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Hankok Medical Science Foundation (since 1971)

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2015
ANNUAL MEETING

KOREAN ASSOCIATION OF ANATOMISTS

제65회 대한해부학회 학술대회

순서 및 초록

2015. 10. 14 ~ 16

고려대학교 의과대학

주관
대한해부학회

후원
한국과학기술인총연합회
한국의학학술지원재단

〈감사의 말씀〉
본 학술대회의 원활한 진행을 위해서 보이지 않는 곳에서 애써주신 분들께 심심한 감사를 표하는 바입니다.
본 학술대회 초록집은 2015년도 한국과학기술단체총연합회 학술활동 지원사업에 의해 인쇄 제작 되었으며, 본 행사는 한국의학학술지원재단의 일부 재정지원에 의하여 이루어졌습니다.

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	12:00 ~ 13:00	점심	
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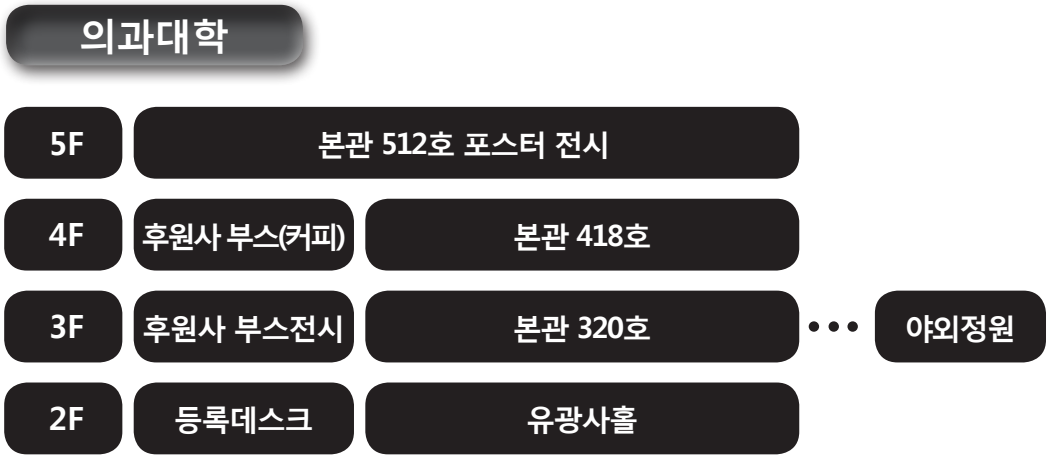
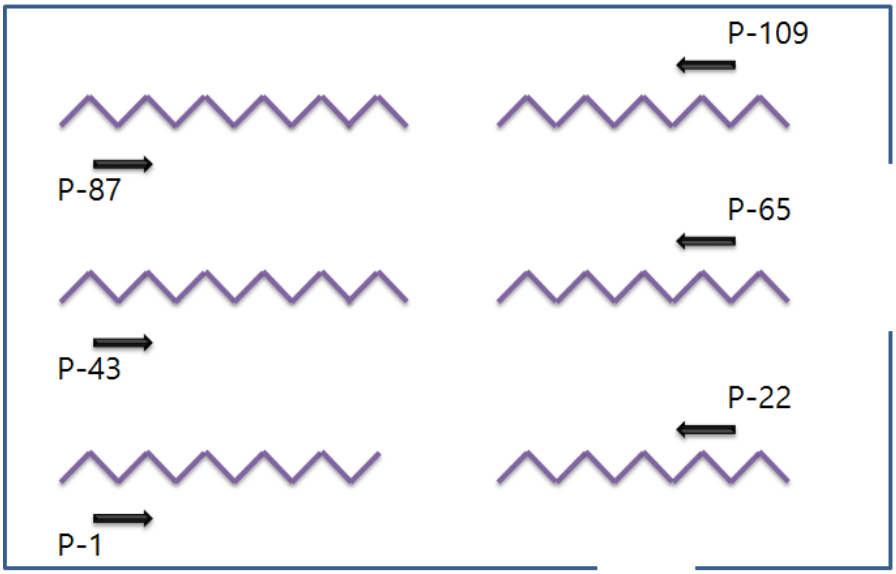
	16:45 ~	제65회 정기총회 (유광사홀)	

학술대회장 배치도



전시발표 배치도 본관 521호: 해부학 실습실

(전시시간: 2015년 10월 15일(목) 오전 7시 – 16일(금) 오후 4시)



Plenary Lecture-1

2015년 10월 15일(목) 11:00 ~ 12:00
유광사홀

좌장 유임주
고려대

PL-1 **11:00-12:00**

Remodeling of Cortical Neuronal Circuits
–Neuron–glia Interaction *in vivo*-

Nabekura Junichi • National Institute for Physiological Sciences

PL-1

Remodeling of Cortical Neuronal Circuits –Neuron–glia Interaction *in vivo*-

Nabekura Junichi /National Institute for Physiological Sciences

Recent advance in two photon excitation microscope enables us to observe the fine structures and neuronal activity in the various organs and tissues in an in vivo condition. Here, we introduce two topics of synapse structural dynamics of mice cortex and the contribution of glia cells, microglia and astrocyte, to these synapse dynamics in pathological conditions.
1) Microglia, immune cells in the brain, selectively and regularly contact onto the synapses in the mature cortex. In the damaged brain areas, e.g. penumbra adjacent to ischemic core, microglia contact became much prolonged in duration, frequently associated with elimination of damaged synapses. In addition, microglia also contact onto the swollen axon of damaged neurons, and rescue the cell death by preventing the depolarizing neuronal excitotoxicity.
2) In chronic pain model mice receiving peripheral sciatic nerve injury, spine turnover (generation and loss) in the primary somatosensory cortex (S1) corresponding to the injured paw markedly increased during an early phase of neuropathic pain, in which pain sensation gradually exaggerated. In the this phase, astrocyte activity was also enhanced. The manipulation of astrocytic activity in vivo with gene manipulation and uncaging of Ca2+ in the targeted astrocyte, affected synapse turnover and chronic pain behavior. Thrombospondin 1 could be proposed molecule released from astrocyte to generate the new spines, which possibly contributes to the synapse remodeling and the development of exaggerated pain sensation after peripheral nerve injury.

Keywords: Microglia, Nerve injury, Thrombospondin 1

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Plenary Lecture-2

2015년 10월 16일(금) 11:00 ~ 12:00
유광사홀

좌장 최완성
경상대

PL-2 **11:00-12:00**

Attenuation of Gliosis by a FAM19A5 Antibody Improves Motor Behaviors of the Nerve-Injured Animals

Jae Young Seong • Graduate School of Biomedical Sciences, Korea University

PL-2

Attenuation of Gliosis by a FAM19A5 Antibody Improves Motor Behaviors of the Nerve-Injured Animals

Jae Young Seong /Graduate School of Biomedical Sciences, Korea University

Although family with sequence similarity 19 member A5 (FAM19A5), a novel neurosecretory polypeptide, was recently identified, roles of FAM19A5 in central nervous system (CNS) have not yet been demonstrated. We observed that FAM19A5 levels are increased in GFAP- and nestin-positive reactive astrocytes in the injured brain and spinal cord. Treatment with blocking anti-FAM19A5 antibody after brain injury attenuated elongation of GFAP-positive reactive astrocytes in the proximal region of the penumbra, resulting in delayed glial scar formation. Unelongated nestin-positive astrocytes and intact survived neurons, however, remain in this region. In addition, the treatment with the FAM19A5 antibody significantly increased axon regeneration in the fibrotic scar. Consistent with the brain histochemical analyses, this antibody significantly improved the functional motor behavior in both brain- and spinal cord-injured animal models. Together, these results suggest a possible clinical uses of a FAM19A5 antibody in brain- or spinal cord-injured patients.

Keywords: FAM19A5, Central nervous system, Axon regeneration, Motor behavior

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Young Scientist Colloquium

2015년 10월 15일(목) 14:00 ~ 15:20
본관 320호

좌장 한기환
이화여대

YSC-1 **14:00-14:20**
Soluble common gamma chain as a novel therapeutic target in rheumatoid arthritis
Changwan Hong • School of Medicine, Pusan National University

YSC-2 **14:20-14:40**
Functional Neuroanatomy of Metabolism Regulation
Hyung Jin Choi • College of Medicine, Seoul National University

YSC-3 **14:40-15:00**
TIMP-1 affects cell survival in animal model of retinitis pigmentosa
Jung–A Shin • School of Medicine, Ewha Womans University

YSC-4 **15:00-15:20**
Possible role in PKCα signaling in a mouse model of Fragile X syndrome
Miyoung Yang • School of Medicine, Wonkwang University

YSC -1

Soluble common gamma chain as a novel therapeutic target in rheumatoid arthritis

Changwan Hong /School of Medicine, Pusan National University

The common γ-chain (γc) plays a central role in signaling by IL-2 and other γc–dependent cytokines. we reported that activated T cells produce an alternatively spliced form of γc that results in secretion of the γc extracellular domain. The soluble form of γc (sγc) was produced only by alternative splicing and not receptor shedding, and directly bound to other γc cytokine receptors on T cells to inhibit their cytokine signaling and promote inflammation. Sγc impaired naïve T cell survival by suppressing IL-7 signaling during homeostasis and enhanced Th17-mediated inflammation by inhibiting IL-2 signaling upon T cell activation, as sγc-overexpressing mice are consequently more susceptible to EAE. Now sγc is being magnified as a novel therapeutic target for autoimmune diseases. Since we showed that sγc dimerization is significantly more functional than monomer, blockade of sγc dimerization would be thus a potential one. However, the dimerization mechanism of sγc is still not fully understood. Today, we will focus on how sγc is dimerized, the dimerization can be blocked and finally how sγc would affect rheumatoid arthritis (RA) pathogenesis with modulation of Th17 differentiation, because Th17 cells are known to play pivotal roles in the pathogenesis of autoimmune RA disease and also high level of sγc was detected in synovial fluid of RA patients. To further study, we are designing sγc inhibitor to block sγc dimerization with peptides, aptamers and chemicals and then testing inhibitory effect in vitro and in vivo autoimmune animal models. Collectively, it is expectable that new development of sγc inhibitor would be applied other autoimmune diseases as well as RA.

Keywords: γ-chain, Th17 differentiation, rheumatoid arthritis, IL-2 signaling

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YSC -2

Functional Neuroanatomy of Metabolism Regulation

Hyung Jin Choi /College of Medicine, Seoul National University

Our research focuses on the functional neuroanatomy of the metabolism regulation, how brain regulates body metabolism. Regulation of body weight homeostasis, food intake and energy expenditure is controlled by central nervous system. Brain cerebral cortex performs higher brain function, integrating external stimuli (sight, smell, taste and etc.), previous experiences, expected rewards and etc. Based on this integrative function, brain makes decisions on what to eat, how much to eat and when to eat. Brain also regulates body temperature and energy expenditure. This integrative regulation is mediated by pathways in the brain involved in cerebral cortex, reward system, hypothalamus, brain stem and autonomic nervous system through multiple hormones and neurotransmitter and afferent/efferent nervous signals. By unraveling these interactions, our research aims to elucidate the major driving pathogenic mechanism of the modern endemic metabolic diseases (obesity, diabetes, osteoporosis and hypertension) and find effective cure and preventive measures. To elucidate the role of brain on metabolism regulation, our translational approach integrates both animal studies and human studies. Our research approach utilizes the unique advantages of each type of study. From animal studies, we can directly manipulate brain function through stereotaxic surgery, drug delivery, gene delivery and disease modeling. We plan to use both rodents and primates, to understand human physiology. From human studies, we can directly measure comprehensive physiologic response to stimuli. Especially, we can directly investigate higher brain function and cognitive/psychologic response phenotype through specially designed survey. In addition, neuroimaging techniques, such as functional MRI, can be used to directly measure regional brain function and connectivity, in response to specific stimuli. From human cadaver study, we can directly detect microscopic distribution of certain molecules and its functional association with other neurons and circuits (especially novel interesting genes found from mouse genome wide profiling study or human GWAS). Finally, we can perform clinical trials to prove the clinical efficacy and safety of novel therapeutic modalities.

Keywords: Brain, Functional neuroanatomy, Metabolism, Stereotaxic surgery, Translational approach

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YSC -3

TIMP-1 affects cell survival in animal model of retinitis pigmentosa

Jung-A Shin /School of Medicine, Ewha Womans University

Retinitis Pigmentosa (RP) is a leading cause of inherited blindness that results from one of many possible gene mutations. Various treatment strategies being explored for RP include gene therapies, administration of neurotrophic factors, retinal pigment epithelium (RPE), photoreceptor and stem cell transplantation. Regardless of these effort, currently, there is no effective treatment that can prevent or reverse the photoreceptor loss in RP. Hence, several animal models are attempted to understand progression of disease and explore treatment strategies. They include Royal College of Surgeons (RCS) rats, which exhibit a defective MERTK gene in the pigment epithelium; the retinal degenerate (rd) mouse model exhibiting a rod-phosphodiesterase gene mutation; the S334ter rat and the P23H rat, which express a rhodopsin mutation found. In this study, S334ter-line-3 rat was used because of the similarity to the rhodopsin mutation in human RP patient. In the rhodopsin S334ter-line-3 rat model of RP, the death of rods induces spatial rearrangement of cones into regular ring mosaics. Using this model, we recently discovered that the ring mosaics are restored to a homogeneous distribution upon application of tissue inhibitor of metalloproteinase-1 (TIMP-1). In this study, we further investigated whether TIMP-1 can prevent a formation of ring like pattern and affect cell survival by early treatment. In this presentation, I will talk about these results.

Keywords: Retinitis pigmentosa, blindness, Metalloproteinase-1, TIMP-1

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YSC -4

Possible role in PKCα signaling in a mouse model of Fragile X syndrome

Miyoung Yang /School of Medicine, Wonkwang University

Fragile X syndrome (FXS) is the most common genetic cause of mental disability, and caused by mutations in the *FMR1* gene. Aberrantly elevated basal level protein synthesis and over-activation of the Gq-coupled glutamate and acetylcholine receptors have been considered as potential mechanisms underlying the pathophysiology in Fragile X syndrome (FXS). Identification of functional downstream target in Gq signaling that affect protein synthesis may aid the development of FXS therapy. Here, we examined the effects of PKCα on the pathogenesis of FXS. Through pharmacological inhibition, we tested the function of protein kinase C (PKC)α in intracellular signaling triggered by the activation of the Gq-coupled metabotropic glutamate receptor 1/5 (mGluR1/5) and muscarinic cholinergic receptors (Gq-mAchR). Following intraperitoneal injection of tamoxifen (TAM), which is known to modulate signaling proteins such PKC and used as anticancer drug, we examined the FXS-related behavioral symptoms and elevated protein synthesis in a mouse model of FXS. TAM suppressed mGluR1/5- and Gq-mAchR-mediated the activation of ERK1/2, whose activity is required for protein synthesis. Administration of TAM and mutation of PKCα corrected multiple FXS-related symptoms including hyperactivity, social behavior and defective memory in *Fmr1* knockout mice. TAM also normalized the elevated protein synthesis in FXS neurons to the wild type level. Our data suggest PKCα as a new therapeutic target and a potential new application of TAM in FXS.

Keywords: Protein Kinase C α, mGluR1/5, Fragile X syndrome, Tamoxifen

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심포지엄-1

2015년 10월 15일(목) 15:30 ~ 18:00
본관 320호

Microscopy– Key tools for morphological research

좌장 배용철 경북대 • 유임주 고려대

S1-1 **15:30-16:00**
Rapid and consistent organ clearing and labeling method for 3D imaging
Woong Sun • College of Medicine, Korea University

S1-2 **16:00-16:30**
Synaptome Analysis of Retinal Ribbon Synapses Using 3D Reconstruction Combined with Serial Section Electron Microscopy and FIB/SEM
In–Beom Kim • College of Medicine, The Catholic University of Korea

S1-3 **16:30-17:00**
Processing of orofacial thermosensation in the brain stem and dental pulp
Yong Chul Bae • School of Dentistry, Kyungpook National University

S1-4 **17:00-17:30**
Cardiac myosin binding protein-C: a structurally dynamic regulator of cardiac contractility
Ji Young Mun • College of Health Sciences, Eulji University

S1-5 **17:30-18:00**
Explore synaptic communication by opto–physiology (The role of CDK5 and Calcineurin at CNS synapses)
Sung Hyun Kim • School of Medicine, Kyung Hee University

S1-1 Rapid and consistent organ clearing and labeling method for 3D imaging

Woong Sun /College of Medicine, Korea University

Three-dimensional (3D) organization of organs or organisms at cellular level is a fundamental challenge in biology. Conventionally, this task has required time- and effort-consuming processes including 1) serial section of the tissues, 2) imaging, and 3) reconstruction of the images into 3D structure. The recent advances of optical tissue clearing techniques allow this process without sectioning, which significantly reduce the efforts and possible error during the reconstruction. However, currently available protocols require long process time. Here, we present a rapid and highly reproducible clearing method that renders tissue or whole-body clearing within a day while preserving tissue architecture and protein-based signals derived from endogenous fluorescent proteins. Especially, our method is compatible with conventional immunolabeling protocol and expedites antibody penetration into thick specimens by applying pressure. Speed and consistency of this method will allow high-content mapping and analysis of normal and pathological features in intact organs and bodies.

Keywords: High-content mapping, Organ clearing, 3-D culture, optical tissue clearing technique

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S1-2 Synaptome Analysis of Retinal Ribbon Synapses Using 3D Reconstruction Combined with Serial Section Electron Microscopy and FIB/SEM

In-Beom Kim /College of Medicine, The Catholic University of Korea

The ribbon synapse is a type of neuronal synapse characterized by extremely fast, precise and sustained neurotransmission, which is critical for the perception of complex senses such as vision and hearing. In the retina, ribbon synapses are formed in photoreceptors and bipolar cells. Molecular machinery and anatomy of the synaptic ribbon, a key presynaptic structure, and its synaptic connectivity have been highlighted and unveiled. Nonetheless, many issues such as postsynaptic elements assigning synaptic efficacy to target remain to be unsolved. Changing the subject, "connectome" refers to the map of connections at the macroscopic and intermediate levels and "synaptome" for the map at the ultrastructural level. Only by combining studies at all three levels can we fully understand the structural plan of the brain as a whole. One of my research interests is to understand retinal circuits for various aspects of visual information such as shape, color and contrast, at ultrastructural level in particular. Here, I will present my two recent synaptome works, axonal ribbon synapse in ON cone bipolar cell and microanatomy of the ribbon synapse in rod spherule, by using 3D reconstruction combined with serial section electron microscopy and focused ion beam/scanning electron microscopy (FIB/SEM). In this symposium, I will talk about comparison between conventional and axonal synapses formed in ON cone bipolar cells through synaptome analysis and its functional implication, and detailed structure of postsynaptic triad at the ribbon synapse in rod spherule.

Keywords: Synaptome, FIB/SEM, Retina, Ribbon synapse

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S1-3

Processing of orofacial thermosensation in the brain stem and dental pulp

Yong Chul Bae /School of Dentistry, Kyungpook National University

Neurons communicate with each other at the synapse. So, elucidation of synaptic connectivities of the specific primary sensory afferents, involved neurotransmitters and receptors may help understand how the specific sensation conveyed via particular sensory afferents is processed at the 1st relay nucleus. Transient receptor potential-melastatin 8 (TRPM8) and -vanilloid 1 (TRPV1) mediate cold and noxious heat respectively, and are expressed in the primary sensory neurons. In this presentation, we will talk about our recent findings on central connectivity of TRPM8-positive (+) and TRPV1+ axons in the trigeminal sensory nuclei (TSN) and existence of glutamate signaling in the TRPM+ pulpal axons. TRPM8 is expressed in unmyelinated C fibers (76%) and small myelinated Aδ fibers (24%). TRPM8+ boutons, show simple synaptic connectivity with one or two dendrites and rarely receive axoaxonic synapse. The fiber type and synaptic connectivity pattern of TRPM8+ fibers in the 1st relay nuclei of the brain stem were unique and different from those of TRPV1+ fibers. In the dental pulp, TRPM8+ fibers coexpressed vesicular glutamate transporter 2 (VGLUT2), but not VGLUT1, which was upregulated following pulpal inflammation. These findings suggest that each specific orofacial sensory information including TRPM8-mediated cold is processed in a unique manner in the brain stem. They also suggest existence of VGLUT2-mediated glutamate signaling in the TRPM8+ neurons that may be underlying mechanism for cold-induced acute pain and hypersensitivity following inflammation.

Keywords: Glutamate signaling, TRPM8, TRPV1, VGLUT2,, Orofacial sensory, Synapse, Thermosensation

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S1-4

Cardiac myosin binding protein-C: a structurally dynamic regulator of cardiac contractility

Ji Young Mun /College of Health Sciences, Eulji University

Myosin-binding protein C (MyBP-C) is an accessory protein of striated muscle thick filaments and a modulator of cardiac muscle contraction. Defects in the cardiac isoform, cMyBP-C, cause heart disease. cMyBP-C comprises eleven immunoglobulinand fibronectin-like domains and a cMyBP-C-specific motif. In vitro studies show that, in addition to binding to the thick filament via its C-terminal region, cMyBP-C can also interact with actin via its N-terminal domains, modulating thin filament motility. Structural observations of F-actin decorated with N-terminal fragments of cMyBP-C suggest that cMyBP-C binds to actin close to the low Ca^{2+} binding site of tropomyosin. This suggests that cMyBP-C might modulate thin filament activity by interfering with tropomyosin regulatory movements on actin. To determine directly whether cMyBP-C binding affects tropomyosin position, we have used electron microscopy (EM) and in vitro motility assays to study the structural and functional effects of N-terminal fragments binding to thin filaments. 3D reconstructions suggest that under low Ca^{2+} conditions, cMyBP-C displaces tropomyosin towards its high Ca^{2+} position, and this movement corresponds to thin filament activation in the motility assay. On the other hand, muscle contraction is regulated by phosphorylation of cMyBP-C within its N-terminal M-domain and patients with heart failure and hypertrophy show a significant decrease in cMyBP-C phosphorylation. Therefore we also studied the effect of phosphorylation on cMyBP-C structure and on its modulation of tropomyosin position on thin filaments. The EM data and 3D reconstruction showed phosphorylation reduces cMyBP-C's displacement of tropomyosin and its activation of thin filaments through their phosphorylation induced structural changes. These results suggest that cMyBP-C may modulate thin filament activity by physically displacing tropomyosin from its low Ca^{2+} position on actin, and phosphorylation affects its regulation.

Keywords: Actin filament activity, Cardiac contractility, Myosin-binding protein C, Tropomyosin

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S1-5

Explore synaptic communication by opto-physiology (The role of CDK5 and Calcineurin at CNS synapses)

Sung Hyun Kim /School of Medicine, Kyung Hee University

The control of neurotransmitter release at nerve terminals is of profound importance for neurological function and provides a powerful control system in neural networks. We take advantage of high fidelity custom-built optical imaging system with presynaptic specific sensor for synaptic vesicle dynamics and fast Ca2+ dynamics. This study reveals that the balance of enzymatic activities of the isoform of the phosphatase calcineurin (CNAα) and the kinase cyclin-dependent kinase 5 (CDK5) has a dramatic influence over single action potential (AP)-driven exocytosis at nerve terminals. Acute or chronic loss of these enzymatic activities results in a sevenfold impact on single AP-driven exocytosis. We demonstrate that this control is mediated almost entirely through Cav2.2 (N-type) voltage-gated calcium channels as blocking these channels with a peptide toxin eliminates modulation by these enzymes. We found that a fraction of nerve terminals are kept in a presynaptically silent state with no measurable Ca2+ influx driven by single AP stimuli attributable to the balance of CNAα and CDK5 activities because blockade of either CNAα or CDK5 activity changes the proportion of presynaptically silent nerve terminals. Thus, CNAα and CDK5 enzymatic activities are key determinants of release probability.

