialoprotein and alkalin phosphatase significantly increased in the extracting mRNA from the defect region. Lastly, the promotion of bone formation in the defect area was observed with a histological analysis, such as H&E, Masson trichrome and Safranin O staining. In this study, we were trying to develop a new bone healing model that complements disadvantages of the existing models. The newly developed model has little side effects, has low significant errors, and has ability to obtain significant results in short amount of time. Thus, we believe the new model developed in this study would help study bone healing better in the future.

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P6

다계통 위축증(MSA) 흰쥐 모델에서 도파민 신경세포와 미세아교세포의 변화에 대한 에리스로포이에틴(EPO)의 효과

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다계통 위축증(multiple system atrophy; MSA)은 파킨슨 증상의 특징, 자율신경계의 기능장애, 소뇌성 운동 실조증과 추체로 징후가 동반되는 중추신경계의 퇴행성질환이다. 본 연구에서는 다계통 위축증 흰쥐 모델에 에리스로포이에틴(erythropoietin; EPO) 투여를 통한 신경방어효과를 행동학적 변화 및 도파민 신경세포(dopamine neuron)와 미세아교세포의 형태학적 변화를 관찰하였다. 실험동물을 Sham 대조군과 MSA군, MSA+EPO군 (EPO군)으로 분류했다. MSA 흰쥐 모델은 내측전뇌다발과 선조체에 각각 6-OHDA (6-Hydroxydopamine hydrobromide)와 QA (Quinolinic acid)를 투여하여 유발하였다. 약물 투여 3주 후 apomorpine 유발 회전실험을 실시하여 시간당 회전수가 300회 이상 동측으로 회전한 동물을 MSA 동물모델로 간주하였다. MSA모델 중에서 MSA군과 EPO군을 무작위로 선발하여 EPO군에 3일 간격으로 EPO (0.125 mg/100 g, i.p.)를 투여 하였으며 하위군으로 1주차군 (2회 투여군)과 2주차군 (4회 투여군)으로 세분하였다. MSA군과 Sham군은 복강 내 투여로 생리식염수 (0.125 ml/100 g, i.p.)를 3일 간격으로 2회와 4회 투여하였고, MSA군과 EPO군의 1주차 군과 2차군은 EPO와 생리식염수 투여 마지막 날 apomorpine 유발 회전실험을 실시하여 행동학적 변화를 관찰하였고 다음 날 관류고정으로 희생시켰다. 면역조직화학 염색으로 TH, Iba-1, α-synuclein을 이용하여 흑색질에서 면역조직학적 변화를 관찰하였다.

Apomorpine 유발 회전실험 결과 MSA군은 시간이 지남에 따라 회전수가 증가했지만 EPO군은 회전수가 감소하였다. 면역조직화학 결과 점진적으로 MSA군은 TH-양성 도파민 신경세포가 감소하였고 1주차군 보다 2주차군에서 더욱 감소하였다. EPO군 에서는 1주차 군과 2주차 군 비교 시 도파민 신경세포가 감소하지 않았다. α-synuclein 항체 면역반응 결과 MSA군에서 α-synuclein이 증가 되는 것을 관찰하였고, EPO군에서는 감소하였다. 또한, MSA군에서 Iba-1-양성 미세아교세포가 증가하였고, EPO투여 군에서는 감소됨을 관찰하였다.

이상의 결과를 종합할 때 MSA 흰쥐 모델에서 EPO의 투여는 행동학적 변화의 완화, 도파민 신경세포의 소실 및 미세아교세포의 증식을 억제하는 신경보호효과가 있는 것으로 사료된다.

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P7

Identification of the trochlea with reference to the lacrimal caruncle, and Its significance as a landmark in oculoplastic surgery

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The purpose of this study was to identify the location of the trochlea in order to prevent injury during oculoplastic surgery, and to determine the reliability of the lacrimal caruncle as a visible external landmark for the trochlea at the superomedial orbital rim. Fifty-one orbits from 27 embalmed cadavers were dissected. The lacrimal caruncle and supraorbital notch/foramen were used as external and bony landmarks, respectively. The location of the trochlea was determined with respect to these structures, and the size of trochlea was

measured. The trochlea was 3.6 mm wide and 5.6 mm long, with a flange width of 5.4 mm. The vertical distance from the apex of the lacrimal caruncle to the superolateral tip of the trochlea (DCT) was 15.8 mm, and that from the top of the supraorbital notch/foramen to the bottom of the trochlea (DST) was 11.4 mm. Since the coefficient of variation and standard deviation were smaller for DCT (11.5 and 1.8, respectively) than for DST (17.0 and 1.9, respectively), it appears that the lacrimal caruncle is a reliable landmark. In contrast to the supraorbital notch, the lacrimal caruncle allows easy identification and serves as a reliable and visible external landmark for prediction of the location of trochlea. The trochlea was located directly at 15.8 mm (i.e., approximately 1.5 cm) superior to the lacrimal caruncle. This anatomical study has yielded accurate measurements of the location of the trochlea, which may facilitate safer oculoplastic surgery by preventing morbidity associated with trochlea injury.

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P8

Low frequency of the lateral thoracic artery originating from the thoracoacromial artery

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Anatomy textbooks define that the lateral thoracic artery (LTA) usually originates from the second part of the axillary artery (AA). The LTA arose from the first or third part of the AA either on its own or as a common trunk with one or more of the other branches. However, recently published study with large cases demonstrated that most of LTA (67.6%, 568/840) arose from the thoracoacromial artery (TAA) and only 17.2% (143/840) of that originated from AA. Here, we studied the branching pattern of the LTA in 189 arms. According to our data, LTA arose directly from second and third parts of AA in 59.7% (113/189) and 9.5% (18/189) of cases, respectively. It also originated from TAA (2.6%, 5/189) and the subscapular artery (21.6%, 41/189). Except the several studies in Caucasians, most of the previous studies demonstrated that LTA from TAA was rare, moreover, LTA arose from the subscapular artery more frequently. Considering the clinical importance of knowledge about its anatomy, the pattern of the LTA should be clarified apparently.

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P9

Dual accessory heads of flexor pollicis longus muscle and its relation to the anterior interosseous nerve

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Among the anatomical variations of the muscles of the forearm, Gantzer`s muscle which is an additional muscle in the forearm as the accessory head of the flexor pollicis longus (FPL) and the accessory head of the flexor digitorum profundus (FDP) have been described its prevalence and morphological variation in the previous studies. Here, we report a rare case which is the presence of dual additional muscles in the forearm and its relation to the anterior interosseous nerve (AIN). Dual accessory heads of the FPL were found in a 73-years old male cadaver during educational dissection. In the right forearm, an accessory head of the flexor pollicis longus muscle (aFPL1) took its origin form the upper surface of the flexor digitorum superficialis muscle. This muscle slip continued about 8 cm more and inserted into the medial border of upper third of FPL. This slip has been called as the Gantzer`s muscle, shown in 50-60% of cases. At the middle third of the FDP, a muscle belly was skirting the AIN and inserted into FPL (aFPL2). Both accessory heads was innervated by the AIN. Considering their anatomical position, accessory heads, especially aFPL2, may induce compression of the AIN, which could cause weakness in the FPL, FDP of the index and middle finger. Accessory head remnants might be caused by partial separation of the flexor mass during forearm development.

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P10

The ileocolic vein passing through the ring-shaped part of ileocolic artery

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Vascular variations in the abdomen have been frequently reported because of its clinical importance. During the educational dissection, we found an ileocolic vein perforating through the annular part of ileocolic artery in the abdomen of a 78 years old male cadaver. The ileocolic artery originated from the superior mesenteric artery as a single branch giving off the ascending colic, anterior cecal, posterior cecal, appendicular and ileal arteries. The ileocolic vein perforated through the circular part of ileocolic artery and drained into the superior mesenteric vein. We reported this rare variation and suggest that the clinicians be aware of this variation for succeeding surgery and making a good diagnosis for the patients.

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P11

A radial artery originating from the thoracoacromial trunk in Korean cadaver

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Variation of arteries of upper limb can be frequent along the axillary, brachial, and radial arteries. Among these variations, the most frequently reported case is high origin of the radial artery from either the axillary or brachial arteries. During the educational dissection, we found an anomalous branch which originated from the thoracoacromial trunk and ran to the distally deep in the deep fascia. It finally coursed like the radial artery, defined as high origin of the radial artery (HRA). A little of the intercondylar line below, the brachial artery gave off small communicating branch to HRA, and continued as the ulnar artery. After that, HRA continued distally as the radial artery in its normal anatomical pathway. We reported this unique variation and discussed its clinical and embryological implication.

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P12

가로막의 다리, 대동맥구멍, 식도구멍의 형태와 분류

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식도(esophagus)와 대동맥(aorta)은 가슴(thorax)을 지나 가로막(diaphragm)을 통과하는 부근에서 끝나는데, 이 때 각각 식도구멍(esophageal hiatus)과 대동맥구멍(aortic hiatus)을 통과함에 따라 이들 구멍의 형태가 식도와 대동맥의 기능에 영향을 줄 수 있다. 본 연구에서는 한국인 성인 시신 26구를 해부하여, 가로막의 식도구멍, 대동맥구멍, 왼다리, 오른다리의 형태를 분석하였다. 오른다리와 왼다리는 허리뼈 몸통의 가쪽면에서 일어나 중심널힘줄(central tendon)에 닿으면서 각각 대동맥구멍의 오른쪽과 왼쪽 경계를 이루었다. 대동맥구멍의 형태는 뚜렷한 꼭대기(apex)를 이루는 삼각형이거나(69.2%) 섬유성 또는 근육으로 된 활모양의 불분명한 꼭대기를 가진 반달모양이었다(26.9%). 대동맥구멍의 최대 너비, 꼭대기로부터 오른쪽끝까지의 거리, 꼭대기로부터 왼쪽끝까지의 거리는 각각 40.3 ± 7.9 mm, 59.0 ± 12.6 mm, 29.0 ± 8.3 mm였다. 대동맥구멍의 꼭대기로부터 복강동맥(celiac artery)의 뿌리 부분까지의 거리는 9.4 ± 8.3 mm, 위창자간막동맥(superior mesenteric artery)의 뿌리 부분까지의 거리는 22.4 ± 10.1 mm였다. 대동맥구멍의 오른쪽과 왼쪽경계를 따라 오른다리와 왼다리의 근육섬유들은 중심널힘줄을 향해 곧바로 달리거나, 반대쪽으로 갈라져 식도구멍을 휘감았다. 모든 표본에서, 오른다리의 일부가 대동맥구멍의 꼭대기를 넘어가 식도구멍의 왼쪽 테두리를 이루었으며, 50.0%에서는 왼다리의 일부도 같은 방식으로 식도구멍의 오른쪽 테두리를 이루었다. 따라서 식도구멍의 왼쪽 테두리는 오른다리와 왼다리 모두에서 온 근육섬유로 이루어졌고, 오른쪽 테두리는 오른다리에 의해(50.0%), 양쪽

다리에 의해(42.3%), 또는 왼다리에 의해(7.7%) 이루어졌다. 식도구멍의 형태는 양쪽 가로막다리의 근육섬유들이 구성하는 양상에 따라 네 가지 유형으로 나뉘었다. 50.0%에서는 오른다리의 일부가 대동맥구멍의 앞위쪽을 가로질러 왼다리로 합쳐져 식도구멍의 왼쪽 테두리를 이루면서 오른다리의 나머지부분은 오른쪽 테두리를 이루었다. 34.6%에서는 오른다리의 일부와 왼다리의 일부가 서로 엇갈려 반대쪽의 식도구멍 테두리를 이루었다. 7.7%에서는 오른다리의 일부가 왼다리와 합쳐져 식도구멍의 왼쪽테두리를 이루기 위해 대동맥구멍을 가로지르는 부분이, 오른다리와 합쳐져 오른쪽 테두리를 이루기 위해 가로지르는 왼다리의 섬유에 의해 관통되었다. 나머지 7.7%에서는 오른다리의 일부가 왼다리와 합쳐져 식도구멍의 왼쪽테두리를 이루면서 오른쪽테두리는 오른다리가 관여하지 않고 왼다리의 일부로만 이루어졌다.

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P13

OPG, RANKL and TRAIL expression in periodontal ligament cells under orthodontic force

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The response of periodontal ligament (PDL) cells to mechanical stimulation is important in the periodontal tissue remodeling during orthodontic tooth movement. The aim of this study was to determine if the compressive stress affected the expression of receptor activator nuclear factor kB ligand (RANKL), osteoprotegrin (OPG) and TNF apoptosis inducing ligand (TRAIL). hPDL cells were obtained from healthy premolars extracted for orthodontic purposes. Cultured hPDL cells were applied for compressive stress (2 g/cm2) for various time durations. Seven week old Sprague Dawley rats were used for in vivo study. Spring was connected from the upper first molar to upper incisor and the orthodontic appliance (50 cN) was left in place for 1, 2 and 6 days. RT-PCR, Western blot and immunofluorescence assay were performed to determine the expression level of genes under stress in vivo and in vitro. The application of compressive force significantly caused an increase of RANKL, TRAIL and a decrease of OPG expression in hPDL cells. In vivo data were same as in vitro. p38 and ERK MAPKs were activated in hPDL after the application of compressive force. Treatment of MAPK inhibitors, SB203580 and U0126 induced the gentle suppression of RANKL expression and the increase of OPG expression under the compressive force. Collectively, PDL cells under compressive force may finely regulate osteoclastogenesis-related genes via the MAPKs pathway for alveolar bone resorption.

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P14

3차원재구성모델을 이용한 한국인 얼굴의 돌출도(편평도) 평가

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한국인의 머리형은 앞뒤길이가 짧고 양쪽 폭이 넓은 짧은머리형으로 서양백인 또는 흑인과도 많이 다르다. 따라서 얼굴도 서양인에 비해 납작한 형태를 갖고 있다는 것은 잘 알려진 사실이다. 이러한 얼굴의 편평도를 평가하기 위하여 그동안은 옆얼굴의 사진을 이용하거나 머리뼈를 이용하여 얼굴의 편평도를 평가해왔다. 사진의 경우 평면이기 때문에 입체적인 돌출도나 편평도를 평가하기엔 어려움이 있었다. 머리뼈를 이용하는 경우 역시 표본수가 적고 일반적으로 나이가 많다는 단점이 있었다. 따라서 본 연구에서는 3차원영상을 통해 한국인 얼굴의 돌출도 또는 편평도를 입체적으로 정확하게 평가하고자 하였다. 재료로는 건국대학교 충주병원에 보관되어 있는 CT자료로부터 재구성한 3차원 머리뼈 모델 100개(남자 50명, 여자 50명, 20~30세, 평균 24.2세)를 이용하였다. 머리뼈 윗면에서의 돌출도를 평가를 위해, 양쪽 Porion사이의 면과 Porion과 눈확아래모서리사이의 면에 수직인 시상면을 기준으로 머리뼈를 고정시켰다. 일정한 위치에서 내려다본 머리뼈를 양쪽 Porion 사이의 선의 중앙점을 기준으로 30° 간격으로 표시선을 그려 머리뼈의 외곽과 맞닿는 점을 표지점으로 삼아 거리를 측정하였다. 머리뼈 옆면에서의 돌

출도 평가를 위해서는 Glabella, Nasion, Rhinion, Anterior nasal spine, Subspinale와 Porion 사이의 거리와 각도를 측정하였다. 3D계측프로그램으로는 OnDemand3DApp (Ver. 1.0, CyberMed)을 이용하였고, 통계분석을 위해 SPSS (Ver. 21.0, IBM, US)를 이용하였다. 30° 간격의 표시선을 기준으로 계측한 결과, 남녀 모두에서 중앙점과 광대활사이의 길이(2D)가 왼쪽이 오른쪽보다 길었다 (남; P=0.000237, 여; P=0.00000531, t-test). 여성에서는 중앙점과 눈확위모서리사이의 거리(2D)도 왼쪽이 우세한 것이 밝혀졌다 (P=0.0067, t-test). 표지점 사이의 직선거리들을 연결한 면적으로 좌우를 비교해 본 결과, 남녀 모두에서 왼쪽의 면적이 우세하여, 머리뼈 위에서 관찰한 한국인의 얼굴 돌출도는 좌우불균형이 존재함을 확인할 수 있었다 (남; 0.037, 여; 0.00693, t-test). 특히 광대활 부분의 돌출각도를 측정한 결과, 왼가쪽 광대활의 각도가 오른가쪽보다 유의하게 작아 왼쪽 광대활의 돌출이 더 도드라짐을 재확인하였다 (남; 0.0000052, 여; P=0.000013, t-test). 반면, 머리뼈 옆면에서 관측한 표지점 사이의 거리와 각도에서는 남녀차, 좌우차가 발견되지 않았다. 지금까지의 계측결과는 소수의 표본을 대상으로 한 선행연구로, 앞으로 표본 수를 늘리고 각 계측항목 사이의 상관관계를 구하여 데이터를 추가할 예정이다.

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P15

Topographic anatomy of the suprascapular and circumflex scapular arteries at the infraspinous fossa

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The aims of the present study were to determine the position of the suprascapular and circumflex scapular arteries at the infraspinous fossa and to analyze the morphology of the arterial anastomosis. The silicone was injected into the suprascapular and circumflex scapular arteries of 59 scapula obtained from 31 cadavers fixed with formalin. The infraspinatus muscle was removed carefully and the periostium of the infraspinous fossa was preserved to maintain the original position of the arteries. Several dimensions were measured using a digital caliper and types of arterial anastomosis were classified. The diameters of the suprascapular, circumflex scapular and ascending branch of circumflex scapular arteries were 1.7 mm, 2.1 mm and 1.7 mm, respectively and there was no significant difference between both genders. Distances from medial point of spine of scapula to the suprascapular artery, from medial border of the scapula to the circumflex scapular artery, from medial point of spine of scapula to the circumflex scapular artery and from the spinoglenoid notch to the circumflex scapular artery were significantly larger in male than in female. Distance from the inferior angle to the circumflex scapular artery was about two-third of the lateral border of the scapula. The suprascapuar artery was distributed to 42.6% and 47.9% of distance from medial point of spine of scapula to the inferior angle in male and female, respectively. The pattern of arterial anastomosis between the suprascapular and circumflex scapular arteries was classified into 2 types and 2 subtypes. The results of the present study could be useful during posterior approach to the scapula and scapular osteocutaneous flap surgery.

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P16

Adipose tissue-derived mesenchymal stem cells cultured at high cell density express BDNF and exert neuroprotective effects in a parkinsonian animal model

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Mesenchymal stem cells (MSCs) secrete neurotrophic factors, and have been reported to improve functional outcomes in animal models of neurodegenerative diseases such as cerebral ischemia, stroke, spinal cord lesions, and Parkinson's disease. Previously, we found

that adipose tissue-derived mesenchymal stem cells (ASCs) cultured at high cell density expressed IFN-b. Here we demonstrate that ASCs expressing IFN-b also express brain-derived neurotrophic factor (BDNF). Growth rates of neuroblastoma cells (SK-N-BE(2)C) were increased when co-cultured with high density ASCs or treated with concentrated medium (CM) obtained from HD-ASCs. The ASC-CM induced AKT phosphorylation in SK-N-BE(2)C cells, and AKT inhibition by Ly294002 reduced cell viability of SK-N-BE(2)C cells. Additionally, a protective effect on SK-N-BE(2)C cells exposed to 6-hydroxydopamine (6-OHDA) was observed in the ASC-CM or BDNF treated cells. The protective effect of the CM obtained from HD-ASCs was neutralized by anti-BDNF antibody. In 6-OHDA-induced Parkinson's disease rat models, ASCs reduced amphetamine-induced rotations and a greater number of tyrosine hydroxylase (TH)-positive cells were observed in the high density cultured ASC-injected group compared with sham controls and the low density cultured ASC-injected group. Moreover, the expression of BDNF, NGF, TH, and PCNA in ipsilateral midbrain tissues including SNc was increased by transplantation of high density cultured ASCs. These data indicate that high density cultured ASCs may induce neuroprotective effects through BDNF expression and subsequent increase of proliferation in neuronal cells both in vitro and in vivo.

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P17

PARP1 activation/expression modulates regional-specific neuronal and glial responses to seizure in a hemodynamic-independent manner

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Poly (ADP-ribose) polymerase-1 (PARP1) plays a regulatory role in apoptosis, necrosis andother cellular processes after injury. Status epilepticus (SE) induces neuronal and astroglial death that show regional-specific patterns in the rat hippocampus and piriform cortex (PC). Thus, we investigated whether PARP1 regulates the differential neuronal/glial responses to pilocarpine (PILO)-induced SE in the distinct brain regions. In the present study, both CA1 and CA3 neurons showed PARP1 hyperactivation-dependent neuronal death pathway, whereas PC neurons exhibited PARP1 degradation-mediated neurodegeneration following SE. PARP1 degradation was also observed in astrocytes within the molecular layer of the dentate gyrus. PARP1 induction was detected in CA1-3-reactive astrocytes, as well as in reactive microglia within the PC. Although PARP1 inhibitors attenuated CA1-3 neuronal death and reactive gliosis in the CA1 region, they deteriorated the astroglial death in the molecular layer of the dentate gyrus and in the stratum lucidum of the CA3 region. Ex vivo study showed the similar regional and cellular patterns of PARP1 activation/degradation. Taken together, our findings suggest that the cellular-specific PARP1 activation/degradation may distinctly involve regional-specific neuronal damage, astroglial death and reactive gliosis in response to SE independently of hemodynamics.

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P18

Cellular and regional specific changes in multidrug efflux transporter expression during recovery of vasogenic edema in the rat hippocampus and piriform cortex

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In the present study, we investigated the characteristics of drug efflux transporters following status epilepticus (SE). In the hippocampus, the expressions of breast cancer resistance protein (BCRP), multidrug resistance protein-4 (MRP4) and p-glycoprotein (p-GP) were decreased 4 days after SE when vasogenic edema was peaked, but subsequently increased at 4 weeks after SE. Multidrug resistance protein-1 (MRP1) expression gradually decreased in endothelial cells until 4 weeks after SE. Enhancements of BCRP, MRP4 and p-GP expressions were mainly detected in astrocytes, neuropils and reactive astrocytes, respectively. In the piriform cortex (PC), BCRP, MRP4 and p-GP expressions were transiently decreased and

subsequently increased after SE. MRP1 expression was gradually decreased in the PC following SE. Up-regulation of BCRP expression was detected in palisade astrocytes around the vasogenic edema lesion. MRP4 expression was increased in neuropils. p-GP expression was up-regulated in endothelial cells. These findings indicate that SE-induced vasogenic edema formation transiently reduced drug efflux pump expressions in endothelial cells. Subsequently, during recovery of vasogenic edema drug efflux pump expressions were differentially up-regulated in astrocytes, neuropils and endothelial cells. Therefore, we suggest that vasogenic edema formation may be a risk factor in pharmacoresistent epilepsy.

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P19

Neuroprotective effect of intermittent fasting on a rat model of focal cerebral ischemia though autophagy activation and apoptosis inhibition

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Evolutionarily, autophagy is a pro-survival mechanism, responsible for the recycling of metabolic substances and the maintenance of intracellular homeostasis. Among the many signals that induce autophagy, starvation has been known as the one of the important trigger. The present study evaluated the neuroprotective effect and its underlying mechanism, which mainly focusing on autophagy and apoptosis, of intermittent fasting (IF) on focal cerebral ischemia using transient middle cerebral artery occlusion (tMCAO) in rat maintained on IF for 2 weeks. For that, we measured the brain infarct volume and neuronal survival fraction of hippocampal CA1 region at 1 day after tMCAO with or without IF using triphenyl tetrazolium chloride (TTC) and cresyl violet staining, respectively. We observed decrease of infarct size and increase of neuronal suvival in the hippocampal CA1 in ischemic rats fed with IF (IF/MCAO) compared with rats fed with ad libitum (AL/MCAO) as control. Furthermore, we demonstrated apoptotic cell death was decreased in cortex and hippocampus of IF/MCAO rats by performing terminal deoxynucleotidyl transferase dUTP nick end labeling assay (TUNEL) and immunoblot. For testing whether IF activated autophagy pathway in ischemic brain, ultramicrostructural observation of autophagosome under transmission electron microscopy (TEM) and immunoblotting for measuring autophagy-related proteins expression were performed in IF/MCAO rats. By these experiments, we demonstrated that IF induced the drastic increase of autophagosome and upregulation of microtubule-associated protein 1 light chain 3 (LC3)-II and beclin-1 in ischemic cortex of IF/MCAO rat. Finally for identifying the roles of autophagy activation on neuronal fate, we inhibited the autophagy using intraventricular injection of 3-methyladenine (3-MA), the chemical autophagy inhibitor, and subsequently measured the neuronal survival morphologically and quantitatively. By these autophagy inhibition, we found the significant abolishment of diminishing effect of IF on the infarct size and apoptosis-relatived protein expression. Taken together, we show that IF exerts neuroprotective effect against ischemic brain injury via at least in part, stimulation of autophagy pathway and inhibition of apoptosis.

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P20

GRS defective axonal distribution as a potential contributor to distal spinal muscular atrophy type V pathogenesis in a new model of GRS-associated neuropathy

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Distal spinal muscular atrophy type V (dSMA-V), a hereditary axonal neuropathy, is a glycyltRNA synthetase (GRS)-associated neuropathy caused by a mutation in GARS. In this study, using an adenovirus vector system equipped with a neuron-specific promoter, we constructed a new GARS associated neuropathy mouse model. We found that wild-type GRS (WT) is distributed in peripheral axons, dorsal root ganglion (DRG) cell bodies, central axon termi-

nals and motor neuron cell bodies in the mouse model. In contrast, the L129P mutant GRS was localized in DRG and motor neuron cell bodies. Thus, we propose that the disease-causing L129P mutant is linked to a distribution defect in peripheral nerves in vivo.

Keywords: Spinal muscular atrophy, axonal degeneration, recombinant adenovirus, glycyl-tRNA synthetase

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P21

Expression profile of aminoacyl-tRNA synthetases (AARSs) in the spinal cord dorsal horn and dorsal root ganglion (DRG) after peripheral nerve injury

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Aminoacyl-tRNA synthetases (AARSs) are essential enzymes that perform the first step of protein synthesis. Beyond their original roles, AARSs possess non-canonical functions, such as in cellular regulatory process and signal transduction. Therefore, AARSs could represent a powerful pharmaceutical target if their non-canonical functions could be controlled. We performed mRNA expression screening in mouse spinal cord dorsal horn and dorsal root ganglion (DRG) using AARS-specific primers. Of 20 AARSs, we found that phenylalanyl-tRNA synthetase beta chain (FARSb), isoleucyl-tRNA synthetase (IARS) and methioninyl-tRNA synthetase (MARS) expression was increased in the injured side of the spinal dorsal horn. Increased FARSb, IARS and MARS expression was found in neurons of the spinal cord dorsal horn, but not in glial cells. In addition found that lysyl-tRNA synthetase (KARS) and glutaminyl-tRNA synthetase (QARS) expression was decreased in the injured sensory neuron cell body of the DRG. Therefore, we suggest the possibility that several AARSs as regulatory molecules, control the transfer of abnormal sensory signals to the brain after peripheral nerve damage.

Keywords: Aminoacyl tRNA synthetases; neuron; spinal cord; dorsal horn; dorsal root ganglion; neuropathic pain

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P22

The effect of agmatine on Alzheimer's disease: agmatine improves brain insulin resistance

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Obesity and type 2 diabetes (T2D) are related disorders with wide range of deleterious effects throughout the body including the brain. Many studies found that persons suffered with T2D are at significantly increased risk for cognitive decline and the development of Alzheimer's disease due to brain insulin resistance. Insulin, the hormone secreted from beta-cells in pancreas, has effect on regulating blood glucose in peripheral tissues, but involving cognitive functions and memory consolidation in brain. Agmatine is an endogenous aminoguanidine compound made from arginine by arginine-decarboxylase(ADC). It is known for neuromodulator as it has affinity for several transmembrane receptors, imidazoline receptors, 2-adrenergic and glutamatergic NMDA receptors and irreversibly inhibits neuronal nitric oxide synthase and downregulates inducible nitric oxide synthase. So, it shows positive effects on widespread diseases, for instance, diabetes, stroke, Alzheimer's disease, depression and so on. Based on previously established methods, we developed type 2 diabetes induced Alzheimer's disease mouse model that exhibits obesity and insulin resistance for investigation the effects of agmatine. Male ICR mice were fed a 60% high fat diet(HFD) for 12 weeks and intraperitoneally injected streptozotocin (100mg/kg) at 4thweek. Then, mice were intraperitoneally administered with agmatine(100mg/kg) for 2 weeks. Following agmatine injection, mice were sacrificed and brains were prepared for immunohistochemistry(IHC) and western blot assay. To determine biochemical changes, we checked blood glucose level, body weights once a week, and conducted oral glucose tolerance test. Blood glucose level and weights of high fat diet group were significantly increased compared with normal diet group over a period of time and had glucose tolerance and insulin resistance. In addition that, the amount of Aβ42 is increased in HFD group. Repeated injection of agmatine alleviated insulin resistance as it increased phosphory-

lation of IRS-1 in brain. Moreover, agmatine lowered the amount of Aβ42, the hall mark of Alzheimer's disease, in brain induced by high fat diet through regulation of PI3K downstream signal pathway.

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P23

Apoptosis signal-regulating kinase 1 mediates 3-nitropropionic acid toxicity and regulates C1q level via astrocyte TGF-beta

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Apoptosis signal-regulating kinase-1 (ASK1), an early signaling element in the cell death pathway, has been suggested to participate in the pathology of neurodegenerative diseases, which may be associated with environmental factors that impact the diseases. The systemic administration of 3-nitropropionic acid (3-NP) facilitates the development of selected striatal lesions and it remains unclear whether specific neurons are selectively targeted in 3-NP infused striatal degeneration. Although not entirely elucidated, the mechanisms of neurotoxicity induced by 3-NP have been shown to include the exhaustion of adenosine triphosphate, mitochondrial membrane depolarization, dysregulation of intracellular calcium homeostasis, calpain activation, and the release of pro-apoptotic proteins from mitochondria. This study investigates that mild and chronic exposure of mitochondrial toxin can modulate the C1q level both in cortex and striatum via regulation of TGF-beta from astrocyte, which is involved in ASK1 pathway. By chronic infusion of 3-NP, reactive oxygen species (ROS) over-produced and correspondingly ASK1 protein amounts and its activity increased both in neuron and astrocyte. Raised ASK1 level was followed by occurring apoptotic cell death in neuron, augmenting the level of TGF-beta in astrocyte, and secreting higher level of C1q in peripheral blood. As a final standard to striatal degeneration, BDNF transcript, protein, and its secretion level were depleted in striatum. When ASK1 was down-regulated, neuronal cell death was ameliorated, astrocyte-derived TGF-beta was also reduced, and C1q level was moderated. Additionally behavioral impairment was improved. We propose the hypothesis that ASK1 may differentially regulate C1q secretion level via active TGF-beta in each brain subregion of cortex and striatum, consequently involved in axon degeneration of corticostriatal projection neuron. When brain is mildly and chronically exposed to mitochondrial toxin, presynaptic neuron (in cortical neuron) degrades first, and then postsynaptic neuron of striatal MSN neuron withers as a consequence of it. Consolidating these results, we suggest that the increased ASK1 is linked to regulation of TGF-beta secreted in astrocytes, and differential C1q expression in neurons triggered by TGF-beta leads depletion of BDNF in striatal neuron in mice brains systemically infused with 3-NP.

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P24

Effect of hydrogen sulfide on schwann cells after peripheral nerve injury

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Hydrogen sulfide (H2S) functions as a physiological gas transmitter in both normal and pathophysiological cellular events. H2S is produced from substances by three enzymes: cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE) and 3-mercaptopyruvate sulfurtransferase (MST). In human tissues, these enzymes are involved in tissue-specific biochemical pathways for H2S production. For example, CBS and CAT/MST are present in the brain, but CSE is not.

Thus, we examined the expression of H2S production-related enzymes in peripheral nerves. Here, we found that CSE and MST/CAT, but not CBS, were present in normal peripheral nerves. In addition, injured sciatic nerves in vivo up-regulated CSE in Schwann cells during Wallerian degeneration (WD); however, CSE was not up-regulated in peripheral axons. Using an ex vivo sciatic nerve explant culture, we found that the inhibition of H2S production broadly prevented the process of nerve degeneration, including myelin fragmentation, axonal degradation, Schwann cell dedifferentiation and Schwann cell proliferation in vitro and in vivo. Thus, these results indicate that H2S signaling is essential for Schwann cell responses to peripheral nerve injury.

Keywords: Hydrogen sulfide, Schwann cells, cytstathionine-γ-lyase (CSE), demyelination, Wallerian degeneration, axonal degradation

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P25

Comparison of cerebral blood flow dynamic between two mouse strains using indocynine green

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C57Bl/6 and Balb/c mice have known to have a different collaterals between anterior cerebral artery and middle cerebral artery. However, it has not known the difference of the blood flow dynamics of two mouse strains. In this study, the cerebral blood flow dynamics were measured using indocynine green (ICG) and analysed the difference of four cerebral blood flow (CBF) parameters including arrival time, rising time and mean transit time of a bolus and blood flow index based on time and intensity information of ICG fluorescence dynamics. Mice were injected with indocynine green (ICG) via tain-vein. Time-series near-infrared fluorescence signals were imaged overhead by a charge-coupled device. We calculated four CBF parameters on time and intensity information of ICG fluorescence dynamics. We take two areas, lateral arterial area and middle sinus area, to analyzed for four parameters. We demonstrated that C57Bl/6 has longer arrival time gap and arrival time gap between two areas, and lower BFI ratio between two areas than Balb/c. These results suggest that, although C57Bl/6 has more collaterals in cerebral artery, velocity of blood from artery to venus sinus of C57Bl/6 is slow than that of Balb/c. and C57Bl/6 has wider difference of overall blood volume of two areas than Balb/c.