Keywords: CDK5, Calcineurin, neurotransmitter, Calcium channels

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심포지엄-2

2015년 10월 15일(목) 15:30 ~ 18:00
본관 418호

대사 작용 조절인자와 실험동물모델

좌장 박인선 인하대

S2-1 **15:30-16:15**
Separation of lipogenesis from LXR-mediated reverse cholesterol transport by modulating hepatic TRAP80
Seung Whan Kim • University of Ulsan College of Medicine

S2-2 **16:15-16:50**
Regenerative medicine for treatment of diabetes
Hee Sook Jun • Gachon University, Lee Gil Ya Cancer and Diabetes Institute

S2-3 **16:50-17:25**
Clusterin, an intriguing biological regulator of the pancreatic beta cells
In Sun Park • School of Medicine, Inha University

S2-4 **17:25-18:00**
Functional Annotation of Metabolic Syndrome-related Genes Through Mouse Phenotyping
Je Kyung Seong • College of Veterinary Medicine, Seoul National University

S2-1

Separation of lipogenesis from LXR-mediated reverse cholesterol transport by modulating hepatic TRAP80

Seung Whan Kim /University of Ulsan College of Medicine

Atherosclerosis is the leading cause of mortality in developed countries, and is poised to become a worldwide health problem. Liver X receptor (LXR) is an attractive target for treating atherosclerosis, due to its ability to enhance ATP-binding cassette A1 (ABCA1)-dependent reverse cholesterol transport (RCT). RCT is a pathway by which excess cellular cholesterol is transported from peripheral tissues to the liver for excretion in the bile and ultimately the feces, thereby helping to prevent atherosclerosis. However, LXR also upregulates sterol regulatory element binding protein-1c (SREBP-1c) expression, leading to increased hepatic triglyceride synthesis, which is an independent risk factor for atherosclerosis. In this talk, data will be presented on the novel strategy of separating the favorable and unfavorable effects of LXR by exploiting its coactivator, thyroid hormone receptor-associated protein 80 (TRAP80). Interestingly, TRAP80 selectively promoted the transcription of SREBP-1c but not ABCA1. We found that in a chromosomal context, TRAP80 was selectively recruited to the LXR responsive element (LXRE) of the SREBP-1c gene, but not to the LXRE of ABCA1 gene. Moreover, Ad-shTRAP80 inhibited LXR-dependent SREBP-1c expression and RNA polymerase II recruitment to the SREBP-1c LXRE, but not the ABCA1 LXRE. Furthermore, liver-specific knockdown of TRAP80 ameliorated liver steatosis and hypertriglyceridemia induced by LXR activation and maintained RCT stimulation by the LXR ligand. Taken together, these results demonstrate that TRAP80 is a selective regulator of hepatic lipogenesis and is required for LXR-dependent SREBP-1c activation. The discovery of novel ways to inhibit the TRAP80-LXR interaction should facilitate the development of LXR agonists that effectively prevent atherosclerosis.

Keywords: Atherosclerosis, TRAP80, Liver X receptor, SREBP-1c, LXR responsive element

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S2-2

Regenerative medicine for treatment of diabetes

Hee Sook Jun /Gachon University, Lee Gil Ya Cancer and Diabetes Institute

Diabetes is characterized by hyperglycemia and results from absolute or relative deficiency of insulin which is released from pancreatic beta-cells. Therefore, restoration of functional beta-cells is the key goal for the therapy of diabetes. *In vitro* differentiation of stem cells into beta-cells or *in vivo* regeneration from intra islet cells (alpha or beta-cells) and extra islet cells (acinar, ductal, or pancreatic progenitor cells) have been investigated as a possible strategies for restoration of beta-cell mass. In vivo generation of functional beta-cells might be a promising strategy for a cure of diabetes in the future. Regeneration of beta-cells by growth factors such as glucagon-like peptide-1 (GLP-1) results in the remission of diabetes in both type 1 and type 2 diabetic mice. New beta cells were generated from both existing beta-cells and non-beta cells in diabetic mice treated with recombinant adenovirus expressing GLP-1 (rAd-GLP-1). Both *in vivo* and *in vitro* studies indicated that GLP-1 increased pancreatic alpha-cell transdifferentiation to new beta-cells. In this lecture the molecular mechanisms for the generation of new beta-cells via replication of alpha-cell by GLP-1 will be discussed.

Keywords: Diabetes, GLP-1, Regenerative medicine, Transdifferentiation

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S2-3

Clusterin, an intriguing biological regulator of the pancreatic beta cells

In Sun Park /School of Medicine, Inha University

Insulin–producing beta cell of the pancreas is considered as a key target for current stem cell study and regenerative medicine. Clusterin is an intriguing glycoprotein expressed in association with a variety of pathophysiological conditions in various tissues including pancreas. We have illustrated clusterin function in pancreatic tissues, particularly regarding with the biological feature of insulin secreting beta cells. We have reported the transient expression of clusterin and its modification along with the islet cell development as well as its up-regulation upon cytotoxic insult of beta cells. Recently, we found that this protein is involved in regeneration of pancreatic endocrine cells following various types of tissue injuries and involved in the neogenic regeneration and reorganization of pancreatic tissue. Over-expression of clusterin induced a significant increase of beta cell differentiation, and deletion of secreted clusterin in the culture medium gave rise to a lazy transformation of insulin secreting cells from duct explants, implying a growth factor-like action of clusterin and its paracrine nature. Although mechanisms of clusterin action have not been defined, clusterin is known to be regulated by growth factors. Clusterin directly interacts with the intracellular segment of TGF-beta receptors inducing their phosphorylation. It implies that clusterin may rather function as a signaling molecule for inducing proliferation and differentiation with the help of growth factors. More recently, using clusterin transgenic ($CLU^{+/+}$) and knock-out ($CLU^{-/-}$), we confirmed cooperative action upon beta cell function and survival opposing diabetic condition. Based on these data, we can conclude that clusterin is an important biological regulator of insulin-secreting beta cells in reference to their survival, regeneration as well as their endocrine function.

Keywords: Clusterin, Pancreas, Regeneration, Diabetes

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S2-4

Functional Annotation of Metabolic Syndrome-related Genes Through Mouse Phenotyping

Je Kyung Seong /College of Veterinary Medicine, Seoul National University

Mouse models are crucial for the functional annotation of human genome. Gene modification techniques including gene targeting and gene trap in mouse have provided powerful tools in the form of genetically engineered mice (GEM) for understanding the molecular pathogenesis of human diseases. Several international consortium and programs are under way to deliver mutations in every gene in mouse genome. The information from studying these GEM can be shared through international collaboration. However, there are many limitations in utility because not all human genes are knocked out in mouse and they are not yet phenotypically characterized by standardized ways which is required for sharing and evaluating data from GEM. The recent improvement in mouse genetics has now moved the bottleneck in mouse functional genomics from the production of GEM to the systematic mouse phenotype analysis of GEM. Enhanced, reproducible and comprehensive mouse phenotype analysis has thus emerged as a prerequisite for effectively engaging the phenotyping bottleneck. We found differentially expressed proteins and transcripts during adipocyte differentiation using proteomics and DNA microarray. To validate these proteins, we developed several lines of knock-out mice. Among them, we found obesity-related phenotypes from AHNAK knockout mouse. To investigate the functional role of AHNAK in lipogenesis, HFD(High fat diet) and LFD(Low fat diet) were fed for 12 weeks to AHNAK knock-out mice and its age matched wild type mice. Even though AHNAK knock-out mice revealed a reduced body weight at birth compared with wild type mice, ratios of major organ weight to body mass was almost same of wild type mice. Body weight of HFD-fed AHNAK mice showed significantly reduced with the rate of weight gain compared to HFD-fed wild type mice despite an identical food intake when normalized to body mass. HFD-fed AHNAK mice display a reduced epididymal fat mass. From discovering differentially expressed proteins in disease models to validate its function involved in the onset of disease, phenotypical characterization of knockout mice is one of essential issues leading to disease.

Keywords: AHNAK, Functional annotation, GEM, Knock-out, Mouse model

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심포지엄-3

2015년 10월 16일(금) 14:00 ~ 16:30
본관 320호

해부학 교육의 임상의학 활용하기

좌장 박대균 순천향대

S3-1 **14:00-14:45**
해부학교육에 임상의학 활용하기 : 심포지엄 준비배경과 순천향대학교 사례
Dae-Kyoon Park • College of Medicine, Soonchunhyang University

S3-2 **14:45-15:20**
임상의학교수의 해부실습 활용 : 건국대학교 사례
Wu Chul Song • School of Medicine, Konkuk University

S3-3 **15:20-15:55**
해부학실습에 임상의학 활용하기
Youngbuhm Huh • Department of Anatomy and Neurobiology, Kyung Hee University

S3-4 **15:55-16:30**
해부학교육에 임상표현 활용하기 : 충남대학교 사례
Sooil Kim • School of Medicine, Chungnam National University

S3-1 해부학교육에 임상의학 활용하기 : 심포지엄 준비배경과 순천향대학교 사례

Dae-Kyoon Park /College of Medicine, Soonchunhyang University

2004년부터 시행된 의학 및 법학분야의 대학원 도입정책에 의해 2005년부터 2009년까지 전국 41개 의과대학 중에서 27개 대학이 의학전문대학원 체제를 도입하였다. 이 중에서 13개 대학은 학부와 대학원 체제를 절반씩 섞어서 운영하였다. 6년으로 진행되던 의학 교육이 4년으로 축소되면서 의학교육의 개편이 이루어졌고, 기초의학 분야의 수업이 임상과 통합되는 변화를 겪었다. 그런데, 2009년 구성된 의학교육제도개선위원회에서 대학이 자율적으로 전문대학원과 의과대학 체제를 선택하기로 결정하자, 36개 대학이 의과대학 체제를 선택하게 되어 또 한번 의과대학 교육의 대대적인 개편이 예상되고 있다. 이번 심포지엄은 교육과정의 개편에도 불구하고 효과적인 해부학 교육은 임상의학을 적절히 활용하는 것이라는 전제하에 마련되었다. 의과대학 체제를 꾸준히 유지한 대학, 의학전문대학원으로 전환한 뒤 그 체제를 그대로 유지하려는 대학, 의학전문대학원으로 전환하였다가 다시 의과대학 체제로 전환하는 대학에서 발표자를 선정하였다. 순천향대학교는 의과대학 체제를 유지하면서 전통적인 해부학교육을 유지하고 있으며 임상의학의 활용은 초보단계이다. 100분인 2시간 강의와 180분인 3시간 실습으로 구성되어 있고, 7주간은 화, 목 금요일, 7주간은 화, 목에 해부학 수업이 진행되며, 시험기간을 포함한 수업계획서에는 해부학 교육시간이 190시간이다. 머리와 목부위 실습에 신경외과와 이비인후과 교수의 수술 경험을 공유하고 있다. 건국대학교는 의학전문대학원 체제를 유지하기로 결정되었고 해부학 실습에서 임상의학을 적절히 활용하고 있는 단계라고 할 수 있다. 경희대학교와 충남대학교는 의학전문대학 체제에서 의과대학으로 전환할 예정으로, 경희대의 경우 해부학 교육에의 임상의학 활용은 체계를 거의 완성한 단계인 것으로 알려져 있고, 충남대학의 경우 임상표현(clinical presentation) 중심의 교육을 도입하고 있다고 한다. 심포지엄에서 발표될 각 대학교의 사례 중에서 어떤 것이 정답이라는 결론을 내리기는 어려울 것이다. 그러나 이 사례들을 통해 앞으로 교육과정을 개편하거나 해부학교육을 수행하는데 있어서 각 대학교의 상황에 맞게 해부학 교육을 수행할 수 있는 단초를 제공할 수 있을 것으로 기대한다. 급변하는 교육과정의 개편 속에서도 해부학 교육에 대한 고민들이 대한해부학회에서 더욱 활발하게 이루어지기를 기대해 본다.

Keywords: 해부학교육

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S3-2 임상의학교수의 해부실습 활용 : 건국대학교 사례

Wu Chul Song /School of Medicine, Konkuk University

최근 의학교육 변화로 해부학교육에 임상의학을 접목시키고자 하는 요구가 많다. 건국대학교는 2005년 의학전문대학원으로 전환 직후 의학교육이 대대적으로 개편되었고 이후로는 큰 변화 없이 약 10년 정도 유지되어 왔다. 의학전문대학원 전환 초창기에 학교측의 요구로 통합교육을 실시해 해부학 뿐 아니라 많은 기초의학과목과 임상의학과목의 통합강의가 이루어졌다. 그러나 한 학기에 모든 기초과목을 끝내는 무리한 강의계획으로 1년 만에 해부학교육은 임상의학과 통합교육을 포기하고 맨눈해부학은 발생학과 합쳐져 '인체의 구조와 발생' 이라는 과목으로 통합되어 현재까지 운영되고 있다. 건국대학교에서는 해부학 수업시간이 비교적 많아 초창기부터 임상의학교수를 활용한 강의를 시도했었다. 초기에는 주로 영상의학과, 정형외과에서 강의에 참여하였으나 대부분의 임상의학교수는 학생의 수준을 고려하지 않고 2학년 이상 수준의 강의를 본인 위주로 시행하여 기초의학 지식이 부족한 1학년 학생에게 너무 어려웠고 강의평가는 매우 낮은 수준이었다. 이후 한동안 임상의학과목은 해부학강의에서 빠지게 되었으나 약 3년 전부터 강의시간이 아닌 해부학실습시간에 임상의학교수를 활용하고자 하였고, 참여교수를 탐색하여 참여하는 목적을 자세히 설명하고 그 목적에 동의하여 기꺼이 참여하겠다는 교수를 모집하였다. 수업조건으로 강의시간이 아닌 실습시간이라는 점, 학생들에게 많은 지식을 전달하지 말 것, 해부학의 중요성을 일깨워 줄 것, 공식적이고 쉬운 용어를 사용할 것, 실습시간에 실제 수술법이나 검사법을 시연해 줄 것 등이었다. 진행은 각 주제별로 해부학의 중요성을 알려주는 강의 약 20분, 시신에서의 술기 시연 30분, 질의응답 10분으로 전체 60분 이내로 제한하였다. 3년 전에는 12명의 임상교수로 시작하였으나 교실의 수업취지에 맞지 않거나, 수업취지와는 맞으나 학생들이 너무 어려워하거나 흥미를 얻기 어려운 주제는 이후 빠지게 되었다. 올해 진행된 주제는 허리통증 및 디스크(정형외과), 양악수술(성형외과), 코성형수술(성형외과), 코안과 코골이(이비인후과), 사시교정(안과), 심장판막수술(흉부외과), 콩팥이식(외과), 여성골반(산부인과) 등이었다. 몇 년의 시행결과 학생들은 이전 임상교수가 강의에 참여했던 것 보다 더 큰 흥미와 관심을 갖게 되었고 앞으로도 계속 되었으면 좋겠다는 의견이 대부분이었다. 특히 환자를 대상으로 하는 것과 비슷한 방법으로 수술방법 및 시술을 시신에서 비슷하게 시연하는 것에 만족했다. 또한 참여한 임상교수의 만족도도 높았다. 이와 같은 결과가 나온 것은 여러 이유가 있겠으나 해부학교실 자체평가로는 강의가 아닌 실습이라는 점과 참여하는 임상교수들에게 취지를 충분히 설명하고 다짐을 받았기 때문이라고 본다. 학교마다 실습시간의 차이가 있겠지만 강의가 아닌 실습시간에 임상교수를 활용하는 것은 학생, 해부학교수, 임상교수에게 매우 매력적이고 효과가 좋은 교육방법이 될 것이다. 해부학교육에서 선제적으로 임상교수를 실습에 참여시키는 것은 의학교육의 주도권을 잡는다는 점에서도 의미가 있을 것이다.

Keywords: 해부학 교육, 해부학실습, 의학교육, 임상의학교수

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S3-3 해부학실습에 임상의학 활용하기

Youngbuhm Huh /Department of Anatomy and Neurobiology, Kyung Hee University

최근 임상의학교육은 실습과 실기를 중시하는 방향으로 바뀌고 있으며, 기초의학교육도 임상연계된 교육이 강조되고 있다. 해부학은 임상의학과 밀접한 관련이 있는 학문으로 임상의학과 연계된 교육이 쉬운 기초의학 분야이다. 우리학교는 2011년부터 해부학실습을 임상연계된 내용으로 변경시켰고, 기초의학 강의시간 조정과정에서 짧아진 실습기간과 해부학실습을 지도할 조교 및 교수가 부족한 현실에 맞추어 실습지도방법도 변경하였다. 이러한 몇 가지 해부학실습 교육변경의 경험을 소개하고자 한다. 해부학실습에 임상의학 교육을 접목하기 위해 정형외과, 응급의학과, 영상의학과, 이비인후과가 실습전 30분씩 임상강의를 시행하고 있다. 해부학실습에서는 이비인후과에서 내시경장비를 활용해서 코의 내부구조에 대한 수술시야와 구조설명을 하였고, 목과 귀의 실습에서는 학생실습에 참여하였다. 영상의학과에서는 무릎관절, 뇌, 콩팥 실습표본을 MRI로 촬영하여 실습강의에 활용하였다. 정형외과에서는 팔과 다리의 해부실습한 시신을 만들어 학생들이 팔과 다리의 구조를 확인하는 표본모델로 활용하였다. 최근에 임상강의는 학생의 관심을 끌 수 있는 주제로 강의내용을 축소해서 진행하였고, 실습시험을 볼 때 임상강의 내용도 평가하여 수업에 대한 집중도를 높였다. 해부학실습은 실습시작 전에 학생이 실습의 전반적인 내용을 미리 예습하고 실습할 구조를 파악하여 실습지도 조교나 교수에 크게 의존하지 않도록 진행하였다. 학생의 해부학실습 예습은 해부실습동영상(e-Anatomy)과 실습강의를 활용하였고, 실습이 시작되면 학생들이 미리 알고 있는 실습구조물을 찾는 작업을 시행하였다. 학생들은 실습 진행 중에 찾은 구조물들은 사진으로 저장하여 실습평가 발표에 사용하였다. 실습평가는 조별로 구두로 발표하는 내용과 작성된 파워포인트 파일의 해부한 구조물 사진의 상태 등을 고려하여 평가하였다. 실습이 완료된 후 학생들이 제출한 발표 자료에 있는 해부사진을 활용한 땡시험을 시행하여 전체 해부학실습 내용을 복습할 수 있도록 하였다. 이와 같이 짧은 해부학실습 시간을 나누어서 e-Anatomy등 해부실습동영상의 활용, 임상교수의 실습참여, 학생실습 자료를 활용한 실습평가를 하였다. 이러한 실습지도방법은 학생이 실습에 주도적으로 참여하며, 실습지도교수의 부담을 줄이는 해부학 실습교육의 한 예가 될 것으로 생각된다.

Keywords: 해부학실습, 해부실습동영상

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S3-4 해부학교육에 임상표현 활용하기 : 충남대학교 사례

Sooil Kim /School of Medicine, Chungnam National University

충남대학교 의학전문대학원에서는 현재 임상의학 통합교육과정에서 2013학년도 부터 임상표현 (clinical presentation) 수업과정을 도입하여 점차 그 비율을 높여가고 있다. 임상표현 수업과정은 실제 환자의 문제해결을 할 수 있는 능력을 키우고 학생 스스로가 깊은 학습이 이루어지도록 돕고자 설계한 수업방법으로 성과바탕교육의 철학을 가장 잘 반영한 수업으로 볼 수 있다. 충남대학교 의학전문대학원의 임상표현 수업은 개념틀의 소개 → 자율증례토의 → 핵심질환소개 → 도전 증례 및 평가의 순서로 진행하게 된다. 그러나 각 진행요소 중 임상표현의 성격 및 성과목표에 따라 변경하거나 생략하여 진행할 수 있다. 2015학년도는 임상의학 통합교육과정에서 과목별로 2~3개의 임상표현을 진행하고 있지만 점차 전체 강의시간의 30%까지 높이고 의과대학 의예과 학생들이 의학과 1학년으로 진입하는 2017학년도부터는 임상의학 통합수업의 교과과정을 8개 영역의 임상표현 통합과정으로 개편하고 99개의 임상표현을 학생들이 스스로 습득하도록 할 예정이다. 또한 5~10개의 핵심임상표현을 선정하여 충남대학교 의학전문대학원을 졸업생들은 핵심임상표현에 해당하는 환자를 숙련된 정도로 자신 있게 진료할 수 있도록 깊이 있는 학습이 이루어지게 할 예정이다. 해부학교육에서의 임상의학 활용은 기초의학 통합교과과정에서 임상 예를 강의시간에 소개하여 임상의학을 접하게 하고 기초지식을 응용하여 임상적인 측면에서 생각하게 하고, 1학년말의 선택 교과목인 임상해부학(clinical anatomy)에서 임상케이스를 조별로 발표하게 하여 임상의학의 이해를 돕고 있다. 임상의학의 교과과정이 임상표현 통합과정으로 바뀌는 2017학년도부터는 각각의 임상표현과정에 해당하는 "기본의학교육 학습성과(과학적 개념과 원리 중심)"의 기본개념을 기초의학통합교과목에 적용하여 임상표현과정과 연계하여 학습할 수 있는 기초를 다질 수 있게 할 예정이다.

Keywords: 해부학실습, 임상표현

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심포지엄-4

2015년 10월 16일(금) 14:00 ~ 16:30
본관 418호

Immunology and metabolism

좌장 이동섭 서울대

S4-1 **14:00-14:45**
Helper T cells at the Cross-road of Atherosclerosis and Autoimmunity
Yeonseok Chung • College of Pharmacy, Seoul National University

S4-2 **14:45-15:20**
The nuclear receptor PPARγ controls effector T cell functions to prevent autoimmunity in gender different way
Je-Min Choi • College of Natural Sciences, Hanyang University

S4-3 **15:20-15:55**
Adipose tissue immune cells: Key players in metabolic syndromes
Kae Won Cho • Soonchunhyang Institute of Medi-Biosciences (SIMS), Soonchunhyang University

S4-4 **15:55-16:30**
Adipose Tissue Dysregulation and Insulin Resistance in Obesity
Jae Bum Kim • School of Biological Science, Seoul National University

S4-1

Helper T cells at the Cross-road of Atherosclerosis and Autoimmunity

Yeonseok Chung /College of Pharmacy, Seoul National University

Patients with systemic autoimmune diseases show increased incidence of atherosclerosis. However, the contribution of proatherogenic factors to autoimmunity remains unclear. We found that atherogenic mice (herein referred to as LDb mice) exhibited increased serum interleukin-17, which was associated with increased numbers of T helper 17 (Th17) cells in secondary lymphoid organs. The environment within LDb mice was substantially favorable for Th17 cell polarization of autoreactive T cells during homeostatic proliferation, which was considerably inhibited by antibodies directed against oxidized low-density lipoprotein (oxLDL). The uptake of oxLDL induced dendritic-cell-mediated Th17 cell polarization by triggering IL-6 production in a process dependent on TLR4, CD36, and MyD88. Self-reactive CD4+ T cells that expanded in the presence of oxLDL induced more profound experimental autoimmune encephalomyelitis. In addition, ApoE-deficient mice fed on high-fat diet exhibited exaggerated germinal center reactions associated with enhanced follicular T helper (Tfh) responses. ApoE-deficient recipients of lupus-prone BXD2 bone marrow had remarkably elevated amounts of autoantibodies to dsDNA and histone. These findings demonstrate that proatherogenic factors promote the polarization and inflammatory function of autoimmune Th17 cells and Tfh cells, which could be critical for the pathogenesis of atherosclerosis and other related autoimmune diseases.

Keywords: Atherosclerosis, Low-density lipoprotein, CD4+ T cell, Autoimmunity

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S4-2

The nuclear receptor PPARγ controls effector T cell functions to prevent autoimmunity in gender different way

Je-Min Choi /College of Natural Sciences, Hanyang University

Members of the nuclear receptor superfamily function as transcription factors within the cells that are sensing hormones or lipid metabolites, etc. These receptors regulate expression of specific genes controlling the development, homeostasis, metabolism, and inflammation. Peroxisome proliferator-activated receptor gamma (PPARγ), which is a type II nuclear receptor, is mainly expressed in adipose tissue, colon, and macrophages. It plays diverse roles in cellular differentiation, development, metabolism, and also in immune system. Although its ligands have demonstrated anti-inflammatory function in various diseases, its role in T cells is not fully elucidated. Recent studies using specific ligand treatments and T cell specific PPAR knockout mice have revealed its important roles in effector T cell functions and autoimmune diseases. Here, we investigated the roles of PPARγ in effector $CD4^+$ T cell differentiation such as Th1, Th2, Th17, Th9, Treg, and Tfh cells by using CD4-$PPAR\gamma^{KO}$ mice. The female but not male 1-year-old CD4-$PPAR\gamma^{KO}$ mice spontaneously developed moderate autoimmune phenotype by increased activated T cells, follicular helper T cells (Tfh cells) and germinal center B cells with glomerular inflammation and enhanced autoantibody production. Sheep red blood cell immunization more induced Tfh cells and germinal centers in CD4-$PPAR\gamma^{KO}$ mice and the T cells showed increased of Bcl-6 and IL-21 expression suggesting its regulatory role in germinal center reaction. Increased ERK and AKT phosphorylation and diminished expression of IkBa, Sirt1, and Foxo1, which are inhibitors of NF-kB, was observed in PPARγ-deficient T cells suggesting its intrinsic regulation of T cell receptor signaling. Collectively, these results suggest that PPARγ controls T cell activation and differentiation including Tfh cells to prevent autoimmunity in female and it would be an important target to regulate autoimmune diseases.

Keywords: PPARγ, CD4+ T cell differentiation, Autoimmunity

최제민 | 한양대학교 생명과학과 • 02–2220–4765 • jeminchoi@hanyang.ac.kr

S4-3

Adipose tissue immune cells: Key players in metabolic syndromes

Kae Won Cho /Soonchunhyang Institute of Medi-Biosciences (SIMS), Soonchunhyang University

Adipose tissue plays a crucial role in whole-body lipid and glucose metabolism. Dysfunction of adipose tissue such as lipodystrophy and obesity leads to metabolic diseases including insulin resistance and type 2 diabetes. Over the past few years, it has been established that chronic inflammation of hypertrophic adipose tissue depots in obese individuals leads to obesity-associated insulin resistance and is mediated by cells of the innate immune system, particularly adipose tissue macrophages (ATMs). More recently, cells of the adaptive immune system, CD4+ T lymphocytes in adipose tissue, have also emerged as important regulators of glucose homeostasis. However, it has been unresolved how ATMs interact with CD4+ T cells and the importance in generating adipose tissue inflammation and contributing glucose homeostasis. In this talk, I will introduce novel mechanisms responsible for crosstalk of ATMs with CD4+ T cells during the development of obesity-induced inflammation and insulin resistance. Furthermore, more comprehensive model of immunometabolism will be discussed.

Keywords: Adipose tissue macrophages, Glucose homeostasis, Immunometabolism

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S4-4

Adipose Tissue Dysregulation and Insulin Resistance in Obesity

Sung Sik Choe, Jin Young Huh, Jong In Kim, In Jae Hwang, Jae Bum Kim*

School of Biological Science, Seoul National University

Adipose tissue plays key roles in whole body energy homeostasis. Furthermore, adipose tissue serves as an endocrine tissue by producing various adipokines such as leptin, resistin, and adiponectin. Increased adipose tissue is one of hallmarks of obesity which is closely associated with metabolic diseases including hyperlipidemia, hypertension, atherosclerosis, insulin resistance, cardiovascular diseases and type 2 diabetes. Recent findings have suggested that various immune cells are infiltrated into adipose tissue of obesity, accompanied with adipose tissue inflammation and insulin resistance. Adipose tissue inflammation in obesity is associated with adipose tissue macrophage infiltration and an adipose tissue macrophage M1-like proinflammatory polarization state. Upon adiposity, adipose tissue show different population of adipose tissue macrophages and various immune cells. Although recruitment kinetics has not been clearly elucidated, total numbers of T cells, B cells, macrophages, neutrophils and mast cells are increased in adipose tissue of obese animals. On the other hand, specific subsets of T cells (Th2, Treg and iNKT) and eosinophil numbers are decreased. Therefore, adipose dysfunction and inflammation are characterized by altered immune cell infiltration in obesity. To date, several mechanisms have been proposed to explain the initiation of adipose tissue inflammation and disrupted tissue homeostasis in obesity. These include increased ER stress, oxidative stress and adipose tissue hypoxia. Unfolded protein responses activated by adipose tissue ER stress cause stimulation of JNK and IKK/NF-kappa B pathways, which are critical pro-inflammatory responses. Oxidative stress increases in the adipose tissue of obese animals and can enhance inflammatory gene expression and blunt insulin signaling in adipocytes. In rapidly expanding adipose tissue of obese subjects, local hypoxia stimulates hypoxic responses, enhancing inflammatory gene expression and insulin resistance. It is likely that each of these stress responses interacts to accelerate adipose tissue inflammation and dysfunction. In this presentation, I will discuss the role of adipocytes to mediate adipose tissue inflammation and insulin resistance in obesity.

Keywords: Adipose tissue, Inflammation, Insulin resistance, Obesity, ER stress

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구연발표

2015년 10월 15일(목) 09:00 ~ 10:45
구연발표 1 (O1–1~7) 본관 320호
구연발표 2 (O2–1~6) 본관 418호

2015년 10월 16일(금) 09:00 ~ 10:45
구연발표 3 (O3–1~7) 본관 320호
구연발표 4 (O4–1~8) 본관 418호

01-1~7 맨눈해부학 분야
좌장 복진웅
연세대

02-1~6 신경과학 분야
좌장 선 웅
고려대

03-1~7 종양, 면역, 콩팥, 기타 분야
좌장 박정현
강원대

04-1~8 영어 구연발표
좌장 김현수
고려대

구연발표 1 맨눈해부학 분야 (O1–1∼7)

2015년 10월 15일(목) 09:00∼10:45, 본관 320호

좌장: 복진웅 (연세대)

01-1 ---------- 30

얼굴동맥의 가지들: 체계적 고찰

Branches of the Facial Artery: A Systematic Review

Kun Hwang[1,*], Geun In Lee[2], Hye Jin Park[2]

[1]Department of Plastic Surgery, Inha University School of Medicine, [2]Inha University School of Medicine

01-2 ---------- 30

Histomorphometric assessment of posterior superior alveolar artery with reference to maxillary sinus floor elevation

Sun-Kyoung Yu, Heung-Joong Kim*

Department of Oral Anatomy, College of Dentistry, Chosun University

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

Anatomical Structures to be Concerned during Peripherally Inserted Central Catheters (PICC) Procedure

Dasom Kim[1], Jin Yong Kim[1], Sung Bum Cho[2], Im Joo Rhyu[1,*]

[1]Department of Anatomy, Korea University College of Medicine, Practical Anatomy Research Institute, [2]Department of Diagnostic Radiology, Korea University College of Medicine

01-4 ---------- 31

법의학적 얼굴복원을 위한 3차원 얼굴근육 템플릿 개발

Dong-Ho Kim[1], Won-Joon Lee[2], U-Young Lee[1,*]

[1]Department of Anatomy - Catholic Institute for Applied Anatomy, College of Medicine, The Catholic University of Korea, [2]Institute of Forensic Science, College of Medicine, Seoul National University

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

The histological study of the fat compartments in the infra-orbital area and the orbicularis retaining ligament

Sang-Hee Lee[1], Hong-Ki Lee[2], Hee-Jin Kim[1,*]

[1]Division in Anatomy and Developmental Biology, Department of Oral Biology, Human Identification Research Institute, BK21 PLUS project, Yonsei University College of Dentistry, Seoul, South Korea, [2]Image Plastic and Aesthetic Surgery Clinic

01-6 ---------- 32

해면정맥굴 주변에 외과적으로 접근하기 위한 방법을 간단한 그림, 절단면영상, 3차원영상으로 설명하기

Beom Sun Chung[1], Jin Seo Park[2,*]

[1]Department of Anatomy, Ajou University School of Medicine, [2]Department of Anatomy, Dongguk University School of Medicine

01-7 ---------- 33

뼈의 부피와 겉넓이를 이용한 성별판별

Ho-Jung Cho, Dai-Soon Kwak*

Department of Anatomy/Catholic Institute for Applied Anatomy, The Catholic University of Korea

구연발표 2 신경과학 분야 (O2–1∼6)

2015년 10월 15일(목) 09:00∼10:45, 본관 418호

좌장: 선 웅 (고려대)

02-1 ---------- 33

Primary Cilium Plays Crucial Roles in Mediating Shh Signaling to Control Cochlear Growth and Hair Cell Differentiation

Kyeong-Hye Moon[1], Hongkyung Kim[1], Sun Myoung Kim[2], Ping Chen[2], Doris K Wu[3], Hyuk Wan Ko[4], Jinwoong Bok[1,*]

[1]Department of Anatomy, Yonsei University College of Medicine, Seoul 120-752, [2]Department of Cell Biology, Emory University School of Medicine, Atlanta, GA 30322, USA;, [3]Lab of Molecular Biology, National Institute on Deafness and other Communication Disorders, Bethesda, MD 20892, USA, [4]Dongguk University College of Pharmacy, Goyang 410-820

02-2 ---------- 34

Indocyanine green을 이용한 뇌혈관 및 혈류 분석: Strain, 뇌허혈, 노화 연구에 활용

Hye-Min Kang, Inkyung Sohn, Chan Park*

Department of Anatomy and Neurobiology, College of Medicine, Kyunghee University

02-3 ---------- 34

Follistatin is Required for Patterning of Mechanosensory Hair Cells in The Apical Cochlea

Hei Yeun Koo[1,2], Ji-Hyun Ma[1,2], Jeong-Oh Shin[1], Harinarayana Ankamreddy[1,2], Jinwoong Bok[1,2,*]

[1]Department of Anatomy, [2]BK21 PLUS Project for Medical Science, Yonsei University College of Medicine

02-4 ---------- 35
Expression of SOCS2 mRNA and Protein in the Ischemic Core and Penumbra after Transient Focal Cerebral Ischemia in Rats
Yoo-Jin Shin*, Tae-Ryong Riew, Joo-Hee Park, Ha-Jin Pak, Mun-Yong Lee
Department of Anatomy, Catholic Neuroscience Institute, College of Medicine, The Catholic University of Korea, 37-70, Seoul, Korea

02-5 ---------- 35
Calretinin Immunoreactivity In The Cerebral Cortex Of The Guinea Pig After Chronic Prenatal Hypoxia
Yonghyun Jun, Jongjoong Kim, Yoonyoung Chung*
Department of anatomy, School of Medicine, Chosun University

02-6 ---------- 35
Effective Botulinum Toxin Injection Point For Treatment Of Headache
You-JIn Choi*, Won-Jae Lee, Hyung-Jin Lee, Kang-Woo Lee, Hee-Jin Kim, Kyung-Seok Hu
Division in Anatomy and Developmental Biology, Department of Oral Biology, Human Identification Research Institute, BK2 PLUS project, Yonsei University College of Dentistry, Seoul, South Korea

구연발표 3 종양, 면역, 콩팥, 기타 분야 (O3-1~7)
2015년 10월 16일(금) 09:00~10:45, 본관 320호

좌장: 박정현 (강원대)

03-1 ---------- 36
Methionine sulfoxide reductase B3 (MsrB3) gene deletion ac celerates vitamin D-induced vascular calcification
Baek JongHo[1], Che Xiangguo[2], Hwa-young Kim[3], Je-Yong Choi[2], Kwon Moo Park[1,*]
[1]Department of Anatomy and BK21 Plus, Kyungpook National University School of Medicine, [2]Departments of Biochemistry and Cell Biology and BK21 Plus, Kyungpook National University School of Medicine , [3]Departments of Biochemistry and Molecular Biology, Yeungnam University College of Medicine

03-2 ---------- 37
An Oriental Medicine, Hyungbangpaedok-san Attenuates Motor Paralysis in an Experimental Model of Multiple Sclerosis by Regulating the T cell Response
Jong Hee Choi, Min Jung Lee, Minhee Jang, Eun-Jeong Kim, Woo-mi Yang, Ik-Hyun Cho*
Department of Convergence Medical Science, College of Oriental Medicine, Kyung Hee University, Seoul 30-70, Republic of Korea

03-3 ---------- 37
Sulforaphane Ameliorates 3-Nitropropionic Acid-Induced Striatal Toxicity by Activating the Keap1-Nrf2-ARE Pathway and Inhibiting the MAPKs and NF-κB Pathways
Minhee Jang, Ik-Hyun Cho*
Department of Convergence Medical Science, College of Oriental Medicine, Kyung Hee University, Seoul 30-70, Republic of Korea

03-4 ---------- 38
High ω3-polyunsaturated fatty acids in fat-1 mice prevent streptozotocin-induced Purkinje cell degeneration through BDNF-mediated autophagy
Dong Ho Bak[1], Enji Zhang[2], Min-Hee Yi[2], Do-Kyung Kim[1], Kyu Lim[2], Dong Woon Kim[2], Jwa-Jin Kim[1,*]
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Liyao Cong[1], Sang-Hee Lee[1], Tanvaa Tansatit[2], Hee-Jin Kim[1,*]

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Md Ariful Islam[1], Syeda Ridita Sharif[1], HyunSook Lee[1], Dae-Hyun Seog[2], Il Soo Moon[1,*]

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01-1

얼굴동맥의 가지들: 체계적 고찰
Branches of the Facial Artery: A Systematic Review

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본 연구의 목적은 얼굴동맥 가지들의 이름과 분지형태를 고찰하고, 각 얼굴동맥가지가 얼마나 존재하는 지 체계적으로 알아보는데 있다. PubMed 에서 1. (facial), AND 2. (artery), AND 3. (classification OR variant OR pattern) 용어들을 사용하여 검색하였다. IBM SPSS Statistics 20 system을 이용하여 분석하였다. 500편의 논문 중 18편을 선택하여 체계적으로 고찰하였다. 대부분의 논문들은 종말가지에 따라 분류에 초점을 맞추었다. 몇몇 저자는 종말가지에 따라 얼굴동맥을 분류하였으나 '종말가지'를 정의하지는 않았다. 분류방법에 혼동이 있었다: 아래입술동맥이 없는 경우 세 종류의 다른 분류가 사용되었다. 가쪽코가지(lateral nasal branch) 대신에 콧방울가지(alar beanch)나 코가지(nasal branch)를 사용하기도 하였다. 눈구석동맥(angular branch)은 몇 개의 각기 다른 가지를 일컫는데 사용되기도 하였다. 그레이 해부학에 기술된 얼굴동맥의 가지들(깨물근앞가지, 아랫입술동맥, 위입술동맥, 가쪽코가지, 눈구석동맥)의 존재는 각각 달랐다. 어느 가지도 100% 존재하지는 않았다. 위입술동맥(95.7%)을 가장 흔하게 찾아볼 수 있었다. 고, 눈구석동맥(53.9%)과 깨물근앞가지(53.8%)가 가장 적게 발견되었다. 얼굴동맥 가지들의 존재빈도는 외과적 시술에 참고할 수 있을 것이다.

Keywords: Carotid artery, External; Classification; Face

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01-2

Histomorphometric assessment of posterior superior alveolar artery with reference to maxillary sinus floor elevation

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The maxillary sinus floor elevation is frequently used for stable maintenance of implant. The intraosseous anastomosis between the posterior superior alveolar artery and the infraorbital artery supplies the maxillary molar, the maxillary sinus, and the Schneiderian membrane. The aim of this study was to investigate an anatomical features of the intraosseous branch of the posterior superior alveolar artery by histomorphometric analysis. Thirty five hemimaxillae from 25 cadavers were used (19 males, 6 females, mean death age 59 years). The specimens obtained from the first premolar to the second molar were embedded in paraffin, stained with hematoxylin-eosin, and observed on the light microscope. The location, shape, and diameter of the intraosseous branch of the posterior superior alveolar artery were measured by using image-processing software. The mean height from the maxillary sinus floor to the intraosseous branch was 5.24, 4.44, 6.35, and 3.00 mm according to tooth site, respectively. The shape of bony wall where the intraosseous branch presented was groove at the molar region, converted into canal toward the premolar region. The mean diameter of the intraosseous branch was 0.62±0.39 mm, the mean diameter of the canal containing it and its surrounding connective tissue was 1.17±0.58 mm, and the mean thickness of the lateral wall of the maxillary sinus at the level of the intraosseous branch was 2.95±1.34 mm. These results on the intraosseous branch of posterior superior alveolar artery are expected to provide critical information for surgical planning for the maxillary sinus floor elevation.

Keywords: Posterior superior alveolar artery, Maxillary sinus floor elevation, Histomorphometric analysis

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01-3

Anatomical Structures to be Concerned during Peripherally Inserted Central Catheters (PICC) Procedure

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Central line has been used for drug and nutrition supply and regular blood sampling of chronic disease patients frequently. However, this procedure access to the highly sensitive area and several problems also rise. Peripherally Inserted Central Catheters (PICC) technique is frequently employed. The advantage of PICC is to be used in long period, economic and safe term use. This procedure could be performed by not only doctors, but also trained nurses. Although PICC procedure is increasing, the anatomy for safe procedures was not properly established yet. Therefore, we studied basic anatomical information for the safe procedures. We used 20 fixed cadavers (40 arms), which were donated to the Korea University College of Medicine. The mean age was 76.75 years (48 to 94 years). After dissection of each arm, the distribution pattern of basilic vein and close structures were recorded by digital camera and some important lengths based on bony landmarks were measured. In addition to linear parameters, number of vein branch (catheter route) and basilic v. diameter were also checked. The mean length of insertion site ~ right atrium was 38.39±2.63cm (left), 34.66±3.60cm (right) and basilic v. diameter was 4.925±1.18mm (left), 4.075±1.49mm (right). These data showed significant differences between left and right arm ($p<0.05$). Especially, mean distance of basilic v. to brachial a. was 8.05±2.42mm and distance of basilic v. to ulnar n. was 5.46±1.67mm. According to this result, PICC procedure is more efficient to perform on right arm. Larger diameter of left basilic v. could facilitate PICC procedure, although its route is longer than right approach. In addition, ulnar nerve and brachial a. were located very closely lateral or behind to insertion site. Therefore, to avoid damaging these important structures, special attentions are required during this procedure.

Keywords: Central line, PICC, Basilic vein

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01-4

법의학적 얼굴복원을 위한 3차원 얼굴근육 템플릿 개발

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법의학적 얼굴복원은 유전자나 지문감식 등의 방법을 이용한 신원확인이 어려운 경우의 신원불상자의 머리뼈로부터 얼굴 형태를 만들어내는 방법이다. 이를 통해 유럽이나 북미 국가들의 경우 신원확인이 되지 않았던 미제사건 해결 등의 소득을 거두었다. 전통적인 얼굴복원방법은 뼈에 찰흙을 붙이는 방법이었으나, 최근에는 3차원 모델을 이용한 복원 사례들이 증가하고 있다. 얼굴근육 기준모델로 구성된 3차원 모델 템플릿은 컴퓨터를 이용한 얼굴복원 과정을 빠르고 정확하게 할 수 있게 해준다. 객관적으로 제작된 기준모델을 사용할 경우, 복원가의 해석에 따른 형태 왜곡을 방지할 수 있고 매 복원 작업마다 근육모델을 새로이 제작해야하는 번거로운 과정을 단축시켜 준다. 이에 한국인 얼굴근육의 형태자료를 이용한 3차원 얼굴근육 템플릿을 제작하였다. 가톨릭응용해부연구소의 20명 (남자 10명, 여자 10명)의 머리부위 컴퓨터단층촬영 데이터를 이용하여 총 20개의 머리뼈 및 얼굴 모델을 제작하여 사용하였다. 3차원 좌표를 이용하여 얼굴근육의 형태와 크기를 파악하고, 얼굴근육의 위치를 나타내기 위한 지수를 계산하였다. 계측 대상은 얼굴복원에 필요한 최소한의 근육 12개를 선정하였다 (눈둘레근, 위입술콧방울올림근, 위입술올림근, 관자근, 큰광대근, 작은광대근, 입둘레근, 턱끝근, 아랫입술내림근, 입꼬리내림근, 볼근, 깨물근). 얼굴근육의 형태와 크기를 측정하기 위해, 닿는곳 – 이는곳의 폭과 근육의 안쪽길이, 가쪽길이를 측정하였다. 얼굴근육의 위치는 정면과 측면 관찰로 나누어, 정면일 때는 정중시상면 – 광대점의 수직거리와 코점 – 턱끝점의 수직거리를 기준으로 하였고, 측면일 때 관상면 – 코점의 수직거리와 코점 – 턱끝점의 수직거리를 이용하여 위치를 설명하였다. 이러한 수치자료를 참조하여 얼굴근육의 3차원 형태를 변형하였고, 템플릿을 제작하여 각 근육모델을 범용 모델 파일 형태인 STL(stereolithography)로 저장하였다. 이번 연구에서 제작한 템플릿을 이용하여 한국인에 적합한 얼굴복원의 자료로 사용할 수 있을 것이며, 또한 얼굴복원 작업을 보다 빠르게 할 수 있으리라 기대한다. 향후 좌표기반 계측 장비(Coordinate Measuring Machine)를 해부된 얼굴근육의 형태자료 획득 과정에 적용하여 이번에 제작된 얼굴근육 템플릿을 검증하고 정확한 모델로 발전시킬 계획이다.

Keywords: 얼굴복원, 법의인류학

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01-5

The histological study of the fat compartments in the infra-orbital area and the orbicularis retaining ligament

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The aim of this study was to elucidate the nature of the fat compartments in the infraorbital area and the orbicularis retaining ligament (ORL) with histological method, and investigate anatomical basis of the morphological change in the infraorbital area. Eight specimens of the skin in the infraorbital area with and without festoon were used in the present study. The full thickness specimens with the bony structure were stained with Masson trichrome or hematoxylin and eoisin. The feature of the fat tissue in the infraorbital skin varied according to the parts relative to the orbital rim and the orbicularis oculi muscle (OOc). A few strands of the fibrous structure which is considered as the ORL were observed distinctly between the preseptal and the prezygomatic part. The specimen with festoon appeared the tugged OOc and the thickened fatty layer at the same level of the orbital rim. A few strands of fibrous structure constitute the ORL and it attaches the deep aspect of the orbicularis oculi muscle (OOc) to the periosteum of the orbital rim. The fascicular system was observed in the superficial and deep fatty layer and it supports the concept of the deep fat compartment. The aging signs of the face originated primarily from the thickening and sagging of the superficial and deep fat tissue, and the tethering effect of the retaining ligament make the signs prominent secondarily.

Keywords: orbicularis retaining ligament, fat compartment

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01-6

해면정맥굴 주변에 외과적으로 접근하기 위한 방법을 간단한 그림, 절단면영상, 3차원영상으로 설명하기

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과거의 많은 연구에서 해면정맥굴 주변에 외과적으로 접근하기 위한 공간을 삼각형으로 정의하였다. 그러나 대부분의 삼각형들은 정의와 이름이 연구마다 다르고, 찾기 매우 어려운 것도 있었다. 또 다른 문제는 이것들을 익히기 위한 교육자료가 부족하다는 것이었다. 이 연구의 목적은 해면정맥굴 주변을 정의한 삼각형을 재정의하고, 이 삼각형을 쉽고, 정확하게 익힐 수 있는 교육자료를 만들어서 제공하는 것이다. 우리는 지난 연구에서 해면정맥굴의 벽을 정의하고, 절단면영상과 3차원영상으로 검증하였다. 이것을 바탕으로 해면정맥굴 주변을 외과적으로 접근하기 위한 공간 열 개를 삼각형으로 정의했고, 각 삼각형의 이름도 정리하였다. 이 삼각형을 쉽게 이해할 수 있는 간단한 그림과 더불어, 정확하게 깨달을 수 있는 절단면영상과 3차원영상을 만들었다. 더불어 삼각형을 통한 대표적인 수술법 네 개를 3차원영상으로 만들었다. 해면정맥굴 삼각형의 간단한 그림은 해부학 강의와 비슷했고, 절단면영상은 자기공명영상과 비슷했고, 3차원영상은 실제 수술과 비슷했다. 따라서 이 자료을 쓰면 해면정맥굴 주변의 삼각형 지식을 쉽고 정확하게 익힐 수 있을 것이다. 이 연구에서 만든 해면정맥굴 삼각형에 대한 절단면영상(TIFF 파일), 3차원영상(PDF 파일)을 홈페이지(anatomy.dongguk.ac.kr/triangles)에서 공짜로 내려받을 수 있다.

사사: 이 연구는 2012년도 정부(미래창조과학부)의 재원으로 한국연구재단의 중견연구과제의 지원을 받아 수행된 연구임(NRF-2012R1A2A2A01012808).