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P26

Delayed migration of inhibitory neuron promotes spasms in infants

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Infantile spasms (IS) is an age-dependent epileptic encephalopathy with severe cognitive dysfunction. A recent clinical study linked severe prenatal stress to increased risk for development of IS. It is also reported that prenatal stress induced early disruption in GABAergic progenitor migration, and responsible for neuronal defect in disorders with the development of these precursors to inhibitory neurons. However, it is unclear how prenatal stress impact GABAergic progenitors that may result in abnormalities in the resulting mature neurons within adult brain networks. We developed the model of spastic seizures triggered by N-methyl-D-aspartate (NMDA) in infant rats prenatally exposed to betamethasone or acute restraint stress. Firstly, we evaluated the developmental expression of glutamic acid decarboxylase isoforms 67 (GAD67), is the rate-limiting step of gamma-Aminobutyric acid (GABA) synthesis after prenatal exposure to stress from embryonic day 12 (E12). The distribution of GAD67 immunopositive cells with the superficial tangential migratory pathway was decreased after prenatal stress. The density of GABAergic progenitors was reduced in the cortical plate of prenatally stressed rats at E16. These results demonstrate that early disruption in GABAergic interneuron migration caused by prenatal stress may enhance susceptibility to develop spasms in infant.

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P27

Astrocytic expression of CTMP following an excitotoxic lesion in the mouse hippocampus

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The PKB (protein kinase B, also known as Akt) is a serine/threonine-specific protein kinases that plays a key role in multiple cellular processes, such as apoptosis, cellular survival, cell proliferation and transformation. PKB is activated by phosphorylation on residues threonine 308, by the protein kinase PDK1 (Phosphoinositide dependent kinase, and Serine 473, by a putative serine 473 kinase. Besides PKB activators, PKB is negatively regulated by endogenous inhibitors which serve as brakes on PKB signaling. The Carboxyl-Terminal Modulator Protein (CTMP) is a novel binding partner and endogenous inhibitor, which binds the carboxyl-terminal regulatory domain of PKB at the plasma membrane and suppresses the phosphorylation and activation of PKB. Although few studies have investigated the roles of CTMP, a negative regulator of PKB/Akt and relationship with multiple cellular function, little is known about CTMP changes in glial cell under neuropathological conditions. In this study, we evaluated the expressions of CTMP and effect on PKB, following the induction of an excitotoxic lesion in mouse brain by kainic acid (KA) injection, which caused pyramidal cell degeneration in the hippocampal CA3 region. In injured hippocampal CA3 region, CTMP was increased in 3 days post injection. Double immunohistochemistry further evaluated that these CTMP were localized in astrocytes not other cells. For the first time, our data demonstrate the injury-induced astrocytic changes in the levels of CTMP in vivo, which may reflect mechanisms of glial cells protection or adaptive response to damage.

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P28

A comparative study between striatal mono- and co-culture systems for investigating medium spiny neuron dendritic spine morphology and plasticity

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The striatum represents the sole input nucleus of the basal ganglia, and is involved in motor and motivational functions. Dendritic spines of striatal medium spiny neurons (MSNs), which represent 90-95% of the neurons within the corpus striatum, undergo structural changes during disease states like Parkinson's and Huntington's diseases. Therefore, primarystriatal neurons showing a full cohort of matured dendritic spines could offer a useful in-vitro model system for studying cellular and/or molecular mechanisms underlying structural and functional plasticity ofMSN dendritic spines. In an effort to evaluate potentials of natural herbs to induce MSN spine morphology and plasticity, we initially focused on optimizing an embryonic culture system that yields MSNs exhibiting matured dendritic spines. In our experiments, we observed the earliest expression of DARPP-32+ MSNs in striatal monoculture at DIV3, with more prominent expressions at DIV12 or later on. We also characterized our striatal single culture with 26% and 27% expressions of DARPP+ MSNs, when maintained in MACS Neuro medium and in MACS Neuro supplemented with 50% glia conditioned medium, respectively. DARPP-32 immunolabeling revealed that monocultured striatal neurons were virtually devoid of dendritic spines. Matured dendritic spines were visible on DARPP-32 labeled striatal MSNs when co-cultured with cortical neurons with or without glial support. Our experimental results conform to the established fact that glutamatergic innervation is required for the formation of dendritic spines on striatal MSNs. Here, we demonstrate that cortico-striatal co-culture with and/or without gilal support offers a suitable in vitro model system for investigating striatal MSN spine morphology and plasticity.

Keywords: Striatum, medium spiny neuron, dendritic spine, DARPP-32, Parkinson's disease

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P29

Edible marine alga exerts neuroprotection against hypoxia/reoxygenation induced hippocampal cell death

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Age related neurological disorders are growing concern among the elderly persons. Natural products with synergistic properties have been increasing attention as potential candidates for the prevention or treatment of neurological disorders induced by oxidative stress. As an effort to explore the natural resources that may have neuroprotective activity, we collected some common marine algae and screened for their neuroprotective activity based on propidium iodide (PI) and lactate dehydrogenase (LDH) assays for the viability of rat primary hippocampal neurons against hypoxia/reoxygenation (H/R) induced cell death. Of the 24 seaweeds examined, the ethanol extract of GCE provided maximum neuroprotection with the optimum concentration of 15 μg/mL, followed by UPE. To elucidate the underlying mechanism of action, we measured reactive oxygen species (ROS) positive cells by fluorescent probe 2',7'-dichlorodihydrofluorescein diacetate (DCF) staining, pohospho-H2AX (early apoptotic marker) by immunocytochemistry, apoptotic cells by Annexin V/PI staining, DNA fragmentation by agarose gel electrophoresis, and mitochondrial membrane potential (MMP) by JC-1 labeling. The results showed that GCE extract pretreatment significantly inhibited the ROS production, the expression of phospho-H2AX, apoptosis, DNA fragmentation, and preserve MMP. Our findings suggest that GCE could exert strong neuroprotection against H/R-induced neuronal death through the prevention of reactive molecules and eventually suppression of apoptosis.

Keywords: Hippocampal Neurons, Marine macroalgae, Hypoxia/Reoxygenation, Apoptosis, and Neuroprotection

P30

Autophagy enhancement contributes to synergistic effect of vitamin D in Temozolomide-based glioblastoma chemotherapy

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Temozolomide (TMZ), an alkylating agent, is recommended as the first-line treatment for high grade glioblastoma. While it is tremendously used, its short half-life and the frequent induction of tumor resistance usually limit its therapeutic efficacy. In the present study, we determined the synergistic anticancer effect of vitamin D (VD) combined with TMZ in glioblastoma and identified the underlying mechanism. By evaluating tumor size and survival rate in rat orthotopic xenograft models, we demonstrated that combining VD with TMZ significantly increased its antitumor effects in vivo. Results of in vitro cell viability, clonogenic, and wound healing assays on C6 glioblastoma cell line incubated with TMZ + VD highly correlated with our in vivo results. Autophagy, which we hypothesized could be the dominant mechanism involved in TMZ-based tumor cell death, was observed in TMZ + VD-treated C6 cells as determined by autophagosome ultrastructural observation, morphologic increase in size and number of microtubule-associated protein 1 light chain 3 (LC3) puncta, and quantitative conversion of LC3-I to -II. Surprisingly, the extent of apoptosis was constant between cells treated with TMZ + VD and those treated with TMZ alone. Most importantly, treatment with 3-MA, used as an autophagy inhibitor, dramatically abolished the synergistic anticancer effect of TMZ + VD. Taken together, our results suggest a chemosensitizing effect of VD on TMZ-based glioblastoma therapy via cytotoxic autophagy enhancement. The use of this combination may be a beneficial strategy.

Keywords: temozolomide, vitamin D, glioblastoma, autophagy, orthotopic xenograft

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P31

Neuroprotective effect of punica granatum in gerbils following global cerebral ischemia/ reperfusion injury

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This study aimed to investigate the effects of punica granatum extract juice (PGJ) in gerbils following global cerebral ischemia/ reperfusion (I/R) injury. I/R model in gerbils was prepared by bilateral common carotid occlusion (BCCAO) for 5 min. PGJ was administered intraorally (i.o) for 2 weeks before the BCCAO. The I/R injury was assessed behaviorally by Morris water maze and histopathologically by evaluating hippocampal cornus ammonius 1 (CA1) pyramidal cell damage. In PGJ groups, congnitive and learning function were intact, number of hippocampal CA1 pyramidal cells were higher than sham-operated group and these results were dose-dependent in general. In addition, expression of apoptosis-related proteins, e.g., caspase-3 and poly [ADP-ribose] polymerase 1 (PARP-1) in hippocampus were lower in PGJ groups. Furthermore, the extent of neuroinflammation was attenuated by i.o PGJ as revealed by immunohistochemistry assay using immunoreactivities against ionizing calcium-binding adaptor molecule 1 (Iba 1) and glial fibrillary acidic protein (GFAP), both of which playing central roles in neuroinflammation. Taken together, we demonstrated the neuroprotective effects of PGJ in gerbils following I/R injury and these effects is due to, at least in part, attenuation of neuroinflammation and apoptosis.

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P32

The indolinone MAZ51 induces cell rounding and G2/M cell cycle arrest in glioma cells without the inhibition of VEGFR-3 phosphorylation: involvement of the RhoA and Akt/GSK3β signaling pathways

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MAZ51 is an indolinone-based molecule originally synthesized as a selective inhibitor of vascular endothelial growth factor receptor (VEGFR)-3 tyrosine kinase. This study shows that exposure of two glioma cell lines, rat C6 and human U251MG, to MAZ51 caused dramatic shape changes, including the retraction of cellular protrusions and cell rounding. These changes were caused by the clustering and aggregation of actin filaments and microtubules. MAZ51 also induced G2/M phase cell cycle arrest. This led to an inhibition of cellular proliferation, without triggering significant cell death. These alterations induced by MAZ51 occurred with similar dose- and time-dependent patterns. Treatment of glioma cells with MAZ51 resulted in increased levels of phosphorylated GSK3β through the activation of Akt, as well as increased levels of active RhoA. Interestingly, MAZ51 did not affect the morphology and cell cycle patterns of rat primary cortical astrocytes, suggesting it selectively targeted transformed cells. Immunoprecipitation-western blot analyses indicated that MAZ51 did not decrease, but rather increased, tyrosine phosphorylation of VEGFR-3. To confirm this unanticipated result, several additional experiments were conducted. Enhancing VEGFR-3 phosphorylation by treatment of glioma cells with VEGF-C affected neither cytoskeleton arrangements nor cell cycle patterns. In addition, the knockdown of VEGFR-3 in glioma cells did not cause morphological or cytoskeletal alterations. Furthermore, treatment of VEGFR-3-silenced cells with MAZ51 caused the same alterations of cell shape and cytoskeletal arrangements as that observed in control cells. These data indicate that MAZ51 causes cytoskeletal alterations and G2/M cell cycle arrest in glioma cells. These effects are mediated through phosphorylation of Akt/GSK3β and activation of RhoA. The anti-proliferative activity of MAZ51 does not require the inhibition of VEGFR-3 phosphorylation, suggesting that it is a potential

candidate for further clinical investigation for treatment of gliomas, although the precise mechanism(s) underlying its effects remain to be determined.

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Keywords: MAZ51, VEGFR-3, VEGFC, G2/M arrest, Glioma cell line

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P33

Reelin secretion by nNOS-positive GABAergic interneurons is repressed in hippocampus of P301L transgenic mice

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Neuronal nitric oxide synthase(nNOS) expressing cells in hippocampus is one of the major subtypes of GABAergic interneurons. Reelin is a secreted extracellular matrix glycoprotein that plays a critical role in neuronal migration in early developmental stage. In the adult brain, it also present particularly in GABAergic interneurons in the cortex and hippocampus and regulates synaptic plasticity and memory. P301L transgenic mice are characterized by high expression of human tau containing frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) mutation and show motor and behavioral deficits together with age-dependent development of neurofibrillary tangles. In the present study, we investigated the reerlin expression in nNOS-positive GABAergic interneurons in the hippocampusand alternation of reelin-expressing nNOS-positive interneurons in P301L transgenic mice. As results, reelin was coexpressed in nNOS-positive GABAergic interneurons andsecreted reelin may affect granular and pyramidal neurons according to analyzing the localization of reelin receptors. In addition, the number of these cells were decreased in P301L mice. By double immunostains, we conclude that reduction of nNOS-positive GABAergic interneurons in hippocampus of P301L mice may be due to tau hyperphosphorylation-induced neuronal cell death.

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P34

Microglia derived AGE-albumin deleterious to dopamine neuronal cell during Parkinson disease progression

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Advanced glycation end products (AGEs) play an important role in pathogenesis of neurodegenerative disease by inducing protein aggregation and crosslink, formation of Lewy body, which could be contributing Parkinson's disease (PD). In this study, we observed that AGE-albumin, the most abundant AGE product in human PD brain, is synthesized in activated microglia and accumulated in the extracellular space. The rate of AGE-albumin synthesis in human activated microglia is distinctly inhibited by ascorbic acid and cytochalasin treatment. Accumulated AGE-albumin upregulate the receptor protein for AGE (RAGE) and leading to apoptosis of human primary dopamine (DA) neurons. In animal experiments, we observed reduced DA neuronal cell death by treatment of soluble RAGE (sRAGE), pyridoxamine. Our study provides evidence that activated microglia is one of the main contributors for AGE-albumin accumulation, deleterious to dopamine neuron in human PD brain, could be used as diagnostic and therapeutic biomarker for neurodegenerative disorder.

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P35

Microglial AGE-albumin is critical in promoting alcohol-induced neurodegeneration in rats and humans

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Alcohol is a neurotoxic agent, since long-term heavy ingestion of alcohol can cause various neural diseases including fetal alcohol syndrome, cerebellar degeneracy and alcoholic dementia. However, the molecular mechanisms of alcohol-induced neurotoxicity are still poorly understood despite numerous studies. Thus, we hypothesized that activated microglial cells with elevated AGE-albumin levels play an important role in promoting alcohol-induced neurodegeneration. Our results revealed that microglial activation and neuronal damage were found in the hippocampus and entorhinal cortex following alcohol treatment in a rat model. Increased AGE-albumin synthesis and secretion were also observed in activated microglial cells after alcohol exposure. The expressed levels of receptor for AGE (RAGE)-positive neurons and RAGE-dependent neuronal death were markedly elevated by AGE-albumin through the mitogen activated protein kinase pathway. Treatment with soluble RAGE or AGE inhibitors significantly diminished neuronal damage in the animal model. Furthermore, the levels of activated microglial cells, AGE-albumin and neuronal loss were significantly elevated in human brains from alcoholic indivisuals compared to normal controls. Taken together, our data suggest that increased AGE-albumin from activated microglial cells induces neuronal death, and that efficient regulation of its synthesis and secretion is a therapeutic target for preventing alcohol-induced neurodegeneration.

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P36

Agmatine modulates the phenotype of macrophage after spinal cord injury

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Agmatine is a decarboxylated arginine by arginine decarboxylase (ADC). Agmatine has been known as a neuroprotective agent. It has been reported that agmatine work in many kinds of CNS injuries as a NMDA receptor blocker or a competitive nitric oxide synthase (NOS) inhibitor. In spinal cord injury, agmatine showed reduction of neuropathic pain, improvement of locomotor function, and neuroprotection. Macrophage is a key cellular component in neuroinflammation, a major cause of impairment after spinal cord injury. Macrophage has subtypes, M1 and M2 macrophages. M1 macrophage induces pro-inflammatory response but M2 inspires anti-inflammatory response. In this study, it is clarified whether neuroprotective effect of agmatine is related with the modulation of macrophage subdivision after spinal cord injury. Spinal cord injury was induced in SD rats with 25.0 gCm contusion by MASCIS. Animals received agmatine (100 mg/kg/day, IP) for 1 week after spinal cord injury. The proportion of M1 and M2 macrophages in the epicenter of injury are confirmed with immunohistochemistry. iNOS+/CD68+ cells were counted as M1 macrophages and CD206+/CD68+ cells as M2 macrophages. The treatment of agmatine increased CD206 expression. These results suggested that agmatine reduce impairment after spinal cord injury through modulating the phenotype of macrophage from M1 to M2 macrophage.

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P37

N-acetyl-D-glucosamine kinase upregulates dendritic architecture which is not dependent on its kinase activity

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N-acetylglucosamine kinase (GlcNAc kinase or NAGK; EC 2.7.1.59) is highly expressed in different brain sections and plays a critical role in the development of dendrites in hippocampal neurons. The overexpression of EGFP- or RFP (DsRed2)-tagged NAGK in rat hippocampal neurons upregulated the dendritic complexity. In contrast, knockdown of NAGK by shRNA induced dendrite degeneration, and this was abrogated by the co-expression of RFP-tagged NAGK. Here, three point NAGK mutants with different substrate binding capacities and reaction velocities were produced. Conversion of Asn36, which plays a role in domain closure by making a hydrogen bond with GlcNAc, to Ala (i.e., N36A) mildly reduced NAGK enzyme activity. Conversion of Asp107, which makes hydrogen bonds with GlcNAc and would act as a proton acceptor during nucleophilic attack on the γ-phosphate of ATP, to Ala (i.e., D107A), caused a total loss in enzyme activity. The overexpression of EGFP-tagged WT or any of the mutant NAGKs in rat hippocampal neurons (DIV 5-9) increased dendritic architectural complexity. Finally, the overexpression of the small, but not of the large, domain of NAGK resulted in dendrite degeneration. These results suggest that NAGK, in particular the small domain, and not its NAGK kinase activity, is instrumental in the formation of neuronal dendrites.

Keywords: N-acetyl glucosamine kinase, culture, transfection, neuron, overexpression, shRNA, mutation, dendritogenesis

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P38

The effect of ASK1 on vascular permeability and edema formation in cerebral ischemia

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Apoptosis signal-regulating kinase-1 (ASK1) is the mitogen-activated protein kinase kinase kinase (MAPKKK) and participates in the various central nervous system (CNS) signaling pathways. In cerebral ischemia, vascular permeability in the brain is an important issue because regulation failure of it results in edema formation and blood-brain barrier (BBB) disruption. To determine the role of ASK1 on vascular permeability and edema formation following cerebral ischemia, we first investigated ASK1-related gene expression using microarray analyses of ischemic brain tissue. We then measured protein levels of ASK1 and vascular endothelial growth factor (VEGF) in brain endothelial cells after hypoxia injury. We also examined protein expression of ASK1 and VEGF, edema formation, and morphological alteration through cresyl violet staining in ischemic brain tissue using ASK1-small interference RNA (ASK1-siRNA). Finally, immunohistochemistry was performed to examine VEGF and aquaporin-1 (AQP-1) expression in ischemic brain injury. Based on our findings, we propose that ASK1 is a regulating factor of vascular permeability and edema formation in cerebral ischemia.

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Keywords: Apoptosis signal-regulating kinase 1 (ASK1), Cerebral ischemia, Vascular permeability, Edema, Blood-brain barrier (BBB), Vascular endothelial growth factor (VEGF), Aquaporin-1 (AQP-1)

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P39

Agmatine regulates the proliferation and differentiation of neural stem cells by controlling miR-Let7A

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Agmatine (decarboxylated arginine) plays multiple roles in various physiological mechanisms. In the central nervous system (CNS), agmatine exerts neuroprotective effects such as neurogenesis in a variety of disorders. Recently, microRNAs have known the relationship with CNS disorders. To determine whether the agmatine modulates the proliferation and differentiation of neural stem cells (NSCs) by regulating microRNA, we first analyzed microarray to screen the related genes and microRNAs on NSC's proliferation. Especially, we investigated the role of microRNA Let7A that has reported as multifunctional microRNA on agmatine treated NSCs. In present study, we investigated the mRNA level of doublecortin (DCX) as a marker of neuron, SRY (sex determining region Y)-box 2 (SOX2) as a marker of neural precursor cell, Feminizing Locus on X-3, Fox-3, Rbfox3, or Hexaribonucleotide Binding Protein-3 (NeuN) as a marker of neuron, Nuclear receptor TLX (TLX) as a transcription factor related with NSC proliferation using quantitative RT-PCR which are involved in the proliferation and differentiation of NSCs. To visualize the expression of DCX, NeuN, SOX2, TLX, we conducted the immunochemical analysis. Moreover, we investigated the various molecular signal pathway using western blot analysis. Taken together, we conclude that agmatine may regulate the proliferation and differentiation of NSCs by modulating microRNA Let7A.

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Keywords: Agmatine, microRNA Let7A, Neural stem cells (NSCs), Proliferation, Differentiation

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P40

Intra-arterial injection of ELP reduces hematoma in rodent model of intracerebral hemorrhage

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Intracerebral hemorrhage (ICH) is one of the devastating diseases and a type of stroke caused by bleeding within the brain tissue itself ?a very life-threatening situation. A stroke occurs when the brain is deprived of oxygen due to an interruption of its blood supply. ICH is most commonly caused by hypertension, arteriovenous malformations or head trauma. Elastin-like polypeptide (ELP) is a thermally responsive biopolymer that reversely aggregates at a pre-defined transition temperature. In this study, we hypothesized that administration of ELPs into the internal carotid artery after collagenase-induced ICH may reduce hematoma size and play an important role in the reorganization of brain structure related to brain plasticity. Here we found that hematoma size was significantly reduced in ELP group compared with saline group 24 hours after ICH. Also The extravasation of rat IgG was higher in saline group than in ELP group. The overall data demonstrate that ELP treatment could be a novel therapeutic strategy for attenuating ICH.

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Keywords: Intracerebral hemorrhage (ICH), Elastin-like polypeptide (ELP), Hematoma

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Three dimensional reconstruction of the postsynaptic triads at the ribbon synapse of rod spherules in the mouse retina

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The ribbon synapse at the photoreceptor terminal is the first synapse in the retina. A key presynaptic structure, synaptic ribbon has been highlighted and recent studies have been unveiling its molecular machinery and anatomy, but relatively little interest and information about the postsynaptic elements at the ribbon synapse of photoreceptors. Therefore, we examined microanatomy of the postsynaptic triad invaginating the rod spherule by Focused Ion Beam Scanning Electron Microscopy (FIB-SEM) combined with 3D image analysis. C57BL/6J mouse retinas were dissected and fixed in 2% paraformaldehyde and 2.5% glutaraldehyde. The tissues were en bloc stained and embedded in Epon. Retinal pieces were cut horizontally through the outer plexiform layer with 30-nm thickness and automatically scanned the cutting surface by FIB-SEM. The scanned images were added one by one and reconstructed with Mimics software. The postsynaptic structure, synaptic triads are composed of one or two bipolar dendrites as the central element and two horizontal cell axon terminals as two lateral elements. All elements entered the rod spherule together as a thin bundle at one side of the synaptic ribbon plate. Afterwards, two horizontal processes ran parallel on either side of the ribbon in an arc, and thus, each process looked 'hook' or 'question' mark. In case that one bipolar dendrite constituted the central element, the bipolar dendrite horizontally expanded like a fan with concave top opposed to the vertical synaptic ribbon. However, in the case of bipolar doublets as the central element, the doublets were vertically expanded and paralleled each other. These results demonstrate that shape of postsynaptic triads at the ribbon synapse within the rod spherule is not only variable but also has consistent features. These results may provide the insights into the ribbon synapse in the rod photoreceptors.

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P42

Hypothalamic, feeding/arousal-related peptidergic projections to the paraventricular thalamic nucleus in the rat

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Based on the importance of paraventricular thalamic nucleus (PVT) as a relay station of energy balance, arousal, and food reward, we aimed in the present study to determine projection patterns of neuropeptide Y (NPY), cocaine- and amphetamine-regulated transcript (CART) peptide, melanin-concentrating hormone (MCH), and hypocretin (Hcrt) to the PVT. First, the distribution of peptidergic axon terminals within the PVT was examined. NPY and CART terminals were confined within the boundary of the thalamic nucleus, exhibiting almost identical distribution. MCH terminals were rarely observed. In contrast, Hcrt terminals were as extensive as NPY/CART terminals, but spread into peri-PVT region including the midline and subventricular surface. Second, neuronal origin of feeding/arousal-related peptides projecting to the PVT was investigated. NPY neurons were observed in the medial subdivision of the arcuate nucleus (Arc), whereas CART cells were in the lateral Arc as well as other hypothalamic regions including the paraventricular hypothalamic nucleus, perifornical region of the lateral hypothalamus, dorsal hypothalamic area, and zona incerta. Both NPY and CART projections to the PVT were bilateral; ipsilateral proportion was 54.0%±3.6% (n=6) for NPY and 57.1%±2.5% (n=6) for CART. The total number of CART neurons projecting to the PVT exceeded that of NPY cells; the ratio of labeled CART neurons to NPY cells was 2.4±0.2 (n=6). In contrast, Hcrt-ergic projection to the PVT exhibited a slight ipsilateral dominance (62.7%±1.6%, n=6), with majority of labeled cells located in the lateral hypothalamus medial to the fornix (72.2%±2.3%, n=6). Finally, with observation of heavy projection from the PVT to the nucleus accumbens shell region, the convergence of NPY and CART terminals on a single PVT neuron was identified. The present observations provided the anatomical evidence that the PVT might play an essential role in the integration of antagonistically-acting, feeding/arousal-related peptidergic inputs on their way to the cortical reward system.

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P43

Activity-dependent interaction of IP3KA and EB3

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End-binding protein 3 (EB3) is asymmetrically accumulated on plus end tips of microtubules by its autonomous recognition of GTP states and it can bind to various proteins including other plus end binding proteins. Through this localized distribution and versatile interactions, EB3 can function as a kind of guidance for dynamic microtubules. Recently, several independent studies reported that the complex of dynamic microtubule and EB3 enters into dendritic spine by activity-dependent manners. However, detailed mechanisms of activity-dependent synaptic invasion are not clear. Neuron-specific protein, inositol 1, 4, 5-trisphosphate 3-kinase A (IP3K-A, alternative name is ITPKA), is both microtubule and F-actin binding protein. It regulates the architecture of dendritic spines by cytoskeletal reorganization. In the present study, we demonstrated that IP3K-A bound directly to EB3 through its N-terminus region of IP3K-A. Their binding affinity was regulated negatively by PKA-dependent phosphorylation of IP3K-A Serine 119. Spatiotemporal distribution of phosphorylated IP3K-A is very dynamic and asymmetric, suggesting that the interaction of EB3 and IP3K-A is strictly regulated by neuron. Like this, after cLTP induction, the interaction of IP3K-A and EB3 was increased intensely and restore to basal status within 30 min. and large portions of IP3K-A and EB3 were observed in dendritic spine and spine head protrusions (SHPs). Additionally, we confirmed that IP3K-A can form as a tripartite complex with EB3 and F-actin in vitro binding assay. These results suggested that IP3K-A and EB3 have a special role to crosslink microtubules and F-actin during the synaptic entry of dynamic microtubules. It is likely that this transient synaptic interaction of two cytoskeletons will contribute a synaptic plasticity enhancement through increased synaptic cargo transports.

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P44

Early gene response 1 (Egr-1) regulates the subunits of GABAA in the hippocampus in an activity-dependent manner

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The homeostatic regulation of neuronal activity in glutamatergic and GABAergic synapses is a critical for neural circuit development and synaptic plasticity. Inductive expression of the transcription factor early growth response 1 (Egr-1) in neurons is tightly associated with many forms of neuronal activity, but the underlying target genes in brain have not been fully elucidated. Here, through quantitative real-time PCR combining in vivo chromatin immunoprecipitation, we find that GABAA receptor subunits, GABRA2 (a2), GABRA4 (a4), and GABRQ (q) genes are transcriptional targets of Egr-1. Transfection of Egr-1 overexpression construct in neuroblastoma cell (Neuro2A) up-regulates a2, a4, and q subunits. Given that Egr-1 knock-out mice display less GABRA2, GABRA4, and GRBRQ mRNAs in the hippocampus and Egr-1 directly binds to their promoters and induces mRNA expression, our findings support a role for Egr-1 as a major regulator of GABAA receptor compositional alteration in homeostatic plasticity by glutamatergic activity-dependent manner.

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P45

Role of inositol 1,4,5-trisphosphate 3-kinase A in regulating emotional behaviors and amygdala functions

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Inositol 1,4,5-trisphosphate 3-kinase A (IP3K-A) is a brain- and neuron-enriched molecule which has ability to reduce the influx of calcium released from endoplasmic reticulum via inositol trisphosphate receptor signaling. Despite its expression in emotion-related structure and functional importance in neural activity, there is no clear evidence that IP3K-A is linked with mood. In the present study, we have found that IP3K-A knockout mice have altered emotional state. Behavioral analyses revealed that mutant animals are more anxious and depressed under basal conditions. In addition, they displayed more robust fear response to both conditioned and unconditioned stimuli, indicating high levels of innate fear in these mice. When exposed to fearful stimulus, IP3K-A deficient mice froze more than wild type littermate and had higher c-fos induction in the central nucleus of the amygdala (CEA), which is a well known structure mediating fear- and anxiety-related behavioral responses. In accordance with these evidences, electrophysiological properties of CEA were also attenuated in brain slices of IP3K-A knockout mice. In conclusion, these findings collectively suggest that IP3K-A has an important role in regulating affective states and activities of CEA neurons in response to aversive stimuli.

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P46

Spatiotemporal expression of SOCS2 mRNA and protein following transient focal ischemia in rats

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Suppressor of cytokine signaling 2 (SOCS2), one of the SOCS family member, has been reported to be possibly involved in astroglial reaction and adult neurogenesis in the ischemic hippocampus. The present study aimed to identify whether SOCS2 is involved in pathophysiology of stroke. A rat focal cerebral ischemia-reperfusion model induced by middle cerebral artery (MCA) occlusion was used to investigate the spatiotemporal regulation of SOCS2 mRNA and protein. Moreover, double- and triple-labeling techniques were used to identify the phenotypes of cells expressing SOCS2. SOCS2 mRNA was localized to the blood vessel or in close vicinity to the blood vessel profiles in the ischemic core region and virtually all of the cells expressing SOCS2 mRNA and protein within the perivascular region were positive for the neural progenitor maker nestin. In contrast, the majority of the SOCS2-expressing cells associated with the vasculature were GFAP-immunoreactive astrocytes in the peri-infarct zone of stroke-lesioned rats, and some cells were activated brain macrophages. In addition, SOCS2 was transiently increased in most GFAP-positive cells of the dorsolateral subventricular zone (SVZ) of the infarcted hemisphere compared with the contralateral hemisphere at 7-14 days after reperfusion. Most cells expressing SOCS2 co-expressed nestin or Ki67 which label cells at all phases of the cell cycle, suggesting that SOCS2 is upregulated in SVZ astrocytes after focal ischemia. These data suggest that SOCS2 may be involved in glial reactions in the ischemic brain and possibly mediate adult neurogenesis after ischemic stoke.

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Keywords: SOCS2, Brain macrophages, Reactive astrocytes, Neurogenesis, Focal ischemia

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P47

Neuroprotective effects of novel antiepileptic drug lacosamide via decreasing glial activation in the hippocampus of a gerbil model of ischemic stroke

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Lacosamide, a novel antiepileptic drug, has been discovered to have some beneficial effects beyond its effectiveness. In the present study, we examined the neuroprotective effect of lacosamide against ischemic damage in the hippocampal CA1 region following 5 min of transient cerebral ischemia in gerbils. The results showed that pre- and post-treatment with 25 mg/kg lacosamide significantly protected neuronal death from transient cerebral ischemic injury. Many H&E positive cells, NeuN-immunoreactive neuronsand a few number of F-JB-positive cells were found in the stratum pyramidale of the CA1 region in the lacosamide-treated-ischemia-operated groups compared with those in the vehicle-treated-ischemia-operated group. In addition, the treatment with 25mg/kg lacosamide markedly attenuated the activation of astrocytes and microglia in the ischemic CA1 region. In brief, these results indicate that both pre-and post-treatment with lacosamide can protect CA1 pyramidal neurons from transient cerebralis chemic injury in the hippocampus and the neuroprotective effect of lacosamide may be related with decreasing the activation of glial cells in the ischemic CA1 region.

Keywords: antiepileptic drug, lacosamide, ischemic stroke, pyramidal neurons, neuroprotection, glial activation

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P48

Reelin signaling through p27kip1 modification controls neuronal differentiation

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During E12~E16 mouse brain, the conversion of Tbr2 → Tbr1 is important in the direct differentiation of IPCs → postmitotic projection neurons. In our data showed that reelin deficiency suppressed Tbr2 expression in SVZ and IZ. Moreover, Tbr1 expressing layer VI neurons also displayed developmental abnormalities in the laminar organization at E16. Recently, several reports indicated that CIP/Kip family p27kip1 is key regulators of neuronal progenitor (NPC) terminal mitosis and differentiation. In addition, p27kip1 directly upregulates Tbr2 expression by stabilizing Neurogenin 2 protein. We first found that, in reelin deficiency, unusual distribution and downregulation of p27kip1 protein was observed in the mouse brain and differentiated neuronal cells. However, p27kip1 expression was recovered via added reelin extracts. We thus conclude that the reelin deficiency suppresses p27kip1 expression in early born preplate neurons and that these neurons wouldn't mature into the postmitotic projection neurons in E12.5 preplate layer. Conclusively, abnormal preplate layer formation induces defect layer VI neuronal positioning and subplates splitting. This result suggests that the reelin may be important for the induction of p27kip1 expression through Cdk5 to control neuronal differentiation in laminar organization.

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P49

SIRT1 deletion in myeloid cells aggravates a high fat diet-induced hepatic steatosis

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Insulin resistance in diabetes induces macrophage inflammation and contributes hepatic injury or fibrosis. Sirtuin 1 (SIRT1) is a mammalian NAD+-dependent protein deacetylase that regulates cellular metabolism and has also been studied in fatty liver disease, however, the macrophage-specific function is largely unknown. Our aim was to determine myeloid-specific SIRT1 deficient mice were protected or adverse against HFD-induced nonalcoholic steatohepatitis (NASH). We employed the myeloid-specific SIRT1 knockout (KO) mice fed a high-fat diet (HFD) or normal diet (ND) for 12 weeks. SIRT1 deletion enhanced HFD-induced changes on body weight gain, fat mass and liver weight, and increased glucose

and insulin resistance. SIRT1 deletion increased acetylated NF-kB expression and the nuclear translocation and exacerbated HMGB1- and TNF-α-mediated inflammation and macrophage infiltration. In addition, SIRT1 deletion increased hepatic fat accumulation by activating lipogenic pathway through SREBP-1 and JNK pathway, which precipitated hepatic fibrogenesis, as indicated by induction of connective tissue growth factor and collagen secretion. Myeloid deletion of SIRT1 stimulates HFD-induced NASH by increasing NF-kB-mediated inflammation and increases a risk of hepatic fibrosis, which suggests that modulating SIRT1 is a potential therapeutic target for treating human NASH.

P50

miR-155 as a proinflammatory regulator via SHIP-1 down-regulation in acute gouty arthritis

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Gout is characterized by episodes of intense joint inflammation in response to intra-articular monosodium urate monohydrate (MSU) crystals. MicroRNA-155 (miR-155) is crucial for the proinflammatory activation of human myeloid cells and antigen-driven inflammatory arthritis. The functional role of miR-155 in gouty arthritis has not been defined. Therefore, the aim of this study was to examine the role of miR-155 in pathogenesis of acute gouty arthritis. Samples from 14 patients with acute gouty arthritis and 10 healthy controls (HCs) were obtained. Peripheral blood mononuclear cells (PBMCs) and synovial fluid mononuclear cells (SFMCs) were cultured in vitro with MSU crystals, and gene expression (human miR-155 and SHIP-1) were assessed by real-time PCR. THP-1 cells and human monocyte-derived macrophages were stimulated by MSU crystals and/or miR-155 transfection. Whole-cell lysates were subjected to Western blot analysis. Human tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-1βin cell culture supernatants were measured by using Luminex. Immunohistochemistry was performed on formalin-fixed gout tissues with anti?SHIP-1 antibody. A C57BL/6J male mouse model of gout was used to analyze the expressions of miR-155, SHIP-1, and inflammatory cytokines. The samples from gouty arthritis were highly enriched in miR-155, with levels of expression being higher than those found in PBMC from HC. miR-155 was strongly induced by stimulation of MSU crystals after 24 hours and their expressions gradually decreased. Stimulating with MSU crystals, the level of SHIP-1 gradually decreased according to the overexpression of miR-155. miR-155 promoted MSU-induced proinflammatory cytokine production such as TNF-αand IL-1β. Consistent with in vitro observations, miR-155 expression was also elevated in the mouse model of gout. The production of inflammatory cytokines was markedly increased in MSU crystal induced peritonitis mice. Overexpression of miR-155 in SFMC leads to down-regulation of SHIP-1 and an increase in the production of proinflammatory cytokines.

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P51

ERRγinduces cardiac hypertrophy by activating GATA4

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Estrogen-related receptor gamma (ERRγ) is an orphan nuclear receptor that has biological roles mainly in metabolism and that controls metabolic switching in perinatal heart. In adult heart diseases, however, the functional roles of ERRγhave not yet been elucidated. In the present study, we aimed to characterize the role of ERRγin cardiac hypertrophy. The functional roles of ERRγin the development of cardiac hypertrophy were examined in primary cultured cardiomyocytes and in animal models. ERRγexpression was increased in hearts from human hypertrophic cardiomyopathy patients and in both cellular and animal models of cardiac hypertrophy. Transgenic overexpression in mouse heart as well as forced expression of ERRγin cardiomyocytes induced hypertrophic phenotypes. Knock-down of ERRγblocked agonist-induced hypertrophic phenotypes. ERRγbound directly to the proximal ERR-responsive element in the GATA4 promoter in a sequence-specific manner and thereby induced transcription. ERRγ-induced hypertrophy was blocked by inhibition of GATA4. GSK-5182, an inverse agonist of ERRγ, completely blocked cardiac hypertrophy in cardiomyocytes. It also prevented aortic banding-induced cardiac hypertrophy and fibrosis in mouse heart. These findings demonstrate a novel ERRγ/

GATA4 signal cascade in the development of cardiac hypertrophy and suggest GSK-5182 as a possible therapeutic.

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P52

GPR40 activation attenuates cisplatin-induced apoptosis

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G-protein-coupled receptor 40 (GPR40) is known to play a role in the regulation of fatty acids, insulin secretion, and inflammation. However, the pathophysiological roles of GPR40 in kidney disease and injury have not yet been identified. Here, we have investigated the expression of GPR40 during cisplatin-induced kidney injury using male Sprague-Dawley rats that were treated with 8 mg/kg cisplatin or vehicle. After cisplatin treatment, the expression of GPR40 protein in the kidney was decreased in association with an increase in serum creatinine and Bax/Bcl-2 expression ratio. To further investigate the function of GPR40, human renal proximal tubular epithelial (HK-2) cells were cultured with cisplatin in the absence or presence of GW9508, a selective GPR40 agonist. In HK-2 cells, the pretreatment with GW9508 attenuated the decreased cell viability by cisplatin treatment. Cisplatin treatment increased the number of cells with condensed nuclei, which was ameliorated by GW9508 pretreatment. TUNEL stain also showed that pretreatment with GW9508 ameliorated cisplatin-induced apoptosis. Cisplatin treatment increased the Bax/Bcl-2 expression ratio, cleaved caspase-3 expression and the activation of nuclear factor-κB (NF-κB). These changes were attenuated by GW9508 pretreatment. Cisplatin-induced activations of reactive oxygen species (ROS) and Src/epidermal growth factor receptor (EGFR)/extracellular signal regulated kinase (ERK) were also counteracted by GW9508 pretreatment. Thus, activation of GPR40 attenuates cisplatin-induced apoptosis through the inhibition of ROS generation, Src/EGFR/ERK signaling pathway, nuclear activation of NF-κB, and pro-apoptotic factors.

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P53

SHP blocks GATA6 for anti-hypertrophic effect

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Small heterodimer partner (SHP; NR0B2) is an atypical orphan nuclear receptor that lacks a conventional DNA binding domain. Through interactions with other transcription factors, SHP regulates diverse biological events, including glucose metabolism in liver. However, the role of SHP in adult heart diseases has not yet been demonstrated. We aimed to investigate the role of SHP in adult heart in association with cardiac hypertrophy. The roles of SHP in cardiac hypertrophy were tested in primary cultured cardiomyocytes and in animal models. SHP null mice showed a hypertrophic phenotype. Hypertrophic stresses repressed the expression of SHP, whereas forced expression of SHP blocked the development of hypertrophy in cardiomyocytes. SHP reduced the protein amount of Gata6 and by direct physical interaction with Gata6 interfered with the binding of Gata6 to GATA binding elements in the promoter regions of natriuretic peptide precursor type A. Metformin, an anti-diabetic agent, induced SHP and suppressed cardiac hypertrophy. The metformin-induced anti-hypertrophic effect was attenuated either by SHP siRNA in cardiomyocytes or in SHP null mice. These results establish SHP as a novel anti-hypertrophic regulator that acts by interfering with GATA6 signaling. SHP may participate in the metformin-induced anti-hypertrophic response.

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P54

RFP mediates Pax7-induced MyoD ubiquitination

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Skeletal muscle atrophy results from the net loss of muscular proteins and organelles and is caused by pathologic conditions such as nerve injury, immobilization, cancer, and other metabolic diseases. Recently, ubiquitination-mediated degradation of skeletal-muscle-specific transcription factors was shown to be involved in muscle atrophy, although the mechanisms have yet to be defined. Here we report that ret finger protein (RFP), also known as TRIM27, works as an E3 ligase in Pax7-induced degradation of MyoD. Muscle injury induced by sciatic nerve transection up-regulated RFP and RFP physically interacted with both Pax7 and MyoD. RFP and Pax7 synergistically reduced the protein amounts of MyoD but not the mRNA. RFP-induced reduction of MyoD protein was blocked by proteasome inhibitors. The Pax7-induced reduction MyoD was attenuated by RFP siRNA and by MG132, a proteasome inhibitor. RFPΔR, an RFP construct that lacks the RING domain, failed to reduce MyoD amounts. RFP ubiquitinated MyoD, but RFPΔR failed to do so. Forced expression of RFP, but not RFPΔR, enhanced Pax7-induced ubiquitination of MyoD, whereas RFP siRNA blocked the ubiquitination. Sciatic nerve injury-induced muscle atrophy as well the reduction in MyoD was attenuated in RFP knockout mice. Taken together, our results show that RFP works as a novel E3 ligase in the Pax7-mediated degradation of MyoD in response to skeletal muscle atrophy.

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P55

The expression of GDF15 in macrophage polarization in skin wound healing

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The macrophage is a prominent inflammatory cell in wounds, beyond increasing inflammation and stimulating the immune system (M1), macrophage also play an important anti-inflammatory role and can decrease immune reactions through the release of cytokines (M2). M2 macrophages decrease inflammation and encourage tissue repair. GDF15 (growth/differentiation factor 15), is a novel member of the TGFβ(transforming growth factor β) superfamily, plays critical roles in regulating inflammatory and apoptotic pathways in injured tissues and during disease processes. Although GDF15 is also expressed in macrophage for regulating inflammatory.its role in healing remains incompletely understood. In this study, we evaluated the expression of GDF15 following an wound in rat skin. In injured rat skin, GDF15 was increased in dermal layer after 1 to 2 day post injury. GDF15 immunoreactive cells were colocalized with Iba1, a marker of macrophages. This data suggest that GDF15 plays an important role on macrophage polarization in skin wound healing, that it would be helpful for wound healing.

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P56

CD200R/Foxp3 signaling as the role of enhancer of alternative activation of microglia

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The main role of the immune system is to protect the organism against damage by ensuring an adequate response against various pathogens and also from damage that may result from inappropriate immune system activation. The immune system, therefore, has to comprise mechanisms that maintain homeostasis, including both activatory and inhibitory mechanisms. CD200 and CD200R, type I transmembraneanchored glycoproteins, are structurally similar to immunoglobulins. CD200/CD200R interaction is crucial inhibitory immune system in alternative activation of microglia (M2). However, the role of CD200/CD200R interaction during alternative activation of microglia has not been described yet. Foxp3 is one of

the most important transcriptional repressor and inhibits activation pro-inflammatory system. We examined the expression of Foxp3 in kainic acid (KA)-induced neurodeneration of the mouse hippocampus and Foxp3 is co-expressed with CD200R, it suggests that Foxp3 is related with alternative activation of microglia. We suggest that Foxp3 may regulate alternative activation of microglia through CD200/CD200R interaction.

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P57

Leptin prevents rat articular chondrocytes against TNF-α-induced cytotoxicity

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Chondrocyte death and the pertinent signaling pathway involved have therefore been the focus of interest recently as pathogenetic factors leading to joint cartilage degradation in OA. TNF-α, a pro-inflammatory cytokine plays a central role in the pathogenesis of articular diseases such as rheumatoid arthritis and OA. Thus, TNF-α has been targeted for therapeutic intervention. Numerous previous studies demonstrated that TNF-α induces articular chondrocytes death. Leptin is a 16 kDa hormone which was originally found in 1994 to be produced by white adipocytes and regulate food intake and energy expenditure. According to the recent findings, leptin is also produced by many other tissues. Leptin can be found in synovial fluid, leptin receptors are expressed within the cartilage and leptin mediates and modulates many inflammatory and destructive responses in cartilage and other joint tissues. Therefore, leptin emerges as an attractive candidate to link obesity and osteoarthritis and serves as a putative drug target for disease-modifying drugs for OA. Although leptin appears to be an important local and systemic factor influencing cartilage homeostasis, the role of leptin in chondrocytes death is largely unknown. We undertook this study to examine whether leptin modulates articular chondrocytes death. In the present study, we observed that leptin prevents TNF-α induced chondrocyte death. We further found that necroptosis mainly contributes to TNF-α induced chondrocyte death. whereas apoptosis partially contributes to TNF-α induced chondrocyte death. In addition, we observed that Leptin exerts anti-TNF-αtoxicity via JNK in rat articular chondrocytes. Based on our findings, we can cautiously assume that leptin present in articular joint fluid of normal person protects articular chondrocytes against cumulative mechanical load and detrimental stress throughout life, delaying the onset of degenerative changes in chondrocytes. We can further assume that leptin protects articular chondrocytes against destructive stimuli even in the joint of OA patients. Taken together our findings suggest that leptin prevents TNF-α induced chondrocyte death. However, further future studies are required to extend these in vitro data to the in vivo situation.

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P58

Resveratrol analogue HS-1793 inhibits adipogenesis in 3T3-L1 via suppression of autophagy

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Obesity is an increasing world problem that may cause several metabolic complications including insulin resistance, hyperlipidemia, hypertension, and atherosclerosis. Development of therapeutic drugs for obesity has been proven difficult. Current strategies for obesity treatment inhibits adipogenesis and lipid accumulation in adipocyte. The polyphenolic compound resveratrol (3,5,4-trihydroxy-trans-stilbene) is a naturally occurring phytochemical found in food products like grapes, peanuts, and various herbs. Resveratrol acts on the process of carcinogenesis by affecting cellular events associated with tumor initiation, promotion, and progression and is also able to active apoptosis. Resveratrol has been documeted to have a wide range of pharmacological effects and inhibits adipogenesis on adipocytes. However, resveratrol is not a potent cytotoxic compound. Therefore, exposure to high doses of resveratrol is required to exert its efficacy. Furthermore, the biological activity of resveratrol

is limited by its photosensitivity and metabolic instability instability. Accordingly, several previous studies were undertaken to obtain synthetic analogues of resveratrol with potent activity. Our previous study demonstrated that a resveratrol analogue HS-1793 showed stronger antitumor activity than resveratrol in various cancer cells. In this study, we investigated whether HS-1793 inhibits adipogenesis like as resveratrol. We undertook Oli red o staining and western blot analysis, HS-1793 as well as resveratrol inhibited lipid accumulation and decreased the expression of the adipocyte differentiation regulator peroxisome proliferator-activated receptor-γ (PPARγ) and fatty acid-binding protein 4(FABP4) genes. As a result, we observed that both drugs inhibits adipogenesis in 3T3-L1. Interestingly, our results show that HS-1793 compared to resveratrol more remarkably inhibited adipogenesis. Recent studies indicate that autophagy is implicated in adipogenesis. Thus, we further tested whether suppression of adipogenesis by resveratrol or HS-1793 involves in autophagy process. We observed that both drugs treatment decreased LC3 II form. Taken together, this data suggest that these two drugs inhibits adipogenesis in 3T3-L1 via autophagy inhibition. Our findings provide their potential therapeutic application in the treatment or prevention of obesity.

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P59

BAG is critical in the development and survival of regulatory T cell

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Naturally occurring regulatory T (Treg) cells are required to sustain immune tolerance and homeostasis by suppressing aberrant or excessive immune responses. The key feature of Treg cells is their expression of the forkhead family transcription factor Foxp3 that is a potently proapoptotic factor. Thus, proapoptotic effects of Foxp3 are counterbalanced by survival signals to normally develop and mature. γc cytokine provide survival signals to Treg cells and protect them from Foxp3 mediated apoptosis in a manner of upregulation of Bcl-2 expression. γc cytokine level in the thymus is physiologically too low to cover Bcl-2-mediated survival from inhibition by Foxp3. Since we found that enhanced Bcl2-associated athanogene (BAG) expression increased CD4 T cell development, BAG seems to play a critical role in Treg survival. BAG which is involved in cell survival has been known as oncogene that prevent cell death and apoptosis. Since BAG is predominantly expressed in muscle cells, their role in immune cells is not known. First, we tested how BAG is expressed in different subset of immune cells such as CD8 T, conventional CD4 T and Treg cells. Interestingly, we found that the mRNA and protein levels of BAG were highly expressed in Treg but not in CD8+ or CD4+CD25- T cells. Although further studies are required, our data indicated that a lethal of Treg cells by Foxp3 could be offset by high level of BAG expression with Bcl-2 upregulation.

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P60

The targeted inhibition of mitochondrial Hsp90 induces mitochondrial elongation via oxidative stress in hepatoma cells

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Hsp90 is of particular interest because its enzymatic ATPase activity is elevated in malignant cells. Particularly, mitochondrial Hsp90 is interacting with another chaperone, TRAP1 (Tumor necrosis factor type 1 receptor-associated protein or Heat-shock-protein 75) to antagonize the cell death promoting properties of the matrix protein, Cyclophilin-D. Previous studies have reported that a Gamitrinib variant containing triphenylphosphonium (G-TPP) binds to mitochondrial Hsp90 and rapidly inhibits its activity, thus inducing the apoptotic pathway in the cells. Mitochondria are dynamic organelles that continually undergo fusion and fission. In mammalian cells, mitochondrial dynamics mediating the fission and fusion processes have been identified as the fission mediators Drp1 and Fis1, as well as the fusion mediators Mfn1 and OPA1. During apoptosis, the mitochondrial network often fragments. We undertook this study to investigate the mechanism underlying the antitumor activity of G-TPP in hepatocellular carcinoma cells. Noticeably, G-TPP induced

mitochondrial elongation in Hep3B cells. We observed that G-TPP reduced Drp1 protein expression level in Hep3B cells undergoing apoptosis. We observed that Hep3B cells showing reduced Drp1 protein expression level were arrested at G2 phase. Depletion of mitochondrial dynamics factors using siRNA affected neither mitochondrial length nor cellular viability in G-TPP treated Hep3B cells. We further observed that G-TPP generated reactive oxygen species (ROS). N-acetyl-cysteine(NAC) pretreatment prevented the activation of caspase-3 and-7 as determined by the production of cleavage procuts, the reduction of mitochodnrial membrane potential, and the generation of mitochondrial ROS. Importantly, NAC not only recovered mitochondrial length but prevented cell viability in G-TPP treated Hep3B cells. Taken together, these findings suggest that G-TPP-induced mitochondrial elongation is mediated by by ROS.

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P61

AGE-albumin from activated macrophage is critical in human BD-MSC survival and critical limb ischemia

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Post-ischemic reperfusion injury (PIRI) triggers an intense inflammatory response which is essential for repair but also implicated in pathogenesis of postischemic remodeling in several organs in human. Recently stem cell therapy emerged as one of the promising way for PIRI in human, however, the satisfactory results did not report in the PIRI including acute myocardial infarction, stroke or critical limb ischemia (CLI). Here we report that human bone-marrow mesenchymal stem cells (hBD-MSC) after inhibition of AGE-albumin from activated macrophages protected the PIRI in CLI model. For PIRI, CLI and reperfusion were generated by tie and reperfusion of femoral artery in C57BL/c mouse. We evaluated the recovery of PIRI-CLI by injection of hBD-MSC with or without sRAGE, the AGE-albumin inhibitor. Our results revealed that activated M1 macrophages synthesize and secrete AGE-albumin with oxidative stress and MAPK pathway, and this was critical in skeletal muscle cell death in PIRI-CLI model through RAGE increase. AGE-albumin also induced hBD-MSC death by RAGE increase. Combined injection of sRAGE and hBD-MSC enhanced the survival of hBD-MSC in PIRI-CLI mouse model and angiogenesis. Our data revealed that AGE-albumin from activated macrophages is critical for skeletal muscle cell death and hBD-MSC death in PIRI-CLI. Taken together, it suggested that AGE-albumin from activated macrophages induced the skeletal muscle cells and hBD-MSCs death through RAGE increase. Inhibition of AGE-albumin with sRAGE protected the apoptosis of both skeletal muscle cells and hBD-MSCs, so the PIRI-CLI protected dramatically with improved angiogenesis. Therefore, regulation of RAGE or AGE-albumin with stem cells could be one of the successful therapeutic strategies for treatment of PIRI including CLI, acute myocardial infarction.

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P62

Five-alpha reductase inhibitor influences expression of androgen receptor and HOXB13 in human hyperplastic prostate tissue

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Objectives: Five-alpha reductase inhibitors (5ARIs) are known as chemopreventive agents in prostate cancer with a risk of high-grade disease. This study evaluated the effects of 5ARI on androgen receptor (AR) and proteins involved in prostate cell growth such as HOXB13 expression in human prostate tissue and LNCaP prostate

cancer cells. **Materials and Methods:** We retrospectively selected 21 patients who underwent TURP between March 2007 and February 2010 for previously confirmed BPH by prostate biopsy. They were grouped into control (group 1, n = 9) and 5ARI treatment (group 2, n = 12) before TURP. AR and HOXB13 expression in prostate tissue was evaluated by immunohistochemical staining. We tested the effect of 5ARI on the expression of AR, prostate specific antigen (PSA) and HOXB13 in LNCaP cells. Cells were assessed by Western blot analysis, MTT in vitro proliferation assay, and ELISA. **Results:** Group 2 showed stronger reactivity for AR and HOXB13 than those of the group 1. MTT assay showed death of LNCaP cells at 25uM of 5ARI. At the same time, ELISA assay for PSA showed that 5ARI inhibited secretion of PSA in LNCaP cells. Western blot analysis showed that 5ARI did not greatly alter AR expression but it stimulated the expression of HOXB13. **Conclusions:** These results demonstrated that 5ARI influences AR and HOXB13 expression in both LNCaP cells and human prostate tissue. In order to use 5ARI in chemoprevention of prostate cancer, we still need to clarify the influence of 5ARI in ARs and oncogenic proteins and its regulation pathway.

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P63

SDC2 hypermethylation is involved in cell cycle dysregulation in colorectal cancer cells

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Syndecan-2 (SDC2) expression is known to be involved in colorectal cancer (CRC) cell tumorigenic activity. However, the association between SDC2 methylation and CRC carcinogenesis is unclear. We investigated SDC2 methylation status and mRNA expression in 42 primary tumor and paired adjacent normal tissues from patients with CRC and in several CRC cell lines by using quantitative methylation-specific polymerase chain reaction (QMSP), reverse transcription-polymerase chain reaction (RT-PCR), and quantitative real time-PCR (RT-PCR). SDC2 hypermethylation was detected in 24 of the 42 CRC specimens (57.1%) and it was statistically different from that observed in paired adjacent normal tissues ($P < 0.001$). Interestingly, SDC2 methylation was associated with tumor moderate/poor differentiation ($P < 0.042$). HCT-116 and DLD-1, two CRC cell lines, showed higher SDC2 methylation, and concomitantly, lower SDC2 endogenous expression. DNA methyltransferase inhibitor, 5-aza-2'-deoxycytidine (5-aza-dC) restored SDC2 mRNA expression in HCT-116 cells ($P < 0.05$). SDC2 promoter (region -322 to 19) activity was confirmed by luciferase assay using the plasmid constructs pGL2-SDC2 and pGL2-Me SDC2 which was methylated in vitro. 5-aza-dC treatment induced G2/M arrest as well as an increase in SDC2 and p21 expression and simultaneous cyclin B1 downregulation. Collectively, these results indicate that SDC2 hypermethylation may play a crucial role in cell cycle regulation in colorectal cancer cells and may be a potential target for epigenetic-based CRC treatment.

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P64

Osteoprotegerin expressed by osteoclasts: an autoregulator of osteoclastogenesis

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OPG is secreted by stromal and osteoblastic lineage cells and inhibits osteoclastogenesis by preventing the interaction of RANKL with RANK. In this study, the expression of OPG in osteoclasts themselves and its biological functions during osteoclastogenesis were investigated for the first time. OPG expression in vivo in the developing rat maxilla was examined by immunofluorescence analysis. OPG expression in osteoclasts during in vitro osteoclastogenesis was determined by RT-PCR, Western blot, and immunofluorescence staining. The function of OPG produced by osteoclasts during osteoclastogenesis was determined by silencing the OPG gene. The effects of

OPG on bone resorbing activity and apoptosis of mature osteoclasts were examined by the assay of resorptive pit formation on calcium phosphate-coated plate and TUNEL staining, respectively. In the immunofluorescence findings, strong immunoreactivities were unexpectedly seen in multinucleated TRAP-positive osteoclasts around the growing and erupting tooth germs in the rat alveolar bone. In vitro, OPG expression was significantly increased during the differentiation of osteoclasts from mouse bone marrow-derived cells treated with a combination of M-CSF and RANKL. Interestingly, it was found that OPG siRNA treatment during osteoclastogenesis enhanced the size of osteoclasts, but attenuated their bone resorbing activity. Also, the increased chromosomal DNA fragmentation and caspase-3 activity in the late phase of osteoclastogenesis were found to be decreased by treatment with OPG siRNA. Furthermore, effects of OPG siRNA treatment on osteoclastogenesis and bone resorbing activity were recovered by the treatment of exogenous OPG. These results suggest that OPG, expressed by the osteoclasts themselves, may play an auto-regulatory role in the late phase of osteoclastogenesis through induction of apoptosis.

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Gambogic acid induces apoptosis in renal carcinoma Caki Cells through down-regulation of cFLIP$_L$

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Gambogic acid (GA), a natural compound derived from brownish gambose resin, shows several bioactivities such as antitumor and antimicrobial properties. Although, GA is already known to induce cell death in variety cancer cells, the molecular basis for GA-induced cell death was not definitely known in renal cancer cells. In this study, we found that GA treatment induced cell death in dose-dependent manner in human renal carcinoma Caki cells. GA treatment of Caki cells decreased the levels of antiapoptotic proteins such as Bcl-2 and XIAP in dose-dependent manners. In addition, GA decreased expressions of cFLIPL protein, which wase down-regulated at the transcriptional level. We also found that z-VAD (pan-caspase inhibitor) partially blocked GA-mediated apoptosis. However, ROS scavenger, N-acetylcystine (NAC) had no effect on GA-induced apoptosis. Restoration of cFLIP attenuated GA-induced cell death in Caki cells.Furthermore Sub-toxic dose of GA sensitizes TRAIL-mediated apoptosis in renal carcinoma Caki cells. Pretreatment of z-VAD completely blocked GA plus TRAIL-mediated apoptosis. However, pretreatment of NAC partially inhibited GA plus TRAIL-induced apoptosis. Taken together, GA induced apoptosis via down-regulation of c-FLIP(L) and sensitized TRAIL-mediated apoptosis in human renal carcinoma Caki cells.

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P66

N-acetyl-D-glucosamine kinase is a component of nuclear speckles and paraspeckles

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N-acetylglucosamine (GlcNAc)-6-phosphate, the main intermediate for UDP-GlcNAc production, can be synthesized through a de novo pathway by using glycolytic intermediates or by a salvage pathway using the enzyme, GlcNAc kinase (NAGK; E.C. 2.7.1.59). NAGK is a ubiquitously expressed kinase enzyme with its characteristic high expression in neurons. Here, by immunocytochemistry (ICC) study of cultured rat hippocampal neurons and HEK293T cells we found that NAGK immune-reactive signals were distinctly present in nucleus and colocalized with snRNPN (small nuclear ribonucleoprotein associated protein N) and p54NRB, a speckle and paraspeckle marker protein respectively. In addition, relative localization of NAGK to Lamin and GlcNAc signals revealed that NAGK encircled the nucleus at the cytoplasmic face of outer membrane. Both in ICC and proximity ligation assay we detected the interaction between

NAGK and snRNPN not only in the nucleus but also at dendritic branches. The association of NAGK with speckle and paraspeckle proteins suggests that NAGK has functional role in splicing and gene expression.

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HOX genes promote tamoxifen resistance in breast cancer

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Endocrine therapy, such as tamoxifen and aromatase inhibitors, has been used to treat both early and advanced estrogen receptor α (ER)-positive breast cancer. Despite improvements in treatment, resistance to the current therapeutics can occur in up to one quarter of all cases and thus presents a serious therapeutic challenge. Multiple mechanisms responsible for endocrine resistance have been proposed, however, the molecular events underlying resistance to therapeutic agents are not clearly understood. Therefore, a better understanding of gene expression alterations associated with the resistance would suggest alternative regimens that overcome endocrine resistance. HOX transcription factors have recently been implicated as strong candidates to control cancer progression and metastasis. Previously we have demonstrated HOX gene dysregulation in breast cancer. To identify HOX genes involved in tamoxifen resistance, here we have generated in vitro model of acquired tamoxifen resistance using MCF breast cancer cells (MCF7-TamR) and analyzed expression pattern of HOX genes. MCF7-TamR cells were more resistant to tamoxifen in MTT assay and exhibited dysregulation of HOX gene expression, in particular HOXB cluster genes including HOXB2, HOXB4, HOXB5, and HOXB6. Interestingly, HOXB5 overexpression or knockdown in ER-positive breast cancer cells, such as MCF7 and T47D, caused altered expression of the ErbB receptor tyrosine kinase family genes, such as EGFR and ERBB2, that are known to be involved in endocrine resistance. In addition, Kaplan-Meier analysis of the overall survival for all patients treated with only endocrine therapy showed the correlation of high HOXB5 expression with a poor response to endocrine therapy. Further analysis of functional role of particular HOX genes in tamoxifen resistance may provide insight into the molecular mechanisms underlying tamoxifen resistance.

Keywords: breast cancer, tamoxifen resistance, HOX genes

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CD99-derived peptidomimetics inactivate EGFR signaling pathway in MCF-7 breast cancer cells

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Epidermal growth factor receptor (EGFR) is a 170 kDa trasmembrane protein, activation of which results in its dimerization and tyrosine autophosphorylation and subsequent recruitment of downstream signaling molecules that mediate cell proliferation, survival, migration and clustering. CD99 protein, a 32 kDa type I transmembrane glycoprotein, plays a role in the regulation of receptor clustering, activation and migration. In this study, we investigated the inhibitory effects of CD99-derived peptidomimetics on EGFR signaling in breast cancer cells and its underlying mechanism. Treatment of MCF-7 cells with CD99-derived peptidomimetics suppressed EGF-mediated clusering and nuclear translocation of EGFR. It abrogated the formation of EGFR-Grb2 and Gab1-SHP2 complex. In addition, it obstructed EGF-mediated ERK1/2 and Akt1 phosphorylation. Interestingly, these inhibitory effects of CD99-derived peptidommetics on EGFR signaling pathway were attenuated by inhibition of SHP2 or ERK activity. Also, It could be blocked

by specific inhibitors of actin filament polymerization (e.g. cytochalasin D). Taken together, these results suggest that CD99-derived peptidomimetics may prevent EGFR signaling pathway through SHP2-ERK pathway-mediated actin cytoskeleton remodeling. Thus, the CD99-derived peptidomimetics might be useful for preventing EGF-mediated tumor cell growth in patients with breast cancer.

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MED30 regulates proliferation and motility of gastric cancer cells

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MED30 is an essential member of the mediator complex, which forms the hub between transcriptional activators and RNA polymerase II. Its expression and roles in cancer have been poorly characterized. In this study, we aim to examine functional roles of MED30 in gastric cancer progression. We found that the MED30 was overexpressed in both gastric cancer patients' tissues and gastric cancer cell lines. MED30 overexpression increased proliferation, migration, and invasion of gastric cancer cells. In contrast, MED30 knock-down exhibited opposite effects. We also found that MED30 overexpression regulated expression of genes related with epithelial-mesenchymal transition (EMT) and induced fibroblast-like morphology. In summary, MED30 has pathophysiological roles in proliferation, migration, and invasion of gastric cancer cells, suggesting that it could be a potent therapeutic target in malignant gastric carcinoma.

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The effect of high glucose levels on the hypermethylation of the protein phosphatase 1 regulatory subunit 3C(PPP1R3C) gene in colorectal cancer

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DNA methylation is an epigenetic event that occurs frequently in colorectal cancer (CRC). Increased glucose level is a strong risk factor for CRC. Protein phosphatase 1 regulatory subunit 3C (PPP1R3C) modulates glycogen metabolism, particularly glycogen synthesis. The aim of this study was to investigate the effect of high glucose levels on the DNA methylation of PPP1R3C in CRC. PPP1R3C was significantly hypermethylated in CRC tissues (76/105, 72.38%, $p<0.05$) and colon cancer celllines($p<0.05$). CRC tissues obtained from the patients with high glucose levels showed that the methylation of PPP1R3C was lower than in patients who had normal levels of glucose. When DLD-1 cells were cultured under conditions of high glucose, the methylation of PPP1R3C was repressed. The expression of PPP1R3C was inversely related to methylation status. In addition, a promoter luciferase assay showed that the transcriptional activity of PPP1R3C was increased in high glucose culture conditions. The number of cells decreased when PPP1R3C was silenced in DLD-1 cells. These results suggest that PPP1R3C, a novel hypermethylated gene in CRC, may play a critical role in cancer cell growth in associated with glucose levels.