Keywords: Cavernous sinus; Cross sectional anatomy; Internal carotid artery; Microsurgery; Neuroanatomy

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01-7

뼈의 부피와 겉넓이를 이용한 성별판별

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한국인 성인 시신 110구의 CT 영상으로 만든 3차원 뼈 모델의 부피와 겉넓이를 이용한 판별분석 (discriminant analysis)을 통해 성별판별을 시도하였다. 모든 뼈의 부피와 겉넓이에서 남녀 사이의 통계적 유의한 차이가 발견되었다 ($p < 0.01$). 개별 뼈를 이용한 판별분석 결과, 팔다리뼈대에서는 자뼈가 부피 (94.5%)와 겉넓이 (94.0%) 모두에서 정확도가 가장 높게 나타났으며, 몸통뼈대에서는 둘째등뼈가 부피 (89.5%)와 겉넓이 (93.7%) 모두에서 정확도가 가장 높았다. 두 개의 뼈를 이용한 판별분석 결과, 팔다리뼈대에서 자뼈와 함께 넙다리뼈, 정강뼈, 종아리뼈의 부피를 이용한 결과가 각각 95.7%로 가장 높았다. 몸통뼈대의 경우 둘째등뼈와 함께 일곱째등뼈, 아홉째등뼈의 겉넓이를 함께 분석한 경우 93.5%로 정확도가 가장 높았다. 몸통뼈대의 면적을 이용한 단계적분석 (stepwise analysis)에서 가장 높은 정확도는 94.7%이었으며, 판별식은 다음과 같았다: (남>0>여) = 0.104 x R06 + (−0.108) x C06 + 0.245 x T02 + (−0.085) x L04 − 8.859. 팔다리뼈대의 면적을 이용한 단계적분석에서 가장 높은 정확도는 99.4%로 판별식은 다음과 같았다: (남>0>여) = 0.060 x clavicle + 0.020 x scapula + 0.045 x humerus + (−0.049) x radius + 0.093 x ulna + (−0.023) x hip bone + 0.091 x patella + (−0.052) x fibula + 0.043 x talus − 11.548. 이 연구를 통해 뼈의 부피와 면적을 이용하여 성별판별이 가능하다는 결과를 얻었으며, 이를 이용하면 디지털 기술을 활용한 객관적 판단 및 자동화 시스템 구축에 기여할 수 있을 것으로 생각된다.

Keywords: Sex determination, Discriminant analysis, Bone model, Korean

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02-1

Primary Cilium Plays Crucial Roles in Mediating Shh Signaling to Control Cochlear Growth and Hair Cell Differentiation

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The primary cilium serves as a signaling center for cellular pathways important for development including Shh, Wnt, and PDGF. Defects in the primary cilium are associated with a range of genetic disorders known as ciliopathies, which include hearing loss. Previous studies showed that ciliary defects resulted in shortened cochlear duct and abnormal hair cell polarization. While the hair cell polarization defect is attributed to defective planar cell polarity (PCP) signaling, the cause for shortened cochlear duct remains unclear. Given the role of Shh signaling in cochlear patterning and growth, we analyzed Shh signaling in inner ears of three different ciliary mutants, *Broad-mined* (*Bromi*) mutant, *Intestinal cell kinase* (*Ick*) KO, and *Pax2-Cre; Ift88*$^{lox/lox}$which all display a shortened cochlear duct. As previously reported, *Ift88* cKO mutants lack the primary cilium. Both Bromi and Ick mutants showed abnormal morphology and increased length of the cilium, respectively. All three mutant cochleae showed a shortened cochlear length, with *Bromi and Ift88* cKO cochleae more severe than that of the *Ick* KO. All three cochleae showed a reduction in expression of *Ptch1*, a readout of Shh signaling, indicating that Shh signaling was compromised. The expression of an apical cochlear marker, *Msx1*, was reduced or absent, also suggesting that the patterning of the apical cochlear region is compromised. *Bromi* and *Ift88* cKO revealed premature haircell differentiation consistent with phenotypes found in Shh mutants and developed ectopic sensory patches containing vestibular-like hair cells in the Kölliker's organ, which are phenotypes associated in reduced Shh signaling.Taken together, our results underscore the complexity of ciliary mutants and the importance of Shh signaling in contributing to the cochlear phenotypes.

Keywords: Primary Cilia , Ciliary Mutant, Shh Signaling, Hair Cell Differentiation, Cochlear Duct

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02-2

Indocyanine green을 이용한 뇌혈관 및 혈류 분석: Strain, 뇌허혈, 노화 연구에 활용

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1956년에 미국 FDA의 승인을 받은 Indocyanine green(ICG)는 간기능 검사와 망막혈관 조영에 이용되어왔다. 최근에 ICG의 기초 연구에 대한 활용에 대한 방법들이 연구 되고 있으나, 실제적인 적용에 의한 연구 결과는 매우 적다. 본 연구실에서 ICG를 여러 동물모델의 뇌혈관 및 혈류 변화연구에 활용하였다. 첫 번째 연구로 ICG를 이용하여 C57BL/6 와 BALB/c의 대뇌 pial artery의 형태를 비침습적으로 관찰하고, ICG의 동역학을 이용하여 두 strain의 대뇌 혈관의 차이에 따른 혈류의 차이를 분석하였다. 두 번째 연구는 photothrombosis에 의한 대뇌 국소허혈 모델에서 ICG이용하여 infarct부분의 뇌혈관의 변화와 손상범위의 변화, 그리고 혈류의 변화를 분석하였다. 세 번째 연구로 12개월된 BALB/c를 이용하여 노화에 따른 대뇌 pial artery의 형태적 변화와 혈류의 변화를 분석하고, 혈관을 구성 하는 collagen 과 elastin의 변화를 분석하였다. 그 결과, 노화에 따른 혈류의 감소가 노화된 쥐에서 보여지는 혈관의 형태 변형과, 혈관의 탄성의 변화와 관련이 있음을 보였다. 이상의 연구는 ICG를 이용하여 비침습적으로 뇌혈관의 형태를 관찰하고 대뇌 혈류를 다양한 parameter로 분석 가능하며, 조직의 변성을 이미지화 하는데 활용될 수 있음을 보여준다. 또한 ICG를 이용하여 다양한 기초연구에 활용될 수 있는 가능성을 제시한다.

Keywords: Indocyanine Green, photothrombosis, pial artery, dynamics

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02-3

Follistatin is Required for Patterning of Mechanosensory Hair Cells in The Apical Cochlea

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The vertebrate cochlea is tonotopically organized, such that hair cells located in the base respond to high frequency sounds and their counterparts towards the apex respond to lower frequencies. Recent studies suggest that the tonotopic organization is established by a series of molecular events that is initiated by a decreasing apex-to-base gradient of Sonic hedgehog (Shh) signaling both in birds and mammals. In chicken, Bmp7 appears to be a key downstream target of Shh signaling. In mouse, however, the downstream mediators of Shh are not known. A likely candidate is Follistatin (*Fst*), which encodes an antagonist for Bmp/TGFβ signaling. The expression pattern of *Fst* is similar to Shh signaling and its expression is regulated by Shh as well. Here, we investigated the role of *Fst* in the tonotopic organization of the mammalian cochlea using *Fst* knockout mouse. In *Fst* KOs, the cochlear length was largely normal, yet its apical end displayed a slightly irregular shape. Within the cochlear duct, an extra row of outer hair cells was evident only in the apical cochlear region and these hair cells appeared more mature than those in the wild type, based on hair bundle morphology and onset of *Atoh1* expression. Importantly, genes that are preferentially expressed in the apical cochlea such as *Msx1* and *Efnb2* were abolished or down-regulated in *Fst* KOs, suggesting that apical cochlear patterning is disrupted in the absence of Fst function. Since the neonatal lethality of *Fst* KOs precludes functional analyses, we generated inner ear-specific *Fst* cKOs, which are viable and closely recapitulate the cochlear phenotypes of *Fst* KOs. We are currently examining hearing function by measuring ABR and DPOAE. Our data suggest that Fst is required for proper organization and differentiation of hair cells in the cochlear apex and is an important downstream mediator of the Shh signaling in the apex to facilitate tonotopy of the mammalian cochlea.

Keywords: Follistatin, Shh, Cochlea, Hair cell

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02-4

Expression of SOCS2 mRNA and Protein in the Ischemic Core and Penumbra after Transient Focal Cerebral Ischemia in Rats

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To elucidate whether Suppressor of cytokine signaling 2 (SOCS2) is implicated in the pathophysiology of stroke, we investigated spatiotemporal regulation and identification of cell phenotypes expressing SOCS2 after transient focal cerebral ischemia. Weak hybridization signals for SOCS2 mRNA were constitutively observed in striatal neurons, and upregulation of SOCS2 mRNA was induced in association with nestin-positive cells in stroke-lesioned rats. Analysis of the characteristics and phenotypes of SOCS2/nestin double-labeled cells revealed spatial differences between infarct and peri-infarct areas. SOCS2/nestin double-labeled cells in the infarct area were associated with the vasculature and were highly proliferative. In contrast, the double-labeled cells in the peri-infarct area were indeed glial fibrillary acidic protein (GFAP)-positive reactive astrocytes forming the glial scar, although nestin-negative reactive astrocytes also exhibited weak SOCS2 expression. In addition, induction of SOCS2 expression was observed in Iba1-positive cells showing a macrophage-like phenotype with amoeboid morphology; these cells were predominantly localized in the infarct area. In the peri-infarct area, only a small proportion of Iba1-positive cells with the morphology of brain macrophages expressed SOCS2, and most activated stellate microglial cells with thick and short processes exhibited weak or negligible SOCS2 expression. Thus, our results revealed the phenotypic and functional heterogeneity of SOCS2-expressing cells within infarct and peri-infarct areas, suggesting the involvement of SOCS2 in astroglial reactions and activation/recruitment of brain macrophages and its potential role in perivascular progenitors/stem cells after ischemic stroke. This research was supported by Basic Science Research Program through the NRF of Korea funded by the Ministry of Science, ICT & Future Planning (NRF-2013R1A1A1057485).

Keywords: Suppressor of Cytokine Signaling 2, Nestin, Brain Macrophages, Reactive Astrocytes, Focal Ischemia

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02-5

Calretinin Immunoreactivity In The Cerebral Cortex Of The Guinea Pig After Chronic Prenatal Hypoxia

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Damage to developing brain produces neurological sequelae such as cerebral palsy, mental retardation and epilepsy. Our recent studies have shown that density of mature neurons in the cerebral cortex is diminished in the hypoxic status. The cellular mechanism underlying this phenomenon is not understood. During hypoxia, the maintenance of calcium homeostasis is essential to control the growth of developing brain. The aim of this study is to examine the immunoreactivity (IR) pattern of calcium-binding protein, calretinin during development of the guinea pig. Chronic hypoxia was induced by unilateral uterine artery ligation at 30 days of gestation (dg: with term defined as ~67dg). Immunohistochemistry was performed with calretinin antibody in the cerebral cortex. The density of calretinin-IR cells lesser in hypoxic fetuses than in control at 60dg ($P<0.05$) but not at 50dg. This result may be associated with previous study result that BDNF level was reduced in ischemic fetus because the availability of growth factor is largely dependent on calcium influx. Thus, these findings indicate that the distribution of calcium-binding protein is related to chronic prenatal hypoxia

Keywords: Calretinin, Hypoxia, Cortex

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02-6

Effective Botulinum Toxin Injection Point For Treatment Of Headache

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This study performed an extensive analysis of published research on the morphology of the temporalis muscle in order to provide an anatomical guideline on how to distinguish the temporalis muscle and temporalis tendon by observing the surface of the patient's face. Twenty-one hemifaces of cadavers (16 males, 5 females; mean age, 81.0 years; age range, 63–93 years) were used in this study. The posterior border of the temporalis tendon was classified into three types according to its location relative to five reference lines: in Type I the posterior border of the temporalis tendon is located in front of reference line L2 (4.8%, 1/21), in Type II it is located between reference lines L2 and L3 (85.7%, 18/21), and in Type III it is located between reference lines L3 and L4 (9.5%, 2/21). The vertical distances between the horizontal line passing through the jugale (LH) and the temporalis tendon along each of reference lines L0, L1, L2, L3, and L4 were 29.74±6.87 mm (mean±SD), 45.06±8.84 mm, 37.76±11.18 mm, 42.50±7.59 mm, and 32.14±0.47 mm, respectively; the corresponding vertical distances between LH and the temporalis muscle were 55.02±8.25 mm, 74.99±9.90 mm, 73.97±10.12 mm, 55.24±13.25 mm, and 47.56±11.41 mm. Sihler's staining shows that the anterior and posterior branches of the deep temporal nerve run through the anterior and posterior fibers of the temporalis muscle, respectively. BoNT-A should be injected into the temporalis muscle at least 45 mm vertically above the zygomatic arch. This will ensure that the muscle region is targeted and so produce the greatest clinical effect with the minimum concentration of BoNT-A. In order to easily identify the temporalis muscle in a clinical setting, the second finger should be placed on the bottom corner of the zygomatic arch; the tip of the thumb will then be located 45 mm from the zygomatic arch.

Keywords: Migraine, Botulinum Toxin Type A, Temporalis, Injection Site, Sihler Stain

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03-1

Methionine sulfoxide reductase B3 (MsrB3) gene deletion ac celerates vitamin D-induced vascular calcification

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Background: Vascular calcification (VC) is common in patients with chronic kidney disease (CKD). Oxidative stress is associated with CKD-associated VC. Methionine sulfoxide reductase B3 (MsrB3) plays as an antioxidant enzyme by reduction of oxidized methionine to reduced methionine. Here, we investigate the role of MsrB3 on high dose vitamin D3-induced VC. **Materials and Methods:** Experiments were conducted using 8-week old male MsrB3 wild type (MsrB3 WT) and MsrB3 knock out (MsrB3 KO) mice. To induce vascular calcification, mice were administered subcutaneously vitamin D_3 (cholecalciferol) for 3 days daily. Seven days after last administration, samples were collected for biochemical and histological studies. **Result:** After vitamin D_3 injection, calcium levels in the kidney, aorta and serum significantly increased when compared with vehicle-injection, and these increases were greater in the MsrB3 KO mice than in the MsrB3 WT mice. Calcium levels in the kidney, aorta and serum after vehicle-treatment were not significantly different between MsrB3 WT and MsrB3 KO. Von kossa and alizarin red stained calcified spots in the kidney and aorta were greater in the MsrB3 KO mice than in MsrB3 WT mice. Vitamin D_3 injection decreased Msrs expression. Vitamin D_3 injection increased vitamin D receptor (VDR), oxidative stress-related proteins (CuZnSOD, MnSOD, catalase, and HNE), runt-related transcription factor 2 (Runx2), and osterix, an osteogenic transcription factor, expressions in the kidney. These increases were greater in the MsrB3 KO mice than in the MsrB3 WT mice. **Conclusion:** MsrB3 gene-deletion accelerates vitamin D_3-induced calcification of kidney and aorta. It indicates that MsrB3 protein plays an important role on VC, suggesting that MsrB3 protein could be considered as a potential target for the treatment of VC.

Keywords: Vascular calcification, Vitamin D, Oxidative stress, Methionine sulfoxide reductase

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03-2

An Oriental Medicine, Hyungbangpaedok-san Attenuates Motor Paralysis in an Experimental Model of Multiple Sclerosis by Regulating the T cell Response

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The preventive and therapeutic mechanisms in multiple sclerosis are not clearly understood. We investigated whether Hyungbangpaedok-san (HBPDS), a traditional herbal medicine, has a beneficial effect in experimental autoimmune encephalomyelitis (EAE) mice immunized with myelin oligodendrocyte glycoprotein peptide (MOG35-55). Onset-treatment with 4 types of HBPDS (extracted using distilled water and 30%/70%/100% ethanol as the solvent) alleviated neurological signs, and HBPDS extracted within 30% ethanol (henceforth called HBPDS) was more effective. Onset-treatment with HBPDS reduced demyelination and the recruitment/infiltration and activation of microglia/macrophages in the spinal cord of EAE mice, which corresponded to the reduced mRNA expression of pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β), iNOS, and chemokines (MCP-1, MIP-1α, and RANTES) in the spinal cord. Onset-treatment with HBPDS inhibited changes in the components of the blood-brain barrier such as astrocytes, adhesion molecules (ICAM-1 and VCAM-1), and junctional molecules (claudin-3, claudin-5, and zona occludens-1) in the spinal cord of EAE mice. Onset-treatment with HBPDS reduced the elevated population of CD4+, CD4+/IFN-γ+, and CD4+/IL-17+ T cells in the spinal cord of EAE mice but it further increased the elevated population of CD4+/CD25+/Foxp3+ and CD4+/Foxp3+/Helios+ T cells. Pre-, onset-, post-, but not peak-treatment, with HBPDS had a beneficial effect on behavioral impairment in EAE mice. Taken together, HBPDS could alleviate the development/progression of EAE by regulating the recruitment/infiltration and activation of microglia and peripheral immune cells (macrophages, Th1, Th17, and Treg cells) in the spinal cord. These findings could help to develop protective strategies using HBPDS in the treatment of autoimmune disorders including multiple sclerosis.

Keywords: experimental autoimmune encephalomyelitis, Hyungbangpaedok-san, T cell

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03-3

Sulforaphane Ameliorates 3-Nitropropionic Acid-Induced Striatal Toxicity by Activating the Keap1-Nrf2-ARE Pathway and Inhibiting the MAPKs and NF-κB Pathways

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The potential neuroprotective value of sulforaphane (SFN) in Huntington's disease (HD) has not been established yet. We investigated whether SFN prevents and improves the neurological impairment and striatal cell death in a 3-nitropropionic acid (3-NP)-induced mouse model of HD. SFN (2.5 and 5.0 mg/kg/day, i.p.) was given daily 30 min before 3-NP treatment (pretreatment) and from onset/progression/peak points of the neurological scores. Pretreatment with SFN (5.0 mg/kg/day) produced the best neuroprotective effect with respect to the neurological scores and lethality among other conditions. The protective effects due to pretreatment with SFN were associated with the following: suppression of the formation of a lesion area, neuronal death, succinate dehydrogenase activity, apoptosis, microglial activation, and mRNA or protein 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 treatment. Also, pretreatment with SFN activated the Kelch-like ECH-associated protein 1 (Keap1)—nuclear factor erythroid 2-related factor 2 (Nrf2)—antioxidant response element (ARE) pathway and inhibited the mitogen-activated protein kinases (MAPKs) and nuclear factor-kappa B (NF-κB) pathways in the striatum after 3-NP treatment. As expected, the

pretreatment with activators (dimethyl fumarate and antioxidant response element inducer-3) of the Keap1-Nrf2-ARE pathway decreased the neurological impairment and lethality after 3-NP treatment. Our findings suggest that SFN may effectively attenuate 3-NP-induced striatal toxicity by activating the Keap1-Nrf2-ARE pathway and inhibiting the MAPKs and NF-κB pathways and that SFN has a wide therapeutic time-window for HD-like symptoms.

Keywords: Huntington's disease, 3-Nitropropionic acid, Sulforaphane, Nuclear factor erythroid 2-related factor 2, Nuclear factor-kappa B

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03-4

High ω3-polyunsaturated fatty acids in fat-1 mice prevent streptozotocin-induced Purkinje cell degeneration through BDNF-mediated autophagy

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There is increasing evidence of central nervous system (CNS) involvement in diabetic neuropathy, which develops due to hyperglycemia and metabolic imbalance. Loss of Purkinje cells has been implicated in the development of diabetic neuropathy, and this degeneration is characterized by impairment of autophagic processes. The contribution of dietary ω3 polyunsaturated fatty acids (ω3-PUFA) to autophagic dysfunction remains unclear. We evaluated whether fat-1 transgenic mice, a well-established animal model that endogenously synthesizes ω3-PUFA, are protected from Purkinje cell degeneration in streptozotocin (STZ)-induced diabetes. We investigated Purkinje cell autophagic response and related signaling pathways in STZ-induced diabetic fat-1 and wild-type mice. STZ-induced diabetic fat-1 mice did not develop hyperglycemia, motor deficits, or Purkinje cell loss. STZ-induced diabetic wild-type mice had higher levels of microtubule-associated protein 1A/1B-light chain (LC3) I, II, Beclin-1 and Sequestosome 1 (SQSTM1/p62) in the cerebellum. In STZ-induced diabetic fat-1 mice, there was more higher levels of LC3I, II and Beclin-1, but lower levels of p62. Moreover, an increase in cerebellar Rab7, Cathepsin D, and ATP6E were found compared to STZ-induced diabetic wild type. There was also increased BDNF expression in Purkinje cells without any changes in TrkB, and phosphorylation of Akt and cAMP response element binding protein (CREB) in the cerebellums of fat-1 mice. Collectively, these findings indicate that STZ-induced diabetic fat-1 mice were protected from Purkinje cell loss and exhibited increased BDNF signaling, enhancing autophagic flux activity in cerebellar Purkinje neurons. These processes may underlie Purkinje cell survival and may be potential therapeutic targets for treatment of motor deficits related to diabetic neuropathy.

Keywords: Diabetes; Autophagy; Purkinje cells; BDNF; Akt

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03-5

생쥐 간세포에 Fumonisin B1 의해 유도된 자가포식 현상

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Fumonisin B1(FB1)은 곰팡이에 의해 생성되는 마이코톡신(mycotoxin)으로 주로 콩팥과 간에 손상을 유발한다. FB1은 세라마이드 합성효소를 억제하여 세포막의 스핑고지질 불균형을 유발한다. 자가포식(autophagy)은 손상 혹은 비정상적으로 변형된 세포성분을 분해하여 제거하는 현상이다. 본 연구에서는 FB1으로 유발된 세포막 불균형과 관련된 자가포식현상을 보고자 했다. C57BL6 생쥐에 FB1을 5mg/kg/day으로 5일간 복강 내에 주사하였고 그에 따른 자가포식을 확인하기 위해 자가포식 과정에 관여하는 항체들을 사용하여 면역조직화학법, 단백질 분석 및 전자현미경으로 미세구조 변화를 관찰하였다. FB1을 투여한 생쥐는 혈액에서 간 기능의 지표인 AST는 정상치의 1.2배, ALT는 1.5배 증가하였다. 형태학적 변화로는 간세포에서 다수의 공포와 세포분열 그리고 국소적인 괴사성 결절이 관찰되었다. 자가포식현상에 관여하는 유전자들인 LC3A/B, Atg3, Atg5, Atg7,

Atg12, Atg16L1, Beclin–1이 FB1을 투여한 간에서 매우 증가하였다. 전자현미경으로 관찰한 결과 대조군에 비해 FB1 투여군에서 이중막 구조로 싸여진 소포(vesicle) 내에 조각난 세포소기관들이 다수 관찰되었으며 일부 소포체는 용해소체(lysosome)와 융합되는 과정이 관찰되었다. 또한 괴사된 세포에 인접한 세포 속에 크기가 다소 큰 세포 조각들이 탐식된 거대자가포식(macroautophagy) 현상도 관찰되었다. 세포 손상과 관련된 세포분열이 유발되었으며 세포분열에 관련된 세포주기 조절인자들은 FB1투여군에서 증가하였다. 이와 대조적으로 세포주기 억제인자들은 감소하였다. 결론적으로 간세포에서 FB1이 자가포식현상에 관여하는 유전자를 활성화함으로써 자가포식을 유발하고, 일부 간세포에서 세포사멸로 의한 보상적인 작용으로 세포증식이 유도됨을 알 수 있었다.