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P71

Telomere shortening and TERT promoter mutation in colorectal precancerous lesions and colorectal cancers

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Telomere length and the mutation in the promoter region of telomerase reverse transcriptase (TERT) have been focused in various cancers. In present study, genetic status of TERT gene and telomere length were investigated in colorectal cancers (CRCs) and their precursor lesions, comprising of tubular adenomas (TAs) and serrated polyps (SPs). Other important molecular markers in CRCs including MSI, KRAS and BRAF mutations were also studied in the selesions. TERT promoter mutation was not found TERT in CRCs and SPs, however it was found in 9.4% (6/64) of TAs. Telomere length was 1.59 ± 1.57, 1.18 ± 0.94 and 1.37 ± 1.13 in CRCs, TAs and SPs, respectively, and it did not have any significant difference. TERT expression level was 0.96 ± 0.50, 0.93 ± 0.78, and 0.78 ± 0.34 in CRCs, TAs and SPs, respectively. It also had no statistical significance. In TAs, telomere shortening was associated with KRAS mutation. In CRCs, telomere shortening and TERT expression had significant association with aggressive characteristics, however, they did not have prognostic value. These data demonstrated that TERT promoter mutation may be an early event in the sequence of tubular adenoma-carcinoma and suggested a potential role for prognostic factor in colorectal carcinogenesis for the first time.

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TERT promoter mutation in gastric cancer: novel mutations and good prognosis?

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The mutation in the promoter region of telomerase reverse transcriptase (TERT) has been focused in various cancers. In present study, the frequency and clinical characteristics of TERT promoter mutation in gastric cancers were studied. We sequenced TERT promoter in 96 gastric cancers. TERT promoter mutation was found in 12.5% (12/96) of gastric cancers. The mutation was found in novel regions more than hot spots regions (-146C>T and -124C>T). It was not associated with clinicopathological characteristics except for gender, highly correlated with female. Surprisingly, the patients with mutations tended to show longer survival result (p = 0.079). These data demonstrated a frequent occurrence of TERT promoter mutation which might have a potential role for prognostic factor in gastric cancers, and it was suggested for the first time.

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P73

Multicellular tumor spheroid model using a calcium-free agarose-collagen-alginate composite hydrogel matrix with enhanced transparency

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It is becoming definitely apparent that monolayer cultures of tumor cells cannot completely represent the characteristics of three-dimensional solid tumors. In this study, we developed a 3D multicellular spheroid tumor model of human ovarian cancer cells and mouse lymphoma cells as an in vivo mimetic tumor model using an agarose-collagen-alginate (ACA). The ACA hydrogel was found

to be compatible for growth of ovarian cancer cells and lymphoma cells. In addition, the ACA hydrogel exhibited an excellent spheroid-forming ability and promoted cell proliferation. In particular, the ACA hydrogel displayed an enhanced transparency, indicating that this hydrogel can potentially be used for the morphological study of cell cultures without using any cell tracking chemicals. Taken together, our unique biophysically crosslinked ACA hydrogel may provide a novel platform to develop functional, biocompatible, and cost-effective scaffolds for 3D culture of various tumor cells including ovarian cancer and lymphoma.

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P74

Constructionand characterization of an agarose/collagen/alginate composite hydrogel matrix for 3D cell culture

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Three dimensional (3D) cell spheroids are a major model of 3D cell culture, thereby attracting increasing attention. Alginate-based hydrogels are extensively used for generation of 3D cell spheroids. However, Ca^{2+}, which acts as ac onventional crosslinker for the preparation of alginate hydrogels, often has toxic effects on various cells. Specifically, we also found that Ca^{2+} exhibits significant cytotoxicity. To circumvent this serious problem, we aimed to fabricate a physically crosslinked hydrogel, an agarose/collagen/alginate (ACA) composite hydrogel, using agarose for use in 3D cell cultures. The physical characteristics of hydrogel were assessed by scanning electron microscope (SEM) analysis, swelling test and Fourier transform infrared spectroscopy (FTIR) analysis. The results of our FTIR analysis of the ACA hydrogels did not yield any new bond between the two polymers, indicating that calcium-free or chemical crosslinker-free scaffolds were successfully constructed. The water absorption profiles of AmCA hydrogels were very similar to the standard hydrogel absorption capacity. Furthermore, the SEM images of ACA hydrogel exhibited distinct, ordered pore s with a high degree of interconnectivity. Importantly, well-formed spheroids of mouse thymic epithelial cells, mouse lymphoma cells and human ovarian cancer cells were generated in the ACA hydrogel matrix, indicating that the pores present in the ACA hydrogels provide the required space for the cells to grow them as in vitro 3D culture models for various cell types. Taken together, this biophysical cross-linking approach for the preparation of alginate-based hydrogels may provide a novel platform technology to develop cytocompatible scaffolds for 3D culture of various normal and cancer cells.

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Encapsulated 3D culture of mouse thymic epithelial cells using a physically cross-linked hydrogel

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Cells grow in three-dimensional (3D) microenvironment in the body. Biomedical researchers have increasingly realized that the limitations of conventional 2D cell culture where most cell studies have been conducted. Thereby, the importance of 3D cell culture is attracting increasing attention since 3D cell culture can provide a more realistic microenvironment where the functional properties of cells can be observed and manipulated. In this study, we developed a 3D multicellular spheroid model of mouse thymic epithelial cells (TECs) using an agarose-collagen-alginate (ACA) hydrogel system. The ACA hydrogel exhibited an excellent spheroid-forming ability and promoted cellular activity. In addition, confocal microscopy of TECs cultured for 7 days in ACA hydrogels showed well-developed actin cytoskeletons and the cell adhesion morphology. The spheroids were uniformly distributed in 3D throughout the entire region of the gel, indicating that ACA hydrogels provide favorable microenvironments for the 3D culture of TECs. Furthermore, we observed

an upregulated expression of thymopoietic genes such as ICAM-1, GM-CSF and TARC in the 3D culture compared to 2D. Taken together, our data demonstrate that the ACA hydrogel can be a useful 3D culture matrix for TECs.

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The function of GPX3 as a putative biomarker for lung cancer in cell proliferation and migration

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Lung cancer is the leading cause of cancer death in men and women in the world, and is among the deadliest cancers with a 5-year survival rate of 15%. The high mortality caused by lung cancer is attributable to a late-stage diagnosis and the lack of effective treatments. This study is to discover, using proteomic analysis, the new biomarkers to detect lung cancer at an early stage. Proteins were pooled separately from both lung tumor and its adjacent normal tissue of 8 non-small cell lung cancer (NSCLC) patients. The two pooled samples were analyzed with a proteomic technology of stable-isotope labeling using TMT, followed by UPLC_LTQ/Orbitrap mass spectrometry. Then, proteins which were expressed more than two folds-increased or decreased between the two pools were selected. We identified 12 increased proteins and 229 reduced proteins in lung tumor vs. its adjacent normal tissue. Of them, we found that a potential biomarker or glutathione peroxidase 3 (GPx3) was produced at lung and secreted into blood (which is contrasted to the fact that the majority of the current serum biomarkers are originated from liver but not from the cancer tissue itself). ELISA was used to individually determine the serum levels of GPx3 in 30 healthy people and 60 NSCLC patients (30 adenocarcinoma and 30 squamous cell carcinoma). The levels of GPx3 were found to be significantly lower in lung cancer patients than in healthy controls ($p < 0.01$). Based on above data, we investigated GPX3 expression levels in six of lung cancer cell lines (H460, H157, A549, H1650, H1299, H1975) and positive control 293T cells. GPX3 mRNA and protein in H460 and H157 were strong expressed, compared with its expression in H1299, A549 and H1650. To explore the function of GPX3 in lung cancer cells, we performed the proliferation assay and migration assay. Cell proliferation and migration in GPX3-downregulated H460 cells by GPX3 shRNA were increased; however, those of GPX3-overexpressed H1299 by GPX3 SECIS vector were reduced. Therefore, GPX3 may role of a putative tumor suppressor and be useful of early diagnosis in lung cancer.

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P77

Effects of light therapy on functional recovery after photothrombotic stroke in mice

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Objective: The effects of low level light irradiation on brain neuronal cell protection after stroke have been presented recently. In the last few years this therapy has been extended for the improvement of more severe conditions such as stroke, myocardial infarctions, neurodegenerative disorders and traumatic brain injury. This study was designed to examine the effects of Low-level light therapy(LLLT) on neuronal protection and motor recovery correlating with cellular response in photothrombosis induced neuronal injury in the sensorimotor cortex. **Methods:** We investigated the neuroprotective effects of LLLT against ischemic brain injury in mice by photothrombosis model and its underlying mechanism in molecular studies. C57 mice(7 weeks old) were assigned to the two experimental groups(Pre-LLLT, Post-LLLT or each no LLLT treated control groups) and photothrombosis was induced in the sensorimotor cortex. We evaluate the behavior function test with rotarod, wire grip, corner, cyliner test and infarct volume. Also the extent of brain

damage was determined by histological evaluation of apoptotic cell death and inflammation in ischemic brain. **Results:** There was a significantly decreased in cortical infarct volume and apoptotic cell death in both Pre-LLLT and Post-LLLT groups compared to each no LLLT treated injury groups (Sham-operated group). Consistent with the infarct volume, Pre-LLLT and post-LLLT significantly improved neurological and sensorimotor function. In molecular studies, the proportion of apoptotic cells, astrocyte and microglia in sensorimotor cortex were markedly decreased in both LLLT groups compared to each sham-operated groups. Quantitative PCR data showed that inflammation mediators (iNOS, Cox-2 and IL-1β)were significantly decreased in LLLT group. **Conclusion:** The data suggest that a noninvasive intervention of LLLT in focal cerebral ischemic injury may provide a significant functional benefit with an underlying mechanism possibly being reduction of apoptotic cell death and neuroinflammation.

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P78

AMP-activated protein kinase is involved in irisin-induced glucose uptake in skeletal muscle cells

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Irisin is a novel adipocytokine produced by adipose tissue, skeletal muscle, and the liver. However, its metabolic role is poorly understood. In the present study, irisin induced glucose uptake in differentiated skeletal muscle cells. It increased AMP-activated protein kinase (AMPK) phosphorylation, and the inhibition of AMPK blocked glucose uptake. It also increased ROS generation, which was blocked by NAC treatment irisin-induced AMPK phosphorylation. Moreover, irisin activated p38 mitogen-activated protein kinase (MAPK) in an AMPK-dependent manner. The inhibition and knockdown of p38 MAPK blocked irisin-induced glucose uptake. A colorimetric absorbance assay showed that irisin induced the translocation of GLUT4 to the plasma membrane, and that this effect was suppressed in cells pre-treated with a p38 MAPK inhibitor or p38 MAPK siRNA. In primary cultured myoblast cells, irisin increased AMPK phosphorylation and induced glucose uptake in an AMPK-dependent manner, implying that irisin has physiological relevance in vivo. Irisin increased the concentration of intracellular calcium in differentiated primary myoblast. Inhibition of calcium with CaMKK inhibitor blocked irisin-induced AMPK phosphorylation. Our results suggest that irisin plays an important role in glucose metabolism via the ROS/calcium-mediated AMPK pathway in skeletal muscle cells.

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Overexpression of NRG1 promotes progression of gastric cancer by regulating the self-renewal of cancer stem cells

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Gastric cancer stem cells (GCSCs) have been successfully isolated from patients. However, the molecular mechanisms underlying the self-renewal of GCSCs and their relationship with the microenvironment are poorly characterized. GCSCs and cancer-associated fibroblasts (CAFs) were cultured directly from gastric cancer patients. The self-renewal of GCSCs was assayed by sphere formation assay and in vivo tumorigenicity. Expression of neuregulin1 (NRG1) was examined by immunohistochemistry and real- time PCR. CAFs increased the self-renewal of GCSCs by secreting NRG1. NRG1 activated NF-κB signaling and this activation regulated the self-renewal. Moreover, NF-κB-active GCSCs were tumorigenic however NF-κB-inactive GCSCs were not. The overexpression of NRG1 in stromal cells and cancer cells was observed in the tumor tissues of gastric cancer patients and was associated with clinical stage, lymph node metastasis, and survival in gastric cancer patients. In addition, we also found that NRG1 can regulate the proliferation and invasion of gastric cancer cells. These results indicate that NRG1, which can be secreted by CAFs or cancer cells, promotes progression of gastric cancer by regulating the self-renewal of GCSCs and its overexpres-

sion is associated with prognosis of gastric cancer patients.

Keywords: NRG1; gastric cancer stem cells; cancer-associated fibroblasts

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P80

AMPKα2 translocates into the nucleus and interacts with hnRNP H: implications in metformin-mediated glucose uptake

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Adenosine monophosphate (AMP)-activated protein kinase (AMPK) is a cytoplasmic protein that plays a critical role in the maintenance of energy homeostasis. However, its role in the nucleus is still largely unknown. Here, we showed that AMPKα2 translocated into the nucleus during muscle differentiation. We also showed that upon treatment with 5-aminoimidazole-4-carboxy-amide-1-D-ribofuranoside (AICAR), an AMPK activator, AMPK rapidly translocated into the nucleus in rat myoblast L6 cells. On the other hand, the AMPKα2 phosphorylation-defective mutant did not translocate into the nucleus. Knockdown of AMPKα2 suppressed the differentiation-induced expression of myogenin, a differentiation marker. A physiological AMPK activator, metformin, also induced the translocation of AMPKα2 into the nucleus. Both inhibition and knockdown of AMPKα2 suppressed metformin-mediated glucose uptake. In addition, AMPKα2 was shown to directly interact with the heterogeneous nuclear ribonucleoprotein H (hnRNP H). AICAR treatment increased the phosphorylation of hnRNP H. Metformin increased the interaction between AMPKα2 and hnRNP H in the nucleus. Knockdown of hnRNP H blocked metformin-induced glucose uptake. In summary, these results demonstrate that AMPKα2 translocates into the nucleus via phosphorylation, AMPKα2 interacts with and phosphorylates hnRNP H in the nucleus, and such a protein-protein interaction modulates metformin-mediated glucose uptake.

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Anti-inflammatory effect of cysteamine in experimental autoimmune uveitis via down-regulation of IL-22 production

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Cysteamine modulates intracellular enzymatic activities involved in inflammation. In this study, we investigated the anti-inflammatory effects of cysteamine on experimental autoimmune uveitis (EAU) in mice. EAU was induced in female C57BL/6 wild-type mice by a footpad injection of human $IRBP_{1-20}$(250μg/mouse) emulsified in complete Freud's adjuvant (CFA). From one day before the IRBP inoculation, cysteamine was daily administered by intraperitoneal injection. Control group received the same amount of vehicle only. After 1 week, the draining lymph nodes were collected, and T lymphocytes were analyzed for cytokine assay by intracellular staining. In addition, when IRBP was rechallenged in vitro in splenocytes of IRBP-induced EAU mice treated with cysteamine, production of IL-22 was reduced. Both clinical and histological examinations showed that ocular inflammation was significantly delayed and decreased in cysteamine-treated mice compared to untreated mice. The amelioration of EAU in cysteamine-treated mice correlated with decreased level of IL-17-positive $CD4^+$TcellsandIL-22Rα. The level of IL-22 was much higher in supernatant from cultured splenocytes in IRBP-induced EAU mice than in control mice and that was much lower in cysteamine-treated mice than in non-treated mice. IRBP treatment was able to stimulate the expression of IL-22Rα. But, cysteamine down-regulated the IL-22Rα expression in vivo and in vitro. We demonstrated that IL-22 can play a key role in the development of EAU. The results also show that cysteamine has an anti-inflammatory effect in EAU which may be associated with the decreased

expression of Th17 cytokines and IL-22. This finding suggests that cysteamine has a beneficial effect for the control of endogenous ocular inflammatory diseases.

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α-Enolase stimulates the cancer cell proliferation via TGF-β production

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It has been recently reported that α-enolase (ENO1) is involved in multiple functions such as glycolysis, cancer metastasis and tumor growth. ENO1 is ubiquitously is expressed both in the cytosol and on the cell surface in cancer. However, it remains to be elucidated the function of ENO1 expressed on cancer cells. Thus, we investigated the role of ENO1 in the various cancer cells. First, it was examined the expression of ENO1 on the cell surface in gastric carcinoma cell line, SNU16, colon cancer cell line, HCT116 and lymphoma cell line, U937. As a result, HCT116 and SNU16 slightly expressed ENO1 on their surface, and ENO1 was highly expressed on the U937 cell surface. To identify whether ENO1 is related to cancer cell proliferation or viability, we performed CCK-8 assay after ENO1 stimulation. ENO1 simulation by anti-ENO1 antibody induced the proliferation of all cancer cells. Since tumor growth factor (TGF)-β is known to regulate cellular proliferation and differentiation in cancer, the level of TGF-β was measured, and its level were increased by ENO1 stimulation. These results suggest that ENO1 on the cancer cell surface is involved in the up-regulation of TGF-β production and cell proliferation.

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P83

Morphological aspects of mitomycin C on urothelial responses in experimentally induced urethral stricture in rats

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We attempted to analyze the urothelial responses with mitomycin c (MMC) treatment following urethral injury in rats since the urothelium might play a role in the pathogenesis of urethral stricture. The male Sprague-Dawley rats were divides into 4 groups (n = 5 / ea): negative control without urethral injury; positive control without further treatment, experimental control with hyaluronic acid, and experimental with MMC after internal urethrotomy. When compared with negative control, positive control showed a significant increase in proliferation and DNA damage whereas a considerable decrease in DNA repair in the urothelium, which results in urethral stricture. Experimental control showed a significant increase in proliferation, DNA damage and DNA repair when compared with negative control. MMC showed a significant decrease in proliferation and DNA damage but a considerable increase in DNA repair when compared with positive and experimental control groups. DNA damage immediately increased after urethral injury, but DNA repair and proliferation showed a belated and upregulated expression, which suggest that MMC might induce healthy re-epithelialization without severe damage in urothelium. These data might provide the possibility of MMC as an adjuvant therapeutic for urethral stricture and also suggest the epithelial role on the process of urethral stricture following urethral injury.

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P84

Insufficiency of vitamin C induces a defect on the fetal growth and maintenance of pregnancy in *Gulo(-/-)* mice

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Developing fetus is particularly susceptible to vitamin C deficiency because rapid growth and immature antioxidant system. So, we investigated the effect of vitamin C on the fetal development using Gulo(-/-) mice. When maternal Gulo(-/-) mice was depleted of vitamin C for 2 weeks during pregnancy, the serum level was vitamin C was half of vitamin C-sufficient Gulo(-/-) mice or wild-type (WT) mice. The number and body weight of fetus was reduced, and the concentration of vitamin C in the amniotic fluid was significantly decreased in the vitamin C-insufficient Gulo(-/-) mice. Moreover, Gulo(-/-) mice showed a loose integrity, an increased expression of matrix metalloproteinase 9 (MMP-9), and a decreased vascular permeability in the placenta. Also, the production of progesterone, a hormone for maintaining pregnancy, was considerably reduced. Therefore, vitamin C insufficiency during gestation could disturb the fetal growth and maintenance of pregnancy.

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앞 · 가쪽복막뒤척추수술에 필요한 혈관 및 신경분포의 해부학적 연구

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앞 · 가쪽복막뒤척추수술(anterior and lateral retroperitoneal surgical approach)은 척추 수술 시 발생할 수 있는 합병증을 최소화하기 위한 최소침습수술(Minimal Invasive Surgery; MIS)이다. 이 수술은 투관침을 통해 작은 시야에서 해부학적 표지점을 기준으로 전체적인 구조를 파악해야하기 때문에 전문적인 해부학 지식이 요구된다. 따라서 이 연구의 목적은 앞 · 가쪽복막뒤척추수술시 손상 받을 수 있는 허리동맥과 척수신경의 해부학적 위치와 분포양상을 밝히는데 있다. 한국인 성인 시신 21구를 이용하여 42쪽(남: 20쪽, 여; 22쪽)에서 뒤배벽을 해부하였으며, 평균연령 75.2세(59–93세)이었다. 각 허리동맥이 배대동맥에서 일어나 큰허리근을 지나 척추사이구멍으로 들어가는 위치를 첫째에서 다섯째 허리뼈몸통의 아래모서리를 기준으로 위치를 관찰하였으며, 허리동맥의 일어나는 혈관의 분포양상 및 척추사이구멍에서 척수신경과의 관계를 관찰하였다. 첫째에서 셋째 허리동맥은 대부분 배대동맥에서 일어났지만, 넷째 허리동맥의 경우 23.1%가 셋째 허리동맥에서 일어났다. 다섯째 허리동맥은 속엉덩동맥에서 일어나는 경우가 81.6%가 가장 많으며, 넷째 허리동맥에서 일어나는 경우가 13.2%, 배대동맥과 온엉덩동맥에서 일어나는 경우가 각각 2.6%이었다. 각 허리동맥이 배대동맥에서 일어나는 위치를 해당 척추뼈몸통의 아래모서리를 기준으로 확인하였을 때, 첫째 허리동맥은 6.5±13.8 mm, 둘째 허리동맥은 5.8±9.6 mm 아래에서 일어났으며, 셋째 허리동맥은 2.1±10.1 mm, 넷째 허리동맥은 16.3±15.5 mm 위에서 일어났다. 그리고 다섯째 허리동맥은 10.2±24.4 mm 아래에서 일어났다. 허리동맥이 배대동맥에서 일어나 큰허리근의 앞모서리로 들어가기 전에 가로막다리의 뒤쪽을 가로질러 가는 경우가 첫째 허리동맥은 91.6%, 둘째 허리동맥은 69.0%, 셋째 허리동맥은 16.7%, 넷째 허리동맥은 2.4%에서 관찰되었다. 각 허리동맥이 척추사이구멍으로 들어가는 위치를 척추뼈몸통의 아래모서리를 기준으로 확인하였을 때, 첫째 허리동맥은 4.7±7.4 mm, 둘째 허리동맥은 4.2±8.4 mm, 셋째 허리동맥은 3.3±7.7 mm 아래로 들어갔으며, 넷째 허리동맥은 1.5±9.2 mm, 다섯째 허리동맥은 5.4±8.1 mm 위로 들어갔다. 첫째에서 넷째 허리동맥은 척수신경의 아래 뒤쪽의 척추사이구멍으로 들어가는 경우가 95.8%로 가장 많았으며 다섯째 허리동맥은 위앞쪽과 위뒤쪽으로 들어가는 경우가 각각 36.1%로 나타났다. 이러한 결과는 앞 · 가쪽복막뒤척추수술 및 복강경, 혈관내시경, 로봇수술(다빈치수술) 등을 시행할 때 허리동맥의 손상을 최소화 할 수 있도록 도움을 주는 자료가 될 것이다.

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팔꿈치굴 아래 아래팔 윗부위에서 자신경 죄임증후군과 관련된 구조들의 형태변이

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말초신경은 신경이 달리는 길 주위에 있는 해부 구조 및 병터 등에 의해 여러 부위에서 조여져서 신경압박 증상이 생길 수 있다. 이 연구는 팔꿈치굴보다 먼쪽 아래팔 부위에서 생길 수 있는 자신경 죄임증후군과 관계있는 구조들을 밝히기 위해 시도하였다. 한국성인시신 21구(남자 11구, 여자 10구, 평균나이 81.9살)의 팔 23쪽을 사용하였다. 먼저 아래팔근막을 제거하여 자쪽손목굽힘근 두 갈래를 확인하였다. 그 후 근육의 두 갈래 사이를 벌려가며 자신경과 주위 구조들의 관계를 관찰하였다. 모든 위치 계측은 안쪽위관절융기를 기준으로 수직거리로 하였다. 자쪽손목굽힘근에서 얕은손가락굽힘근이 연속적으로만 일어나는 경우가 5쪽, 연속적으로 일어난 후 먼쪽에서 떨어져서 일어나는 경우가 17쪽, 그리고 두 근육 사이에 힘살연결이 없는 경우도 한 예 있었다. 먼쪽에서 일어나는 근육다발의 개수는 1–5개 였으며, 자쪽손목굽힘근의 가쪽에서 뒤쪽까지 연결되어 있는 널힘줄에서 각각 얕고 깊게 또는 전체에 걸쳐 일어났다. 깊게 일어나거나 전체에 걸쳐 일어나는 경우 자신경과 접해 있었다. 자쪽손목굽힘근에서 얕은손가락굽힘근 이는곳 중 가장 아래 부분은 안쪽위관절융기에서 평균 64.2±17.8 mm 였다. 자쪽손목굽힘근 두 갈래를 벌렸을 때 먼저 지방과 섞여 있는 얇은 막층이 보였으며, 그 아래에서 자쪽손목굽힘근 깊은 면의 근막이 관찰되었다. 두 층의 구조는 서로 붙어있었으나 집게를 이용하여 쉽게 분리할 수 있었다. 자쪽손목굽힘근 깊은 면을 덮는 근막은 18쪽에서는 얇고 투명하여 그 아래로 지나가는 자신경이 보였지만, 5쪽에서는 불투명하였다. 이 근막의 몸쪽 부분은 자신경을 단단하게 덮고 있었지만, 먼쪽은 상대적으로 느슨하였다. 자쪽손목굽힘근 깊은 면을 덮는 근막과 함께 자신경을 가로지르는 힘줄띠가 관찰되는 경우가 3쪽 있었다. 이 중 2쪽은 자쪽손목굽힘근 위팔갈래쪽에서 비스듬히 자신경을 가로질렀고, 1쪽은 자갈래쪽에서 힘줄섬유다발이 비스듬히 내려와 위팔갈래 쪽 널힘줄과 합쳐져 이룬 쐐기모양의 틈새로 자신경이 지나갔다. 자쪽손목굽힘근 깊은 면의 근막은 얕은 및 깊은손가락굽힘근 근막과 서로 연결되어 자신경이 지나가는 굴을 형성하였으며, 굴의 아래모서리는 안쪽위관절융기에서 59.3±15.0 mm 에서 관찰되었다. 자쪽손목굽힘근 두 갈래 사이를 벌리다보면 안쪽위관절융기로부터 평균 56.2±12.2 mm 에서 힘줄이 시작되는 곳을 확인할 수 있었다. 모든 예에서 이 힘줄은 자신경이 달리는 길을 따라 신경을 덮고 있었으며, 힘줄의 폭은 시작되는 곳, 중간, 그리고 닿는 곳 바로 전에서 각각 평균 7.2±2.1 mm, 7.3±1.5 mm, 8.0±2.2 mm 였다.

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혀밑신경 및 바깥목동맥 가지와 주위 구조의 형태계측학적 연구

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혀밑신경은 뒤통수동맥이나 목빗근동맥을 감고 돈 후 바깥목동맥의 앞면을 가로지른다. 목동맥 내막제거술을 할 때 혀밑신경이 손상되는 사례와 혀밑신경이 뒤통수동맥에 압박되어 마비가 오는 경우가 보고되었다. 이 연구는 한국인 혀밑신경 및 뒤통수동맥과의 국소해부학적 관계 그리고 혀밑신경과 주위 구조와의 위치에 대한 계측자료를 마련하기 위하여 시도하였다. 재료는 한국성인시신 50구 100쪽(남: 60, 여: 40, 평균나이: 71살)을 사용하였다. 목뿔뼈 큰뿔을 지나는 수평선에서 목동맥갈림까지의 길이와 목동맥갈림에서 혀밑신경이 바깥목동맥을 가로지르는 점까지의 길이를 계측하였다. 혀밑신경이 바깥목동맥을 가로지르는 곳에서 위갑상동맥, 혀동맥, 얼굴동맥, 뒤통수동맥, 뒤귓바퀴동맥까지의 거리는 30쪽에서 계측하였다. 혀밑신경이 바깥목동맥을 가로지르는 위치는 뒤통수동맥이나 목빗근동맥이 일어나는 곳보다 아래쪽으로 지나가는 경우가 50%, 일어나는 곳과 접하는 경우가 23%, 뒤통수동맥이나 목빗근동맥이 일어나는 곳보다 위쪽으로 지나가는 경우는 21%였다. 혀밑신경이 뒤통수동맥을 감고 도는 경우는 89%였고, 목빗근동맥을 감고 도는 경우는 11%였다. 목뿔뼈 큰뿔의 수평선이 목동맥갈림보다 위쪽인 경우 이 수평선에서 목동맥갈림까지 수직길이는 평균 9.3mm였고, 아래쪽인 경우는 9.2mm였다. 목동맥갈림이 혀밑신경보다 위쪽인 경우 목동맥갈림에서 혀밑신경까지의 수직길이는 평균 4.7mm였고, 아래쪽인 경우는 10.2mm였다. 혀밑신경이 뒤통수동맥의 이는곳보다 위쪽으로 지나갈 경우 수직길이는 평균 8.5mm, 아래쪽으로 지나갈 경우도 8.5mm였다. 혀밑신경이 목빗근동맥의 이는곳보다 위쪽으로 지나가는 경우 수직길이는 평균 1.0mm였고, 아래쪽으로 지나가는 경우는 3.8mm였다. 혀밑신경이 바깥목동맥을 가로지르는 끝부분에서 위갑상동맥의 이는곳까지의 평균길이는 14.3mm였고, 얼굴동맥까지는 8.6mm, 뒤귓바퀴동맥까지는 25.6mm였다. 혀동맥의 이는곳은 혀밑신경이 바깥목동맥을 가로지르는 끝부분보다 위쪽인 경우 평균길이는 4.0mm였고, 아래쪽은 7.5mm였다. 혀동맥과 얼굴동맥의 이는곳이 바깥목동맥의 한 줄기에서 같이 일어난 경우는 29%였다.

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Effect of bortezomib on dentin-pulp complex

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The proteasome inhibitor, bortezomib, is known to induce osteoblastic differentiation in a number of cell lines, such as mesenchymal stem cells and osteoblastic precursor cells by increasing the cytosolic accumulation and nuclear translocation of b-catenin. Odontoblasts form mineralized tissues and this cell exhibit active Wnt signaling during postnatal life. To address the relationship between wnt signaling and regeneration of dentin-pulp complex, we experimentally studied the effects of bortezomib in in vitro organ cultivation of mouse upper molar at E14 and PN16, as well as in in vivo experiment of cavity preparation. The upper bilateral first molars of PN16 mice were extracted and divided into two pieces and cultured for 0, 1, 3, and 5 days using the Trowel's method, then examined the reactions of dentin-pulp complex after the treatments of Bortezomib. Expression patterns of Wnt related genes and cellular events were examined using RT-qPCR and immunohistochemistry respectively. Quantitative real time-PCR analysis detected the significant altered expression patterns of candidate genes including Tgfb3, Runx2, Snail, Slug, Axin2, Twist, Bmp2, Bmp4, Bmp7, beta-Catenin, Lef1, and Bmp6. Agarose beads, soaked by 1 μM of bortezomib, were embedded into the pulpal cavity of upper molar then sealed the cavity using glass-ionomer and resin using 8-week male mice. After, 1, 3 and 5 days, mice were sacrificed and molars were harvested for further examinations such as micro-CT, histology and immunohistochemstry. Overall, the treatment of 1 μM of bortezomib showed the morphological changes of dentin-pulp complex through alteration of Wnt signaling.

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Morphological variations of the proximal attachment between the superficial flexor muscles of forearm

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The superficial flexor muscles of forearm arise from the medial epicondyle by a common tendon and have additional attachments between the muscles. The attached points of these muscles were variable, but to the best of our knowledge there are no reports regarding their morphology. The aim of this study was to clarify the morphological variations of the proximal attachment between the superficial flexor muscles of forearm. Fifty-eight forearms of 40 Korean cadavers (25 males, 15 females, mean age 79 years) were used for this study. The vertical distance of lowest attached point between the muscles was measured from the medial epicondyle. The mean length of the forearm was 24.4±1.4 cm. The lowest attached points between the pronator teres (PT) and flexor carpi radialis (FCR), between the FCR and palmaris longus (PL), between the PL and flexor carpi ulnaris (FCU) were 9.8±2.3 cm, 8.1±1.5 cm, 6.3±2.6 cm, respectively. And those between the flexor digitorum superficialis (FDS) and FCR, or PL, or FCU were 10.5±1.6 cm, 7.8±1.9 cm, 6.9±1.6 cm, respectively. A tendinous membrane was observed between the FCR and PL in all specimens. The PL was attached to the FCU in only 13.8% of the specimens. The FCU connected with the FDS within three additional muscular bundles. The PL was absent and accessory FCU existed in one case, respectively.

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Roles of Wntless in dentin apposition and root elongation

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Wnt signaling plays an essential role in the tooth morphogenesis of the dental epithelium and mesenchyme. However, it remains unclear if Wnt ligands, produced from dental mesenchyme, are necessary for odontoblast differentiation and dentin formation. Here, we show that odontoblast-specific disruption of Wntless (Wls), a chaperon protein that regulates Wnt sorting and secretion, leads to severe defects in dentin formation and root elongation. Dentin thickness decreased remarkably and pulp chambers enlarged in the mandibular molars of OC-Cre;WlsCO/CO mice. Although the initial odontoblast differentiation was normal in the mutant, odontoblasts became cuboidal and dentin thickness was reduced. In immunohistochemistry, Wnt10a, β-catenin, type I collagen, and dentin sialoprotein were significantly down-regulated in the mutant odontoblasts. In addition, roots were short and root canals were widened. Cell proliferation was reduced in the developing root apex of mutant molars. Furthermore, Osx and β-catenin expression was remarkably decreased in mutant odontoblasts. Deletion of the Wls gene in odontoblasts inhibits odontoblast maturation and root elongation. These results indicate that Wnt ligands produced in odontoblasts are required for dentin apposition and root elongation.

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Site-specific regulation of Osterix in tooth root formation

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Bone and dentin share similar biochemical compositions and physiological properties. Dentin, a major tooth component, is formed by odontoblasts; in contrast, bone is produced by osteoblasts. Osterix (Osx), a zinc finger-containing transcription factor, has been identified as an essential regulator of osteoblast differentiation and bone formation. However, it has been difficult to establish whether Osx functions in odontoblast differentiation and dentin formation. To understand the role of Osx in dentin formation, we analyzed mice in which Osx was subjected to tissue-specific ablation under the control of either Col1a1 or OC promoter. Two independent Osx conditional knockout mice exhibited similar molar abnormalities. Although no phenotype was found in the crowns of these teeth, both mutant lines exhibited short molar roots due to impaired root elongation. Furthermore, the inter-radicular dentin in these mice showed severe hypoplastic features, which were likely caused by disruptions in odontoblast differentiation and dentin formation. These phenotypes were closely related to the temporo-spatial expression pattern of Osx during tooth development. These findings indicate that Osx is required for root formation by regulating odontoblast differentiation, maturation, and root elongation. Cumulatively, our data strongly indicate that Osx is a site-specific regulator in tooth root formation.