Keywords: 간, 자가포식, 세라마이드

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03-6

Inactivation of poly(ADP-ribose) polymerase enhances glycolytic activity in kidney proximal tubule epithelial cells

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After renal injury, selective damage occurs in the proximal tubules as a result of inhibition of glycolysis; but the molecular mechanisms by which the proximal tubule epithelial cells undergo selective injury are not known. Poly(ADP-ribose) polymerase (PARP) activation plays a critical role of cell death in several renal disorders. Here, we studied the role of PARP on glycolytic flux in pig kidney proximal tubule epithelial LLC-PK1 cells using XFp extracellular flux analyzer. Poly(ADP-ribosyl)ation by PARP activation was increased by 10 mM glucose in LLC-PK1 cells, but treatment with 3-aminobenzamide as a PARP inhibitor does-dependently prevented the PARP activation induced by glucose. Treatment with 1 mM 3-aminobenzamide significantly enhanced extracellular acidification rate increased by glucose, but not oligomycin; indicating that PARP inactivation increases only glycolytic activity during glycolytic flux including basal glycolysis, glycolytic activity, and glycolytic capacity in kidney proximal tubule epithelial cells. Glucose increased the activities of all glycolytic enzymes including hexokinase, phosphoglucose isomerase, phosphofructokinase-1, glyceraldehyde-3-phosphate dehydrogenase, enolase, and pyruvate kinase in LLC-PK1 cells. Furthermore, PARP inactivation selectively augmented the activities of hexokinase, phosphofructokinase-1, and glyceraldehyde-3-phosphate dehydrogenase. In conclusion, these data suggest that PARP activation regulates glycolytic activity through poly(ADP-ribosyl)ation of hexokinase, phosphofructokinase-1, and glyceraldehyde-3-phosphate dehydrogenase in kidney proximal tubule epithelial cells.

Keywords: poly(ADP-ribose) polymerase, glycolysis, kidney proximal tubule

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03-7

Stabilization of Microtubule Retards Recovery of Kidney after Ischemia/Reperfusion Injury

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Ischemia/reperfusion (I/R) is a major cause of acute kidney injury (AKI) which progresses toward chronic kidney disease (CKD). I/R injury changes microtubule network which plays important roles in cell shape, cell motility, and cell division. Here, we investigate the role of post-translational modification of microtubule in the recovery of kidney after I/R injury and progression of fibrosis. Mice were subjected to 30 minutes of bilateral renal ischemia. Some mice were administered either saline (vehicle) or paclitaxel (taxol, a microtubule stabilizing reagent by microtubule acetylation) every other day, beginning on 1 day after ischemia until sacrifice. I/R caused microtubule disruption in the kidney tubule cells, tubular cell death, and functional impairments, leading to kidney fibrosis. I/R resulted

in the decreases of acetylated-α-tubulin and α-tubulin acetyltransferase (αTAT) expression and increase of histone deacetylase 6 (HDAC6) expression. Taxol treatment during recovery phase delayed renal functional and histological recovery from I/R injury and exacerbated fibrosis. Taxol retarded tubule cell regeneration with the increases of cell cycle arrest proteins, p21 and p-chk2. In contrast, taxol accelerated interstitial cell proliferation and macrophage accumulation. Taxol increased α-tubulin acetylation in mProx24 cell, mouse proximal tubular cells, and RAW 264.7 cell, mouse monocytes/macrophages. Taxol in mProx24 induced G2/M phase cell cycle arrest and inhibited ERK activation. Conversely, taxol in RAW 264.7 did not induce G2/M phase cell cycle arrest, but activated ERK and increased PCNA expression. In conclusion, I/R injury results in tubulin deacetylation and taxol treatment during recovery phase retards recovery of kidney after I/R, suggesting that microtubule modification could be considered for the treatment of AKI and CKD.

Keywords: Taxol/ Microtubule/ Tubular regeneration/ Ischemia/ reperfusion/ Macrophage

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04-1

Analysis of Dural Sac Thickness in the Human Cervical Spine

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Background Context: The thickness of the dura mater in the human cervical spine may have differences which are dependent on individuals and vertebral levels, and these can result in various clinical outcomes. **Purpose:** To measure and analyze thickness of the cervical dura mater. **Study Design:** Microscopic measurement of tissue from human cadaver. **Methods:** The subjects were 9 human cadavers showing no previous history of spinal deformity or surgery. Fourteen anterior and the same number of posterior dura mater from C1 to C7 cervical vertebrae were obtained. Thickness of the dura mater was measured by an infrared laser-based confocal microscope. Statistical analyses were performed to reveal relation of thickness of the cervical dura mater with vertebral level, age and sex. Results. Overall average thickness of the cervical dura mater was 379.299×10^{-3}mm in this cadavers. Statistical significant difference of thickness was showed between anterior and posterior part ($P<0.0001$). Moreover, thickness at each different vertebral level had significant differences ($P<0.05$). Posterior thickness of the dura mater was the highest at C1 and lowest at C5/6, which was also significantly different at the axial, sub-axial, and lower cervical levels, whereas anterior thickness of the dura mater was relatively constant along levels. A significant correlation was found between thickness and age ($P<0.05$), however, the average thickness of the dura mater between male and female were not significantly different. **Conclusion:** This study shows anatomical differences in thickness of the cervical dura mater with respect to vertebral level and age. These results provide anatomical information for basic research and clinical approaches.

Keywords: cervical, dura mater, thickness, measurement

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04-2

Topographic anatomy of the inferior medial palpebral artery

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The inferior medial palpebral artery (IMPA), which is a branch of the ophthalmic artery (OA), supplies the tarsal plate of the lower eyelids. There were few studies performed in detail about the knowledge of the IMPA topography. The aim of this study was to determine the distribution pattern of the IMPA and to provide precise topographic information of IMPA for various clinical performances. Twelve hemi-faces from 8 Thai cadavers (4 males and 4 females: mean age 73 years) were used in this present study. The various distribution patterns of the IMPA were classified into two types ac-

cording to its relationship with the superior medial palpebral artery (SMPA): type I (58.3%), in which the IMPA and the SMPA arose from the OA at the same point; type II (41.7%), in which IMPA arose from the OA first and then the SMPA divided from the OA. The IMPA located on the tarsal plate in depth of 3.69±1.24mm at the medial epicanthus, and 3.06±0.79mm at the lateral epicanthus. The diameter of the inferior medial palpebral artery was 0.59±0.14mm at the medial epicanthus and was 0.31±0.10mm at the lateral epicanthus. The IMPA became thinner from medial to lateral epicanthus.

Keywords: inferior medial palpebral artery, ophthalmic artery, lower eyelids

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04-3

CTCF negatively regulate tumor suppressor *HOXA10* in breast cancer cells

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HOX genes play important roles in defining body patterning during embryonic development, but also control numerous cellular events in adult cells. Deregulated HOX gene expression in many different cancers and the critical role of several HOX in breast cancer are now increasingly being reported. Given that human HOX clusters are marked with several CTCF binding sites, some of which are known to play a key role in establishing chromatin domains and regulating gene expression, we investigated whether the presence of CTCF in HOX gene cluster is associated directly with gene expression in breast cancer cells. Several HOX genes, such as *HOXA4*, *HOXA5* and *HOXA10*, were deregulated by CTCF overexpression and knockdown in MCF7 cells. Among these genes, HOXA10 is one of emerging tumor suppressors for its role in activation of p53 and in countering tumorigenesis in breast cancer. Here we provided evidences that CTCF functions as a negative regulator of *HOXA10* in breast cancer cells. The putative promoter region of *HOXA10* lies 5.59 kb upstream of its start codon and its promoter activity was negatively regulated by CTCF. Together with in-silico analysis we identified a 20 bp CTCF binding motif flanking with core promoter element of *HOXA10*. The presence of CTCF on the promoter region of *HOXA10* is associated with decreased active histone marks H3K4me3 and increased repressive histone marks H3K27me3. Low expression of *HOXA10* in T47D as compared to BT474 cells is due to the higher enrichment of CTCF at the promoter region of *HOXA10*. 5-aza cytidine treatment of T47D cells significantly upregulated *HOXA10* expression. We propose that the presence of CTCF not only maintains the inactive state of chromatin but also opposes the recruitment of transcription machinery for the expression of *HOXA10*. Epigenetic silencing of HOXA10 by CTCF in breast cancer cells may contribute towards tumorigenesis by decreasing apoptosis and promoting metastasis.

Keywords: CTCF, Tumor suppressor, HOXA10, H3K27me3, Breast cancer

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04-4

Specific Collaboration Between the Microenvironment and Genetic Constitution Regulates the Self-Renewal of Gastric 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, real-time PCR and western blotting. CAFs increased the self-renewal of GCSCs by secreting

NRG1. NRG1 activated NF-κB signaling and this activation regulated GCSC 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 overexpression is associated with a prognosis of gastric cancer.

Keywords: NRG1 Gastric cancer stem cells Cancer-associated fibroblasts

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04-5

Roles of Hedgehog and TGF-beta in The Specification of Middle Ear

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Mammalian middle ear (ME), responsible for transmitting mechanical vibrations from the outer ear to the inner ear, is composed of a chain of ossicles: malleus, incus, and stapes. Any failure of ME function can lead to conductive hearing loss. Malleus and incus are derived from Neural crest cells (NCCs) migrated into branchial arch (BA) 1, while stapes is from NCCs migrated into BA2. However, the molecular mechanisms involved in NCC migration in forming the ME ossicles remain unclear. In order to elucidate the mechanisms, we have used the Cre-loxp system to manipulate signaling pathways specifically in NCCs or pharyngeal endoderm (PE). Hedgehog (Hh) signaling has previously been implicated in NCC differentiation into ME ossicles. When we analyzed MEs of *Wnt1-Cre;Smo*$^{lox/lox}$ mutants, in which NCCs failed to respond to Hh signaling, initial condensation assessed by *Sox9* expression of malleus and incus in BA1 and stapes in BA2 were observed at E10.5, but disappeared at E11.5, suggesting that Hh signaling is not required for initial condensation but for subsequent development of ME ossicles. Constitutive activation of Hh signaling in NCCs in *Wnt1-Cre;Smo*$^{M2/+}$ mutants resulted in enlarged condensation in both BA1 and BA2 at E10.5 and in fused ME ossicles dislocated from the inner ear at E15.5. Interestingly, we observed that initial condensation of stapes in BA2, was closely associated with *Bmp4* expression domain in PE. When TGF-β was inactivated in NCCs using *Wnt1-Cre;Smad4*$^{lox/lox}$ mutants or endodermal *Bmp4* expression was abolished in *Foxg1-Cre;Bmp4*$^{lox/lox}$, NCCs failed to migrate to the prospective stapes region in BA2, but not in BA1, suggesting that Bmp4 signal emanating from PE dictates migration and initial condensation of NCCs to form stapes in BA2. Together, our results suggest that endodermal Bmp4 signal guides NCCs to migrate to the prospective stapes region in BA2, and Hh signal subsequently plays roles in maintenance and further development of ME ossicles.

Keywords: Middle ear, Initial condensation, Hedgehog and TGF-β signaling, Pharyngeal endoderm

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04-6

Spatiotemporal Progression of Microcalcification in the Hippocampal CA1 Region following Transient Forebrain Ischemia in Rats. an Ultrastructural Study

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Calcification is a common finding in several neuropathological disorders including ischemic insults. The present study was designed to examine in detail the onset and spatiotemporal profile of the calcification in the CA1 hippocampal region, where neuronal death has been observed after transient forebrain ischemia. Very little alizarin

red staining was detected in the CA1 pyramidal cell layer until day 28 after reperfusion, while prominent alizarin red staining was detected in CA1 dendritic subfields, especially, in the stratum radiatum, by 14 days. Electron microscopy using the osmium/potassium dichromate method and electron probe microanalysis revealed that selective calcium deposits were first noted within the mitochondria of degenerating dendrites as early as 7 days, with subsequent complete mineralization of whole dendrites, which coalesced to form larger mineral conglomerates of adjacent calcifying neurites by 14 days. Large calcifying deposits were frequently observed at 28 days, when they were closely associated with or completely engulfed by astrocytes. By contrast, no prominent calcification was examined in somata of degenerating neurons located in the CA1 pyramidal cell layer, except that electron-dense precipitates were noted within, but not beyond, mitochondria in some degenerated neurons that became dark and condensed, but retained their compact ultrastructure by 28 days. Thus, our data revealed that microcalcification initially occurred within dendritic mitochondria of degenerating neurons and this led to the extensive calcification associated ischemic injury, while no progression of calcification occurred in their somata, suggesting that dendritic calcified mitochondria may serve as a nidus for further calcium precipitation in the ischemic hippocampus. This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT and future Planning (NRF-2014R1A2A1A11050246).

Keywords: Transient Forebrain Ischemia; Hippocampus; Mitochondria; Dendrites; Somata; Astrocyte

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04-7

Caloric restriction regulates hippocampal calcium signaling and improves diabetes-induced memory deficits in high-fat diet-fed mice

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Diabetes-induced cognitive decline has been recognized in human patients of type 2 diabetes and a mouse model of obesity, but underlying mechanisms or therapeutic targets are not clearly identified. We investigated the effect of caloric restriction (CR) on diabetes-induced memory deficits and searched a molecular mechanism of CR-mediated neuroprotection. C57BL/6 mice were fed a high-fat diet (HFD) for 40 weeks and RNA-seq analysis was performed in the hippocampus of HFD-fed mice. To investigate CR effect on differential expression of genes, mice were fed HFD for 20 weeks and continued on HFD or subjected to CR (2 g/day) for 12 weeks. HFD-fed mice exhibited insulin resistance, neuroinflammation, blood-brain-barrier (BBB) leakage, and memory deficits, in that we identified *neurogranin* (Ng), a down-regulated gene in HFD-fed mice using RNA-seq analysis; Ng regulates Ca^{2+}/calmodulin (CaM)-dependent synaptic function. CR increased insulin sensitivity, reduced HFD-induced BBB leakage and glial activation, and improved memory deficit. Further, CR reversed HFD-induced expression of Ng and the activation of Ca^{2+}/CaM-dependent protein kinase II, calpain, and downstream effectors. Our results suggest that Ng is an important factor of HFD-induced memory deficits on which CR has a therapeutic effect by regulating Ng-associated calcium signaling.

Keywords: caloric restriction; memory deficits; neurogranin; calcium signaling; obesity

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04-8

N-acetyl-D-glucosamine kinase interacts with dynein light-chain roadblock type 1 in dendritic branch points

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N-acetylglucosamine kinase (GlcNAc kinase or NAGK) phosphorylates GlcNAc to GlcNAc-6-phosphate in the GlcNAc recycling pathway in mammalian amino sugar metabolism. Recently it was reported that NAGK plays a noncanonical role in dendritogenesis. In this study, a interaction between NAGK and dynein light-chain roadblock type 1 (DYNLRB1) was found in yeast two-hybrid screening. Immunocytochemistry (ICC) showed NAGK signal to be colocalized with DYNLRB1. A proximity ligation assay (PLA) of NAGK-dynein followed by tubulin or Golgi ICC showed the colocalization of PLA signals with somal Golgi and with Golgi outposts in dendritic branch points and distensions. NAGK-Golgi PLA signals colocalize with DYNLRB1 at dendritic branch points and at somal Golgi, suggesting a three way interaction between NAGK, dynein and Golgi. In addition, the exogenous inclusion of a C-terminal small peptide of DYNLRB1 resulted in the stunting of dendrites in culture. Our data indicate that the NAGK-dynein-Golgi tripartite interaction at dendritic branch points functions to regulate dendritic growth and/or branching.

Keywords: Dynein, DYNLRB1, Golgi outpost, Microtubule, NAGK, Neuron.

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Poster

전시발표-1 (P001-P065)
2015년 10월 15일(목) 13:00 ~ 14:00 본관 521호: 해부학 실습실
- 맨눈해부학 분야: P1~P6
- 신경과학 분야: P7~P58
- 뼈와 치아의 생물학분야: P59~P65

전시발표-2 (P066-P130)
2015년 10월 16일(금) 13:00 ~ 14:00 본관 521호: 해부학 실습실
- 뼈와 치아의 생물학 분야: P66~P69
- 종양발생의 기전과 조절 분야: P70~P87
- 면역학 분야: P88~P97
- 콩팥의 생리와 병리 분야: P98~P104
- 기타: P105~P130

P1

The Feasibility Study of Plantaris Muscle for Delicate Transplantation

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Plantaris muscle is a rudimentary structure in human. Its incidence in a human leg is about 90%. Although it covers the knee joint and ankle joint, its function and importance is unclear. Rather, its presence along the triceps surae in the leg can be an aggravating factor for the Achilles' tendinosis. However, the tendinous part of the muscle can be used for repair of defect in Achilles' tendon, reconstruction of flexors or extensors of fingers, repair of cardiac valves, improving of the facial asymmetry, and fixation of unstable joints. Beyond the use of the muscle confined in its tendinous part, the use of the muscular part of the plantaris would provide a breakthrough of difficulties in reconstructive surgeries because of the availability of the muscle without any certain complication in the leg. In this study, the morphological features of the plantaris muscles from 28 legs of adult Korean cadavers were investigated. Before the removal or division of the gastrocnemius muscle in most legs, the plantaris muscle could be identified as a crescentic appearance in superomedial side of the lateral head of gastrocnemius muscle. The muscles could be separated from each other with ease. In accordance with the results from previous study, the plantaris muscles were grouped into 3 types. It originated from two regions: the lateral supracondylar line and lateral condyle, from single region: the lateral condyle, or from three regions: the lateral supracondylar line, lateral condyle and knee joint capsule. The plantaris muscle was innervated by the branch from tibial nerve. Most of the plantaris muscles received single nerve branch. In conclusion, the plantaris muscle can easily be identified in the leg without leaving any potential damages to other structures. With its motor innervation, the plantaris is available not only for the tendon graft surgery, but also for the delicate muscle transplantation.

Keywords: Graft, Transfer, Soleus, Facial Reanimation, Calcaneal Tendon

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P2

The Study for Relationship of Joint Cavity and Vascular Formation in Wrist Joint of The Developing Mouse

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손목관절은 8개의 뼈가 자리잡고 있는 복잡한 관절로, 윤환관절(synovial joint)중에서 타원관절(ellipsid joint)에 속하며 다른 관절에 비해 손목관절의 발생에 관한 연구는 거의 없는 실정이다. 본 연구에서는 생쥐의 손목관절을 대상으로 먼저 생쥐 손목관절의 발생 시기를 확인 한다. 이후 후기 발생 중 시간경과에 따라 관절공간 확장 과정을 확인하고, 관절공간 형성 시 두 개의 연골 사이부위에 침입되는 혈관들의 발생 경로를 추적하며, 이 혈관들이 관절공간 안 형성에 어떠한 영향을 미치는지 이를 3차원 재구성을 통해 종합적 분석하고자 한다. 이를 위해 태령 제15일부터 태령 제18일까지 생쥐의 손목관절을 채취하여 일반적인 H&E 염색을 통하여 시간 경과에 따른 생쥐 손목관절의 발생과정을 확인하고 각 시기별 조직을 디지털하여 Univ. Colorado에서 개발된 IMOD를 사용하여 3차원적 재구성을 통하여 다음과 같은 결론을 얻었다. 1. 태령 제15일에 손목관절 노뼈(radial bone)쪽에서 세포의 집중(condensation)과 관절틈새(joint cleft)가 관찰되기 시작하였다. 겨드랑동맥(axillary artery)에서 유래된 장차 노동맥(radial artery)이 될 직경이 큰 원시동맥이 손목관절의 관절공간을 향해 들어가는 것은 관찰할 수 없었다. 2. 태령 제16일에 관절공간의 관절틈새가 태령 제15일에 비해 커져 있으며 세포의 집중은 떨어져 있는 소견이 관찰되었다. 태령 제15일과 마찬가지로 관절공간으로 향하는 혈관은 관찰되지 않았다. 3. 태령 제17일에 관절공간의 형상은 뒤집어진 말굽형태의 U자 모양이었으며 U자의 열린 부분이 먼쪽(distal)을 향하고 있었다. 세포의 집중 소견은 보이지 않으면서 관절틈새가 아닌 관절공간의 형태를 갖추었다. 손목관절부위에서 아래팔 동맥 2개를 완전히 식별할 수 있었다. 이들 동맥에서 관절을 향해 가는 가지동맥(branch arterys)들은 관찰되지 않았다. 이는 특히 3차원 재구성을 통해 확인할 수 있었다. 4. 태령 제18일에 관절공간이 완전하게 관찰 되었다. 이상의 결과로 보아 생쥐의 손목관절공간은 태령 제15일에 손목관절 노뼈(radial bone)쪽에서 세포의 집중(condensation)과 관절틈새(joint cleft)가 관찰되기 시작하며 태령 제17일에 완성되어진다. 관절공간을 향하는 혈관은 관찰되지 않아 관절공간의 형성과 혈관과는 특별한 상관 관계가 없다는 것을 알 수 있었다.

Keywords: 손목관절, 발생, 혈관, 관절공간, 3차원 재구성

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P3

The Third and Forth Head of the Biceps Brachii Muscle Originated from the Pectoralis Major Muscle and the Short Head of the Biceps Brachii Muscle

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During an educational dissection, the supernumerary heads of the biceps brachii muscle were found on the left side in a Korean cadaver. The short and long heads were normal: however, the third head and the forth head were found in this case. The third head originated from the pectoralis major muscle and was inserted into the conjoined tendon of the short head of the biceps brachii muscle. And the forth head originated from the middle level of the short head of the biceps brachii and was inserted into the conjoined tendon of the short head of the biceps brachii muscle that so called inferior medial head. The author describes this previously unreported case in Korea and discusses the clinical implications of such a variant.

Keywords: Biceps brachii muscle, Pectoralis Major Muscle, Variation

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P4

Ac cessory Tendon of the Biceps Brachii Muscle Originated from the Pectoralis Major Muscle

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During an educational dissection, accessory tendon of the biceps brachii muscle was found on the right side in a Korean cadaver. The short and long heads showed normal morphology and course: however, narrow tendon was originated from the posterior border of the pectoralis major muscle and was inserted into the conjoined tendon of the long head of the biceps brachii muscle. The author describes this previously novel case report and discusses the clinical implications of such a variant.

Keywords: Biceps Brachii Muscle, Pectoralis Major Muscle, Variation

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P5

기관과 반지연골의 형태계측 연구

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이 연구는 한국인의 기관과 반지연골의 형태계측을 통하여 기관내 삽관, 기관 절개술, 반지 방패막 절개술 등에 필요한 기초자료를 제공하고자 수행하였다. 연구에 사용한 시체는 남자 33구, 여자 15구로 총 48구를 대상으로 실시하였다. 시체의 평균 연령은 남자 70세(50~91세), 여자 74세(47~92세)였다. 기관 연골의 수는 남자가 16.79개, 여자가 18.13개로 남자가 여자보다 적었다. 기관의 길이는 남자가 104±1.41, 여자가 102.3±1.89mm로 남자와 여자 사이에 유의성은 없었다. 첫째, 다섯째, 열째, 열다섯째 기관연골의 앞뒤지름과 가로지름, 기관연골의 높이는 모두 남자가 여자에 비하여 길었다. 앞뒤지름은 첫째와 다섯째, 가로지름은 첫째와 열다섯째, 연골의 높이는 첫째에서 남자와 여자 사이에서 유의한 차이를 보였다. 기관연골의 뒷막넓이는 첫째와 열째, 열다섯째에서 남자가 여자에 비하여 넓었다. 기관연골사이 넓이도 남자가 여자보다 모두 넓었으나 유의한 차이는 1~2째와 10~11째 사이에서 나타났다. 반지연골에서 7가지 계측항목들을 측정하였다. 반지연골의 위쪽면의 앞뒤길이는 남자에서 28.50±0.59mm, 여자에서 23.85±0.98mm, 아래쪽면의 앞뒤길이는 남자에서 18.78±0.47mm, 여자에서 15.97±0.54mm로, 남자가 여자보다 길었다. 반지연골의 가로길이도 남자 17.19±0.40mm, 여자 13.36±0.50mm로 남자가 여자에 비하여 길었다.

앞쪽과 뒤쪽에서의 정중앙의 높이는 남자가 여자보다 각각 약 1.38mm, 2.23mm 높았다. 그러나 앞쪽과 뒤쪽에서 정중앙의 두께는 남자가 여자에 비하여 두꺼웠으나 통계학적 유의성은 없었다. 이상의 결과는 응급의사, 마취의사, 응급 구조사들의 시술에 유용한 임상적 기초자료로 활용될 것으로 생각한다.

Keywords: 기관, 반지연골, 형태계측

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P6

Morphologic Characteristics of the Volar Surface of the Distal Radius in Korean

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Volar locking plate has been commonly used for treatment of distal radius fractures. In depth understanding of the distal radius morphology is mandatory in order to choose a proper implant and to avoid implant-related complications. The purpose of this study was to evaluate the morphologic characteristics of the volar surface of the distal radius in Korean population. Morphologic characteristics of the volar surface of the distal radius were evaluated with 3D computed tomography images from cadavers. Ninety specimens (male:34, female:56) were included in this study. CT scan was performed with 0.75 mm thickness and reconstructed with 3D modelling program (Mimics, Materialise, Belgium). Volar slope angles of the radial and intermediate columns were measured and compared with commercially available volar locking plates. Mean volar slope angle was 23.9 degrees in radial column and 28.1 degrees in intermediate column. Male has larger angles in both columns compared to those of female (26.1 vs 21.5 in intermediate column, 29.9 vs 25.2 in radial column, respectively). Some volar locking plates were protruded in female specimens with low volar slope angles. Larger implants need to have more volar slope angle to accommodate the morphology of the distal radius. Some commercially available implants protrude from the female distal radius in Korean population which may cause flexor tendon complications.

Keywords: Distal Radius, Fracture Locking Plate, Bony Surface Anatomy, Korean

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P7

Early growth response 1 (Egr-1) directly regulates $GABA_A$ receptor α2, α4, and θ subunits in the hippocampus

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The homeostatic regulation of neuronal activity in glutamatergic and GABAergic synapses is critical for neural circuit development and synaptic plasticity. The induced 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 the brain remained to be elucidated. This study uses a quantitative real-time PCR approach, in combination with in vivo chromatin immunoprecipitation, and reveals that $GABA_A$ receptor subunit, *GABRA2* (α2), *GABRA4* (α4), and *GABRQ* (θ) genes, are transcriptional targets of Egr-1. Transfection of a construct that over-expresses Egr-1 in neuroblastoma (Neuro2A) cells up-regulates the α2, α4, and θ subunits. Given that Egr-1 knockout mice display less *GABRA2*, *GABRA4*, and *GRBRQ* mRNA in the hippocampus, and that Egr-1 directly binds to their promoters and induces mRNA expression, the present findings support a role for Egr-1 as a major regulator for altered $GABA_A$ receptor composition in homeostatic plasticity, in a glutamatergic activity-dependent manner.

Keywords: Egr-1; GABRA2 (α2); GABRA4 (α4); GABRQ (θ)

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P8

Early gene response 1 (Egr-1) directly regulates the α2, α4, and θ subunits of the GABAA receptor in the hippocampus

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The homeostatic regulation of neuronal activity in glutamatergic and GABAergic synapses is critical for neural circuit development and synaptic plasticity. The induced 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 the brain remained to be elucidated. This study uses a quantitative real-time PCR approach, in combination with in vivo chromatin immunoprecipitation, and reveals that $GABA_A$ receptor subunit, *GABRA2* (α2), *GABRA4* (α4), and *GABRQ* (θ) genes, are transcriptional targets of Egr-1. Transfection of a construct that over-expresses Egr-1 in neuroblastoma (Neuro2A) cells up-regulates the α2, α4, and θ subunits. Given that Egr-1 knockout mice display less *GABRA2*, *GABRA4*, and *GRBRQ* mRNA in the hippocampus, and that Egr-1 directly binds to their promoters and induces mRNA expression, the present findings support a role for Egr-1 as a major regulator for altered $GABA_A$ receptor composition in homeostatic plasticity, in a glutamatergic activity-dependent manner.

Keywords: Egr-1; GABAA receptor ; GABRA2 ; GABRA4 ; GABRQ ;

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P9

Warburg effect in the high fat diet-fed mouse brain and Alzheimer's pathology

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The amyloid cascade hypothesis, along with amyloid precursor protein and the secretases, argues that beta amyloid is correlated with familiar Alzheimer's disease (AD). Yet, evidences from experimental and clinical studies are compelling that the amyloid at any stage of aggregation is not sufficient to develop sporadic AD. Additionally, not only cancer and diabetes mellitus but also neurodegenerative disorder are recently evaluated as the chronic metabolic diseases. In this study, we investigated the correlation between dysregulation in brain glucose metabolism and early-time pathophysiology in AD using high fat diet (HFD)-fed mouse. The mouse, to detect alteration of glucose metabolism in the AD-like mouse brain, was subjected to dynamic nuclear polarization-enhanced hyperpolarized 13C magnetic resonance spectroscopic imaging (DNP-MRSI), following HFD for 6 months. Specifically, metabolic amounts and its speed of hyperpolarized 13C-labeled pyruvate were 1) temporally analyzed with dynamic MRS and 2) spatially analyzed with chemical shift imaging (CSI) methodology. We also performed immunohistochemistry analyses to detect accumulation of beta amyloid. Firstly, although the HFD-fed mouse for 6 months controlled intact blood glucose levels through pancreatic insulin, abnormal accumulation of beta amyloid was detected in the hippocampal areas. In addition, we observed both the lactate conversion from hyperpolarized 13C pyruvate in the hippocampal areas drastically increased in the HFD-fed mouse brain compared with normal diet-fed mouse. Together, our results demonstrate that the abnormal accumulation of beta amyloid and of lactate residues through Warburg effect in the brain could play a role in the neuropathology of AD.

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Keywords: Warburg effect, Sporadic Alzheimer's disease, Glucose metabolism, Beta amyloid, Hippocampus

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P10

Korean Red Ginseng and Ginsenosides Rb1/Rg1 Alleviate Experimental Autoimmune Encephalomyelitis by Suppressing Th1 and Th17 T Cells and Upregulating Regulatory T Cells

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The effects of Korean red ginseng extract (KRGE) on autoimmune disorders of the nervous system are not clear. We investigated whether KRGE has a beneficial effect on acute and chronic experimental autoimmune encephalomyelitis (EAE). Pretreatment with KRGE significantly attenuated clinical signs and loss of body weight and was associated with the suppression of spinal demyelination and glial activation in acute EAE rats, while onset treatment (daily after the appearance of clinical symptoms) did not. The suppressive effect of KRGE corresponded to the mRNA expression of proinflammatory cytokines (TNF-α and IL-1β), chemokines (RANTES, MCP-1, and MIP-1α), adhesion molecules (ICAM-1, VCAM-1, and PECAM-1), and inducible nitric oxide synthase in the spinal cord after immunization. Interestingly, in acute EAE rats, pretreatment with KRGE significantly reduced the population of $CD4^+$, $CD4^+$/IFN-γ^+, and $CD4^+$/IL-17^+ T cells in the spinal cord and lymph nodes, corresponding to the downregulation of mRNA expression of IFN-γ, IL-17, and IL-23 in the spinal cord. On the other hand, KRGE pretreatment increased the population of CD4+/Foxp3+ T cells in the spinal cord and lymph nodes ofthese rats, corresponding to the upregulation of mRNA expression of Foxp3 in the spinal cord. Interestingly, intrathecal pretreatment of rats with ginsenosides (Rg1 and Rb1) significantly decreased behavioral impairment. These results strongly indicate that KRGE has a beneficial effect on the development and progression of EAE by suppressing T helper 1 (Th1) and Th17 T cells and upregulating regulatory T cells. Additionally, pre- and onset treatment with KRGE alleviated neurological impairment of myelin oligodendrocyte glycoprotein35–55-induced mouse model of chronic EAE. These results warrant further investigation of KRGE as preventive or therapeutic strategies for autoimmune disorders, such as multiple sclerosis.

Keywords: Korean red ginseng, Ginsenosides, Experimental autoimmune encephalomyelitis, T cell

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P11

The potential role of SNX12 and its interaction with Drp1 in endosomal trafficking of neurons

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Dynamin-related protein1 (Drp1) is a large GTPase protein, promoting mitochondrial fission. Recently, the localization of Drp1 has been reported in other membranous organelles such as Golgi complex, peroxisome and endosome. However, the precise mechanisms and the functional contribution of Drp1 on the endocytic vesicle trafficking is yet to be addressed. In this study, we identified Sorting nexin 12 (SNX12) as a putative Drp1-binding protein localized at the endocytic vesicles. SNX12 was highly expressed in the brain and its expression level increased more as neurons became mature. In cultured primary hippocampal neurons, GFP-SNX12 is co-localized with VPS35, a component of heteropentameric retromer complex in early endosome. Interestingly, Drp1 was recruited to the overexpressed SNX12 puncta. Moreover Co-immunoprecipitation further confirmed the interaction of SNX12 with Drp1. Drp1 and SNX12 are co-localized with early endosome marker, EEA1 at neurites of primary hippocampal neurons. Knockdown of Drp1 perturbed the

subcellular localization of SNX12 and they formed large aggregates in primary hippocampal neurons. Therefore, our present data provide preliminary evidence that Drp1 plays a significant role in the endosomal vesicle trafficking through the interaction with SNX12.

Keywords: SNX12, Drp1, retromer, Endosome

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P12

Patterning of neuronal synapse formation by surface-printed microdot array

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Functions of neuronal circuit are fundamentally modulated by its quality and quantity of connections. Assessment of synapse, a basic unit for a neuronal connection, is essential for understanding the nervous system and drug screening for synaptic diseases. However, due to the small size and the spatially random clustering of neuronal synapses, exploration of synapses is labor-intensive and time-consuming in conventional culture systems. In the present study, we propose a novel culture system, in which synapses can be concentrated at desired locations, suitable for the high-throughput assays. We fabricated a negative dot array pattern by coating the entire surface with poly-l-lysine (PLL) and subsequent microcontact printing of the inverse-dot patterns with various masking substrates. Presynapse and postsynapse were markedly concentrated to the PLL-only surface of the dots and closely apposed with each other, forming functional synapses, suggesting that the printing of biologically inactive molecules on the surface of adhesive surface efficiently control the position of synapse formation. The printing of Semaphorin 3F-Fc (Sema3F), a well-known repulsive axon guidance molecule, elicited more profound patterning of neurons including the preferential localization of a soma within the negative dots. This 'synapse concentrating' chip can easily be applied for the various high-throughput assay formats based on the synaptic morphology and function. Thus, our results illustrated that newly designed dot array pattern by microcontact printing can control neuronal morphology and synapse distribution, suggesting its potential usefulness for bio-chip platforms for the assay in synapse-related neurobiological studies.

Keywords: Neuron, Synapse, Microcontact printing, Dot array pattern, Bio-chip

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P13

Agmatine ameliorates high glucose-induced cell senescence via the p53/p21 cascade

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Neuronal senescence caused by diabetic neuropathy is considered a common complication of diabetes mellitus. The deleterious effects of high glucose result in multiple impairments of hypothalamic neurons during aging. Neuronal senescence leads to the secretion of pro-inflammatory cytokines, the production of reactive oxygen species, and the alteration of cellular homeostasis. Agmatine, which is biosynthesized by arginine decarboxylation, has been reported in previous *in vitro* and *in vivo* studies to exert a protective effect against various stresses. The data from our present study suggest that agmatine may inhibit neuronal cell senescence induced by high glucose. Cell death was evident in the brains of mice fed a high-fat diet that induced hyperglycemia. The activation of AMP-activated protein kinase, p53, and p21, which leads to cellular senescence, was inhibited by agmatine. Additionally, agmatine also attenuated the expression of pro-inflammatory cytokines such as tumor necrosis factor alpha, interleukin-6, and chemokine (C-C motif) ligand 2 in high glucose *in vitro* conditions. Moreover, the senescence associated-β-galatosidase's activity in high glucose exposed cells was reduced by agmatine. Here, we propose that agmatine may ameliorate neuronal cell senescence via p53/p21 signaling in hyperglycemia.

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Keywords: Agmatine, High-fat diet(HFD), High glucose, Neuronal cell, Senescence

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P14

Suppression of let-7A microRNA expression by agmatine induces neuronal differentiation

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Neural stem cells (NSCs) effectively reverse some severe central nervous system (CNS) disorders, due to their ability to differentiate into neurons. Agmatine, a biogenic amine, has cellular protective effects and contributes to cellular proliferation and differentiation in the CNS. Recent studies have elucidated the function of let-7a microRNA (miR-let-7a) as a regulator of cell differentiation and proliferation with roles in regulating genes associated with CNS neurogenesis. This study aimed to investigate whether agmatine modulates the expression of crucial regulators of NSC differentiation including DCX, TLX, c-Myc, and ERK by controlling miR-let-7A expression. Our data suggest that high levels of miR-let-7a promoted the expression of TLX and c-Myc, as well as repressed ERK expression. In addition, agmatine attenuated expression of TLX and increased expression of ERK by negatively regulating miR-let-7a. Further research on the mechanistic link between agmatine and miR-let-7a may elucidate the effects of agmatine on neuronal differentiation. Our study therefore enhances the present understanding of the therapeutic potential of NSCs in CNS disorders.

Acknowledgments: This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MEST) (NRF-2014R1A2A2A01006556).

Keywords: Neural stem cell(NSCs), MicroRNA let-7A(miR-let7A), Agmatine, TLX, ERK

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P15

Blocking the PI3K pathway Inhibit the Efficacy for NRG1 Mediates Rescue LTPIimpairment and Neurotoxicities Induced by Ab1-42

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Neuregulin-1 (NRG1) plays critical roles in the development and plasticity of the brain. Furthermore, it is also known to have potent neuroprotective properties. We previously reported that NRG1/ErbB4 has neuroprotective actions against Alzheimer"fs cell models and prevents Amyloid'À(A'À1-42)–induced impairment of long-term potentiation (LTP) in the CA1 region of mice hippocampal slices. A'À peptide is generally believed to play an important role in the pathogenesis of AD. In this study, we investigated the downstream pathways of NRG1/ErbB4 signaling in prevention of LTP impairment and neurotoxicity induced by A'À1-42. By blocking the PI3K pathway, the LTP-restoring action of NRG1 was almost completely negated, suggesting that NRG1/ErbB4 signaling acts through PI3K activation to exert its protective action on LTP. Moreover, Inhibition of PI3K activation blocked the reducing effects of NRG1 on A'À1-42-induced LDH release, TUNEL-positive cells number, and reactive oxygen species accumulation in primary cortical neurons. Collectively, our results demonstrate that NRG1/ErbB4 signaling exerts neuroprotective effects against A'À1-42-induced hippocampal

LTP impairment and neurotoxicity through 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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P16

Effects of Neuregulin1 on Glutamate Uptake by Upregulating Excitatory Amino Acid Carrier1 (EAAC1)

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Neuregulin1 (NRG1) is a trophic factor believed to play critical roles in the development of brain circuitry. Recent studies suggest that NRG1 may regulate neurotransmission, though the mechanisms remain uncertain. In this study, 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 NRG1. By inhibiting ErbB4, this effect was blocked, suggesting ErbB4 involvement in NRG1 regulation of glutamate uptake. By suppressing the expression of ErbB4 by siRNA, the expression of EAAC1 decreased. In addition, the ablation of ErbB4 in parvalbumin (PV)-positive interneurons in PV-ERbB4-/- mice suppressed EAAC1 expression. Furthermore, NRG1 was shown to reduce EAAC1 ubiquitination and degradation. Collectively, these results show that NRG1 regulates EAAC1 via ErbB4 receptors and identifies a novel function of NRG1. These findings link proposed effectors in schizophrenia: NRG1/ErbB4 signaling perturbation, EAAC1 deficit, and neurotransmission dysfunction.

Keywords: Neuregulin 1 (NRG1), Excitatory amino acid carrier 1 (EAAC1), ErbB4, Glutamate

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P17

Three-dimensional assessment of bystander effects of mesenchymal stem cells carrying a cytosine deaminase gene on glioma cells

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Stem cells carrying a suicide gene have emerged as therapeutic candidates for their cytotoxic bystander effects on neighboring cancers, while being non-toxic to other parts of the body. However, traditional cytotoxicity assays are unable to adequately assess the therapeutic effects of bystander cells. Here, we report a method to assess bystander effects of therapeutic stem cells against 3-dimensionally grown glioma cells in real time. U87 glioma cells were stably transduced to express a green fluorescence protein and co-cultivated with mesenchymal stem cells engineered to carry a bacterial cytosine deaminase gene (MSC/CD). Following addition of a 5-fluorocytine (5-FC) prodrug to the co-culture, fluorescence from U87 cells was obtained and analyzed in real time. Notably, the IC_{50} of 5-FC was higher when U87 cells were grown 3-dimensionally in soft agar medium for 3 weeks, as compared to those grown for one week in two-dimensional monolayer cultures. Additionally, more MSC/CD cells were required to maintain a similar level of efficacy. Since three-dimensional growth of glioma cells under our co-culture condition mimics the long-term expansion of cancer cells *in vivo*, our method can extend to an *in vitro* assay system to assess stem cell-mediated anti-cancer effects before advancing into preclinical animal studies.

Keywords: Mesenchymal stem cell, Cytosine deaminase, Glioma cell, Bystander effect, 3-dimensional culture

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P18

Developmental changes in axonal translatome

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Local mRNA translation mediates extrinsic cue-induced axonal guidance and survival. What mRNAs are translated in axons in vivo remains a key unanswered question. We developed Axon-TRAP, a technique to isolate mRNAs translating in mouse retinal axons in vivo and performed deep sequencing of the entire set of translating mRNAs (translatome) at different developmental stages. Bioinformatic analyses reveal that functionally distinct classes of mRNAs are translationally co-regulated during axon elongation, the initial phase of synapse formation, and postnatal synaptic refinement. This result suggests that an RNA-based mechanism operates in the distal axon, which enables a prompt and autonomous to control over the local proteome to meet the current biological demands.

Keywords: translatome, axon, retinal development

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P19

Inositol 1,4,5-trisphosphate 3-kinase A, a Gene Enriched in the Amygdala, Regulates Fear- and Anxiety-related Behavior

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Inositol 1,4,5-trisphosphate 3-kinase A (IP_3K-A) is a molecule enriched in the brain and neurons that regulates intracellular calcium levels via signaling through the inositol trisphosphate receptor. Despite its expression in emotion-related neural structures and its functional importance in neural activity, no clear evidence has shown that IP_3K-A is associated with emotional state. In the present study, we found that IP_3K-A expression is highly enriched in the central nucleus of the amygdala (CeA), which plays a pivotal role in the processing and expression of emotional phenotypes in mammals. Genetic abrogation of IP_3K-A altered amygdala gene expression, particularly in genes involved in key intracellular signaling pathways and genes mediating fear- and anxiety-related behaviors. In agreement with the changes in amygdala gene expression profiles, IP_3K-A knockout (KO) mice displayed more robust responses to aversive stimuli and spent less time in the open arms of the elevated plus maze, indicating high levels of innate fear and anxiety. In addition to behavioral phenotypes, decreased excitatory and inhibitory postsynaptic current and reduced c-Fos immunoreactivity in the CeA of IP_3K-A KO mice suggest that IP_3K-A has a profound influence on the basal activities of fear- and anxiety-mediating amygdala circuitry. In conclusion, our findings collectively demonstrate that IP_3K-A plays an important role in regulating affective states by modulating metabotropic receptor signaling pathways and neural activity in the amygdala.

Keywords: Inositol 1,4,5-trisphosphate 3-kinase A, amygdala, emotion

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P20

Down-Regulation of Acetylcholinergic Neurotransmission in Medial Habenular Cholinergic Cells Induces Anhedonia

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The habenula modulates several brain functions via regulation of monoaminergic neurotransmitters such as dopamine, norepinephrine, and serotonin. Recent studies suggest that the habenula is involved in debilitating mental disorders related with fear, anxiety and depression. However, little information is available at the molecular levels about the transcriptional alterations that aversive stimuli cause in the habenula. Using genome-wide microarray we identified differentially expressed genes in rat habenula from chronic restraint stress and learned helplessness models. Among them, medial habenula-enriched acetylcholinergic signaling-regulating genes are down-regulated in both rat models. These stress-induced down regulation of acetylcholinergic genes is occurred in the habenuli of depressed rats induced with learned helplessness and human suicide victims that suffered with major depressive disorder. Acetylcholine-related genes are enriched in the ventral medial habenula and its transmission is mainly occurred in the synapses innervated into interpeduncular nucleus which projects axons into serotonergic neurons in raphe. Notably, administration of AAV virus, which express interference RNA reducing rat cholineacetyltransferase (ChAT) gene, shows the depression-like behaviors. Here, we report that acetylcholinergic signaling in medial habenular cholinergic neurons is important for regulation of anhedonic mood and this signaling is a new pharmacological target for depressive psychiatry.

Keywords: Habenula, Stress, Acetylcholine, Depression, Suicide

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Abnormal Synaptic Plasticity and Behaviors of Inosito 1, 4, 5-Triphosphate 3 Kinase A(IP3K-A) Transgenic Mouse

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Inositol 1,4,5-trisphosphate 3-kinase A (IP3K-A) is a brain specific enzyme whose expression is regulated by altered neuronal activities such as learning and seizure. IP3K-A is known to control dendritic spine formation via modulation of actin or tubulin cytoskeletons. Our previous study showed that IP3K-A null mice exhibited defects in some forms of learning, impaired synaptic plasticity such as long-term potentiation, and changed actin dynamics in hippocampus. To further explore the function and mechanism of IP3K-A on the neuronal plasticity, we generated transgenic (Tg) mice whose expression of IP3K-A was inducible in the forebrain region including hippocampus using Tet-on system. As a result, IP3K-A Tg mice showed defects in spatial memory (WT, n = 11; Tg, n = 10) and higher efficacy of evoked synaptic transmission at CA1 synapses than wild type (WT) mice. In electrophysiology data, IP3K-A Tg mice showed enhanced early phase long-term potentiation and reduced metabotropic glutamate receptor-dependent long-term depression (WT, n = 20 cells; Tg, n = 18 cells). Interestingly, however, there was no change in dendritic spine density or synaptic molecule level in IP3K-A Tg mice. Instead, IP3K-A Tg mice had increased number of synaptic vesicles at CA1 synapses. Now we are investgating the molecular mechanism underlying the abnormal synaptic plasticity. Our data suggest that IP3K-A might regulate hippocampal CA1 synaptic plasticity by modulating presynaptic release process in hippocampus, rather than by changing cytoskeletons.

Keywords: IP3K-A. Transgenic Mouse. Synaptic Plasticity. Behaviors

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Bangladeshi Medicinal Plants for Neuronal Differentiation and Axodendritic Complexity

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In Bangladesh, a large number of valuable medicinal plants have been used as folkloric medicine for treatment of brain related disease but there is no scientific evidence of use of these plants. Neurotrophic factors are essential for neuronal differentiation, development and survival, and their combined actions may reduce the risks of neurodegenerative disease progressions. Therefore, to explore plants of natural origins having neurotrophic factors, 21 medicinal plant leaf samples was collected from Bangladesh and evaluated their effect on central nervous system (CNS) neurons regarding neurotrophic properties. The primary culture of embryonic hippocampal neurons was prepared and incubated with the ethanol extract of plants leaf. Cultures were then fixed and immunolabeled to visualize the neuronal morphology. Morphometric analysis was performed using Image J software. The results revealed that CGE promoted most promising neurite outgrowth activity in a concentration dependent manner with an optimal concentration of 7.5 μg/mL. As a very initial effect, CGE significantly enhanced the neuronal differentiation and subsequently increased the formation of axodendritic arbor complexity. It is note that CGE not only promotes the neuronal differentiation but also facilitates axodendritic maturation in developing neurons. The findings manifested CGE can be used as a promising candidate for the prevention or treatment of neurological disorders.

Keywords: Neuronal development, Hippocampal neuron, Axodendritic arborization, Medicinal plant

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P23

Neural Stem/Progenitor Cells Overexpressing Arginine Decarboxylase Gene Promotes Intracellular Ca2+ - Induced Neural Differentiation After Ischemic Injury

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The third acid resistance system, arginine decarboxylase (ADC) is highly conserved gene but poorly understood in CNS diseases. Here, we reported *vh*ADC for therapeutic use in cell replacement therapy, could stimulates the cell cycle arrest and neuronal differentiation in NSPCs after ischemic damage *in vitro* and *in vivo* CNS models. Highly expressed *vh*ADC were promotes cell cycle arrest by intracellular Ca^{2+} induced CDK4 activation and nucleocytoplasmic shuttling of phosphorylated pRB and E2F1. Together with, *vh*ADC resisted mitochondrial membrane potential ($\Delta\Psi_m$) collapse against accumulated intracellular Ca^{2+} in mNSPCs. In addition, *vh*ADC displayed enhanced neural differentiation by increasing pSTAT1 expression regulated with pP38 MAPK and pCREB signaling in mNSPCs. Following these results, transplanted *vh*ADC-mNSPCs consequently promoted neuronal differentiation, synapse formation and motor functional recovery in transient cerebral ischemia. These results suggest that *vh*ADC-mNSPCs have relevant cell therapeutics for various CNS diseases.