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Identification strategy of single copy gene OCA2 from ancient human bones

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We utilized three strategies to identify the production of the in-

tended human OCA2 region from aDNA samples: First, we checked Tms of all the real-time PCR products. We did not accept Tms deviated more than ± 2 Tms from the average Tm of reference of each polymerase. The Tm analysis is used as evidence for the specific PCR product in qPCR analysis. Second, products of incorrect size based on the agarose gel electrophoresis analysis were not included in the further analysis. Third, we checked the identity of PCR products of 46 aDNA samples with a probe-based real-time PCR. We verified the probes' capability for the differentiation of the OCA2 polymorphic alleles using DNA sequencing. The probe-based real-time PCR with the verified probes did not show any ambiguous or failed product identification in all the products. The potential PCR inhibition status of these 46 samples was evaluated based on ECFL value analysis. The ECFL values of the samples can provide information about PCR inhibition, observing their changes compared with those of reference DNAs under the same PCR conditions applied. We could estimate the degree of PCR inhibition of aDNA samples using ECFL analysis in this study. Inhibitory molecules may be polymerase type-dependent, which can be explained either by their different origins or by mutations. Therefore, we attempted to make a blend of Ex Taq HS and PicoMaxx HF according to Hedman's suggestion. However, the blended polymerases showed no significant difference in their amplification of aDNA samples compared to that of the individual DNA polymerases. The use of blended polymerases may be convenient but can also be costly.

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진료용 그림 및 활용시스템 개발

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가톨릭응용해부연구소에서는 한국보건복지정보개발원의 의뢰를 받아 환자 진료에 필요한 그림과 활용시스템을 개발하고 있다. 2007~2009년 보건의료정보표준화 사업의 세부사업으로 시작된 진료용 인체그림 제작 사업은 인체의 외형을 나타내기 위한 전신 체형 그림 31종, 머리/목 부분의 세부 그림 48종, 내부 장기 등 계통해부학 그림 56종 등 총 135종의 그림이 제작되어 배포 및 사용되고 있다. 제작된 그림은 범용 그림 파일 규격인 JPG 형식과 더불어 확대 / 축소가 자유로운 벡터 그래픽 형식(EMF)을 도입하고 있다. 사용자의 요구에 적합하게 부분 확대, 잘라내기, 수정 등 편집 작업에도 품질 저하를 최소한으로 유지할 수 있게 제작되었다. 또한 같은 부분 다른 시야의 그림에서는 그림 상호간 축척 정보를 최대한 유지하여 그림간 연동시 활용 효율성을 높이도록 제작하였다. 2013년 추가로 수행된 사업에서는 치료, 수술 등 의료행위에 대한 그림, 질환을 기록하거나 설명하기 위한 그림 205종이 추가되어 총 340종의 진료용 그림이 배포되어 사용되고 있다. 제작된 진료용 그림은 보건의료정보표준용어(KOSTOM, KOrea Standard Terminology Of Medicine, 보건복지부 고시 예정)와 연동이 가능하여 전자의무기록 등 전산 시스템에서 용어와 그림을 연결시켜 사용 가능하다. 진료용 그림은 의료계 종사자들 사이의 의사소통, 환자와 의료진사이의 소통에 효율적으로 사용될 수 있을 것으로 기대하고 있다. 또한 현재 의료기관에서 사용되고 있는 출처가 불분명한 그림을 대체하여 지적재산권 문제 발생을 방지할 수 있다. 진료용 그림은 보건의료정보표준관리시스템 홈페이지(www.hins.or.kr)에서 누구나 다운로드하여 사용할 수 있다.

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Lobar variations of the lung in human cadavers : its clinical significance

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Our present study was performed to research both lung specimens about the morphological fissures and lobes, to record the variations, to compare them with previous studies and to find their clinical significance. **Introduction:** Lobar anatomy and bronchiopulmonary segments can be appreciated better with knowledge of variations that abound in fissures of the lungs. Anatomically, amongst the pair of lungs in the thoracic cavity, the right lung has two fissures, dividing it into three lobes by an oblique and a horizontal has been called the upper, middle and lower. The left lung has one fissure, dividing it into two lobes by an oblique has been called upper and lower. **Mate-**

rials and methods: The lung of twenty-nine cadavers of both sexes [male: female ratio 22: 7], aged 40-88, were studied in the dissecting laboratory of the Det. of Anatomy, school of medicine, Kyungpook national university. The thoracic wall of properly embalmed and 10% formalin fixed cadavers was dissected and the lungs were exposed to study the morphological features including number, lobes, and fissures. Total number of specimen was examined fifty-eight. **Result:** The horizontal fissure was absent in three right-sided lungs (10.34%) and hence were absent of middle lobe, has one fissure (oblique fissure) and two lobes (upper and lower lobe). In 3 cases (10.34%) incomplete horizontal fissure could be detected, were incomplete either at its beginning or at its end or both. Amongst right specimens, were displayed an incomplete oblique fissure (3.45%). Four specimens (13.79%) were showed presence of accessory fissure. The oblique fissure was incomplete in 3.45% of left specimens and three specimens (10.34%) showed presence of accessory fissure. **Conclusion:** Segmental localization is essential knowledge for a thoracic surgeon and knowledge of accessory fissures is a great usefulness to cardiothoracic surgeon for the pre-operative planning of pulmonary lobectomy and segmental resections. Our present case of variations in the fissures might help to explain certain unusual radiological image of the lung. Considering the usefulness of these anomalies, clinicians and radiologists should have the anatomical knowledge with prior awareness of variant fissures in the lungs.

Keywords: Lobar variation, bronchopulmonary segment, accessory fissure

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Presence of melanosomes in the dermal papilla may be associated with cause of androgenetic alopecia

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Androgenetic alopecia (AGA) is highly heritable condition and the most common form of hair loss in humans. Although androgens are known to be the primary cause of AGA, the actual mechanism is not known yet. In our preliminary study, we found that melanosome-like materials were increased in the dermal pailla (DP) of the balding region compared with the non-balding region. The aim of this study was to evaluate the effect of melanosomes on DP cells and investigate the association of melanosomes in DP and the cause of AGA. To confirm the presence of melanosomes in DP of the hair follicle, Fontana-Masson's stain was performed in the human scalp tissues. After melanosomes were treated in the SVDP cells, a kind of immortalized DP cells, cell viability and β-catenin expression in the cells were evaluated. We confirm that melanosomes were increased in the DP of the balding region compared with the non-balding region. Cell viability of the SVDP cells was not different significantly after melanosomes treatment. However, β-catenin, a key molecule for hair growth, expression was decreased in the SVDP cells after melanosomes treatment. Our data suggests that presence of melanosomes in the DP may be associated with cause of AGA by reducing β-catenin activity.

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신경이식을 위한 겨드랑신경과 노신경의 형태학적 특징

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겨드랑신경(axillary nerve)의 정보는 팔신경얼기 손상(brachial plexus injury) 등의 외상으로 인해 어깨세모근(deltoid)의 기능이 저하되었을 때, 회복을 위해 노신경(radial nerve)을 신경이식(nerve transfer)하기 위하여 꼭 필요하다. 이에 본 연구진은 한국인의 겨드랑신경과 노신경의 국소해부학적 관계를 밝히고자 하였다. 성인시신(남 34, 여 15; 평균 나이 75.8 세)의 겨드랑 49쪽(오른쪽 24, 왼쪽 25)에서 겨드랑신경이 작은원근(teres minor)의 아래모서리를 지나는 곳부터 근육에 들어가는 곳까지 해부하여 겨드랑신경의 분지 양상과 크기를 조사하였고, 이를 같은 쪽의 노신경의 분지 양상과 크기를 조사하여 결과와 비교하여 분석하였다. 어깨세모근의 이는곳을 기준으로 빗장부분, 봉우리부

분, 가시부분으로 구별하여 각 부분에 분포하는 가지의 수, 각 가지가 분지하는 위치, 근육으로 들어가기까지의 거리를 계측하였다. 겨드랑신경은, 모든 경우에서 네모공간을 지나기 전에 앞가지와 뒤가지로 나뉘었다. 뒤가지는 작은원근에 분포하는 가지는 1.6(1–3)개로 항상 관찰되었고 또한 어깨세모근에 분포하는 경우도 65%였다. 작은원근에 분포하는 가지의 길이는 39mm였다. 어깨세모근의 빗장부분과 봉우리부분은 겨드랑신경의 앞가지가 항상 신경분포를 하였다. 어깨세모근의 가시부분은 앞가지와 뒤가지가 함께 분포하는 경우가 50%이고, 앞가지만 분포하는 경우는 35%, 뒤가지만 분포하는 경우는 15%였다. 가시부분으로 향하는 가지의 개수는 2(1–4) 개이고, 지름은 1.2mm이다. 봉우리부분과 빗장부분에 분포하는 가지의 개수는 각각 4.6(2–9) 개와 4.5(1–8)개이다. 가지가 분지되어 근육으로 들어가기까지의 길이는 가시부분(40.0mm)에서 빗장부분(9.5mm)으로 갈수록 짧아졌다. 겨드랑신경이 어깨세모근으로 들어가는 위치는 근육 길이의 28.2–46.3 백분위 지점이었으며, 봉우리 끝점으로부터 아래로 평균 57.1 mm였다. 노신경은 위팔세갈래근에 각 부분에 분포하였는데 가쪽갈래, 긴갈래, 안쪽갈래, 그리고 가쪽갈래와 안쪽갈래로 함께 가는 가지로 나뉘어졌다. 위팔세갈래근으로 가는 4개의 가지가 다 있는 경우는 61.2%로 가장 많았고, 가쪽갈래와 안쪽갈래로 가는 가지가 없는 경우, 안쪽갈래로 가는 가지가 없는 경우, 가쪽갈래로 가는 가지가 없는 경우는 각각 26.5, 8.2, 4.1%였다. 큰원근(teres major)의 아래모서리에서 나와 근육으로 들어가는 갈래가 나뉘어 지기 전까지의 신경의 길이는 긴갈래로 가는 가지가 가장 짧았고(19.5mm) 안쪽갈래로 가는 가지가 가장 길었다(51.20mm). 신경의 굵기는 안쪽갈래와 가쪽갈래로 함께 가는 것이 가장 굵었고(1.67mm) 안쪽갈래로 가는 가지가 얇았다(1.36mm). 신경개수는 긴갈래로 가는 가지가 가장 많았고(2.10mm)것이 가쪽갈래와 안쪽갈래로 함께 가는 가지가 적었다(0.78). 작은원근의 아래모서리와 큰원근의 아래모서리의 길이가 평균 37.6 mm이기 때문에 신경이식을 하기 위해서는 이것보다는 길어야 한다. 따라서 긴갈래로 가는 가지보다는 안쪽갈래와 가쪽갈래로 함께 가는 가지를 쓰는 것이 낫고 만약 안쪽갈래와 가쪽갈래로 함께 가는 가지가 없을 때는 가쪽으로 가는 가지를 쓰는 것이 좋을 것이다. 겨드랑신경과 노신경 가지의 굵기 및 길이는 수술성공에 중요한 요인이 되기 때문에 이를 참고 한다면 신경이식의 성공률을 높이는 데에 도움이 될 것이다.

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3차원 얼굴스캔 이미지와 해부학적 얼굴표지점 좌표분석을 이용한 개인식별 방법 연구

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연구배경: CCTV 등 영상감시기기 사용의 보편화로 사건현장에서 촬영된 범인의 얼굴을 이용하여 용의자를 특정해야 하는 감정 사례가 급증하고 있다. 하지만 우리나라에서 설치 · 운영되는 다수의 CCTV는 얼굴 식별에 사용하기에는 화질이 낮아 감정에 적용하는 데에 많은 문제를 야기하고 있다. 이를 극복하고자 해부학적 얼굴표지점과 3차원 스캐너나 모형제작 프로그램 등 3차원 이미지 분석기기를 이용한 일대일(1 : 1) 얼굴이미지 분석과 개인식별 방법 개발의 필요성이 대두되고 있다. **연구목표:** 3차원 얼굴스캔 이미지와 해부학적 얼굴표지점 분석을 이용한 개인식별 방법을 개발하고 그 유용성을 시험해 보고자 하였다. 개인식별의 기본이 되는 동일인 특정 분석을 위한 객관적 · 정량적 기준으로 주요 해부학적 얼굴표지점 좌표를 이용하고 동일인에서 얻은 각기 다른 화질과 각도의 얼굴이미지를 연구에 사용하였다. 최종적으로 3차원 얼굴이미지와 해부학적 얼굴표지점 좌표를 이용한 개인식별 실무작업에 적용할 수 있는 분석방법과 절차를 마련하는 것을 목표로 하였다. **재료와 방법:** 20명의 한국인 성인 남성에게서 얻은 3차원 얼굴스캔 이미지에 주요 해부학적 얼굴표지점을 위치시키고 이를 다른 얼굴이미지와 비교 시 기준으로 사용하였다. 기준과 대조할 비교이미지는 동일인의 3차원 얼굴스캔 이미지를 다양한 각도와 세 종류 화질의 2차원 사진 이미지로 변환하여 적용하였다. 해부학적 얼굴표지점의 위치는 10명의 치과교정전문의가 시행하였다. 마지막으로 표지점이 위치된 기준얼굴이미지와 비교얼굴이미지를 중첩하여 두 얼굴이미지의 공통 얼굴표지점 간의 거리 차이를 측정하여 통계적 분석을 통해서 동일인 특정을 위한 기준치를 확보하고자 하였다. 결과 및 **고찰:** 기준얼굴이미지와 비교얼굴이미지 사이의 공통표지점 간 거리분석을 통하여 동일인특정에 보다 유용한 해부학적 얼굴표지점을 알아낼 수 있었고 다른 표지점들 또한 통계분석을 통해서 그 편차를 확인할 수 있었다. 향후 실제 감시영상장비에서 얻은 이미지를 적용한 추가 연구가 필요하지만, 본 연구 결과를 토대로 영상물을 이용한 실제 얼굴특정 작업의 표준화된 기준과 절차 확립에 기여하고 분석결과의 정확성을 높여 수사의 효율과 신뢰도를 높일 수 있을 것으로 기대된다. 또한 이 결과는 향후 영

상을 바탕으로 한 개인식별 작업의 디지털 · 자동화 연구와 기법 개발의 기초자료로 활용 가능하고 관련 연구를 주도 할 수 있는 토대를 마련할 수 있을 것으로 사료된다.

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해부학 수업에서 학생들의 이해를 돕는 키노트 기능 두 가지

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전통적으로 가장 많이 사용되는 교육방법은 강의식 방법이다. 단시간에 다양한 지식과 내용을 학습자에게 전달할 수 있는 등의 장점으로 인하여 강의식 방법을 선호하지만 추상적인 개념 전달에는 한계가 있다. 이러한 한계점을 보완하기 위해 수업교재, 동영상자료 등 다양한 수업방법 등을 사용하고 있지만 이 중 가장 많이 사용되는 방법은 PPT(파워포인트)이다. PPT를 사용하는 것은 교재의 내용을 전달하거나 동영상을 구동하는 등 다른 수업방법들을 통합하여 제공할 수 있기 때문이다. 이러한 프레젠테이션 프로그램을 운영하는 컴퓨터 운영체계는 크게 Window OS와 Mac OS으로 나뉜다. Window OS에서는 PPT, Mac OS에서는 Keynote(키노트)이다. 일반적으로 PPT는 범용성이나 확장성, 자동화에서 강점이 있고, Keynote는 디자인이나 사용자 중심의 편의성에서 강점을 가진다. 그림이나 사진 등을 사실적으로 설명해야 하는 해부학 강의 특성을 반영하여 보다 효과적으로 전달하기 위한 키노트 기능 중 두가지를 소개하고자 한다. 첫번째는 매직무브(magic move) 기능이다. 이 기능은 그림을 쉽게 zoom in?out(단순한 확대가 아닌 동적인 확대와 축소를 의미)을 구현해 준다. 하나의 그림을 정적 상태로 설명하기 보다는 구조물에 대한 동적인 접근을 함으로서 교육효과를 높일 수 있다.

두번째는 애니메이션(animation) 기능이다. 해부학적 구조를 알려주면서 스크린에 레이저빔을 사용하여 해당 부위를 가르키는 것보다 구체적인 영역을 애니메이션으로 표시하여 설명한다면 학생들이 구조물을 정확하게 이해하는데 도움이 될 것이다. 애니메이션 기능은 PPT에서도 가능하지만, 키노트는 사용자가 쉽게 만들어서 구현할 수 있다는 강점도 있다.

해부학구조물을 처음 접하는 학생들에게 정확하고 섬세하게 사람의 구조를 이해시키는 일은 해부학수업에서 매우 중요하다. 이를 수행하는데 있어서 키노트의 매직무브와 애니메이션 기능은 매우 유용하고, 또한 사용자들도 이를 쉽게 제작할 수 있다.

아이폰이나 아이패드에서도 키노트가 구동된다. 따라서 Mac 컴퓨터 없이도 키노트를 구현할 수 있다.

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Thickness of the cervical dura mater in the human cadavers

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The thickness of the human spine dural sac can show differences between individuals and levels, and these differences may affect clinical outcomes. Therefore it needs to analyze dural thickness of the cervical spinal cord. We performed anatomical study of human cadavers. The subjects of this study were nine human cadavers with no prior history of spinal surgery or deformity. Seventeen specimens from C1 to C7 vertebra were obtained from each of nine cadavers. Microscopic measurements were taken with an infrared laser-based confocal microscope to determine the mean dural sac thickness at each level. Relations of dural sac thicknesses at different levels were analyzed with respect to gender, age and cervical vertebral level. Overall mean dural sac thickness was 379.299×10-3mm in this human cadaver series. There existed significant differences of thickness between anterior and posterior parts ($P<0.0001$). And, significant differences were found between dural sac thicknesses at each different levels ($P=0.0199$). Posterior dural thickness was the highest at C1 and lowest at C5/6, these were also significantly different at the axial, subaxial, and lower cervical levels, where as anterior dural thickness was similar among levels. Overall, a significant correlation was found between dural thickness and age ($P=0.287$). However, the mean dural thickness of men and women were not significantly different ($P=0.347$). This study identifies anatomical differences in the cervical dural sac thickness with respect to spinal level and age. These results provide useful physiological information of the dural sac.

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P100

Anti-neuroinflammatory effects of new herbal formula PMC-12 on amyloid β-induced cognitive deficits

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PMC-12, a new Korean medicinal formulation, is a mixture of four herbal medicines, consisting of Polygonum multiflorum, Rehmannia glutinosa, Polygala tenuifolia, and Acorus gramineus, which have been reported to have various pharmacological effects on age-related neurological disease. Alzheimer's disease (AD), which is characterized by progressive cognitive impairment, is the most common neurodegenerative disease. In the present study, we investigated whether PMC-12 treatment improves cognitive deficits associated with decreased neuroinflammation on amyloid-β-induced mice model and the anti-neuroinflammatory peoperties of PMC-12 in lipopolysaccharide (LPS)-stimulated murine BV2 microglia. Intracerebroventricular injection of Aβ25-35 in C57BL/6 mice resulted in a significantly increased escape latency time and swimming distance in the target quadrant compared to control group, whereas oral administration of PMC-12 (100 and 500mg/kg) for 4 weeks significantly reduced escape latency time and swimming distance dose-dependent manner compared to vehicle. In addtion, PMC-12 reduced Aβ-induced increases of Aβ, Iba-1 and GFAP imuunoreactivity. Quantitative PCR data showed that inflammation mediators (iNOS, COX-2, IL-1β, IL-6, TLR-2 and TLR-4)were significantly decreased by administration of PMC-12inAβ-injected brain. Consistent with in vivo data, PMC-12 significantly reduced the inflammatory mediators, including iNOS, COX-2, IL-1β and IL-6 in LPS-stimulated BV2 cells without cell toxicity. Moreover, PMC-12 exhibited anti-inflammatory properties by down-regulation of extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK) pathways. These finding suggest that PMC-12 may offer substantial therapeutic potential for the treatment of AD that are accompanied by decreased neuroinflammation.

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Anti-neuroinflammatory effects of Probucol in LPS-induced BV2 microglia cells and focal cerebral ischemic mice

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Probocol, a lipid-lowering agent with anti-oxidant properties, has been implicated in protection against atherosclerosis, whereas its anti-neuroinflammatory effects on ischemic brain injury has not been fully elucidated. In the present study, we investigated the anti-neuroinflammatory properties of Probucol in lipopopolysaccharide (LPS)-induced murine BV2 microglia and its beneficial effects on focal cerebral ischemia in C57BL/6J and hyperlipidemic mice. To determine whether Probucol improved the tissue outcome after focal cerebral ischemia, C57BL/6J mice received 1 h of middle cerebral artery occlusion (MCAO) followed by 23 h of reperfusion. Probucol administered orally (3, 10, and 30 mg/kg) for 4 days before arterial occlusion significantly decreased the cerebral infarct volume in a concentration-dependent manner. To examine the anti-neuroinflammatory effects of Probucol on focal cerebral ischemia, we assessed iNOS, COX-2, TLR-2, and TLR-4 mRNA levels in the ischemic brain. iNOS, COX-2, TLR-2, and TLR-4 mRNA levels were significantly decreased by the treatment of Probucol in the ischemic brain. Moreover, Probucol exhibited the down-regulation of AKT and JNK phosphorylation in focal cerebral ischemic brain. Finally,

we examined the beneficial effects of Probucol on ischemia stroke with hyperlipidemia. MCAO resulted in significantly larger infarct volumes in ApoE KO provided with high-fat diet compared to ApoE KO fed a regular diet, which was significantly reduced by Probucol. Consistent with a small infarct size, Probucol improved neurological and motor function. Taken together, Probucol inhibits LPS-induced production of pro-inflammatory mediators and prevents cerebral ischemic damage, suggested that Procucol may have therapeutic potential for prevention and treatment if ischemic stroke accompanied by microglia activation.

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Inhibition of a-syn secretion by Rab11 overexpression in SH-SY5Y cells

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Parkinson's disease (PD) is a progressive neurodegenerative movement disorder. The motor symptoms of PD result from the death of dopaminergic neurons in the substantia nigra. The symptoms are tremor, rigidity, bradykinesia. Accumulation of misfolded alpha-synuclein (a-syn) into Lewy bodies (LBs) and Lewy neurites (LNs) is a major neuropathological feature of PD. Recent studies showed that a-syn can be secreted and transmitted to cell to cell, play a role in propagation and spreading of pathology. To understand the trafficking and spreading of a-syn in cells, we decided to look at the involvement of rab family proteins. Rabs are small GTPase peripheral membrane proteins involved in the vesicular trafficking and membrane fusion. We prepared recombinant adenoviral vectors of Rabs (Rab5, 7, 9, 11) WT and dominant negative forms and compared their effect on a-syn transmission and trafficking. Rab11, a Rab protein known to be involved in recycling of endosomes, was shown to increase a-syn secretion and transmission upon inactivation by dominant negative form of Rab11. Overexpression of WT Rab11 decreased the aggregation and secretion of a-syn. These results suggest that the a-syn trafficking and exocytosis may be inhibited by recycling endosome pathway and inhibition of recycling may trigger the yet unknown a-syn secretory pathway.

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Increased COX-2 and NF-κB/p65 expression in the mouse hippocampus after systemic administration of Tetanus toxin

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In the present study, we observed changes in the immunoreactivities and protein levels of cyclooxygenase-2 (COX-2) and nuclear transcription factor kappa-B (NF-κB/p65) in the mouse hippocampus proper (HP, CA1-3 regions) and dentate gyrus (DG) after systemic treatment of 100 ng/kg of tetanus toxin (TeT), an exotoxin. Any neuronal damage or loss in any subregions of the hippocampus was not found after TeT. We found that, in the control-group, moderate COX-2 immunoreactivity was shown in the stratum pyramidal (SP) of the CA2-3 region and hardly found in the CA1 region and DG. COX-2 immunoreactivity was increased in the SP and granule cell layer (GCL) of the DG with time after TeT treatment. At 24 h post-treatment, COX-2 immunoreactivity in the SP of the CA1 region and in the GCL of the DG was strong, and COX-2 immunoreactivity in the SP of the CA2/3 region was the strongest. On the other hand, we observed that NF-κB/p65 immunoreactivity was also changed in the hippocampus after TeT treatment. NF-κB/p65 immunoreactivity was apparently increased in the SP and GCL 6, 12 and 24 h after TeT treatment. In addition, NF-κB/p65 was newly expressed in astrocytes after TeT treatment. In brief, our results in-

dicate that the increased COX-2 and NF-κB/p65 expression in the mouse hippocampus after systemic treatment of TeT may be related with inflammation in the brain induced by exotoxin.

Keywords: exotoxin, inflammatory mediator, pyramidal cells, granule cells, astrocytes

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Changes of expression pattern of glutamate, GABA, and their receptors correlated with calcium-sensing receptor in a rat model of glaucoma

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The calcium sensing receptor (CaSR) activated by extracellular calcium level is implicated in synaptic plasticity and neurotransmission in the brain. CaSR is expressed in the ganglion cell and displaced amacrine cell subpopulations in the ganglion cell layer of the retina. In our previous study, CaSR expression showed increase at 1 and 2 weeks but a little reduce at 4 and 8 weeks glaucomatous retina, compared to the normal and contralateral control retinas. The present study is aimed to examine expression pattern of major excitatory and inhibitory neurotransmitters, glutamate and GABA, and their receptors correlated with CaSR expression in an experimental glaucoma model of rat, for a better understanding on the glaucoma pathogenesis. Experimental model was made by electrical cauterization of three episcleral veins on the same side eyes of Sprague-Dawley rats aged of 8 weeks. Experimental time points were set at 1 week, 2, 4, and 8 weeks post-operation. Expression pattern and its alteration of glutamate, GABA, their receptors, and CaSR were evaluated by double immunofluorescent staining and confocal microscopy. Glutamate is expressed in the outer plexiform layer (OPL), the inner plexiform layer (IPL), and bipolar cells in the inner nuclear layer at the normal. In glaucomatous retinas, glutamate expression decreased in the IPL and increased in the outer nuclear layer along the experimental time lapse. Metabotropic glutamate receptors (mGluRs) 5 in the Mueller cells of the normal showed reduced reactivity in the glaucomatous retinas along the time lapse. On the other hand, glutamate receptor 2, 3 appeared faintly in the proximal radial processes and cell bodies of Mueller cells, but also even in the distal processes in the OPL at 4 and 8 weeks glaucomatous retina. The other kinds of iGluRs, NMDAR2B appeared in laminas 2 and 4 of the IPL and faintly in the OPL at the normal and increased moderately and gradually during glaucoma. GABA is expressed in the amacrine cells, displaced amacrine cells, and their processes in the IPL, especially laminas 2 & 4 at the normal. Along the experimental time lapse, GABA reactivity in the cell body and their processes reduced, but the radial processes of Mueller cells showed newly GABA reactivity. GABAAR1α and GABABR1 are expressed faintly in the laminas 2 & 3, and in laminas 1,2,3 and 4, respectively at the normal. During glaucoma, GABAAR1α appeared newly in the Mueller cell processes and GABABR1 showed increased reactivity in the laminas at 4 and 8 weeks glaucomatous retinas. These findings suggest that glaucomatous injury evokes the fluctuation in the extracellular calcium level in the nuclear layers, and thereby glutamate and GABA intracellular neurotransmission are abnormally deviated throughout the whole retina via altered expression of neurotransmitters and their various receptors.

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Neuroprotection and spatial memory enhancement of new formula PMC-12 in HT22 hippocampal cells and a mouse model of focal cerebral ischemia

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A new prescription was formulated using four traditional Korean

medicinal herbs (PMC-12), Polygonum multiflorum, Rehmannia glutinosa, Polygala tenuifolia, and Acorus gramineus. PMC-12 was standardized to contain 3.09% 2,3,5,4'-tetrahydroxystilbene-2-O-β-D-glucoside, 0.35% 3',6-disinapoyl sucrose, and 0.79% catalpol by HPLC analysis. In HT22 cells, pretreatment with PMC-12 resulted in significantly reduced glutamate-induced apoptotic cell death. Pretreatment with PMC-12 also resulted in suppression of ROS accumulation in connection with cellular Ca^{2+} level after exposure to glutamate. Expression levels of phosphorylated p38 mitogen-activated protein kinases (MAPK) and dephosphorylated phosphatidylinositol-3 kinase (PI3K) by glutamate exposure were recovered by pretreatment with either PMC-12 or anti-oxidant N-acetyl-L-cysteine (NAC). Expression levels of mature brain-derived neurotrophic factor (BDNF) and phosphorylated cAMP response element binding protein (CREB) were significantly enhanced by treatment with either PMC-12 or NAC. Combination treatment with PMC-12, NAC, and intracellular Ca^{2+} inhibitor BAPTA showed similar expression levels. In a mouse model of focal cerebral ischemia, we observed higher expression of mature BDNF and phosphorylation of CREB in the hippocampus and further confirmed improved spatial memory by treatment with PMC-12. Our results suggest that PMC-12 mainly exerted protective effects on hippocampal neurons through suppression of Ca^{2+}-related ROS accumulation and regulation of signaling pathways of p38 MAPK and PI3K associated with mature BDNF expression and CREB phosphorylation and subsequently enhanced spatial memory.

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P106

Protease activated receptor-1 antagonist ameliorates the clinical symptoms via stabilization of blood brain barrier in experimental autoimmune encephalomyelitis

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To evaluate whether protease activated receptor-1 (PAR-1) antagonist is a potential therapeutic target in multiple sclerosis, we treated EAE (experimental autoimmune encephalomyelitis) mice with two PAR-1 antagonists KC-A0590 and SCH-530348. Treatment with both antagonists showed significant decrease of clinical characteristics of EAE mice by suppressing demyelination and infiltration of inflammatory cells in the spinal cord and brain. Thrombin and TNF-α were significantly increased in the spinal cord and brain of EAE mice and these expressions were also reduced by treatment with both antagonists. When we analyzed vascular breakdown, profound leakage of dextran were observed in the brain of EAE mice. But PAR-1 antagonist stabilized vascular endothelial cell and reduced blood brain barrier (BBB) breakdown with neuroinflammatory response. PAR-1 antagonist also down-regulated MMP-9 expression and preserved occludin and ZO-1. Finally, we treated PAR-1 antagonists in primary cultured astrocytes to evaluate whether PAR-1 antagonists reduce thrombin-induced MMP-9. PAR-1 antagonist suppressed thrombin-induced MMP-9 secretion in the astrocytes. Collectively, our data suggest that inhibition of PAR-1 by two antagonist involve in stabilizing the BBB in EAE mice and imply a therapeutic potential for multiple sclerosis.

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P107

Effects of abnormal neurotransmissions in the hippocampus following Febrile Seizure (FS)

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Febrile seizure (FS) induced by fever is most frequent seizure type in the infant and young child, it is impacted in developmental abnormality of hippocampal neuronal circuitry and thus contributed

toward the development of temporal lobe epilepsy (TLE). Many previous investigators demonstrated that an imbalance of excitatory and inhibitory neurotransmissions was involved to wide spreading of seizure attack in the brain. Therefore, we in the present study investigated whether the expressional changes and the functional alterations of hippocampal interneuons involved to epileptogenesis following FS. In the present results, EEG and Timm's staining was shown differentially alterations depend on time courses after FS in the hippocampus. In addition, $GABA_A$-α1 and calretinin (CR) expressions in the hippocampal interneurons were significantly altered during recurrent seizure period after FS. Briefly, $GABA_A$-α1 immunoreactivity was markedly enhanced for a period of 11 - 12 weeks following FS and significantly down-regulated as compared to control groups after 13 week following FS. On the other hand, CR expression were significantly enhanced in the hippocampal interneurons of 7 - 8 weeks after FS, after that it was down-regulated more than control group in 13 week after FS. Indeed, in order to examined regarding the main cause of $GABA_A$-α1 changes in recurrent seizures after FS, we investigated the 5-bromo-2-deoxyuridine (BrdU), vesicular GABA transpoter (VGAT) and GABA transporter 1 (GAT1) expressions. At the recurrent seizure stage following FS, BrdU expression was migrated from subgranular zone to hilus of dentate gyrus (DG) and enhanced its expression, while VGAT positive GABAergic interneurons were significantly increased at DG. Moreover, GAT1 expression at the same time was elevated and an abnormality of excitatory postsynaptic potential (EPSP) also observed in the recurrent seizure period after FS. Therefore, these results in the present study revealed that time-dependent alterations of hippocampal neuronal circuit by the abnormality of interneruonal activities may involved to the imbalance of excitatory and inhibitory neurotransmission in the hippocampus following FS. Thus, it may lead to the epileptogenesis and the spreading of seizure activity in the hippocampal neuronal circuit of brain.

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P108

Distribution and effect of Phospholipase C beta-1 (PLCβ-1) immunoreactivity in the hippocampus of Mongolian gerbil following ischemic attack

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Selected neuronal cell death induced in the hippocampal CA1 pyramidal neurons following transient global ischemia and cause cognitive damages in rodents, primates, and humans. This phenomenon is known for a variety of mechanisms, including excitotoxicity, free radical stress and apoptotic. Phospholipase C (PLC) activation occurs via receptor activation coupled to a G protein. Also, PLC activation is neuronal intracellular signal transduction cascade part in an intricate. Moreover, PLC activation increases intracellular Ca2+ and may play a role in delayed neuronal death after ischemia/reperfusion. Therefore, in order to confirm the distributions of PLCβ-1 expression in the gerbil hippocampus after ischemia insult. In the present study, we investigated the time-course changes in PLCβ-1 expression in the gerbil hippocampal CA1 and DG region after ischemia /reperfusion. In sham-operated group, PLCβ-1 immunoreactivity slightly detected interneurons in the CA1 and DG regions. In the hippocampal CA1 region, PLCβ-1 expression was detected in the neuronal processes at the 24h. PLCβ-1 immunoreactivity was significantly increased interneurons at the 4day after ischemia /reperfusion. In addition, this expression was co-localized with PV-positive interneurons. On the other hand, in the hippocampal DG region, at the 24h PLCβ-1 immunoreacitivity was increased interneurons in the sub-granular cell layer. However, at the 4day after ischemia/reperfusion, the PLCβ-1 immunoreactivity enhanced interneuron in the hilar region. In addition, the PLCβ-1 expression was confirmed CR-positive intenrneuron at the 4day after ischemic insult. Thus, PLCβ-1 may play a role in the ischemia-induced neuronal cell death and the function of interneurons in the gerbil hippocampus.

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P109

Alterations of Phospholipase C (PLC) beta1 in the rat hippocampus following pilocarpine-induced status epilepticus

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Status epilepsy (SE) is characterized by without recovery and telogen of seizures and induces neuronal disorder. Pilocarpine was muscarin acetylcholin agonist, widely used as experiment for SE Phospholipase C (PLC) beta was a component of cell membrane lipids to produce a pair of second messengers, activates IP3 receptors to gather Ca^{2+} from the smooth endoplasmic reticulum(sER) For these reasons, PLC beta is important components of signal transduction processes in the brain Thus, activation of the PLC beta pathway produces important effects on cellular function, differentiation and activity Because recent studies have suggested that PLC beta1 and PLC beta4 may be associated with many kinds of seizures, we investigated whether the distributional alterations of PLC beta1 immunoreactivities in the hippocampus following pilocarpine-induced SE PLC beta1 immunoreactivities were decreased depending on time course following SE. At 5 days after SE, PLC beta1 immuoreactivity was markedly decreased in hippocampus We were confirmed NeuN and PLC beta1 double immunofluorescence for the PLC beta1 is to make sure that the normal operation after SE NeuN immunoreactivity was colocalized within PLC beta1 positive neurons and decreased as similar to PLC beta1 expression following SE We study correlation between GABAergic interneuron and PLC beta1. Parvalbumin (PV) positive neuron, one of the GABAergic interneuron, was diminished following SE At 2week after SE, PV immunoreactivity was almost disappeared in the hippocampus We study electrophysiology for confirm comparison of the neuronal function in normal state and SE state So we were recording electroencephalogram (EEG), excitatory post synaptic potential (EPSP) The electrophysiology result was dissimilar to each other situation. Therefore, these results in the present study revealed that PLC beta may change following SE and induce an abnormal neuronal function Thus we considered that PLC beta1 abnormal condition was relation SE and this situation trigger the disorder of neuronal function.

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P110

Development of parameters to determine in vivo safety of adult human neural stem cells and hTERT-immortalized neural stem cells for preclinical and clinical trials

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There has been no complete therapeutic treatment for neurodegenerative diseases such as stroke, Alzheimer's disease, Parkinson's disease, and spinal cord injury. Stem cell-based regeneration is considered as a promising option for neurodegenerative diseases. To develop stem cell-based therapy, evaluating in vitro and in vivo safety of stem cells is required for the pre-clinical and clinical efficacy of stem cell therapy. To develop reproducible and standardized in vivo safety test, tumor formation assay was conducted using three types of immunodeficient mouse models, Balb-c/nu, NOD/SCID, and NOG mouse. First of all, to develop standard method of in vivo tumorigenicity, U-87MG, which was known as highly aggressive glioblastoma cell line was injected into neonatal and adult BALB/c-nu, NOD/SCID, and NOG mice. Tumor cells were injected into mice subcutaneously (SC) or intracranially (IC). When U-87MG cells were injected into BALB/c-nu mouse, the duration of tumor formation was shortened in the case of IC injection compared to SC injection. There was no difference between neonatal and adult mice. To confirm sensitivity of tumorigenic potential, primary glioblastoma cells were injected into neonatal and adult NOD/SCID and NOG mouse. The highest tumorigenicity was observed in neonatal NOG mouse. To determine in vivo tumorigenicity of stem cells, adult human neural stem cells (ahNSCs) and hTERT-immortalized NSCs were injected into NOG mouse. When ahNSCs and hTERT-immortalized NSCs were injected into NOG in neonatal and adult

NOG mice, no tumor was formed during long-term observation. In conclusion, we suggest highly sensitive standard method to evaluate in vitro and in vivo tumorigenecity for pre-clinical and clinical application.

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P111

Mesenchymal signalings in developing palatal epithelium

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Secondary palate consists of anterior bony hard palate with keratinized covering and posterior muscular soft palate without keratinized layer. Soft palatal mesenchymal cells are composed of paraxial mesoderm derived myogenic cells and NCC derived osteogenic and fibrogenic cells. There have been a lot of reports to unveil the developmental mechanisms during palatogenesis but there is a lack of information for soft palate morphogenesis. In order to evaluate the detailed process of soft palate development, firstly we analyzed and characterized the non-keratinized soft palate by histology and protein localization patterns such as E-Cadherin, CK4 and CK10 along with A-P axis of developing palate. From recombination assay, we speculated that Fgf7 as a mesenchyme-derived signaling factor could make the differences between anterior and posterior palatal epithelium during soft palate development. In addition, laser-microdissection-aided microarray results also suggested that a range of mesenchymal factors related with myogenesis, cell cycle regulation, osteogenesis, GPCR pathway as well as ECM molecules would involve in region-specific differentiation. From the gene expression patterns and differential epithelial development would suggest that region-specific mesenchymal factors along A-P axis regulate keratinization of palatal epithelium and determine the hard and soft palate during development.

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P112

Melatonin promotes long-term memory via CREB signal pathway in hippocampal cells

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Memory decline is one of the many characteristics of aging. The individual older develop cognitive deficits or age-associated long-term memory impairments. Reduced long-term memory is thought to be responsible for this decline, although the precise mechanisms underlying long-term memory (LTM) in the old remain unclear. The cAMP response element-binding (CREB) has been known to play a central role in the LTM that activates gene expression required for the formation of LTM in animal models such as Aplysia, Drosophila, and rodents. This study has shown that gain or loss of CREB function improves and impairs in the formation of LTM. In addition, the activation of CREB is highly significant biomarker in the formation and enhancement of memory. The aim of the present study is to determine the effects and molecular mechanisms by which phosphorylated of cAMP-response element?binding protein (p-CREB) in affecting memory function by melatonin regulates in hippocampal cells. In this study, cellular aging is accompanied by the loss of CREB in HT-22 cell of hippocampal cell lines, whereas treatment of melatonin leads to CREB phosphorylation and mediates its up-downstream signaling pathway including p-ERK, p-p90RSK, BDNF via the MT1 receptor in senescent cellular state. In conclusion, the activation of CREB signaling pathway by melatonin has shown that CREB plays essential roles in memory processes and enhancement of memory. CREB signaling pathways are thought to be a potential target for drug discovery to improve brain disorders displaying memory impairments in aging.

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P113

Blocking the PI3K pathway inhibit the efficacy for NRG1 mediates rescue LTP impairment and neurotoxicities induced by Ab1-42

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Neuregulin-1 (NRG1) plays important roles in the development and plasticity of the brain, and it is also reported to have potent neuroprotective properties. We previously reported that NRG1/ErbB4 has neuroprotective actions against Alzheimer's cell models and prevents Amyloidβ(Aβ1-42)-induced impairment of long-term potentiation (LTP) in the CA1 region of mice hippocampal slices. Aβ peptide is generally believed to play a critical role in the pathogenesis of AD. In this study, we investigated downstream pathways of NRG1/ErbB4 signaling in prevention of LTP impairment and neurotoxicity induced by Aβ1-42.This LTP-restoring action of NRG1 was almost completely abolished by blocking PI3K, suggesting that NRG1/ErbB4 signaling acts through PI3K activation to exert its protective action on LTP. Moreover, Inhibition of PI3K activation blocked the reducing effect of NRG1 on Aβ1-42-induced LDH release, TUNEL-positive cellsnumber, andreactive oxygen species accumulation in primary cortical neurons. Collectively, our results demonstrate that NRG1/ErbB4 signaling exerts neuroprotective effects against Aβ1-42-induced hippocampal LTP impairment and neurotoxicity via the PI3K activation, which suggests the neuroprotective potential of NRG1/ErbB4 in AD.

Keywords: Alzheimer's disease, Neuregulin 1, PI3K, Amyloid beta peptide, Long-term potentiation

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P114

Neuregulin 1 controls glutamate uptake by upregulating excitatory amino acid carrier 1 (EAAC1)

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Neuregulin 1 (NRG1) is a trophic factor that is thought to play important roles in the development of brain circuitry. Recent studies suggest that NRG1 may regulate neurotransmission, though the mechanisms remain elusive. Here, we show that NRG1 controls glutamate uptake by increasing the protein level of excitatory amino acid carrier (EAAC1). Our data indicates that NRG1 induced the up-regulation of EAAC1 in primary cortical neurons with a concurrent increase in glutamate uptake. These in vitro results were corroborated in the PFC of mice given NGR1. This effect was blocked by inhibition of ErbB4 suggesting the involvement of ErbB4. The suppressed expression of ErbB4 by siRNA led to a decrease in the expression of EAAC1. In addition, the ablation of ErbB4 in parvalbumin(PV)-positive interneurons in PV-ErbB4-/- mice suppressed EAAC1 expression. Furthermore, NRG1, was shown th reduce EAAC1 ubiquitination and degradation. Taken together, these of NRG1. These findings link proposed effectors in schizophrenia: NRG1/ErbB4 signaling perturbation, EAAC1 deficit, and neurotransmission dysfunction.

Keywords: schizophrenia, EAAC1, NRG1, ErbB4, parvalbumin

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P115

CD44 expression in microglia of chicken retina and cerebellum

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CD44 is a transmembrane glycoprotein which acts as a receptor for

adhesion molecule and as a cell surface receptor for hyaluronic acid. Many studies have showed that CD44 was localized in astrocyte lineage cells in developing CNS of the chick embryo, and developing CNS of the rat and mouse. Besides the CNS, CD44 expression was also reported in the retina. In mature retina, CD44 expressed on M?ller glial cells. Localization of CD44 in microglia has been reported in ischemic brain lesion of the rat. Despite of many studies, the type of cells expressing CD44 remains to be clearly elucidated. The aims of the present study were to examine whether the CD44 was expressed in the brain and retina of adult chicken and to examine the type of CD44-expressing cells. Further, we examined whether CD44 was upregulated by lipopolysaccharide (LPS) stimulation. Post-hatch day 120 chicken were used in this study. Eyes and the cerebellum were taken, fixed with 4% paraformaldehyde, and fronzen-sectioned into 10-20 um thickness. Immunohistochemical staining for CD44, RCA-1, GFAP, neurotrace (NT), and glutamine synthetase (GS) was performed. As a result, in the adult retina and cerebellum, CD44-immunoreactive cells were colocalized with RCA-1-immunoreactivity, a marker for microglia, but not with GFAP for astrocytes, NT for neurons or GS for M?ller glial cells. CD44-expressing cells in the retina were mainly localized in the nerve fiber layer, inner plexiform layer, and outer plexiform layer. In the cerebellum, CD44-expressing cells were observed in both molecular layer and granular layer. LPS-stimulation upregulated CD44 expression in activated microglia. Taken together, the present results showed that CD44 was expressed in microglia of chicken brain and retina even in the resting state as well as in activated state, which suggested that a specific epitope of the CD44 molecule could be a useful marker for the microglia.

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P116

Studies on the animal model of post-stroke depression as a subtype of vascular depression with high validity

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The existence of a causal relationship between depression and vascular deficits has been hypothesized clinically as a vascular depression, but has not been established in proper animal model. To investigate whether cardiovascular abnormalities such as ischemic stroke develops to ideal animal model of vascular depression by additional chronic mild stress (CMS) procedure, we performed behavioral and immunohistochemical analysis in middle cerebral artery occlusion (MCAO), CMS and combined group with MCAO and CMS. In all antidepressant screening tests involving sucrose preference test, forced swim test, open filed test, and spatial learning test-morris water maze, MCAO+CMS group showed significantly less depressive symptoms compared to MCAO group. In the immunohistochemical analysis, MCAO+CMS group showed an increase of proliferative cells, demyelination and dopaminergic neuronal injuries compared with CMS group. These results suggest that combined treatment with MCAO and CMS shows more severe depressive symptoms than MCAO and CMS each treated group and this model may be available to vascular depression research.

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P117

Role of Follistatin in inner ear development

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Follistatin (Fst) encodes a cystein-rich protein that inhibits the activity of Activins, BMPs, and other TGF-β superfamily. It has been shown that Fst knockout mice exhibit several developmental defects including growth retardation, craniofacial defects, and abnormal intercostal muscles, which lead to neonatal lethality, suggesting that Fst plays crucial roles in normal development of multiple organs in mammals. However, its role in inner ear development has not been explored. We have previously reported that Fst is expressed in

a specific temporal and spatial expression pattern during cochlear development; Fst expression is observed in the apical cochlea region as soon as the cochlear primordium emerges from the inner ear anlagen, the otocyst, at E10.5, and maintained throughout embryogenesis and until postnatal 8. This specific expression pattern suggests that Fst plays an important role in the apical cochlear patterning. To test this hypothesis, we analyzed the cochlea of Fst knockout mice. We observed slightly sharpened apical end of cochlea duct, extra rows of outer hair cells(OHC) in the apical regions, but no significant change in total length of cochlea duct, and when compared to control, mutant cochlea shows premature hair cell(HC) differentiation. In addition, hair cell(HC) marker, Atoh1, originally starts its expression at around E13.75-E14.0, from the midbase region of cochlea duct and then expand bidirectionally to the base and apex. WT mice at E15.5, there is no or very weak Atoh1 expression at apex region. Mutants however, expression of Atoh1 has been expanded toward the apex, and the entire intensity of expression is higher than that of WT. Besides, the cochlea duct of Fst mutants lacked the expression of Msx1, an apical cochlea marker, and shows decreased expression level of EphrinB2(Efnb2), also an apical marker. This indicates the possibility that Fst mutants lose their apical identity of cochlea duct. To make sure the reason why the hair cells differentiate prematurely, we will see the expression of Atoh1 at E13.75-E14.0 so as to confirm the early-onset of HC differentiation. Later on, we will focus on the timing of cell cycle exit in order to identify whether the premature hair cell differentiation is due to premature cell cycle exit. To summarize, our results indicate that follistatin could be the promising candidate which regulates the timing of hair cell differentiation and give the apical identity to the cochlea duct.

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P118

Primary cilia play crucial roles in mediating Shh signaling during cochlear development

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Primary cilia is a microtubule-based organelle that project from the surface of vertebrate cells classified as non-motile cilia and have been recognized for its importance as a cellular signaling center of many pathways. These pathways include Sonic hedgehog(Shh), Wnt, PCP, FGF and PDGF, all of which are important in development. Defective primary cilia are shown to cause a range of genetic diseases collectively known as ciliopathy, which displays symptoms such as Hydrocephaly, Craniofacial abnormalities, Retinal degeneration, Hearing loss, Anosia, Cystic organs, polydactyly, and Obesity. To understanding the role of Primary cilia in inner ear development, we analysed the inner ears of a ciliopathy mouse model, in which primary cilia is elongated due to the missense mutation of Broad-minded encoding an uncharaterized ciliary protein. Bromi mutants exhibit a variety of inner ear defects, which can be attributed to defective Shh signaling transduction due to the elongated primary cilia, such as shortened cochlea duct. we continuously investigated the regional identity of Bromi mutants, to confrim the shortened cochlea are whether truncated or not fully elongated. Cochlear apical marker such as Msx1 and Fst, which requires strong level of Shh, are observed in Bromi mutants although not strong enough, suggesting that cochlea of Bromi mutant are not fully elongated. Additionally, Atoh1, one of the early marker of Hair cell fate, is expressed prematurely indicating compromised inhibition of hair cell formation by Shh. Multiple rows of hair cells were obseved in apical region of Bromi mutants, by the failure of convergent extension of prosensory domain. However, kinocilium of Bromi mutant is at the abnueral side of Hair cells, with normal orientation of stereocilia bundle. Interestingly, Bromi mutants develope apical sensory hair cell patches containing Vestibule-like hair cells in K?lliker's organ, similar with the phenotype in Gli3Δ699/Δ699 mutants, the model of Compromised Shh signaling. In addition, Primary cilia of supporting cells are selectively disappeared in Bromi mutants. Our results are attributed to impaired Shh signaling transduction due to abnormal ciliary morphology and function, also implying the general mechanism of cochlear elongation.

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P119

6-Hydroxydopamine induced dopaminergic neurodegeneration is ac companied with galectin-3 and activating transcription factor 3 expression

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Parkinson's disease (PD) is a common age-related neurological motor disorder, marked by the relatively selective and progressive neuronal degeneration of dopaminergic (DA) neurons in the substantia nigra (SN). 6-hydroxydopamine (6-OHDA) is able to induce retrograde degeneration of the nigrostriatal DA neurons and has been the most widely used tool for replicating a PD pathology. Galectin 3, a member of the galectin family of β-galactoside binding lectins, has been known to take part in cell to cell adhesion, human embryogenesis, inflammatory cascades, tumor growth and angiogenesis. Recently, growing evidences indicated that galectin-3 also paly an important role in the anti-apoptotic pathway. Activating transcription factor 3 (ATF3), a member of CREB/ATF family, is induced in a variety of tissues by various types of insults and suggested to be an important immediate early gene to initiate the signal cascades. To elucidate the significance and functional role of these genes in DA neuronal degeneration caused by 6-OHDA insults, we examined temporal and spatial profiles of galectin-3 and ATF3 expression in DA neurons of SN and ventral tegmental area (VTA). Following 6-OHDA injection into the striatum, both galectin-3 and ATF3 were found in the tyrosine hydroxylase-immunoreactive (TH-ir) neurons in the ipsilateral SN, but not in those of the contralateral SN. The number of galectin-3 and ATF3-positive DA neurons was increased by 3-7 days post-lesion, and then progressively decreased. The number of ATF3-positive DA neurons outnumbered that of galectin-3. Concomitant co-localization of galectin-3 and ATF3 in the same TH-ir neuron was also demonstrated by triple immunofluorescence labeling. Taken together, these results suggest that galectin-3 and ATF3 may be closely participating in 6-OHDA induced neurodegenration. This is the first in vivo demonstration that DA neurons undergoing neurodeneration in SN and VAT following 6-OHDA lesions express galectin-3 and ATF3.

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P120

Goα protein modulates the neuritogenesis in primary neurons

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Heterotrimeric G-proteins mediate signal transduction generated by numerous neurotransmitters and hormones. Among all G-proteins, Goα, a member of the Go/i family, is the most abundant G protein in brain. Although Goα has been implicated in neuronal differentiation, the mechanism of how Go modulates neuronal differentiation has not been defined. We previously showed that Goα may modulates neurite outgrowth in F11 cells. Expression of Goα decreased the average length of neurites but increased the number of neurites per cell by interfering cAMP-PKA-CREB signaling (Ghil et al., 2000 and 2006). In this study, we investigated the roles of Goα during the neuritogenesis in primary cultured neurons through the aspects of cytoskeletal filament such as microtubule and F-actin. Short protrusions or neurites were found to be less extended in Goα knock-out neurons. Our data showed that the formation of protrusions/neurites is delayed in the absence of Goα. The data also suggest that Goα may induce the formation of protrusions/neuritis at earlier time. Further, we will discuss the mechanisms by which Goα regulate the neuritogenesis during differentiation and maturation of neuronal cells.

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P121

Determination of Xnr1 response element on mixer promoter during the early endoderm formation of Xenopus laevis

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Mixer play an important role in boundary formation in the Xenopus gastrula, upregulated upon by Xnr1 and VegT signal involved in endodermal fate of Xenopus embryonic cells. However, transcriptional regulation of activated mixer by Xnr1 and VegT was poorly understood. Here, we identified genome size of about 4.5 kb fragmenet of mixer which included 2.7 kb size of 5 ' flanking region, three of exons and two of introns by yeast one hybrid method, and 2.7kb 5 'flanking region of mixer was cloned into the pGL2-reporter vector and performed luciferase assay. As a result, the promoter activity of mixer was very high at stage 12 in vegetal region, and was increased by VegT and Xnr1 in animal cap assay. In particular, the expression of mixer by Xnr1 was induced in a direct manner through cycloheximide treatment. Furthermore, in luciferase activity of mixer promoter deletion constructs, -1614 ~ -1420 upstream from the transcriptional start site was included Xnr1 response element. In this study, we identified 5' flanking region of mixer and identified its Xnr1 response element which induced mixer expression in a direct manner. The sequence may provide us with a clue to understand how to process (that) the downstream signals of Xnr1 activate mixer expression in endodermal development.

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P122

Calcium chelation by ethyl pyruvate is responsible for inhibition of HMGB1 phosphorylation and release in neurons and microglia

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Ethyl pyruvate (EP), a simple aliphatic ester of pyruvic acid, has been shown to have anti-inflammatory effects and to confer protective effects in various pathological conditions. Recently, a number of studies have reported EP inhibits high mobility group box 1 (HMGB1) secretion and suggested this might contribute to its anti-inflammatory effect. Since, EP is used in a calcium-containing balanced salt solution (Ringer's solution), we wondered if EP directly chelates Ca2+ and it is related with the EP-mediated suppression of HMGB1 release. Calcium imaging assays revealed that EP significantly and dose-dependently suppressed high K+-induced transient [Ca2+]i surges in primary cortical neurons and similarly, fluorometric assays showed that EP directly scavenges Ca2+, as the peak of fluorescence emission intensities of Mag-Fura-2 (a low-affinity Ca2+indicator) was shifted in the presence of EP at concentrations of ≥ 7 mM. Furthermore, EP markedly suppressed the A23187 (a calcium ionophore)-induced intracellular Ca2+ surge in BV2 cells (a microglia cell line) and under this condition, A23187-induced activations of Ca2+-mediated kinases (protein kinase C alpha and calcium/calmodulin-dependent protein kinase IV), HMGB1 phosphorylation, and subsequent secretion of HMGB1 were also suppressed. Moreover, the above-mentioned EP-mediated effects were obtained independent of cell death or survival, which suggests that they are direct effects of EP. Together these results indicate that EP directly chelates Ca2+, and that it is, at least in part, responsible for the suppression of HMGB1 release by EP.

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P123

Arginine-Glycine-Aspartate-containing osteopontin icosamer peptide affords neuroprotective effect in the postischemic brain via pro-angiogenic functions

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Osteopontin (OPN) is a phosphorylated glycoprotein that is secreted into body fluid after being synthesized in various cells and tissues. OPN contains arginine, glycine, aspartate (RGD)-motif, through which it binds to several cell surface integrins, that mediates a wide range of cellular processes, such as, the adhesion, migration, and survival of a variety of cell types. In the present study, authors examined the pro-angiogenic effects of a RGD-containing, 20 amino acids OPN peptide (OPNpt20) in HUVECs and in a rat model of focal cerebral ischemia, induced by middle cerebral artery occlusion (MCAO). We found that OPNpt20 exerts a robust pro-angiogenic effect in HUVECs, including proliferation, migration, and tube formation. OPNpt20 also induced blood vessel formation in a Matrigel plug assay in mice. However, a mutant peptide (OPNpt20-RAA), in which RGD was replaced by RAA, failed to activate all of pro-angiogenic processes, indicating that the RGD motif is required for its pro-angiogenic effect. In OPNpt20-treated HUVECs, PI3K/AKT signaling was activated. Moreover, blocking avb3 integrin by antibody or treating OPNpt20 after pre-incubating it with avb3 integrin suppressed OPNpt20-mediated pro-angiogenic function, indicating that OPNpt20 stimulates angiogenesis via avb3/PI3K/AKT signaling pathway in HUVECs. Pro-angiogenic function of OPNpt20 was further confirmed in the postischemic brain, wherein significant inductions of RECA-1 immunoreactivity as well as angiogenesis-associated proteins, such as, VEGF, MMP-9, and smooth muscle actin, were also observed in cortex penumbras of OPNpt20-administered animals. Together these results demonstrate that RGD-containing OPN peptide has a robust pro-angiogenic effects and it might contribute to a robust neuroprotective effects in the postischemic brain.

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P124

High accumulation and affinity with iron in supraoptic nucleus of the mouse hypothalamus

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Iron is an abundant metal in the brain and an essential factor for brain cells. Neuroglial cells demand large amount of iron for lipid and cholesterol biosyntheses. Neurons also require iron for metabolism and biosynthesis of neurotransmitters. However, intracellular iron is potentially detrimental to cells since it may produce hydrogen superoxide free radicals through the Fenton reaction which triggers oxidative damage involving lipid peroxidation of the cell membrane. Oxidative damage to the cell membrane increases calcium ion influx and lead to cell death. Therefore, although iron is an essential factor involved in neurotransmitter production in neurons, there are few nuclei containing high concentration of iron. We recently found high iron accumulation in the supraoptic nucleus (SON) of the mouse hypothalamus using intensified iron histochemistry and densitometry. The iron content of the SON was approximately twice higher than those of other forebrain regions including the lateral hypothalamic area, the globus pallidus, the reuniens thalamic nucleus, and the corpus callosum. Furthermore, iron-overload experiment showed that increased rate of iron accumulation in the SON was significantly higher in comparison with those in other forebrain regions, indicating that the SON has high affinity with iron. Our results suggest that the SON are required for high iron content for their normal function and may serve as an iron reservoir for the brain.

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P125

Bee venom acupuncture alleviates experimental autoimmune encephalomyelitis by upregulating regulatory T cells and suppressing Th17 and Th1 responses

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The protective and therapeutic mechanism of bee venom acupuncture (BVA) in neurodegenerative disorders is not clear. We investigated whether treatment of BVA (0.25 and 0.8 mg/kg) into Zusanli (ST36) acupoints, lateral from the anterior border of the tibia, has

a beneficial effect in a myelin basic protein (MBP)68-82-induced acute experimental autoimmune encephalomyelitis (EAE) rat model. Pretreatment (every 3 days from 1 hour before immunization) of BVA was more effective than post-treatment (daily after immunization) in clinical signs (neurological impairment and loss of body weight) of acute EAE rats. Treatment of BVA into ST36 acupoint of normal rats did not induce the clinical signs. Pretreatment of BVA suppressed demyelination, glial activation, expression of cytokines (IFN-γ, IL-17, IL-17α, TNF-α, and IL-1β), chemokines (RANTES, MCP-1, and MIP-1α), and iNOS, and activation of p38 MAPK and NF-kB (p65 and phospho-IkBα) signal pathways in spinal cords from acute EAE rats. Pretreatment of BVA decreased the numbers of CD4+,CD4+/IFN-γ+, and CD4+/IL-17+ T cells, but increased numbers of CD4+/Foxp3+ T cells in spinal cords and lymph nodes from acute EAE rats. Treatment of BVA into two non-acupoints (gulteal region and base of proximal tail) of acute EAE rats did not positive affect neurological impairment, spinal demyelination, and immune cell recruitment/infiltration. Interestingly, onset- and post-treatment of BVA into ST36 acupoint markedly attenuated neurological impairment in myelin oligodendrocyte glycoprotein (MOG)35-55-induced chronic EAE mice. Our findings strongly suggest that treatment of BVA into ST36 acupoint could delay or attenuate the development and progression of EAE by upregulating regulatory T cells and suppressing Th17 and Th1 responses. These results warrant further investigation of BVA as a treatment for autoimmune disorders of the central nervous system.

Keywords: bee venom acupuncture, experimental autoimmune encephalomyelitis, immune cell

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P126

The effects of LRRK2 mutations in cell-to-cell transmission of a-synuclein aggregates

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The Parkinson's disease (PD) is caused by loss of dopaminergic neurons in the substantia nigra of the midbrain. the main clinical symptoms in motor function occurred, such as resting tremor, bradykinesia, rigidity. And a PD is pathologically characterized by the presence of Lewy bodies (LBs) and Lewy neurites (LNs) in the substantia nigra. The the accumulation of a-synuclein aggregates, major component of LBs and LNs has been implicated in the onset and the progress of PD. Previous studies showed that a-synuclein can be accumulated in the neuronal cells and be transmitted into neighboring cells, suggesting that the transcellular transmission of a-synuclein aggregates can cause the progress of Lewy pathology. Leucine-rich repeat kinase-2 (LRRK2), the most common gene led to early-onset Parkinson's disease (EOPD) in an autosomal dominant manner. However, the effect of mutation in LRRK2 gene on the cell-to-cell transmission of a-synuclein aggregates remains unclear. Herein, we hypothesize that the mutations in LRRK2 kinase activity domain can increase the lewy pathology into the larger brain region thereby enhancing the transcellular transmission of a-synuclin aggregates. To test this, we generated the adeno virus construct of LRRK2 (WT, G2019S kinase active mutant and D1994A kinase dead mutant). We demonstrated that the transduction of LRRK2 G2019S to a-synuclein stable cell line by using adenovirus infection increased the cell-to-cell transmission of a-synuclein aggregates. These result suggested that the mutation in LRRK2 kinase domain could increase lewy body pathology thereby accelerating the cell-to-cell transmission of a-synuclein aggregates.

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P127

일차배양된 신경세포에서 Botulinum neurotoxins (BoNTs)로 유발된 synaptophysin 발현감소의 BDNF (Brain Derived Neurotrophic Factor)에 의한 회복에 관한 연구

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Botulinum neurotoxins (BoNTs) 중 가장 강력한 항원형인 BoNT/A는 연접소포(synaptic vesicle)의 당단백질(glycoprotein

2, SV2)을 수용체로 활용하여 신경세포 속으로 들어간 후, synaptosome-associated protein인 SANP-25를 분해한다. 또한 SV2, synaptophysin, synaptotagmin I, VAMP2와 같은 연접소포단백질 복합체들은 BoNT/A와 BoNT/B의 연접소포수용체로서 상호작용하는 것으로 알려져 있다. 본 연구의 선행연구에서는 BoNT/A가 synaptophysin의 발현을 유의하게 감소시킴을 확인하였다. Synaptophysin은 연접소포에 풍부하게 존재하며 신경연접(synapse)의 형성과 endocytosis를 조절하는 역할을 한다. 한편 synaptophysin은 synaptic modification을 촉진시키는 이차매게체(second messenger)의 하위표적일 가능성이 높다. 한편 신경영양물질(neurotrophic factor) 중의 하나인 BDNF(brain derived neurotrophic factor)의 경우 정확한 기전은 밝혀지지 않았으나 연접전말단(presynaptic terminal)에서의 연접가소성(synaptic plasticity)과 밀접한 관련이 있다. 따라서 본 연구의 목적은 BDNF가 BoNT/A로 유발된 synaptophysin 발현의 감소를 회복시키는지 여부를 확인함으로써 BDNF가 synaptophysin 의존적인 신경연접 안정화에 필요한 상위신호물질로 작용할 수 있음을 제시하는 데 있다. 본 연구에서는 특히 synaptic vesicular trafficking과 recycling에 필수적인 munc18-1의 유전자변형 생쥐(munc18-1+/+&+/-)를 신경세포일차배양(primary neural culture)에 활용하여 BDNF의 synaptophysin 발현감소에 대한 회복효과와의 연관성을 알아보았다. 배양된 신경세포로의 BDNF 도입은 BDNF를 배양액에 직접 첨가하는 방법과 lentivirus을 이용한 BDNF 과발현(overexpression) 방법을 함께 활용했다. 본 연구의 결과에서 BDNF를 배양액에 첨가하거나 과발현시킨 신경세포에서는 BoNT/A에 의한 synaptophysin 발현감소가 상당 수준 회복된 것을 확인할 수 있었다. 한편 munc18-1이 결핍된 신경세포의 경우 BDNF를 배양액에 첨가한 경우와 과발현시킨 경우의 결과가 일치하지 않는 경향을 보였다. 따라서 본 연구결과에서 나타난 synaptophysin에 대한 BDNF의 효과가 구체적으로 munc18-1과 어떤 연관성이 있는가에 대해서는 관련연구가 더 진행돼야 할 것으로 판단된다.

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P128

Galectin-3 expression is accompanied with microglial activation in medial forebrain transection PD model

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Neuroinflammation is a innate response of neural tissue against the diverse insults (infections, trauma, stroke, toxins etc.) within the CNS and is now regarded as both an early event and a prime mover in the pathobiology of neurodegenerative disease. Neuroinflammation is associated with gliosis, in particular microglial activation. Therefore, it is important to understand the molecules involving activation of microglia in various neurodegenerative disease, including PD, for understanding the underlying mechanism of the progress of pathogenesis and developing therapeutic interventions. Previous studies have shown that a specific subset of activated microglia express the lectin galectin-3/Mac-2, a member of the galectin family of β-galactoside binding lectin. Moreover, there is emerging evidence that galectin-3 positive microglia may have a role beyond myelin phagocytosis. We have also presented microarray data that galectin-3 expression is highly up-regulated in the substantia nigra (SN) following medial forebrain bundle (MFB) transection and the main cell types expressing galectin-3 are microglia. In this study, to elucidate the significance and functional role of galectin-3 during microglial activation, we conducted time course study assessing the dynamic expression profiling of galectin-3 in the activated microglia following MFB transcetion. Neurodegenration in the SN was induced by unilateral MFB transection. Galectin-3 positive cells were first observed in the ipsilateral SN as soon as day 1 after MFB transection and their number is significantly increased at day 3 and peeked at day 7. By day 14, the number of galectin-3 positive cells was decreased but this is still significant. Quantitative real time PCR and western blot results were in consistent with that of immunohistochemistry. To further study the role of galectin-3 expression in microglia, we conducted double immunofluorescence of galectin-3 antibody with other antibodies: clone of antibody that detects major histocompatibility complex (MHC) class II antigens (OX6) for MHC class II and CD 68 (ED1) for pahgocytic activity. Galectin-3 expression is always concomitant with MHC class II expressing (OX6) and phagocytic (ED1) activated microglia. This study suggest that galectin-3 expression precedes microglial activation and seems

to triggering the myeline or cell debris phagocytosis.