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Keywords: Human Arginine decarboxylase (vhADC), Neural Stem/Progenitor Cells (mNSPCs), Intracellular Ca2+ Level, Mitochondrial Membrane Potential, Neuronal Differentiation

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Radix Puerariae promotes neuronal cytoarchitecture and synaptogenesis in cultured rat hippocampal neurons

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Natural or synthetic molecules with potential neurotrophic effects offer means of preventing or treating neurodegenerative disorders. We therefore investigated the neurotrophic effects of a traditional ethnomedicine, Radix *Puerariae* and its active constituent, puerarin on the development of central nervous system neurons. For this purpose, rat embryonic (E19) brain neurons cultured with the ethanolic extract of Radix *Puerariae* (RPE) or puerarin were assessed for neuronal morphologies by immunostaining and for neuronal proteomes by MALDI-TOF-MS/PMF and measuring immunofluorescent intensities. Results showed that RPE and puerarin alone promoted maximum neurite outgrowth at concentrations of 1 μg/ml and 5 μM, respectively. Moreover, RPE and puerarin provided neurotrophic support by promoting axo-dendritic arbors and synapse formation in cultured neurons. Proteomic study revealed that RPE and puerarin both up-regulated a number of proteins, including dynein light chain 2 (DLC2) and elongation factor 2 (EF2), which are associated with neuritogenesis and synaptic potentiation. Taken together, our study suggets that RPE and puerarin should be considered potentially valuable preventative therapeutics for brain disorders due to their abilities to promote neuronal cytoarchitecture and synaptic connectivity, which are possibly associated with dynein-dependent regulation of cytoskeletal structures and up-regulation of translation machinery.

Keywords: Dynein, Elongation factor 2, Neuritogenesis, Radix Puerariae, Synaptogenesis

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P25

Shh Expressed In Apical Spiral Ganglion Neurons Is Necessary For Otic Neurogenesis And Survival In Spiral Ganglion Neurons

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The inner ear is complex organ developed to perceive sound, motion, and orientation. These perceived information in inner ear are transmitted by CVG, consisting of vestibular ganglion neurons (VGNs) and spiral ganglion neurons (SGNs), from inner ear to the brainstem. SGNs are specified for neuroblasts that delaminate from otic cup and otic vesicle between embryonic day (E) 8.5 to 12.5 in the mouse. *Neurogenin1* (*Neurog1*), member of the basic helix-loop-helix (bHLH) family of transcription factor, is required for otic neurogenesis. In previous study, *Shh* knockout mouse showed that *Neurog1* and *Nuerod1* were significantly down-regulated in anteroventral side of otocyst. Although midline source, notochord and floor plate, of Shh is involved in otic neurogenesis and survival of SGNs, little is known about neurogenesis of apical SGNs. Recently, it was reported that all SGNs had expressed Shh transiently during embryonic development, suggest that Shh is important for SGNs development. Thus, we examined to identify the roles of Shh expressed in apical SGNs for apical SGNs neurogenesis. To investigate the roles of Shh expressed in apical SGNs, we spatially and temporally inactivated Shh signaling in SGNs using *Neurog1-CreERT2*; $Smo^{lox/lox}$ mcie. Additionally, we used $Foxg1^{Cre}$; $Smo^{lox/lox}$ mice, which is inactivated Shh signaling in otic epithelium and SGNs. We found that expression of *Neurod1* is not detected in apical SGNs, and *Foxg1* expression is also absent in apical SGNs but not in middle and base SGNs in $Neurog1\text{-}CreER^{T2}$; $Smo^{lox/lox}$ mutant mice by E10.5 tamoxifen treatment. The absence of *Neurod1* and *Foxg1* expression in apical SGNs region means that apical SGNs neurogenesis was not occurred or apical SGNs was not survival in the cochlea after tamoxifen treatment on E10.5. In $Foxg1^{Cre}$; $Smo^{lox/lox}$ mutant mice, otic neurogenesis is similar to compared wild type mice at E11.75. These results suggest that Shh expressed in apical SGNs is necessary for apical SGNs neurogenesis and survival of SGNs.

Keywords: Neurogenesis, Spiral ganglion neuron, Neurogenin1, Shh, Foxg1

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Keywords: CTCF, Inner ear, Morphogenesis, Neurogenesis, Hair Cell Maintenance

P26

Role of CCCTC-binding Factor (CTCF) In The Mammalian Inner Ear

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The inner ear is comprised of diverse cell types that are specialized to convert sound waves into electrical stimuli and to convey the signals to the brain. Organization of the inner ear requires tight regulations of genes important for patterning, morphogenesis, and cell differentiation. Recent advancements of epigenetics demonstrated that "non-genetic" regulations such as changes of chromatin conformation are also important for development and function. CTCF is a key molecule for chromatin organization that promotes cellular diversity. Nothing is known about its role in inner ear. Here, we examined inner ear-specific (*Pax2-Cre*) or hair cell-specific (*Gfi1-Cre*) conditional knockouts of *Ctcf*. *Pax2-Cre*; $Ctcf^{lox/lox}$mutants showed that morphogenesis was severely disrupted, such that anterior and lateral semicircular canals and cristae were absent and the cochlear duct was malformed. Expression analyses indicated that neurogenesis was severely impaired and hair cell differentiation occurred prematurely with disorganized pattern. Microarray analyses of the *Pax2-Cre*; $Ctcf^{lox/lox}$ otocysts confirmed that neurogenesis-related genes including Neurog1 were significantly downregulated. We found several CTCF putative binding sites in the *Neurog1* locus, and confirmed that CTCF binding induced a DNA looping between the enhancer and the promoter sequences of the *Neurog1*. *Gfi1-Cre*; $Ctcf^{lox/lox}$mutants were viable and displayed normal hair cell differentiation. However, *Gfi1-Cre*; Ctcflox/loxmutants exhibited progressive hearing loss when examined by ABR test. DPOAE measurements and scanning electron microscopy confirmed that the hearing loss is mainly due to degeneration of the hair cells, suggesting that CTCF is required for hair cell maintenance. Our data suggest that CTCF plays crucial roles in inner ear development and function. We are currently investigating the mechanisms by which CTCF regulates inner ear morphogenesis, neurogenesis, and hair cell maintenance.

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Ac celeration of Transcellular Transmission of Alpha-Synuclein Aggregate is Caused by Lysosomal Dysfunction

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Lysosomal pathway has a key role in the long-lived protein degradation. Lysosomal dysfunction affects to pathogenesis in the Parkinson's disease (PD) and other neurological disease. Pathological and genetic studies suggested lysosomal dysfunction as one of the common features of PD. In recent studies, transcellular transmission of α-synuclein (α-syn) aggregates has been suggested as an underlying mechanism of the progression of Lewy pathology. Growing bodies of evidence showed that α-syn aggregates secreted from damaged neurons can be transferred to neighboring cells via the endolysosomal pathway and broken down in lysosomes. To examine whether lysosomal defects can accelerate transmission of α-syn, by leading to the massive accumulation and secretion of α-syn aggregates, we generated *ATP13A2*-/- and *CTSD*+/- cell lines. Though the depletion of *ATP13A2* did not alter the lysosomal activity, the heterozygous mutation in *CTSD* gene resulted in the accumulation of autophagic vacuoles and the lysosomal substrates. These results indicate that the haploinsufficiency of *CTSD* is enough to occur lysosomal dysfunction. Consistent with these results, the heterozygous deficiency of cathepsin D accelerated the transcellular transmission of α-syn though *ATP13A2* depletion showed no effects on the transmission of α-syn aggregates. These results showed that depletion of specific lysosomal enzyme can increase transcellular transmission of α-syn aggregates by blocking endo-lysosomal degradation pathway of

transmitted α-syn aggregates. Therefore, this studies suggest that the regulation of lysosomal activity can be a major therapeutic target of propagation of Lewy pathology.

Keywords: Parkinson's disease, alpha-synuclein, Lysosome, Cathepsin D, Cell-to-cell transmission

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P28

Analysis of Cell-to-Cell Transmission Mechanism Using Laser Microdissection Technique

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Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease (AD). Pathologically, PD is chracterized by the loss of dopaminergic neurons in the substantia nigra pars compacta and is associated with abnormal protein accumulation in the forms Lewy bodies (LBs) and Lewy neurites (LNs), both of which contain α-synuclein(α-syn) as a main component. Recent studies suggest that α-syn aggregates can be secreted from neurons via exocytosis and then these extracellular α-syn aggregates are internalized into neighboring cells. However, the effects of transmitted a-syn on disease propagation are still unclear. To understand the detailed mechanisms of α-syn transmission, we have utilized Laser capture microdissection technique to isolate transmitted acceptor cells vs. non-transmitted cells in the same co-culutre system containing α-syn overexpressing donor cells and the recipient cells. Total RNA was purified and amplified from these isolated cells and were submitted for microarray analysis to compare gene expression patterns of transmitted vs. nontransmitted cells. Several interesting changes have been observed and we are currently validating these results.

Keywords: Parkinson's Disease, Alpha-Synuclein, Cell-to-Cell transmission, Laser Microdissection

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Cell Type-Specific Proteome Labeling in Mammalian Cells by Genetic Code Expansion

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Analyzing gene expression of specific cells in a living organism is crucial in understanding complex biological systems. It has not been possible, however, to isolate the proteome of specific cells in vertebrates. Genetic code expansion is a rising technique to label newly synthesized proteins. We expanded the genetic code of mammalian cells by introducing the pyrrolysine tRNA/tRNA synthetase system of *Methanosarcina barkeri*. An alkyne-modified pyrrolysine analog specifically incorporated into the de novo proteome of these cells. Using the alkyne-azide cycloaddition we could visualize these proteome in situ and after biochemical purification. These results provide a promising direction for a new technique to isolate the proteome of a specific cell type from a living animal.

Keywords: Genetic code expansion, Proteome labeling

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P30

Analysis Of Synaptic Vesicle Pooling In Culture Hippocampal Neuron With Electron Tomography

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The synaptic vesicle is a specialized structure in presynaptic terminals that stores various neurotransmitters. The actin filament has been proposed as an important role in mobilizing synaptic vesicles. To understand the role of actin filament on synaptic pooling, we characterized synaptic vesicles and actin filament after BDNF treatment or Latrunculin A treatment on primary cultured neuron from rat embryo hippocampus (E18). Immunocytochemical analysis showed that BDNF treatment increased expression of synapsin I compared to the control. Incubation of latrunculin A decreased expression of F-actin and synapsin. Latrunculin A treatment after BDNF pretreatment restored expression F-actin and synapsin I slightly compared to latrunculin A treatment group. Also, Western blots showed increased expression of the synapsin I, post synaptic density 95 and phospho GluR1 in cells treated with BDNF. Ultrastructural and 3D tomography showed that more synaptic vesicles localized near the active zone after treatment of BDNF. But synaptic vesicles were dispersed in presynpatic terminal and loss of filamentous network was observed after latrunculin A application. Latruculin A treatment after preincubation of BDNF group showed that synaptic vesicle number was similar to that of BDNF treatment group, but filamentous structures were not restored. These data suggest that actin filament play a significant role in synaptic vesicle pooling in presynaptic terminal.

Keywords: Synapse, Synaptic Vesicle, Electron Microscopy, Tomography

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P31

ZL006, an Inhibitor of the Neuronal Nitric Oxide Synthase-Postsynaptic Density 95 Interaction, Ameliorates Pathology in a Mouse Model of Alzheimer's Disease

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Excessive calcium influx via over-stimulation of N-methyl-D-aspartate receptors (NMDAR), which are triggered by extracellular amyloid-β accumulation, and the resulting neuronal nitric oxide synthase (nNOS), are crucial for neuropathologies in Alzheimer's Disease (AD). As a scaffolding protein, the postsynaptic density 95 (PSD95) participates in this process by mediating the binding of NMDARs with nNOS at excitatory synapses. Given that novel compound ZL006 can selectively interrupt the interaction of nNOS with PSD95, we examined whether ZL006 might attenuate the behavioral and morphological deterioration in a mouse model of AD, which were established by intra-hippocampal injection of amyloid-β oligomer (AβO). We observed that single injection of 10mg/kg ZL006 via intraperitoneal (*i.p*) route significantly ameliorated the cognitive impairments being tested by three different sets of behavioral assessments: Morris water- and Y-maze task and passive-avoidance task. Morphologically, *i.p* injection of ZL006 protected the AβO injection-evoked neuronal loss in various sub-divisions of hippocampus, sparing synaptic integrities, which were revealed by performing immunohistochemical detection of synaptophysin (presynaptic marker) and PSD95 (postsynaptic marker). Applying semi-quantification and co-immunoprecipitation approaches onto hippocampal homogenates, we demonstrated that the AβO injection caused the translocation of cytosolic nNOS to membrane as well as increase of nNOS-PSD95 binding affinity. However, *i.p* injection of ZL006 significantly blocked both changes. Consequently, we suggested that ZL006 could ameliorate the AD-related pathologies via inhibition of nNOS-PSD95 interaction in hippocampal neurons. It is likely that this study provide new insight of developing nNOS-PSD95 interaction inhibitor as a novel strategies against AD.

Keywords: Alzheimer's disease, nNOS, PSD95, ZL006

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P32

Neuroprotection and Reduced Gliosis by Atomoxetine Pretreatment in a Gerbil Model of Transient Cerebral Ischemia

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Atomoxetine(ATX) is a non-stimulant selective norepinephrine reuptake inhibitor that is widely used for the treatment of attention-deficit/hyperactivity disorder(ADHD). In this study, we firstly examined neuroprotective effects of pre- or post-treatment with 15 and 30 mg/kg ATX against ischemic damage in the gerbil hippocampal CA1 region subjected to 5 min of transient cerebral ischemia using cresyl violet staining, neuronal nuclei immunohistochemistry and Fluor-J B histofluorescence staining. We found that only pre-treatment with 30 mg/kg ATX protected CA1 pyramidal neurons from ischemic insult. In addition, pre-treatment with 30 mg/kg ATX, which had neuroprotective effect against ischemic damage, distinctly attenuated the activation of astrocytes and microglia in the ischemic CA1 region compared with the vehicle-treated ischemia group by glial fibrillary acidic protein (for astrocytes) and ionized calcium-binding adapter molecule 1 (for microglia) immunohistochemistry. In brief, our present results indicate that ATX has neuroprotective effect against transient cerebral ischemic insult and that the neuroprotective effect of ATX may be closely associated with attenuated glial activation.

Keywords: Atomoxetine; Selective Norepinephrine Reuptake Inhibitor; Transient Cerebral Ischemia; Hippocampus; Neuroprotection

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P33

Primary Cilium Regulates Inflammation In Hippocampus Through TLR4-induced NFkB Signaling

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The primary cilium is an organelle acting as a master regulator of cellular signaling. Cilium components and signal transduction proteins are transported as parts of multimeric protein complexes called IFT, which require motor and adaptor proteins for trafficking in anterograde and retrograde directions. KIF3a, one of component of KINESIN-2 complex, moves IFT particles and their protein cargoes along the axoneme toward the ciliary tip. However, the role of KIF3a on cilia length in neuroinflammation remains yet. Here, we examined LPS-induced primary cilia length in hippocampal cell line (HT22) transfected with si_KIF3a. Cilia length was decreased with si_KIF3a but reversed by LPS treatment. LPS treatment induced decrease of IkB-a expression and increase of phosphorylation of RelA/p65. Next we examined the primary cilia length in pyramidal cell of hippocampus in wild type and TLR4 knockout mice. Primary cilia length and protein level were decreased in the hippocampal pyramidal cell of LPS-treated wild type mice, and these expression were recovered in TLR4 knockout mice. The expression of iNOS and COX2, inflammatory indicator, were decreased in TLR4 knockout mice. Collectively, we demonstrated that blockade of the primary cilium formation by si_KIF3a regulates TLR4-induced NFkB signaling. We proposed that the locality of primary cilia have a critical role for regulation of neuroinflammation including NFkB signaling events, tuning signaling as appropriate.

Keywords: Primary cilia, NFkB signaling, Inflammation, KIF3a

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P34

Neuroprotection of Ischemic Preconditioning is Mediated by Thioredoxin 2 in the Hippocampal CA1 Region Induced by a Subsequent Transient Cerebral Ischemia

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Thioredoxin 2 (Trx2), which is a small protein with redox-regulating function, and shows cytoprotective roles against oxidative stress. Here, we had focused on the role of Trx2 in ischemic preconditioning (IPC)-induced neuroprotection against oxidative stress followed by subsequent lethal transient cerebral ischemia. **Results:** A significant loss of neurons was found in the stratum pyramidale (SP) of the hippocampal CA1 region (CA1) in the ischemia-operated-group 5 days after ischemia-reperfusion; in the IPC+ischemia-operated-group, pyramidal neurons in the SP were well protected. In the IPC+ischemia-operated-group, Trx2 and TrxR2 immunoreactivities in the SP and its protein level in the CA1 were not significantly changed compared with those in the sham-operated-group after ischemia-reperfusion. In addition, superoxide dismutase 2 (SOD2) expression, superoxide anion radical (O2·-) production, denatured cytochrome c expression and TUNEL-positive cells in the IPC+ischemia-operated-group were similar to those in the sham-operated-group. On the other hand, the treatment of auranofin to the IPC+ischemia-operated-group significantly increased cell damage/death and abolished the IPC-induced effect on Trx2 and TrxR2 expressions. Furthermore, the inhibition of Trx2R nearly cancelled the beneficial effects of IPC on SOD2expression, O2·- production, denatured cytochrome c expressionand TUNEL-positive cells. Innovation: IPC conferred neuroprotection against ischemic injury by maintaining Trx2. This study suggests that the maintenance or enhancement of Trx2 expression by IPC may be a legitimate strategy for therapeutic intervention of cerebral ischemia.

Keywords: Ischemia-Reperfusion, Delayed Neuronal Death, Thioredoxin 2, Superoxide Dismutase 2, Superoxide anion; Cytochrome c

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Ginsenoside Rb1 Attenuates Acute Inflammatory Nociception by Inhibiting Neuronal ERK Phosphorylation by Regulating the Nrf2 and NF-κB Pathways

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Ginsenoside-Rb1 (Rb1) has anti-inflammatory effects. However, the potential anti-nociceptive value of Rb1 for the treatment of acute inflammatory nociception is still unknown. Here, we examined whether Rb1 has any anti-nociceptive effects on acute inflammatory nociception in Sprague Dawley rats given intrathecal (i.t.) introduction of Rb1 (2, 10, and 50 μg) 20 minutes before injection of formalin (5%, 50 μl) into the plantar surface of the hind paws. I.t. introduction with Rb1 significantly decreased nociceptive behavior during phase II (16-60 minutes), but not phase I (0-10 minutes), after formalin stimulation, corresponding to the reduced activation of c-Fos in the L4-L5 spinal dorsal horn after formalin stimulation. Rb1 also reduced the phosphorylation of extracellular signal-regulated kinase (ERK) in the neurons, but not the microglia and astrocytes. Microscopic examination of the microglia and astrocytes revealed no morphological changes due to formalin stimulation and i.t. introduction with Rb1. Interestingly, Rb1 activated the Nrf2 pathway and inhibited NF-κB pathways. Our findings indicate that i.t. introduction of Rb1 may effectively inhibit formalin-induced acute inflammatory nociception by inhibiting neuronal ERK phosphorylation, which is thought to regulate the Nrf2-NF-κB pathways in the spinal dorsal horn, suggesting therapeutic potential for suppressing acute inflammatory pain.

Keywords: ginsenoside-Rb1, inflammatory nociception, phospho-ERK, nuclear factor erythroid 2-related factor 2, nuclear factor-kappa B

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P36

REP Attenuates the Blood-Brain Barrier Disruption on Collagenase-induced Intracerebral Hemorrhage Model in Rat

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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. Also, ELP is known to have less immuno- and cytotoxicity and inflammatory responses than other synthesized biomaterials. Although the biocompatibility of this pentapeptide reflects chemical similarity to human tropoelastin, an elastin precursor, and is highly suitable with living cells, the low cell adhesive properties of ELP and its lack of biological function are limitations in their application to cell growth. To circumvent the properties of low affinity to cells, modified ELP that has themo-sensitive but high affinity to cells, TGPG[VGRGD(VGVPG)6]20WPC, named REP, was developed. Moreover, REP has an ability to highly promote the adhesion and proliferation of neuronal cells on a poorly adherent organic scaffold. In this study, we hypothesized that the administration of REP into the internal carotid artery(ICA) after collagenase-induced intracerebral hemorrhage may reduce the volume of hematoma and plays an important role in the reorganization of brain structure which is related to its plasticity. Here we found that the administration of REP reduced hematoma volume, decreased the number of activated microglia, attenuated the von Willebrand factor(vWF) expression and prevented the leakage of IgG into a cerebral parenchyma region without any other occlusion of intact microvessels in an acute phase rat model of ICH. Taken together, the overall data demonstrate that REP treatment could be a novel therapeutic strategy for attenuating the intra-cerebral hemorrhage injury.

Keywords: Intracerebral Hemorrhage(ICH), REP, Biomaterial, BBB, Hematoma

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P37

Differential Expression of the Calcium-Sensing Receptor in the Ischemic Core and Penumbra after Transient Focal Cerebral Ischemia in Rats

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G-protein-coupled calcium-sensing receptor (CaSR) has been recently recognized as an important modulator of diverse cellular functions, beyond the regulation of systemic calcium homeostasis. To identify whether CaSR is involved in the pathophysiology of stroke, we studied the spatiotemporal regulation of CaSR protein expression in rats undergoing transient focal cerebral ischemia, which was induced by middle cerebral artery occlusion. We observed very weak or negligible immunoreactivity for CaSR in the striatum of sham-operated rats, as well as in the contralateral striatum of ischemic rats. However, CaSR expression was induced in the lesion in ischemic rats. Six hours post-reperfusion there was an upregulation of CaSR in the ischemic core, which seemed to decrease after seven days. This upregulation preferentially affected some neurons and cells associated with blood vessels, particularly endothelial cells and pericytes. In contrast, CaSR expression in the peri-infarct region was prominent three days after reperfusion, and with the exception of some neurons, it was mostly located in reactive astrocytes, up

to day 14 after ischemia. On the other hand, activated microglia/macrophages in both the core and border zones were devoid of specific labeling for CaSR at any time point after reperfusion, despite their massive infiltration. Our results show heterogeneity in CaSR-positive cells within the core and border zones, suggesting that CaSR expression is regulated in response to the altered extracellular ionic environment caused by ischemic injury. Thus, CaSR may have a multifunctional role in the pathophysiology of ischemic stroke, possibly in vascular remodeling and astrogliosis. This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT and future Planning (NRF-2014R1A2A1A11050246).

Keywords: Pericytes; Calcium-Sensing Receptors; Reactive Astrocytes; Corpus Striatum; Stroke; Endothelial Cells; Microglia; Vascular Remodeling

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P38

Iron is responsible for production of reactive oxygen species regulating vasopressin expression in the mouse paraventricular nucleus

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Reactive oxygen species (ROS) are mostly described as important initiators and mediators of cell death in pathological process. While ROS are essential factor for biological activities and biochemical functions which are interrelated to cell signaling and physiological pathways. Recently, ROS have been shown as signaling molecules for maintaining homeostasis particularly the regulation of body-fluid balance. However, there has been little discussion about source of ROS generation in osmoregulatory system. We, therefore, examined the amount of iron contents in the paraventricular nucleus (PVN) and investigated the relationship between iron contents and ROS production regulating vasopressin (VP) expression in this study. Intensified iron histochemistry and densitometry analyses revealed that the iron content of the PVN was significantly higher than other forebrain regions of the hypothalamus. We also found that the PVN has high iron affinity through iron-overload and chelation experiments. Furthermore, ROS production and VP expression of iron-overload group were significantly increased as compared with the control, although ROS production and VP expression were not changed in iron-chelation group. However, iron did not change expression of nitric oxide synthase (NOS) known as another modulator of VP synthesis and secretion. These results suggest that high iron contents in the PVN induce VP expression via production of ROS, independently of NO signaling.