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Therapeutic effect of neurally induced mesenchymal stem cells in the ischemic rat brain

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Mesenchymal stem cells (MSCs) have been shown to improve a variety of neurological dysfunction by their paracrine effects. Neurogenin-1 (Ngn1) is a proneural gene that directs neuronal differentiation of progenitor cells during development. In recently study, intracranial injection of Ngn1-expessing MSCs showed the remarked improvement of motor dysfunction in stroke model compared to MSC and PBS treated group. However, intracranial injection is not feasible method to use in clinical field. Therefore, we conducted the study to investigate that intra-arterial injection of Ngn1-expressing MSCs can improve motor deficit in ischemic rat model. Fifteen Sprague-Dawley rats were subinjected to transient middle cerebral artery occlusion(tMCAo) of 2 hours. Magnetic resonance image (MRI), including diffusion-weighted imaging (DWI) and T2-weighted imaging was performed at 2, 7 and 28days after withdrawal of the suture. Motor function evaluation including ratarod test and adhesive removal test was performed at 1, 7, 14 and 28 days. Rat injected with MSC-Ngn1 showed the tendency of motor dysfunction improvement compared to MSC-LacZ and control groups. The induction of neural stem cell number were greater in MSC-Ngn1 injected rat than in other groups. Intra-arterial injection of MSC-Ngn1 cell in stroke model showed the remarkable improvement of motor dysfunction . Intra-arterial injection can be the feasible method of stem cell transplant.

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P130

An improved method for a mouse focal ischemic stroke model : assessment of cerebral blood flow and functional impairment

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Stroke is one of the commonest causes of death and disability. Despite extensive efforts, therapeutic options for improving stroke recovery remain limited due the complexity of pathophysiology, which could be unraveled with ischemic models of genetically modified mice. Here, we optimized the procedure for mouse stroke model where blood flow in the middle cerebral artery was blocked with an intraluminal suture for 60 minutes and the ischemic injury was verified by using indocyanine green (ICG). The animals exhibited the increased survivability after optimization of the occluding procedures and administration of antibiotics and consistent induction rates. On batteries of behavioral test to assess the functional impairments, animals showed the maximal severity during the first week but spontaneously recovered starting from the second week. In conclusion, we developed an improved approach which allows us to investigate the role of the cell death related molecules in the disease progression and to evaluate the modes of action of candidate drugs.

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Overexpressed E46K, a missense mutation of a-synuclein, suppresses neurite outgrowth with down-regulation of cdc42ep2 in SK-N-SH, human neuroblastoma cell line

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a-Synuclein (aSN) is one of the major etiological genetic factors in Parkinson's disease (PD), a second major neurodegenerative disorders. Although a lot of study about pathophysiological functions have investigated, it is still elusive. Recently, in contrary to the pathological involvement in PD, aSN also has been known to induce neuritogenesis as a protective role. Wild type (WT) and two missense mutants, A30P and A53T, of aSN up-regulate neurite outgrowth. However the effect and mechanism of another mutant, E46K is poorly understood. In this study, aSN (E46K) overexpression suppressed neurite outgrowth in SK-N-SH human neuroblastoma cell line in contrast to WT, A30P and A53T. Comparing the altered gene expressions in aSN transfectants by real-time RT-PCR and Western blotting, cdc42ep2 (cdc42 effector protein2) was down-regulated in aSN (E46K) trasnfectant. Cdc42ep2 protein is known to activate cdc42, a small GTPase acting in neurite outgrowth. However, the interrelationship among cdc42EP2, cdc42, and neurite outgrowth has not been revealed. Application of cdc42ep2 siRNA suppressed neurite outgrowth in aSN (WT and A53T) transfected SK-N-SH. With above results, we conclude that cdc42ep2 is a key regulator in aSN-induced neuritogeneis. Difference in mechanism of aSN (E46K) with other mutations need to study further to elucidate the functional mechanism in neuroprotection and neuronal development.

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P132

Expression of ARL13B and adenylyl cyclase III in the ventricular system of mouse brain

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ADP-ribosylation factor-like protein 13B (ARL13B) is localized in the cilia and plays a role in formation and maintenance of cilia. Adenylyl cyclase III (ACIII) localizes to primary cilia on neurons, choroid plexus cells, and some astrocytes in the brain. The aim of this study is to compare the expression of ARL13B and ACIII in the ventricular system in mouse brain. Immunofluorescence staining for ARL13B and ACIII was performed in the mouse brain. ARL13B immunoreactivity was found in the primary cilia of the choroid plexus cells, ependymal cells, and in the primary cilia of the non-neuronal (glial) cells around the ependyma. ACIII immunoreactivity was similar to the ARL13B immunoreactivity, except that ACIII immunoreactivity was not found in the ependymal cells in the corner of the ventricle. These data shows that ARL13B and ACIII are good markers for primary cilia in the cells consisting the ventricular system, the expression pattern between ARL13B and ACIII is slightly different in the mouse ventricular system.

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P133

High-fat diet exacerbates kainic acid-induced hippocampal cell death

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Obesity has deleterious effects on the brain, and recent study suggests that metabolic dysfunction exacerbates the outcome of seizures and brain injury. However, it has not been determined whether obesity affects excitotoxicity-induced neuronal cell death. The purpose of this study was to investigate the effects of high-fat diet (HFD) on neuroinflammation and ER stress in the hippocampus of kainic acid (KA)-treated mice. Mice were fed a HFD for 8 weeks, followed by systemic injection of KA. Mice fed a HFD showed hyperinsulinemia, hypercholesterolemia, and insulin resistance. Comparing with mice fed a normal diet, the neurons of KA-treated mice fed a HFD showed more susceptibility to KA-induced neuronal cell death, as demonstrated by fast appearance of seizure induction and increased TUNEL-positive cells, as wells as neuroinflammation. It was also showed that KA increases HFD-induced ATF4 expression in the hippocampus. These findings implicate a link between metabolic dysfunction and excitotoxicity-induced neuronal cell death.

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Purslane suppresses osteoclast differentiation and bone resorbing activity via inhibition of Akt/GSK3β-c-Fos-NFATc1 signaling in vitro and prevents lipopolysac charide-induced bone loss in vivo

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Purslane (Portulaca oleracea L.) is popular as a potherb in many areas of Europe, Asia, and the Mediterranean region and is widely distributed around the globe. It has a wide range of pharmacological effects, such as antibacterial, anti-aging, anti-inflammatory, and antioxidative properties. Although the extract of purslane has numerous beneficial pharmacological effects, its effect on osteoclasts remains unknown. We aimed to investigate the anti-osteoclastogenic activity in vitro and in vivo and to elucidate the underlying mechanism. The effect of purslane on the differentiation and function of bone marrow-derived macrophages (BMMs) into osteoclasts was examined using a phenotype assay such as TRAP staining, F-actin staining, and pit assay and followed by confirmation by real-time RT-PCR and western blot analysis. To address the effect of purslane in vivo, the inflammatory, LPS-induced osteolysis mouse model was chosen. Bone volume and bone microarchitecture were evaluated by micro-computed tomography and histologic analysis. Purslane inhibited RANKL-stimulated osteoclast differentiation accompanied by inhibition of Akt/GSK3β signaling, which could underlie purslane-induced downregulation of c-Fos and nuclear factor of activated T cells 1 (NFATc1) expression levels, transcription factors that regulate osteoclast-specific genes, as well as osteoclast fusion and resorption-related molecules. Moreover, in vivo studies further verified the bone protection activity of purslane in the lipopolysaccharide-induced (LPS) osteolysis animal model. Purslane could exhibit its anti-osteoclastogenic activity by inhibiting Akt/GSK3β-c-Fos-NFATc1 signaling cascades. Therefore, purslane is a potential natural medicine for the treatment of osteoclast-related diseases.

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P135

Ampelopsis brevipedunculata extract prevents bone loss by inhibiting osteoclastogenesis in vitro and in vivo

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Osteoclasts play a critical role in bone resorbing disorders such as osteoporosis, periodontitis, and rheumatoid arthritis. Therefore, discovery of agents capable of suppressing osteoclast differentiation may aid the development of a therapeutic access for the treatment of pathological bone loss. Ampelopsis brevipedunculata has been used as herbal folk medicine to treat liver diseases and inflammation in Asia. However, its effects on osteoclast differentiation are unknown. We were aimed to investigate the anti-osteoclastogenic activity in vitro and in vivo and to elucidate the underlying mechanism of

Ampelopsis brevipedunculata extract (ABE). In this study, ABE inhibited receptor activator of NF-kappa B ligand (RANKL)-induced osteoclast differentiation, the formation of filamentous actin rings and the bone resorbing activity of mature osteoclasts. ABE inhibited RANKL-induced p38 and IkB phosphorylation and IκB degradation. Also, ABE suppressed the mRNA and protein expression of nuclear factor of activated T cells c1 (NFATc1) and c-Fos, and the mRNA expression of genes required for cell fusion and bone resorption, such as OSCAR, TRAP, cathepsin K, DC-STAMP, β3-integrin and OC-STAMP. Furthermore, results of micro-CT and histologic analysis indicated that ABE remarkably prevented lipopolysaccharide (LPS)-induced bone erosion. These results demonstrate that ABE prevents LPS-induced bone erosion through inhibition of osteoclast differentiation and function, suggesting the promise of ABE as a potential cure for various osteoclast-associated bone diseases.

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Ostericum koreanum extract prevents LPS-induced bone loss through inhibition of osteoclastogenesis

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The roots of Ostericum koreanum (OK) Maximowicz have traditionally been used to produce an herbal medicine reported to possess anti-inflammatory, antioxidant, antimicrobial, and antitumor activities; however, its effect on bone metabolism has not yet been reported. The present study examined the effects of OK extract on lipopolysaccharide (LPS)-induced bone loss in mice by investigating bone structure and the levels of the receptor activator of nuclear factor kappa-B ligand (RANKL) and osteoprotegerin (OPG) in serum and bone marrow fluid (BMF). The effects of OK extract on osteoclastogenesis were also investigated in mouse bone marrow macrophages by examining the formation of tartrate-resistant acid phosphatase (TRAP)-positive cells, the actin ring, and bone resorption activity. OK reduced LPS-induced bone destruction in vivo via a decrease in the RANKL/OPG ratio. Furthermore, it suppressed the formation of TRAP-positive cells and the actin ring, and reduced the bone-resorbing activity of mature osteoclasts. OK also significantly downregulated the expression of various osteoclast-specific genes. However, it did not affect osteoblast differentiation, or the expression of genes involved in this process. These results demonstrated that OK prevented LPS-induced bone loss by decreasing the RANKL/OPG ratio in serum and BMF, and inhibited osteoclast differentiation and function, suggesting that OK represents a potential therapeutic drug for the treatment of osteoclast-associated bone diseases.

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P137

Aconitum pseudo-laeve var. erectum inhibits receptor activator of nuclear factor kappa-B ligand-induced osteoclastogenesis via the c-Fos/nuclear factor of activated t-cells, cytoplasmic 1 signaling pathway and prevents lipopolysac charide-induced bone loss in mice

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Aconitum pseudo-laeve var. erectum has been widely known to have therapeutic effect on the inflammatory condition in oriental medicine. However, there is no evidence about the relation between the extract of *Aconitum pseudo-laeve var. erectum* (APE) and bone metabolism. In this study, we priorly confirmed that the administration of APE recovered normal skeletal condition in bone loss murine model. Next, we investigated the effect of APE on RANKL-induced the differentiation of bone marrow macrophages (BMMs) and bone resorbing action of mature osteoclasts to acquire its underlying

molecular mechanisms. As a results, APE blocked TRAP-positive cells formation, as well as, extracellular matrix resorption. Moreover, APE attenuated the activation of nuclear factor of activated T cell c1 (NFATc1) and c-Fos without any phosphorylation of early signal, dependent on RANKL induction. Subsequently, APE significantly down-regulated the expression various genes, exclusively expressed in osteoclasts. Taken together, this present study confirms that APE suppresses bone erosion through the inhibition of osteoclast differentiation and functional activity.

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Mollugin suppresses receptor activator of nuclear factor-kB ligand-induced osteoclastogenesis and bone resorbing activity in vitro and prevents lipopolysac charide-induced bone loss in vivo

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Osteopenic diseases, such as osteoporosis, are characterized by progressive and excessive bone resorption mediated by enhanced receptor activator of nuclear factor-kB ligand (RANKL) signaling. Therefore, down regulation of RANKL downstream signals may be a valuable approach for the treatment of bone loss-associated disorders. In this study, we investigated the effects of the naphthohydroquinone mollugin on osteoclastogenesis and its function in vitro and in vivo. Mollugin efficiently suppressed RANKL-induced osteoclast differentiation of bone marrow macrophages (BMMs) and bone resorbing activity of mature osteoclasts by inhibiting RANKL-induced c-Fos and NFATc1 expression. Mollugin reduced the phosphorylation of signaling pathways activated in the early stages of osteoclast differentiation, including the MAP kinase, JNK, Akt, and GSK3β and inhibited the expression of different genes associated with osteoclastogenesis, such as OSCAR, TRAP, DC-STAMP, OC-STAMP, integrin av, integrin b3, cathepsin K, and ICAM-1. Furthermore, mice treated with mollugin showed significant restoration of lipopolysaccharide (LPS)-induced bone loss as indicated by micro-CT and histological analysis of femurs. Consequently, these results suggested that mollugin could be a novel therapeutic candidate for bone loss-associated disorders including osteoporosis, rheumatoid arthritis, and periodontitis.

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P139

Depletion of CTCF is disadvantageous for the survival of breast cancer cell

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Breast cancer is the second most common cancer worldwide and the leading cause of cancer death in women. Because there is a high degree of diversity between and within tumors and this heterogeneity makes it difficult to conquer them with the same treatment, context dependent actions of druggable molecule in breast cancer should be considered. CTCF (or CCCTC-binding factor) is a ubiquitous 11-zinc finger multifunctional protein involved in different unrelated functions including regulation of transcription, enhancer-blocking activities and X chromosome inactivation. CTCF emerged as a major player in maintenance of epigenome and cellular identity and its dysregulation affects cell cycle regulation, apoptosis and cell fate. In breast cancer cell lines, it has been recently shown that higher CTCF level gives cancer cells a survival advantage by conferring protection against apoptosis and inhibiting BCL2-Associated X Protein (Bax). Here, we confirmed that CTCF knockdown induced gradual inhibition of cellular growth of MCF7 and MDA-MB231 cells than normal cells over the same time period. Acceleration of apoptosis and induction of TP53, p21 and Bax were observed in CTCF knocked down MCF7 cells. To demonstrate context-specific effects of CTCF in breast cancer by closely mimicking cancer microenvironment in vitro, we manipulated the level of CTCF in breast cell co-culture system, a mixture of MCF7 (ER^+Breastcancercellline) and MCF10A (normal

breast epithelial cell line) or MDA-MB231 (ER Breastcancercellline) and MCF10A. For this purpose, MCF7-GFP (MCF7 cell line stably expressing GFP) cells were generated to allow simple visual discrimination between normal and cancer cells. CTCF knockdown in co-cultured cells preferentially induced apoptosis in cancer cells, whereas normal cells were more predominant. In addition, the colony forming ability of MCF7-GFP cells in co-culture was reduced. In conclusion, we propose that depletion of CTCF may selectively kill breast cancer cells and can be considered for its benefits of using as a drugs.

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P140

Anti-andropause effects of the dandelion and rooibos in the aging male rat

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Many aging male suffer various andropause symptoms including loss of physical and mental activities. This study examined apparent mitigation effects of dandelion and rooibos on the andropause symptomatology. The cell viability of TM3 Leydig cells (TM3 cells) was treated with dandelion and rooibos was examined established on typical physiological stress. After rats were orally administrated with dandelion and rooibos flour daily for 4 weeks, Samples were collected from 18-week-old male rats and then the level of testosterone, physical activity and both the number and motility of sperm was measured. On the whole, we examined protective effect of dandelion and rooibos on the levels of serum restriction and oxidative stress associated with activation of ERK and Akt pathways in the TM3 cells. The level of testosterone and vitality of spermatogenesis in the aging male rats were evidently enhanced. Futhermore, physical activies motor ability was outstandingly improved. In consequence, it was appeared potential of dandelion and rooibos as a safe and efficacious natural product complex for decreasing or mitigating andropause symptomatology.

Keywords: Leydig cell, testosterone, dandelion and rooibos, spermatogenesis, andropause

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P141

In vitro assays to measure bystander effects of therapeutic stem cells on glioma cells

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Glioblastoma multiform (GBM) is the most severe cancer in the nervous system. Despite the progress has been made in treating GBM, the most effective therapy including combination of chemotherapy and radiotherapy has remained as a palliative cure. Recently, stem cells carrying suicide gene have emerged as the therapeutic candidates for the bystander effects on neighboring cancer cells while limiting cytotoxicity to other cells. Here, we report a method to accurately measure the bystander effects in co-culture system. Stable transduction of reporter genes such as green fluorescent protein (GFP) did not alter the sensitivity of glioma cells to 5-fluorouracil, product converted from a nontoxic prodrug, 5-fluorocytosine (5-FC) by a suicide gene, cytosine deaminase (CD). Unlike conventional mitochondrial enzyme-based assays, image analysis of fluorescence signals from GFP-labeled glioma cells allowed separation of surviving glioma cells from co-cultured therapeutic stem cells expressing CD. The results indicate that our experimental approach to determine the bystander effect of therapeutic stem cells against glioma cells in the presence of 5-FC. Furthermore, our method can be expanded as an in vitro assay for screening anti-cancer drugs or for determining effectiveness of candidate drugs before advancing into animal studies.

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Human adipose-derived stem cells attenuate inflammatory bowel disease in IL-10 knockout mice

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Inflammatory bowel disease (IBD) is a complex immunological disorder characterized chronic inflammation caused by mainly unknown factors. The interleukin-10 knockout (IL-10 KO) mouse is a well-established murine model of IBD which develops spontaneous intestinal inflammation that resembles Crohn's disease. In the present study, human adipose-derived stem cells (hAMSCs) were administrated to IL-10 KO mice to evaluate the anti-inflammatory effects of hAMSCs that may attenuate the progress of or treat IBD. After IBD was induced by feeding the IL-10 KO mouse a 125-250 ppm piroxicam mixed diet for 1 wk, 2×106 hAMSCs were injected into the peritoneum and the mice were switched to a normal diet. After 1 wk, the mice were sacrificed and tissue samples were harvested. Tissue scores for inflammation and inflammation-related genes expression were determined. The hAMSC-treated group showed significantly reduced inflammatory changes in histological analysis. Reverse transcription-PCR analysis showed that RANTES, Toll-like receptor, and IL-4 expression levels were not significantly different between the groups while IL-12, INF-γ, and TNF-α levels were significantly decreased in the hMMSC -treated group. hAMSC attenuated IBD induction in the IL-10 KO mice by suppressing inflammatory cytokine expression, which might be mediated by the type 1 helper T cell pathway. Even though only a single injection of hAMSCs was delivered, the effect influenced chronic events associated with inflammatory changes and demonstrated that hAMSCs are a powerful candidate for IBD therapy.

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The effects of bone marrow derived-mesenchymal stem cells in adriamycin-induced nephropathy in the rat

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Objectives: Adriamycin (ADR) induce nephropathy is widely used animal model of progressive chronic renal disease resulting in glomerulosclerosis, podocyte injury and fibrosis. The present study investigated the protective effects human bone marrow derived-mesenchymal stem cells (hBMSCs) on the ADR induced nephropathy rat model. **Methods:** Male Sprague-Dawley rats were divided into normal control (Nomal), ADR+Vehicle (CON) and ADR+hMSCs (MSC) groups. Nephropathy was induced by single injection of ADR (4 mg/kg, i.v.). Four days later, 0.5 ml of saline with or without 2 x107h BMSCs was injected via tail vein for CON or MSC group. The rats were sacrificed 1 week and 6 weeks after ADR injection. hBMSCs were characterized by cell surface CD marks express ion as well as differentiation induct ion into osteoblasts and adipocytes. To evaluate homing of hBMSCs, the cells were labeled with CFSE (5(6)-Carboxyfluorescein N-hydroxysuccinimidyl ester) and examined several tissues 3 h after injection. Kidney and body weight, as well as serum level of protein, albumin, cholesterol, triglycerides and creatinine were measured at 1 week and 6 weeks. Western blotting for inflammatory cytokines, nephrin, type I collagen was carried out. Eelectron microscopic and light microscopic observation was done for structural analysis. **Results and Conclusions:** The hBMSCs were highly observed in lung, liver and spleen but hardly detected in kidney. There was no significant difference in body and kidney weight as well as serum levels of protein, albumin, cholesterol, triglycerides and creatinine between CON and MSC groups. Pro-inflammatory cytokine (COX2, TNF-a, INF-g and IL-12) expression was decreased in MSC compared to CON but nephrin expression was increased. Podocytes preservation was observed in MSC. Our data shows that hMSCs have little effect for improve nephropathy by direct regeneration but preserve kidney by indirect systemic anti-inflammatory effect.

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EPA attenuates ultraviolet radiation-induced downregulation of aquaporin-3 in human keratinocytes

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Eicosapentaenoic acid (EPA) is an omega-3 polyunsaturated fatty acid (ω-3 PUFA) that protects against photodamage and photocarcinogenesis in mammals. Aquaporin-3 (AQP3) is a water/glycerol transport protein that is found in basal layer keratinocytes. In this study, we have investigated the protective effect of EPA against ultraviolet B (UVB)-induced AQP3 downregulation in human keratinocytes. EPA treatment was found to increase AQP3 gene and protein expression in human epidermal keratinocytes (HaCaT). Using a specific inhibitor, we observed that the effect of EPA on AQP3 expression was mediated by extracellular signal-regulated kinase (ERK) activation. UVB radiation induced AQP3 downregulation in HaCaT cells, and it was found that EPA treatment attenuated UVB-induced AQP3 reduction and the associated cell death. UVB-induced downregulation of AQP3 was blocked by EPA and p38 inhibitor SB203580. Collectively, the present results show that EPA increased AQP3 expression and that this led to a reduction UVB-induced photodamage.

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Flowers of Rosa rugosa inhibit α-MSH-induced melanogenesis by suppression of the CREB/MITF signaling in melanoma cells

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Rosa rugosa Thunb., belonging to the family of Rosaceae, is a plant native to eastern Asia. Its flowers have been used to effectively help in expansion of blood vessels and improvement of microcirculation. The present study aimed to investigate the molecular events underlying the anti-melanogenic activity of ethanol extracts from Rosa rugosa flowers (ERR) in alpha-melanocyte stimulating hormone (α-MSH)-stimulated B16-F10 melanoma cells. In this investigation, ERR effectively reduced α-MSH-stimulated melanin synthesis by suppressing expression of tyrosinase (TYR). On the other hand, the expressions of tyrosinase-related protein-1 (TRP-1) and tyrosinase-related protein-2 (TRP-2) were not affected by treatment with ERR. ERR inhibited the expression of microphthalmia-associated transcription factor (MITF) as a key transcription factor for tyrosinase expression regulating melanogenesis. The upstream signaling pathways including cAMP response element-binding protein (CREB) and MAPKs were also inhibited by ERR. Collectively, the present results show that the anti-melanogenic activity of ERR is correlated with the suppression of tyrosinase gene through CREB/MITF pathway.

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MsrA gene-deletion aggravates fibrosis after unilateral ureteral obstruction in mice

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Background: Methionine sulfoxide reductases (Msrs) catalyze the reduction of methionine sulfoxide (Met-O) to methionine. The primary function of Msrs is to repair oxidative damaged protein. Methionine sulfoxide reductase A (MsrA), one of Msrs, plays as an antioxidant enzyme to copy with oxidative stress. Progression of fibrosis resulting from unilateral ureteral obstruction (UUO) is aggravated by reactive oxygen species (ROS). Here, we investi-

gated the role of MsrA in kidney fibrosis induced by UUO in mice. **Method:** Mice were subjected to either UUO or sham-operation in MsrA -knockout (MsrA-/-)and wild-type(MsrA+/+) mice. Kidneys were harvested 5 or 7 days after UUO. Expression of an tioxidant enzymes and fibrogenic changes were determined using western blotting analysis. Sirius red staining was performed to determine the area of collagen deposition. **Results:** UUO increased collagen deposition in the interstitium, and this increase was more severe in the -/- mouse kidneys than the +/+ mouse kidneys. Expression of α-SMA and collagen III were also greater in the -/- mouse kidneys than the +/+ mouse kidneys. In addition, MsrA KO more significantly enhanced the increase of F4/80, Ly6G and myeloperoxidase (MPO) expression after UUO in the kidney when compared with MsrA wild. **Conclusion:** MsrA negatively regulates UUO-induced kidney fibrosis, likely by suppressing fibrogenic and inflammatory responses.

Keywords: Methionine sulfoxide reductase A (MsrA), kidney fibrosis

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P147

Positive effects and its underlying mechanism of whole body vibration therapy on functional recovery after rat model of sciatic nerve injury

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Despite beneficial effects of Exercise is intensively investigated, however therapeutic application of exercise (esp. voluntary movement like running, swimming) is frequently restricted due to patient's immobilization. Therefore, we investigated the long-term effects of whole body vibration (WBV) which is the sort of passive exercise, on rat model of peripheral nerve injury. In these study, sciatic nerve contusion as used as a model of peripheral nerve injury produced the gait disturbance, muscle atrophy, diminishment of α-motor neuronal soma size, and spinal cord expression of synaptic markers (synaptophysin and postsynaptic density-95) of rat. Adversely, WBV for 10 days (with schedules of 30 min * 2 times per day) induced the time-dependent recovery of functional deficit, muscle hypertrophy, enlargement of α-motor neuronal soma size, and synaptic reinforcement as revealed by foot print analysis, H-E staining, confocal microscopy, and quantitative immunoblotting, respectively. Taken together, we concluded that WBV exerts a positive effects on functional recovery via protecting loss of synaptic integrity in spinal α-motor neurons after peripheral nerve injury. Further studies for elucidating upstream causes of WBV's long-term beneficial effects on peripheral nerve injury (e.g., strengthening of serotonergic neurons which usually modulates electrical firing of spinal α-motor neuron) are needed.

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HMGB1-binding heptamer suppresses synergy between HMGB1 and LPS by direct binding with HMGB1

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High mobility group box 1 (HMGB1) is an endogenous danger signal molecule. In the postischemic brain, HMGB1 is massively released during NMDA-induced acute damage and triggers inflammatory processes. Moreover, it has been reported HMGB1 augments proinflammatory function of LPS by direct interacting. In previous studies, the authors demonstrated that intranasally delivered HMGB1 binding heptamer peptide (HBHP; HMSKPVQ) affords robust neuroprotective effects in the ischemic brain after middle cerebral artery occlusion (MCAO) and that HBHP exert anti-inflammatory effect. In the present study, the authors investigated whether HBHP suppresses synergy between HMGB1 and LPS. In primary microglial cultures, low dose LPS (5 ng/ml) and recombinant HMGB1 (rHMGB1, 10 ng/ml) activate microglial cells synergistically, wherein HMGB1-LPS binding was detected. In addition, synergistic NO production by LPS (5 ng/ml) and HMGB1 accumulated in NMDA-conditioned medium (NCM) was also ob-

served in primary microglial cultures along with the direct binding between HMGB1 and LPS. Co-treatment of HBHP with LPS and rHMGB1 (or NCM) or treatment of rHMGB1 (or NCM) with LPS after pre-incubating it with HBHP markedly suppressed synergistic activation of microglial cells. Results indicate that HBHP might be able to suppress synergistic action of HMGB1and LPS. Interactions between rHMGB1 and LPS or between HMGB1 in NCM and LPS were suppressed by HBHP in a dose-dependent manner, suggesting that inhibiting HMGB1-LPS interaction might be an underlying mechanism. We also found that LBP-mediated LPS transfer to CD14 was inhibited after HBHP treatment. Together these results demonstrate that HBHP confers anti-inflammatory effects, in particular, inhibiting synergistic action between HMGB1 and LPS.

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P149

Altered expression of transcriptional coactivator with PDZ-binding motif (TAZ) in the human placenta with pregnancy-induced hypertension (PIH)

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Transcriptional co-activator with PDZ-binding motif (TAZ) was identified as a 14-3-3-binding protein. TAZ binds to a variety of transcription factors to control cell differentiation and organ development. Placenta plays critical role in fetal development. The purpose of this study was to examine the expression of TAZ in normal and pregnancy-induced hypertension (PIH) placenta. Human placenta tissues were processed for immunohistochemistry and immunoblot analysis. TAZ and 14-3-3 were localized mainly in the cytoplasm of cytotrophoblasts and syncytiotrophoblasts in normal full-term placenta. In PIH placenta, TAZ was expressed in the nucleus of cytotrophoblast and 14-3-3 was expressed in the nucleus of syncytiotrophoblast. The quantity of TAZ was increased in PIH placenta, but 14-3-3 was unchanged. Interestingly, nuclear TAZ stained cytotrophoblasts were also expressed PCNA. In contrast, nuclear 14-3-3 stained syncytiotrophoblasts showed TUNEL staining positive and did not expressed PCNA. These results suggest that TAZ and 14-3-3 are inactive in normal placenta. However, cells loss their balance and TAZ overexpressing cells are destined to proliferate, and 14-3-3 overexpressing cells have a tendency to go to apoptosis in PIH placeanta. In conclusion, altered expression of TAZ may play an important role in the pathophysiology in human placenta.

Keywords: TAZ, 14-3-3, placenta, PIH

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P150

CTCF-mediated chromatin organization at the Hoxc locus in mouse embryonic fibroblast cells

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In mammals, sequential expression of Hox genes at a specific time and space control the anteroposterior body axis during embryogenesis. However, the precise mechanisms underlying the collinearity of Hox gene expression is not fully understood. CTCF is a key molecule for chromatin structural changes that forms chromatin loops through binding to DNA. Since CTCF-mediated chromosomal organization has become crucial epigenetic mechanism for transcriptional regulation, we examined whether CTCF activity is involved in 5' Hoxc gene expression in Akt1 null MEFs compared to the wild type cells not expressing these genes. Semi-quantitative RT-PCR results showed no differences in the CTCF expression level between MEFs and Akt1 null MEFs. To determine the putative CTCF binding sites, ChIP-sequencing was done with anti-CTCF antibody in the presence or absence of Akt1. Four CTCF putative binding sites (C1, C2, C3, C4) identified through in silico analysis were validated with ChIP-PCR, and 3C analysis was performed to determine long-range interactions among these CTCF binding sites. The long range interaction frequencies among the sites were similar in MEFs and Akt1 null MEFs. Interestingly, however, C1-C2 and C1-C4 sites form strong DNA-looping interaction in Akt1 null MEFs, where hy-

pomethylation at the C1 site was detected. Demethylation at the C1 site probably increases CTCF binding affinity at this region, which subsequently induced the posterior Hox gene expression.

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P151

CD99-peptidomimetics suppress the activity of β1 integrin by decreasing the formation of focal adhesion complex through the ERK1/2-PTPN12 signaling pathway in human breast carcinoma

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CD99 is a 32kDa glycosylated transmembrane protein which is expressed on the surface of most mammalian cell types. The interaction of CD99 with the natural ligands, such as PILR and CD99 itself, has been implicated in regulating various cellular responses, including cell adhesion, migration and thymocyte differentiation. Previous studies have shown that β1 integrin has been known to play a crucial role in cell adhesion, growth, spreading, migration, proliferation, and survival of a variety of cells, as well as in developmental process. In this study, we investigated how CD99 regulates the activity of β1 integrin in breast cancer cells, and its underlying mechanisms. In human breast cancer (MCF-7) cells, CD99-peptidomimetics (CD99-derived peptides) suppressed β1 integrin activity in a dose-dependent manner and induced phosphorylation of ERK1/2, but not Akt1. CD99-peptidomimetics-mediated suppression of β1 integrin activity was ablated by transfection of siRNA targeting SHP2, RasGAP1, HRas and dominant-negative Raf, and by treating with ERK inhibitor, PD98059. Consequently, activation of the Ras/Raf/Erk signaling pathway induced the phosphorylation of FAK S910, resulting in the binding of PTPN12 and PIN1 to FAK and dephosphorylation of FAK Y397. Moreover, CD99-peptidomimetics inhibited the clustering of FAK and paxillin, which led to the disruption of focal adhesion complex and inactivation of β1 integrin. Additionally, treatment with PTPN12 siRNA abolished the suppression of integrin β1 activation and dephosphorylation of FAK Y397, which were induced by CD99-derived peptide. Taken together, these results represent that PTPN12 plays a critical role in suppression of β1 integrin activity through the HRas-ERK1/2-FAK signaling pathway induced by CD99-peptidomimetics.

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P152

Reduced expression of CD99 and CD99L2 secretory isoforms in rheumatoid arthritis patients

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The rheumatoid arthritis (RA) is an autoimmune disorder that leads to progressive inflammatory reaction and destruction of diarthrodial joint. Human CD99 and CD99L2 are known to regulate infiltration of immune cells into the inflammed loci. They generate nine isoforms including secretory forms by alternative splicing, respectively. Our previous data showed that a secretory isoform, CD99L2-VI, functions as a CD99 agonist. In this study, we investigated the change of CD99 and CD99L2 isoform mRNA levels in RA patient group compared to healthy controls using quantitative polymerase chain reaction. Our results revealed that there is significant differences between heathy males(n=15) and females(n=15) in the mRNA expression levels of CD99-IX secretory isoform. The mRNA expression levels of secretory isoform CD99-IX were two times higher in healthy females than in males ($p < 0.001$). We compared CD99 and CD99L2 isoform mRNA levels in peripheral white blood cells between RA patients and healthy controls. The mRNA levels of secretory isoforms, CD99-IX and CD99L2-VI, were significantly downregulated in female RA patient group (n=23) compared to normal female group ($p<0.01$ and $p<0.001$, respectively). However, in male RA patient group (n=3) compared to normal male group. ($p<0.01$), only the mRNA level of CD99L2-VI was downregulated.

These results suggest that reduced expression of CD99 and CD99L2 secretory isoforms may prevent them from controlling extravasation of immune cells, and that secretory isoforms of CD99 and CD99L2 may be ideal RA therapeutic agents.

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P153

A MITF antagonist peptide (SE207C) inhibits melanogenesis by suppression of MITF activity in B16F1 melanoma cells and human epidermal malanocytes

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Melanin is synthesized in melanosomes present in melanocytes by the action of a variety of stimulators, α-melanocyte stimulating hormone (α-MSH) and cyclic AMP (cAMP)-elevating agents or by absorbing ultraviolet light. These external stimulators activate adenylyl cyclase and upregulate intracellular cyclic AMP level, which subsequently activates microphthalmia-associated transcription factor (MITF) that is a transcription factor for melanocyte-specific enzymes, including tyrosinase (TYR), tyrosinase-related protein-1 (TRP-1), and tyrosinase-related protein-2 (TRP-2). In this study, we investigated anti-melanogenic activities of a MITF-derived antagonist peptide (SE207C) and its underling mechanism in B16F1 melanoma cells and primary human epidermal melanocytes (HEMs). Treatment of melanocytes with SE207C inhibited α-MSH-induced melanin production, TYR activity and proliferation. Furthermore, SE207C reduced the expression of melanin-related genes at both mRNA and protein levels in a dose-dependent manner. On the other hand, the mRNA and protein expression of MITF were not changed by treatment with SE207C. The upstream signaling pathways including cAMP response element-binding protein (CREB), glycogen synthase kinase-3β (GSK-3β), and Akt for activation were also not affected by SE207C. Interestingly, we found that the SE207C inhibited MITF from binding to the promoter region of tyrosinase gene. Moreover, SE207C decreased the formation of MITF-β-catenin and MITF-CREB a complex, which led to a decrease in melanin synthesis. Collectively, these results suggest that SE207C might be a promising candidate for the treatment of MITF-associated disorders.

Keywords: Peptides, Melanogenesis, MITF, Tyrosinase, B16F1

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P154

Vandetanib controls the migration through regulation of ADAM and MAPK in EBV-infected Human retina pigment epithelial cells

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Choroidal neovascularisation (CNV) occurs during wet age-related macular degeneration (AMD), which is the main cause of blindness elderly people. Vandetanib is a multiple tyrosine kinase inhibitor that specifically blocks VEGFR2, EGFR-related signaling pathway. EBV-infected APRE19 cell (ARPE19-EBV) over-expressed VEGFR2, EGFR, a disintegrin and metalloproteinase (ADAM), and various signaling molecules, that induce angiogenesis and migration. This study investigated the effect of anti-migration of vandetanib on ARPE19-EBV cells as a model of CNV.Vandetanib inhibited the expression of VEGFR2, EGFR, ADAM10 and ADAM17 expression and migration. ADAM inhibitor also blocked the migration of ARPE19-EBV after treatment with VEGF. Furthermore, vandetanib attenuated MAPK signaling pathway. In addition, vandetanib regulated EMT markers, including E-cadherin, N-cadherin, vimentin and snail. These results suggest that vandetanib modulate through the inhibition of VEGFR2, EGFR via ADAM expression and MAPK signaling pathway.

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P155

Unmethylation of the CHRNB4 gene is an unfavorable prognostic factor in non-small cell lung cancer

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Objectives: Lung cancer is the leading cause of cancer-related deaths and is currently a major health problem owing to difficulties in diagnosis at the early stage of the disease. Changes in DNA methylation status have now been identified as a critical component in the initiation of lung cancer, and the detection of DNA methylation is expected to be an important method for the early diagnosis of lung cancer. Nicotine, the principal tobacco alkaloid, directly contributes to lung carcinogenesis through the activation of nicotinic acetylcholine receptors (nAchRs). **Materials and Methods:** To investigate the role of the CHRNB4 gene, which encodes the nAchR b4 subunit that is ubiquitously expressed on lung epithelial cells, we analyzed its methylation status in 266 patients with non-small cell lung cancer (NSCLC) by using methylation-specific polymerase chain reaction and compared it with clinicopathological parameters. **Results and Conclusion:** The frequency of CHRNB4 unmethylation was 13.5% and 8.3% in malignant and nonmalignant tissues, respectively. CHRNB4 demethylation was associated with upregulation of its mRNA expression and was more frequent in squamous cell carcinoma and pathological stage II?IIIA disease than in adenocarcinoma and pathological stage I disease, respectively (P = 0.003 and P = 0.01, respectively). Univariate and multivariate analyses showed that CHRNB4 unmethylation was significantly associated with unfavorable overall survival in the entire patient group as well as in men and ever-smokers. These results suggest that epigenetic regulation of CHRNB4 may affect tumor progression and survival in patients with NSCLC. Further investigation into the molecular basis of the role of CHRNB4 in the progression of NSCLC is warranted.

Keywords: Non-small cell lung cancer; Nicotinic acetylcholine receptors; CHRNB4; Unmethylation; Methylation-specific polymerase chain reaction; Prognosis

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Body mass index (BMI)-associated global DNA methylation change in healthy Korean women

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Obesity is known to be strongly associated with cardiovascular disease and cancer, the leading causes of mortality worldwide, and develops owing to interactions between genes and the environment. DNA methylation can act as a downstream effector of environmental signals, and analysis of this process therefore holds substantial promise for identifying mechanisms through which genetic and environmental factors jointly contribute to disease risk. Global DNA methylation of peripheral blood cells has recently been proposed as a potential biomarker for disease risk. Repetitive element DNA methylation has been shown to be associated with prominent obesity-related chronic diseases, but little is known about its relationship with weight status. In this study, we quantified the methylation of Alu elements in the peripheral blood DNA of 244 healthy women with a range of body mass indexes (BMIs) using pyrosequencing technology. Among the study participants, certain clinical laboratory parameters, including hemoglobin, serum glutamic oxaloacetic transaminase, serum glutamic-pyruvic transaminase, total cholesterol, and triglyceride levels were found to be strongly associated with BMI. Moreover, a U-shaped association between BMI and Alu methylation was observed, with the lowest methylation levels occurring at BMIs of between 23 and 30 kg/m2. However,there was no significant association between Alumethylationandage, smoking status,or alcohol consumption. Overall,we identified a differential influence of BMI on global DNA methylation in healthy Korean women,indicating that BMI-related changes in Alumethylation might play a complex role in the etiology and pathogenesis of obesity. Further studies are required to elucidate the mechanisms under lying this relationship.

Keywords: Methylation, Alu1, BMI, Pyrosequencing, U-shape

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Hyper-O-GlcNAcylation in human Cervical Carcinogenesis

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O-GlcNAcylation is a process of reversible posttranslational modification of serine or threonine residue of protein and plays important roles in cancer metabolism. Levels of O-linked N-Acetyl glucosamine (O-GlcNAc) are increased in cancer cells, which regulate various biological processes. Our previous researches showed that O-GlcNAcylated HCF-1 induces the expression of Human Papilloma Virus (HPVs) E6/E7 oncogenes, which modulate the epigenetic modification of tumor genes in cervical cancer. Here, we investigate the further effects of O-GlcNAcylated HCF-1 in human cervical carcinogenesis in vivo and in vitro. Hyper-O-GlcNAcylated HCF-1 enhances the expression of EZH2, chromatin remodeling protein, and induces cell cycle progresses by regulation of cell cycle regulating proteins, such as FoxM1, p27 and p16 in human cervical cancer tissues. We also found that hyper-O-GlcNAcyclation increased the expression of secretory clusterin (sClu) gene, which induces the carcinogenesis and drug-resistance in cancer therapy. Knock - down of O-GlcNAc transferase(OGT) using rentiviral shOGT transduction shows the anti -tumor effect. shOGT transduced Hela cells decreased the expression of epigenetic modulator genes and cell cycle progressing genes compared to Hela cell. Expression of sClu which induces the drug-resistance was also decreased in shOGT Hela cells. Our results suggest that O-GlcNAcylated HCF-1 increases the sClu expression which induces carcinogenesis and drug-resistance in cervical cancer.

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P158

Burkitt's lymphoma exosome-mediated delivery of miR-155 to retinal pigment epithelial cells

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Exosomes are extracellularly secreted vesicles ranging 50-100 nm in diameter and thought to play important roles in intercellular communications. Exosomes contain numerous proteins, mRNAs, miRNAs, and lipids that can affect the status of recipient cells in various pathological conditions. MicroRNAs (miRNAs) are small non-coding RNAs that play a major role in post-transcriptional gene silencing by interacting with the 3'-untranslated regions (UTRs) of target genes. Epstein-Barr virus (EBV) infection induces sustained elevation of cellular miRNAs such as miR-21, miR-146a, and miR-155 via NFκB. We hypothesized that miRNAs delivered by exosomes might affect angiogenesis of retinal pigment epithelial (RPE) cell. Here we demonstrated that co-culture of EBV-positive Burkitt's lymphoma cells (BL, Raji) with retinal pigment epithelial cells (ARPE-19) increased the level of miR-21, 146a, and 155 in recipient cells while no major difference was detected in co-culture with EBV-negative BL cells (Ramos). With PEG 6000 or Exo-SpinTM, exosomes were isolated from both Raji and Ramos cells and isolated exosomes were treated to recipient ARPE-19 cells for 1-3 days. Increased transcriptional and translational levels of VEGF-A, a major angiogenic factor, were detected by quantitative PCR and ELISA, which pretreatment of endocytosis inhibitor e.g. sodium azide annulled these effects of treated exosomes. Roles of delivered miR-155 in angiogenesis were tested using exosomes loaded with miR-155 mimics and inhibitors. MiR-155 transferred exosomes from Ramos and HEK293 increased VEGF-A level in recipient ARPE-19 cells. Consequently our results demonstrate that sustainedly accumulated miRNAs might affect remote recipient cells such as retinal pigment epithelial cells via exosomes.

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P159

Celecoxib down-regulates angiogenic factor of retinal pigment epithelial cells in hypoxic state via HIF-1α degradation

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Age-related macular degeneration (AMD) is a common disease causing blindness in the aging population. There are two forms of AMD, the wet form and the dry form. AMD affects central regions of the retina and choroid that can lose vision. This disease starts with drusen between retinal pigment epithelium (RPE) and Bruch's membrane. The RPE is an epithelial monolayer located between the choroid and the photoreceptors. Its function is necessary supporting vision. Hypoxic state is deeply associated with abnormal vessel formation in AMD. Hypoxia accumulate hypoxia-inducible factor-α (HIF-1α) and induce angiogenesis. In this study, we investigated that HIF-1α was up-regulated in RPE cells which was exposed hypoxic states. Increasement of HIF-1α was degraded after treatment with celecoxib, an inhibitor of cyclooxygenase-2 (COX-2), on hypoxic RPE cells. We also observed that celecoxib blocked vascular endothelial growth factor (VEGF) induction in hypoxic RPE cells. We investigated that celecoxib might regulate degradation by proteasome. Taken together, we suggest that these effects of celecoxib down-regulate angiogenesis through HIF-1α degradation and can support prevention of neovascularization of AMD.

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The Epstein-Barr virus causes epithelial-mesenchymal transition in human corneal epithelial cells via Syk/Src and Akt/Erk signaling pathways

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Purpose: Although Epstein-Barr virus (EBV)-associated keratitis is rare, it can cause acute corneal necrosis and neovascularization. We aimed to examine the signaling mechanism by which EBV causes epithelial-mesenchymal transition (EMT) in human corneal epithelial cells (HCECs) in vitro. **Methods:** The cellular response to EBV was assessed by real-time polymerase chain reaction, Western blot, migration assay, invasion assay, inhibitor assay, and ELISA assay. **Results:** A model of EBV-induced EMT was established in HCECs. EBV induced morphological changes in the cells; the loss of epithelial markers E-cadherin, ZO-1, and β-catenin; and an increase in the mesenchymal markers N-cadherin, Vimentin, Snail, and TCF8/Zeb1. EBV infection also led to the nuclear translocation of Snail and TCF8/Zeb1; enhanced the secretion of IL-6, IL-8, VEGF, TGF-β1, TNF-α, and MCP-1; and up-regulated the expression of MMP2 and MMP9. EBV-infected HCECs exhibited increased migration and invasiveness compared to uninfected HCECs. We measured the involvement of Syk, Src, PI3K/Akt, and Erk signaling, but not Smad, in EMT by EBV-induced TGF-β1. We demonstrated that treatment with TGF-β1, TGF-β receptors, Syk, or Src inhibitor blocked TGF-β1, Syk, or Src signaling activation and EMT development by EBV. Moreover, these inhibitors prevented PI3K/Akt and Erk activation. **Conclusion:** EBV infection in HCECs can lead to a mesenchymal fibroblast-like morphology and cause EMT through the activation of PI3K/Akt and Erk by TGF-β1-mediated Syk and Src signaling. This phenomenon may have implications for EBV-associated keratitis and molecular approaches to treatment.

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P161

Trail mediates erlotinib-induced apoptosis in non-small cell lung cancer cell

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Three-dimensional (3D) cell culture has mimic in vivo cells and microenvironment compared to conventional two-dimentional (2D) culture. Spheroids are one tool for creating 3D model. Here, we investigated that phenotypic and functional differences between 2D and 3D cultures of human non-small cell lung cancer (NSCLC). Erlotinib, a tyrosine kinase inhibitor (TKI), induced apoptosis in 3D spheroid cell, but not in 2D monolayer cell. The proapoptotic BH3-only BCL-2 family protein Bim was increased in 3D spheorid cell. This finding indicates that Bim expression is associated with apoptosis in NSCLC. Moreover, we found that 3D spheroid cells expressed TNF-related apoptosis-inducing ligand (TRAIL), whereas the expression of Fas / FasL was not changed in 3D spheroid cells. Silencing of TRAIL inhibited anti-tumor activity of erlotinib in 3D spheroid cells. These findings suggest that 3D cell spheroid culture changes the cellular response to drug and may be effective therapeutic approaches for the natural NSCLC.

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지속적인 고농도 카페인 노출이 사춘기 수컷 쥐의 골격 성장에 미치는 영향

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목적: 임신 중 카페인 섭취는 태아의 골화를 지연시켜 골격 성장을 저해하는 것으로 알려져 있다. 그러나 골 성장이 급속히 이루어지는 시기인 사춘기 동안 고농도 카페인 섭취가 어떠한 영향을 미치는지 여부는 명확히 알려진 바가 없다. 따라서 본 연구에서는 지속적인 고농도 카페인 노출이 사춘기 골 성장에 미치는 영향을 알아보고자 하였다. **실험방법:** 미성숙한 수컷 쥐를 이용하여 대조군(n=17) 및 카페인 120mg/kg(n=16), 180mg/kg(n=14) 투여군으로 분류하여 매일 오전에 정해진 양의 카페인을 위장관 내로 4주간 투여하였다. 실험 기간 동안 체중 변화 및 식이 섭취량을 관찰하였으며, 실험이 종료되기 전 날 Dual energy X-ray absorptiometry(DEXA)와 PET-CT로 체성분 및 경골에서의 18F-NaF uptake를 분석하였다. 실험 종료 후에는 대퇴골과 경골을 분리하여 실제 길이와 무게를 계측하여 기록하였으며, 추가적으로 경골 말단부의 조직 소견을 분석하여 비교 관찰하였다. **결과:** 본 연구 결과, 카페인 투여량에 따른 체중 증가량의 감소로 4주 후 대조군 및 카페인 투여군의 몸무게는 각각 242.2±12.6g 및 190.5±15.3g와 183.8±12.2g으로 유의한 차이가 관찰되었다($p<0.001$). 마찬가지로, 식이섭취량에 있어서도 카페인 투여군에서 감소하는 소견을 보였다. 이는 카페인 투여 4주째 측정한 체성분 검사 결과와도 일치하는 소견으로, 카페인 투여군에서 전반적인 체지방 및 제지방 질량(lean body mass)의 현저한 감소가 확인되었다. 한편, 신체 전체의 골밀도 및 골 무기질함량에 있어서도 카페인 투여군에서 유의하게 감소하는 소견이 관찰되었다. 특히 뼈의 길이 성장을 확인하는데 유용한 양측 경골에서도 골 무기질함량(g)이 대조군 및 카페인 투여군에서 각각 0.17±0.02 및 0.14±0.02와 0.14±0.02, 골밀도(g/cm2)는 0.195±0.01 및 0.182±0.05와 0.179±0.01로 카페인 투여군에서 유의한 감소를 보였으며($p<0.01$), 카페인 투여 용량에 따른 차이는 관찰되지 않았다. 카페인 투여군에서의 경골 골밀도 및 골 무기질함량의 감소와 마찬가지로 경골 성장판에서 측정한 18F-NaF uptake의 감소가 관찰되었다 (대조군, 4.20±0.83, 카페인 투여군, 3.51±0.31와 3.66±0.37)($p<0.05$). 또한 카페인 투여군에서 장골(대퇴골, 경골)의 무게와 길이 및 전체 척추 길이의 현저한 감소가 관찰되었으며, 이러한 장골 성장 저해는 경골 성장판의 조직학적 변화를 동반하는 것으로 확인되었다. **결론:** 사춘기 시기는 신체의 발달과 골격이 빠르게 성장하는 시기이다. 그러나 이 시기의 지속적인 고농도 카페인 섭취는 식욕을 감퇴시키고 신체 발달에 필요한 지방과 골 무기질함량을 감소시켰다. 특히, 고농도 카페인으로 인해 경골 성장판 내의 chondrocyte의 활성이 저해되었고, 정상조직과 다른 불규칙적인 배열을 보였으며, 뼈의 성숙과 성장이 일어나는 골단에서 골의 길이 성장을 방해하는 것으로 보인다.

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Renal inducible nitric oxide synthase is induced only in the interstitial cells in various renal injury rat models

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Although inducible nitric oxide synthase(iNOS) is known to play significant roles in the kidney, its localization has long been controversial. We previously demonstrated the precise localization of iNOS in LPS-treated rat kidneys(J Histochem Cytochem 60:301-15,2012). Here, we extended the localization of renal iNOS to the several experimental models of renal injury; ischemia reperfusion(1, 3 & 7 days), unirateral urethral obstruction(5, 10 & 21 days), streptozotocin-induced diabetes mellitus(30 & 40 weeks) and adriamycin-induced nephropathy(12 week) rat models. In all the models after injury, iNOS-immunoreactivities were shown only in the exfoliated tubular cells, some of the interstitial cells and cortical tubular cells. However, unlike interstitial cells, both exfoliated tubular cells and cortical tubular cells showed no iNOS-reaction in the cytosolic portion but in the mitochondria. Electron microscopy for NADPH-diaphorase revealed that the reaction products were localized to the mitochondria of the exfoliated cells and cortical tubular cells, moreover, immunoelectron microscopy demonstrated that iNOS-immunoreactions were restricted to swollen mitochondria. Qantitative real-time reverse transcriptase polymerase chain reaction showed there was low basal expression of iNOS mRNA from dissociated tubules even after injuries. In contrast, there was increases in iNOS mRNA from renal tissues after injuries. These findings suggest that renal iNOS may be induced only in interstitial cells not in the tubular cells after renal injury of four experimental models, and that low basal expression of iNOS mRNA in the tubular cells may be the source of mtNOS in the tubular cells.

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P164

Combined modulation of actin rearrangement and transcription by eupatilin cures osteoporosis

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Eupatilin, a active flavone derived from the Artemisia plants, has been revealed to have pharmaceutical efficacy on inflammation, tumor, cancer, allergy, and oxidation. Also, eupatilin is a main constituent of stillen which is a anti-peptic ulcer drug dominantly used in Korea. However, the correlation between eupatilin and bone metabolism has not been identified. In this study, we priorly confirmed that eupatilin significantly suppressed the formation of TRAP-positive multinucleated cells in bone marrow macrophages (BMMs) dose dependently via modulating the phosphorylation of IκB, Akt, and its downstream, GSK3? pathway. This blockade of signal transduction was accompanied by the attenuation of c-Fos and nuclear factor of activated T cell c1 (NFATc1) activation. Subsequently, eupatilin deteriorated rearrangement of actin ring and bone resorbing activity of mature osteoclasts. Furthermore, the administration of eupatilin has both preventive and therapeutic effects in a murine model of lipopolysacharide (LPS)-induced bone loss and has the improvement effect in a mice model of ovariectomy-induced bone loss in vivo. Surprisingly, eupatilin suppressed the differentiation of human blood mononuclear cells (HBMCs) into osteoclastic giant cells via inhibiting the phosphorylation of Akt, GSK3?, and IκB which are coincide with anti-osteoclastogenic activity of eupatilin in BMMs. Taken together, our study verified that eupatilin could be worth a novel therapeutic agent against bone loss-related diseases including osteoporosis, rheumatoid arthritis, and periodontitis.

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Reduced expression of CD99 and CD99L2 secretory isoforms in rheumatoid arthritis patients

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The rheumatoid arthritis (RA) is an autoimmune disorder that leads to progressive inflammatory reaction and destruction of diarthrodial joint. Human CD99 and CD99L2 are known to regulate infiltration of immune cells into the inflammed loci. They generate nine isoforms including secretory forms by alternative splicing, respectively. Our previous data showed that a secretory isoform, CD99L2-VI, functions as a CD99 agonist. In this study, we investigated the change of CD99 and CD99L2 isoform mRNA levels in RA patient group compared to healthy controls using quantitative polymerase chain reaction. Our results revealed that there is significant differences between heathy males(n=15) and females(n=15) in the mRNA expression levels of CD99-IX secretory isoform. The mRNA expression levels of secretory isoform CD99-IX were two times higher in healthy females than in males ($p < 0.001$). We compared CD99 and CD99L2 isoform mRNA levels in peripheral white blood cells between RA patients and healthy controls. The mRNA levels of secretory isoforms, CD99-IX and CD99L2-VI, were significantly downregulated in female RA patient group (n=23) compared to normal female group ($p<0.01$ and $p<0.001$, respectively). However, in male RA patient group (n=3) compared to normal male group. ($p<0.01$), only the mRNA level of CD99L2-VI was downregulated. These results suggest that reduced expression of CD99 and CD99L2 secretory isoforms may prevent them from controlling extravasation of immune cells, and that secretory isoforms of CD99 and CD99L2 may be ideal RA therapeutic agents.

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A hydrogel-based 3D cell culture promotes malignancy of mouse T cell lymphoma

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Lymphoma is one of the most perplexing and complicated types of cancer which accounts for about 10 percent of human neoplasm. Malignant lymphoma has highly variable clinical course and prognosis. Malignancy includes growth, metastasis, cell-to-matrix and cell-to-cell interaction, intracellular signaling, and resistance to chemotherapy and radiation therapy. Since it is believed that spatial organization may profoundly affect tumor cell behavior, we established a 3D encapsulated culture model of mouse T cell lymphoma (EL4) using an agarose-collagen-alginate hydrogel matrix, and analyzed various cellular activities associated with its malignancy in this study. Morphological and histological examination of the 3D cultured cells confirmed the formation of well-established multicellular spheroids. RT-PCR, western blot, immunoflorescence and FACS analysis also revealed that expression of various genes related to drug resistance and malignancy was significantly upregulated in EL4 cells after 3D culture compared to 2D culture. Furthermore, EL4 cells cultured in the 3D hydrogel matrix exhibited a difference in cell proliferation activity compared to those in the 2D monolayer culture both with and without treatment of anticancer agents. Altogether, our data demonstrate that spatial organization strongly influences the response to malignancy of EL4 cells, supporting the use of our 3D models for the testing of therapeutic agents in lymphoma.

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A hydrogel-based 3D cell culture enhances malignancy and chemoresistance of human ovarian cancer

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Two-dimensional (2D) monolayer cultures have predominantly been used for biomedical researches, but they have serious flaws since are unable to recapitulate are alistic three-dimensional (3D) environment where the functional properties of cells can be observed and manipulated. In this study, we developed a 3D multicellular spheroid tumor model of human ovarian cancer cells using an agarose-collagen-alginate (ACA) composite hydrogel. The A2780 human ovarian cancer cells efficiently formed multicellular tumor spheroids (MTS) with uniform distribution, and showed a feature of budding formation which is suggestive of malignant transformation in ACA hydrogels. The hypoxic zone of the A2780 MTS was distinguished by the high expression of HIF-1α at the center of the spheroids with marked induction of cleaved caspase-3. Moreover, the expression of genes related with epithelial-to-mesenchymal transition (EMT) and cancer stem cells (CSCs) including Notch-1, Notch-2, Notch-3,Notch-4, Hes-1, Snail, vimentin, CD44, HIF-1α, and ET-1, was upregulated in the A2780 cell spheroids. Subsequently, the A2780 spheroids showed a marked resistance to paclitaxel and curcuminas compared to 2D cell culture. The drug diffusion assay confirmed that drug was homogeneously distributed throughout the whole area of the spheroids. Notch-1 and Notch-3expression was upregulated in 3D culture of A2780 cells after treatment with a selected dose of paclitaxel. Taken together, this study will provide useful information toward the development of improved biomimetic invitro human ovarian tumor models for pre-clinical drug development using ACA hydrogel culture system.

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Hydrogen sulfide ac celerates functional and morphological recovery of kidney after ischemia/ reperfusion injury in mice

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Hydrogen sulfide (H2S), at hird novel biological gas, plays a protective role in ischemia/reperfusion(I/R)-induced acute kidney injury. However, the role of H2S in the repair process after kidney injury remains to be defined. Here, we investigated the role of H2S in recovery of kidney function and morphology following I/R injury. Mice were subjected to either 30min of bilateral renal ischemia or sham operation. Some mice were administered with NaHS, an exogenous H2S donor, and propargylglycine(PAG), an inhibitor of cystathionine gamma lyase(CSE) which is a major H2S producing enzyme in the kidney, beginning at 2 day after ischemia until sacrifice daily. I/R resulted in severe tubular cell damage and functional loss in the kidney as evaluated by PAS staining and plasma creatinine (PCr) concentration, respectively. Eight days after the transient ischemia, the kidney was functionally recovered with a partial restoration of damaged tubules. I/R reduced expression, and activities of CSE and cystathionine beta synthase (CBS). The reduced activities and expression were gradually recovered over time. Administration of NaHS accelerated return to normal level of PCr, whereas administration of PAG delayed that. Furthermore, NaHS treatment decreased mortality of mice after I/R, whereas PAG treatment increased that. Administration of NaHS accelerated 5-Bromo-2′-Deoxyuridine (BrdU) incorporation into the tubular epithelial cell, whereas PAG delayed that. Our findings demonstrate that H2S accelerated restoration of damaged tubules following I/R, suggesting that H2S could be a therapeutic target for acute kidney injury.

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Zuckerkandl's tubercle of the thyroid gland: a description of its location in the anatomical position, and comparative morphology of the same specimens before and after fixation

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Objective: The aim of this study was to elucidate the definition of

the borders and surface of the thyroid lobe in the anatomical position, and to compare the morphology of Zuckerkandl's tubercle (ZT) in fresh and fixed states. **Materials and Methods:** Fifty thyroid lobes of 25 fresh Korean cadavers were used. **Results:** The lateral border of the thyroid lobe could be defined as the most lateral margin of its anterior aspect when in the anatomical position. The posteromedial border was the margin that projected toward the trachea or tracheoesophageal groove. The lateral and posteromedial borders, and the posterior surface between these borders of the thyroid lobe could usually be identified in fixed cadavers. The posterolateral border could only be identified in the thyroid lobe by compression of the internal carotid artery in cross-sectioned specimens and CT images. The ZT was identifiable in 84% of both the fresh and fixed specimens. The ZT was identified mainly at the posteromedial border of the thyroid lobe when in the anatomical position, and extended to the tracheoesophageal groove or esophagus. In the fresh state, the ZT projected as a rounded cone with a usually semicircular base, but its shape varied diversely in the fixed state. **Conclusion:** In the present study the ZT was found to be located at the posteromedial border or posterior surface of the thyroid lobe in both the fresh and fixed states, contrary to most previous reports. The location of the ZT should be established in the anatomical position to avoid confusion.

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Role of mast cell in a murine asthma model

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Mast cells are thought to be important in the cause of allergic diseases, but the role of mast cells in the airway remodeling of chronic long-term asthma remains controversial. In this study, using the mast cell "nock in" strategy to get the mast cell-deficient WBB6F_1-W/W^vmice(W/W^v) selectively reconstituted bone marrow-cultured mast cells (BMCMCs) from normal congenic wild-type mice (+/+) (+/+BMCMCs→W/W^vmice), mice were employed to study the roles of mast cell in a murine asthma model. The mice were sensitized with ovalbumin (OVA) and challenged with OVA for 14 weeks. The mice were assessed airway reactivity by PenH. The lungs and trachea were stained with H-E for pathologic alteration, toluidine blue for mast cell, congo red for eosinophil, PAS for goblet cell and Masson's-trichrome for fibrosis. Mast cells were not observed in the lungs of control and OVA-sensitized and challenged W/W^V mice, but OVA-sensitization and challenge increased mast cell number in +/+ mice and +/+BMCMCs→W/W^V mice. OVA-sensitization and challenge could enhance airway reactivity, pathologic alteration, eosinophil infiltration, goblet cell hyperplasia and fibrosis in +/+ mice. The pathologic changes of OVA treated W/W^V mice were less than that of +/+ mice, but +/+BMCMCs→W/W^V mice could restore the reaction to OVA-sensitization and challenge of +/+ mice. These results indicate that the mast cell play an important role in the OVA-induced chronic murine asthma model.

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Effect of sorafenib on pulmonary fibrosis induced by lipopolysac charide

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Acute respiratory distress syndrome (ARDS), which occurs by various insults such as pneumonia and trauma, causes significant mortality and morbidity. Especially fibroproliferative response is associated with high mortality and diminished quality of life among ARDS survivors. Sorafenib, one of multi-kinase inhibitors, showed anti-fibrotic effect through antagonizing tissue TGF-β1-mediated epithelial mesenchymal transition in experimental model. So in this study, we investigated whether SA-1 show similar anti-fibrotic effect on fibroproliferative phase of lipopolysaccharide (LPS) induced

acute lung injury (ALI) model in mice. Also we try to reveal the potential effect of sorafenib on the early phase of ALI by measuring pro-inflammatory cytokine and growth factor. Histopathology was done using hematoxylin-eosin and masson-trichrome staining, and real time PCR for mRNA expression and ELISA assay for various cytokines production were measured using BAL fluid and tissue lysate. mRNA and protein expressions of TGF-β1 and epithelial and mesenchymal cell markers were measured in lung tissue lysates of 1week. Sorafenib attenuated the acute inflammatory response and fibrosis induced by LPS treatment on histologic examination. Sorafenib suppressed the increased gene expression of IL-6, 8, MCP-1 and VEGF in lung tissue lysate of 48 hrs and 1 week. Also, sorafenib decreased the concentration of IL-6, 8, MCP-1, VEGF, TGF-β1, and TNF-α which were increased by LPS injection. In lung tissue of 1week, sorafenib suppressed the LPS induced increased gene expression of TGF-β1 and mesenchymal cell markers, and increased the expression of epithelial cell marker, E-cadherin. Taken together, in this LPS-induced acute lung injury model, sorafenib attenuated both acute inflammatory and fibroproliferative response by suppressing various mediators related to acute and late phase of ALI.

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Volitional suppression of cortical theta without sensory feedback in rats

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Rhythmic activity of the brain reflects cognitive and behavioral function. Neurofeedback therapy which aims at the voluntary control of brain rhythms has shown its effectiveness to many psychiatric disorders such as ADHD and depression in humnas. However, well-controlled animal studies are required to elucidate neurofeedback and its effect on brain rhythms. Here, we examined feasibility of voluntary control of rhythmic activity in rats. Parietal theta rhythms were conditioned using brain stimulation reward (electrical excitation of medial forebrain bundle (MFB)). Since MFB stimulation give rise to elevated theta rhythms, rats were rewarded whenever suppressing theta rhythms. Theta band was divided into overlapping three sub-bands (4-8 Hz, 6-10 Hz and 8-12 Hz). Sensory feedback which signals the state of the rhythms instantly was completely omitted. Reward increased theta rhythms of 6 to 12 Hz while rats trained to suppress theta of 8-12 Hz band showed significantly reduced theta rhythms compared to yoked control rats. Spectral analysis revealed that suppressed theta was correlated with the shift of spectral peaks. Furthermore, rhythmic activity could be volitionally modulated within a single daily session without sensory feedback. Data suggest that rats could successfully modulate rhythmic activity when band ranges and spectral peak dynamics are considered under our experimental framework. This might contribute to expand the understanding of human neurofeedback as well as the development of the animal model for self-regulation of brain activity.

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