Keywords: Iron, Reactive oxygen species, Paraventricular nucleus, Vasopressin

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P39

Alpha B crystallin protects oligodendrocyte precursor cells under oxidative stress via Akt signaling

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Alpha B-crystallin (aBC) is a member of small heat shock protein family. aBC is expressed in mature myelinating oligodendrocytes in the central nervous system. Oigodendrocyte-lineage cells are more susceptible to oxidative stress than any other neural cells. Recently, we identified *in vitro* that oligodendrocyte precursor cells (OPCs) are more susceptible to oxidative stress than aBC-expressing mature oligodendrocytes. Therefore, we investigated whether aBC overexpression in OPCs could protect these cells under oxidative stress condition in this study. We used an aBC recombinant lentiviral vector (pLVX-aBC) for aBC overexpression in OPCs. MTT assay and hoechst staining analysis clearly demonstrated that the survival rate of aBC-overexpressing OPCs was higher than that of the control under oxidative stress condition. aBC overexpression suppressed caspase-3 and Bax activities under oxidative stress in OPCs. We also

identified the effect of aBC overexpression on Akt pathway. Under oxidative stress condition, the phosphorylated Akt (p-Akt) levels of the control were decreased as compared with those under normal condition. However, p-Akt levels of aBC-overexpressing OPCs were not changed under oxidative stress condition. These results suggest that aBC overexpression has a protective effect against oxidative stress-induced apoptosis in OPCs and this protective effect of aBC may be related to the Akt pathway.

Keywords: alpha B crystallin, oligodendrocyte, oxidative stress, protection, lentiviral vector

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P40

Measurements of the Distance from Sacral Hiatus to Termination of Dural Sac and Conus Medullaris in Korean Population using Magnetic Resonance Imaging

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The purpose of this study is to provide basic biometric data about Korean people by measuring the distance between the sacral hiatus and the termination of dural sac and the distance between the sacral hiatus and the conus medullaris through magnetic resonance imaging, which is very important for the performance of epidural neurolysis and epidural neuroplasty. As research subjects, this study selected a total of 200 patients, 88 males and 112 females, among neurosurgical outpatients with back pain. The patients with spine fracture, significant spinal deformity or spondylolisthesis were excluded. We measured the distance by using T2-weighted images of MRI and analyzed the correlation of these distances by gender and height. The mean distance between the sacral hiatus and the termination of dural sac was 62.83±9.41 mm, and the mean distance between the sacral hiatus and the conus medullaris was 232.2±21.87 mm. The mean height was 161.34±9.60 cm. The minimum distance and the maximum distance between the sacral hiatus and the termination of dural sac were 34.80 mm and 93.90 mm, respectively. Both the distance between the sacral hiatus and the termination of dural sac and the distance between the sacral hiatus and the conus medullaris in the female patients was shorter than those in the male patients, which was statistically significant. Both the distance between the sacral hiatus and the termination of dural sac and the distance between the sacral hiatus and the conus medullaris showed a significant correlation with the height. The distance between the sacral hiatus and the termination of dural sac was not significant by age, but the distance between the sacral hiatus and the conus medullaris showed a significant correlation with age, while getting shorter as the patients was older.

Keywords: acral Hiatus, Termination of Dural Sac, Conus Medullaris, Magnetic Rresonance Imaging, Korean.

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P41

Goα protein, heterotrimeric GTP binding protein, modulates the neuritogenesis

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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 involved in neuronal differentiation, the mechanism of how Go modulates neuronal differentiation has not been defined clearly. We previously showed that Goα may regulates 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 gain/loss of function by Goα during the neuritogenesis in F11 cells and primary cultured neurons respectively via 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 impeded in the absence of Goα. The data also suggest that Goα may induce the formation of protrusions/neuritis at earlier time of neuronal differentiation. Further, we will discuss the mechanisms by which Goα regulate the neuritogenesis during differentiation and maturation of neuronal cells.

Keywords: Goα protein, PKA, Neuritogenesis

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P42

A Zingerone Attenuates MPP^+-Induced Cell Death via Activation of ERK and VMAT2 in a Parkinson's Disease Model

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Parkinson's disease (PD) is characterized by a progressive and selective loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and striatum. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is used to produce an animal model for PD, and it is converted to 1-methyl-4-phenylpyridine (MPP^+) in animals. MPP^+ accumulation leads to neuronal cell death. Vesicular monoamine transporter 2 (VMAT2) regulates the accumulation of monoamine neurotransmitters into synaptic vesicles and is involved in neuroprotection against neurotoxin-induced cell death. Recently, zingerone has been reported to reduce oxidative stress and inhibit inflammation. Therefore, we examined the effect of zingerone on neuronal cell death in a PD model. In an MPP^+ and MPTP-mediated PD model, neuronal cell survival was increased by zingerone without modifying neuroinflammation or reactive oxygen species generation. Zingerone also induced ERK activation and VMAT2 expression, leading to the attenuation of MPP^+-induced neuronal cell death. Our current results suggest that zingerone has a neuroprotective effect in a PD model.

Keywords: Zingerone; Parkinson's disease; MPTP/MPP+; VMAT2; ERK

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P43

Effect of GABAA receptor for recurrent seizure stage following Febrile seizures (FS)

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Febrile seizure (FS) is the most common seizure type in the infant and young children. It is contribute to the alteration in developmental abnormality of hippocampal circuitry. These changes may sustain enhanced excitability of hippocampus and thus contributed toward the development of temporal lobe epilepsy (TLE).In previous study, $GABA_A$-α1 receptor expression was abnormally enhanced in recurrent seizures stage at FS. Chloride channels (ClC) following activation of $GABA_A$ receptor is important role in regulating chloride ion and chloride extrusions play a key role in susceptibility of neurons to epileptiform activity. Therefore, these studies identify the effects of $GABA_A$ receptor at recurrent seizures following FS through that compared $GABA_A$ receptor antagonist and agonist drug models. In the present results, EEG was shown distinction of amplitude in each model. In addition, we were investigated filed excitatory postsynaptic potential (fEPSP) and paired-pulse responses in the hippocampus for identifying the distinct functions of GABAergic inhibition at $GABA_A$ receptor drugs and FS models. In the bicuculline and FS, the slope of fEPSP is markedly reduced than control and paired-pulse response is enhanced as compared to control. Moreover, chloride channels immunoreactivity was significantly changed in the CA1 and dentate gyrus of hippocampus. In the CA1 of hippocampus, ClC-2 expressions were declined at muscimol and FS groups more than control group. Whereas, ClC-2 positive interneurons of DG were decreased in muscimol models, its expression was enhanced in bicuculline and FS groups. As well, ClC-3 positive interneurons were increased in bicuculline and FS groups compared to control group.

Therefore, these results may be that increasing of CLC expression is compensatory for $GABA_A$ receptor-mediated depolarization and it is leads to an enhancement of intracellular Ca^{2+} concentration and susceptibility seizures at recurrent seizures following FS.

Keywords: GABAA receptor , Febrile seizure, Chloride channel

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P44

Effects of ethyl pyruvate on Schwann cell dynamics during peripheral nerve degeneration

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Ethyl pyruvate (EP), as a pyruvate derivative, has the protective effect on oxidative stress-mediated cellular injury. In previous studies, it has been reported that EP provides protection against neuronal injury in brain, for example transient cerebral ischemia. However, the inhibition effect of EP on peripheral nerve injury is still unknown. Here, we investigated the inhibition effect of EP in Schwann cell dedifferentiation and proliferation during Wallerian degeneration using ex vivo sciatic nerve explant system. We demonstrated that EP inhibits p-ERK1/2, p75NGFR and LAMP1 as factors implicated in Schwann cell dedifferentiation during Wallerian degeneration. In addition, EP is sufficient to inhibit Schwann cell proliferation during Wallerian degeneration. Together, these findings suggest that EP has a strong protective effect on Wallerain degeneration.

Keywords: Ethyl pyruvate; Wallerian degeneration; sciatic explant; Schwann cell dedifferentiation; Schwann cell proliferation

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P45

A correlation with altered synaptic plasticity and Phospholipase C (PLC) beta expression in the hippocampus following pilocarpine-induced status epilepticus

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Epilepsy is a group of neurological diseases characterized by epileptic seizures. Above all, status epilepticus(SE) was chronic seizure, characterized without recovery and telogen between the seizure. So, SE was induces neuronal abnormality including functional and anatomical disorder. Phospholipase C (PLC)β was important components of signal transduction processes and intimately related with synaptic plasticity in the brain. Thus, activation of the PLCβ pathway produces important effects on cellular function, differentiation and activity. So PLCβ 1 may be associated with many kinds of abnormal neuronal situation. Therefore we investigated whether the correlations of PLC beta immunoreactivities with synaptic plasticity in the hippocampus following SE induced pilocarpine. For study about neuronal functional disorder, we recording electrophysiology for identification neuronal condtion; electroencephalogram (EEG), population spike in the hippocampus. Electrophysiology result was dissimilar to control situation and confirmed induced SE. Population spike was confirmed for GABAergic inhibition in the hipocampus. And SE animal was not regulated inhibitional function for recording popualtion spike in the DG. PLC beta 1 immunoreactivities were decreased dependent time passed in the hippocampal CA1 and DG. But early time induced pilocarpine, PLCβ 1 immunoreactivity was slightly increased. And after 2month induced SE, PLCβ 1 immunoreactivities were almost disappeared in the hippocampus. And neuronal degeneration marker fluoro jade b (FJB) immunoreactivity was increased in this time. Parvalbumin (PV) positive neuron was diminished following SE in the hippocampus. So status epilepticus induced PLCβ 1 abnormal regulation and this situation was induced neuronal fuction was more excitement and not regulated about inhibition. Thus we consider that PLCβ 1 functional disorder was triggered abnormal neuronal condition and this disorder was correlative with SE.

Keywords: Status epilepticus, Pilocarpine, PLCβ 1

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P46

Growth Differentiation Factor 15 Expression in Astrocytes After Excitotoxic Lesion in the Mouse Hippocampus

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Growth differentiation factor 15 (GDF15) is, a member of the transforming growth factor β (TGF-β) superfamily of proteins. Although GDF15 is well established as a potent neurotrophic factor for neurons, little is known about its role in glial cells under neuropathological conditions. We monitored GDF15 expression in astrocyte activation after a kainic acid (KA)-induced neurodegeneration in the ICR mice hippocampus. In control, GDF15 immunoreactivity (IR) was evident in the neuronal layer of the hippocampus; however, GDF15 expression had increased in activated astrocytes throughout the hippocampal region at day 3 after the treatment with KA. LPS treatment in astrocytes dramatically increased GDF15 expression in primary astrocytes. In addition, LPS treatment resulted in the decrease of the IκB-α degradation and increase of the phosphorylation level of RelA/p65. These results indicate that GDF15 has a potential link to NF-κB activation, making GDF15 a valuable target for modulating inflammatory conditions.

Keywords: Growth differentiation factor 15 (GDF15), Kainic acid (KA), NF-κB activation, Astrocyte

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P47

Effects of natural derived compounds on APP processing and beta-amyloid degradation enzymes in Neuro2a neuroblastoma cells

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Alzheimer's disease (AD) is the most common form of dementia over 65 years of age. The novel drug of Alzheimer's disease has been not still developed yet because the candidates of synthetic drugs have had side effects. Recently, natural compound has been tried as a novel candidate for AD therapeutics without the side effect. Here, we evaluate mechanism of beta-amyloid reduction by resveratrol and its derivatives, oxyresveratrol and piceatannol using Neuro2a cells. High concentration of resveratrol, oxyresveratrol and piceatannol treatment activated caspase-3 and induced increase of LC3-II conversion and decrease of p62 at 24 hr, which indicate induction of apoptosis and autophagy. Next, endogenous APP processing was examined using immunoblot. sAPPs and NICD were decreased after the treatment of resveratrol, oxyresveratrol and piceatannol for 24 hr and CTFalpha was increased only by resveratrol, but was decreased by other compounds. In exogenous assay of secretase activity using exogenous fluorogenic substrate, activities of alpha-secretase and gamma-secretase were increased from treatment of compounds, but activity of beta-secretase did not show significant changes except piceatannol treated cells. Finally, changes of beta-amyloid degrading enzymes (IDE, NEP, cathepsin B, and MMP-9) by treatment compounds were determined. The protein level of IDE did not show significant change by compounds and activity of NEP was only increased by high dose of oxyresveratrol. The activity of cathepsin B was increased by high dose of piceatannol and activity of MMP-9 was increased by all doses of resveratrol and low dose of piceatannol. Although the detail mechanisms of beta-amyloid reduction are not still elucidated, these results suggest some mechanistic clues of beta-amyloid reduction for the therapeutic strategy of AD.

Keywords: Alzheimer's disease, Beta-amyloid, Natural compound, Autophagy

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P48

Increased Expression of Osteopontin in Retinal Degeneration Induced by Blue-Light-Emitting Diode Exposure in Mice

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Osteopontin (OPN) is a multifunctional adhesive glycoprotein implicated in a variety of proinflammatory as well as neuroprotective and repair-promoting effects in the brain pathophysiology. In this study, we examined changes in OPN expression in an animal retinal degeneration (RD) model induced by a blue light-emitting diode (LED) exposure. OPN is weakly expressed in ganglion cells of the ganglion cell layer in the normal mouse retina. On the other hand, OPN expression was increased in blue LED-induced RD retinas during experimental period. In RD retinas, OPN expression in ganglion cells appeared to be similar to that in the normal retina, while new OPN expression was apparently observed in additional cells mainly located in the outer nuclear layer, the outer plxiform layer, and the subretinal space. Double-labeling immunofluorescence with anti-Iba-1, a microglial cell marker, showed that OPN was always colocalized with Iba-1 in these cells in RD retinas, indicating that OPN was expressed in activated microglia. These results suggest that OPN is produced by activated microglia as RD progresses, and plays an important role in RD pathogenesis.

Keywords: Osteopontin, Retinal degeneration, Inflammation, Microglia

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P49

Dual projections of single orexin- or CART-immunoreactive, lateral hypothalamic neurons to the nucleus ac cumbens shell and paraventricular thalamic nucleus in the rat

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The paraventricular thalamic nucleus (PVT) is a major relay station to the limbic forebrain regions including the nucleus accumbens shell (NAcSh). Both the PVT and NAcSh are known to receive arousal/feeding-related peptidergic fibers such as orexin (ORX), cocaine-and-amphetamine-regulated transcript (CART), and neuropeptide Y (NPY). As a sequel to our previous observation on the distribution of feeding/arousal-related peptidergic terminals in the PVT (Lee et al., 2015), we examined neuronal components of these peptides in the NAcSh. The density of ORX-, CART-, or NPY-immunoreactive axon terminals in the NAcSh was lower than that in the PVT. The NAcSh is the only striatal region that contains both CART and NPY cells. The majority of CART neurons were located in the rostral NAcSh, while only a small number were in the caudal part. In contrast, NPY cells were observed in the entire rostro-caudal extent of the NAcSh with the largest number in the caudal part. We further addressed the question of whether single ORX, CART, or NPY neurons in various hypothalamic regions provided dual projections to the PVT and NAcSh. ORX neurons projecting to both the PVT and NAcSh were found mainly in the medial portion of the lateral hypothalamus (LH), representing an average of 1.6% of total ORX cells in the area. CART neurons with dual projections were observed in the LH, zona incerta (ZI), and retrochiasmatic nucleus (RCh, which is often considered as a rostral extension of the arcuate nucleus), accounting for a mean of 2.5% of total CART cells in these nuclei. None of the CART or NPY cells in the main portion of the arcuate nucleus had dual projections. These data suggested that through dual projections, a portion of ORX neurons in the LH (or CART cells in the LH, ZI, and RCh) might concurrently modulate the activity of neurons in the PVT and NAcSh during reward-seeking behaviors related with arousal, stress, and feeding.

Keywords: Paraventricular thalamic nucleus, Nucleus accumbens shell, Orexin, Cocaine- and amphetamine-regulated transcript

(CART), Neuropeptide Y(NPY)

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P50

Functional and Morphological Evaluations of Blue Light-Emitting Diode-Induced Retinal Degeneration in Mice

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Retinal degeneration (RD) is a general cause of blindness. To study its pathogenesis and evaluate the effects of new therapeutic agents for RD before clinical trials, it is essential to establish reliable and stable animal models. We established and characterized an RD model created by exposing mice to a blue light-emitting diode (LED), which induced photoreceptor cell death. Electroretinographic recordings showed that both a- and b-waves were decreased in the retinas after blue LED exposure in an illuminance-dependent manner. Hematoxylin and eosin staining, terminal deoxynucleotidyl transferase dUTP nick end labeling assay, and electron microscopy showed massive photoreceptor cell death by apoptosis in the central region of the retina. Retinal stress and inflammation were detected by increased expression of glial fibrillary acidic protein and by electron microscopy findings demonstrating microglia infiltration in the outer nuclear layer and subretinal space. In addition, increased labeling of 8-hydroxy-2'deoxyguanosine, a marker for oxidative stress, was observed in the retinas from blue LED exposure. These results suggest that blue LED-induced RD may be a useful animal model to study the pathogenesis of RD, including age-related macular degeneration, and to evaluate the effects of new therapeutic agents before clinical trials where oxidative stress and inflammation are the underlying RD mechanisms.

Keywords: Retinal Degeneration, Blue Light-Emitting Diode, Photoreceptor, Apoptotic Cell Death, Animal Model

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P51

Enhanced Expression of Calcium-Sensing Receptor in Reactive Astrocytes of the Rat CA1 Hippocampus following Transient Forebrain Ischemia

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G-protein-coupled calcium-sensing receptor (CaSR) is an important modulator of diverse cellular functions, beyond the regulation of systemic calcium homeostasis. CaSR has recently been reported to be associated with the pathogenesis of ischemic stroke, possibly in the vascular remodeling and astrogliosis as response to ischemic injury. To further substantiate whether CaSR is involved in the overarching astroglial reaction common to ischemic insults, we investigated temporal regulation and identification of cell phenotypes expressing CaSR in the hippocampus after transient forebrain ischemia. Constitutive expression of CaSR was localized in neurons of the pyramidal cell and granule cell layers, whereas increased immunoreactivity for CaSR occurred only in reactive astrocytes within the vulnerable region of the post-ischemic hippocampus, especially, in the CA1 hippocampus, where severe neuronal death occurs following ischemia. Astroglial induction of CaSR occurred by day 3 after reperfusion, and appeared to increase progressively up to at least day 28. These immunohistochemical data were compatible with the post-ischemic upregulation of CaSR protein in the CA1 hippocampus, which was detected by immunoblot analysis. On the other hand, activated microglia/macrophages in the CA1 hippocampus were devoid of specific labeling for CaSR at any time point after reperfusion, despite their massive infiltration in this area. These results indicate that the expression of CaSR in astrocytes is regulated in response to ischemic insults, suggesting that the induction of CaSR is related to the astroglial reaction in the ischemic hippocampus. This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT and future Planning (NRF-2014R1A2A1A11050246).

Keywords: Calcium Sensing Receptor (CaSR); Reactive Astrocytes; Transient Forebrain Ischemia; Neurons; Hippocampus

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Electroacupuncture Promotes Oligodendrogenesis via Functional Expression of Neurotrophin-4/5 in Prolonged Cerebral Hypoperfusion Model of Mice

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White matter injuries caused by cerebral hypoperfusion may contribute to the pathophysiology of vascular dementia, but its precise mechanisms of injury/repair remains unclear. This study was investigated whether electroacupuncture (EA) could promote oligodendrogenesis and remyelination with improvement of cognitive function in prolonged cerebral hypoperfusion model. Animal model was prepared by bilateral common carotid artery stenosis (BCAS) using microcoil and EA stimulation was applied at two acupoints, Baihui (GV20) and Dazhui (GV14). EA stimulation improved memory functions in BCAS model as measured by Morris water maze and passive avoidance tests. EA stimulation also enhanced oligodendrocyte differentiation from oligodendrocyte precursor cells (OPCs) with recovered myelinated cells in the corpus callosum. Moreover, the newly differentiated OPCs were colocalized with phosphorylated CREB in EA treated mice. For the qPCR array of mouse growth factors, levels of some genes were significantly upregulated by EA stimulation, especially level of neurotrophin-4/5 (NT-4/5). Expression of NT-4/5 were confirmed by real-time PCR and immunohistochemical analysis in the corpus callosum. Expression of TrkB, NT-4/5 receptor, were also showed similar patterns. However, treatment with selective TrkB antagonist ANA blocked in partly recovered myelination and memory functions. Our results suggest that EA stimulation promotes functional recovery from white matter injuries through oligodendrogenesis involving NT-4/5/TrkB signaling pathway. We demonstrated new curative effects of EA for vascular dementia as an additional therapy, and EA treatment may provide another therapeutic approach for this disease.

Keywords: Electroacupuncture, Neurotrophic factor, Oligodendrocyte, Remyelination, Vascular dementia

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P53

Effects of caloric restriction on memory deficits in the hippocampus of ob/ob mice, a model of obesity-induced diabetes

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Diabetes may adversely affect memory function, although the specific underlying mechanisms are unknown. On the other hand, caloric restriction (CR) increases longevity and improves memory. We examined the effects of CR on serum metabolic parameters and hippocampal protein expression in ob/ob mice, a model of obesity-induced diabetes. We found that CR reduced hepatic steatosis and insulin resistance in ob/ob mice. In the hippocampus of ob/ob mice, CR increased expression of O-GlcNAc and GlcNAc transferase and decreased expression of calcium/calmodulin-dependent protein kinase II. CR decreased hippocampal lipocalin-2 and phosphorylated tau in ob/ob mice. Furthermore, CR improved memory deficits in ob/ob mice. These findings indicate that CR may reverse obesity-related brain glucose impairment and intracellular Ca^{2+} dysfunction and improve memory in diabetes.

Keywords: Caloric restriction; O-GlcNAc; Calcium homeostasis; Memory deficit; Hippocampus

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P54

Cilostazol, Selective Phosphodiesterase 3 Inhibitor, Shows Anti-depressant Effects on Post-stroke Depression

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We investigated the question of whether selective phosphodiesterase 3 inhibitor cilostazol would have an antidepressant effect on chronic mild stress (CMS)-treated mice after ischemic stroke. An animal model of post-stroke depression was developed by additional CMS procedures in middle cerebral artery occlusion. An animal model of post-stroke depression was developed by additional CMS procedures in middle cerebral artery occlusion. We performed behavioral, histological, TUNEL, immunohistochemical, Western blot and ELISA assay. In the open field, sucrose preference, forced swim and Morris water maze test, treatment with cilostazol resulted in reduction of all depressive behaviors examined, particularly in the Morris water maze test. Treatment with cilostazol reduced prominent atrophic changes in the striatum and hippocampus of CMS-treated ischemic mice through inhibition of neuronal cell death and microglial activation. In addition, treatment of CMS-treated ischemic mice with cilostazol resulted in significantly increased phosphorylation of cAMP response element binding protein (CREB) and expression of mature brain-derived neurotrophic factor (BDNF) with its receptor B in these regions. Phosphorylation of CREB was also demonstrated in the dopaminergic neurons of midbrain. Treatment with cilostazol also resulted in an increased number of newly formed cells and enhanced differentiation into neurons in the ipsilateral striatum and hippocampus. Our results suggest that selective phosphodiesterase 3 inhibitor cilostazol may have anti-depressant effects on post-stroke depression through inhibition of neurodegeneration in the primary lesion and secondary extrafocal sites and promotion of neurogenesis. These beneficial effects on post-stroke depression may be involved in activation of CREB/BDNF signaling.

Keywords: Cilostazol, Depression, Stroke, Chronic Mild Stress, CREB, BDNF

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P55

Beneficial Effects of Treadmill Training and Electroacupuncture on Deficits of Neonatal Hypoxia–Ischemia in Sprague-Dawley Rats

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We investigated whether treadmill training and electroacupuncture could have autonomous or synergistic beneficial effects on deficits of neonatal hypoxia–ischemia in Sprague-Dawley rats. Hypoxic–ischemic rats underwent treadmill training and electroacupuncture (EA) stimulation from 4 to 8 weeks of age. Conventional electroacupuncture (CEA) and scalp electroacupuncture (SEA) were employed by electrical stimulation (2Hz, 1mA) at traditional acupoints and at scalp to primary motor area, respectively. For behavioral examination, markedly improved performances of rota-rod test were observed in rats treated with treadmill and co-treated with treadmill and CEA compared to hypoxic-ischemic rats and passive avoidance test in rats treated with treadmill and EA. For Western blot analysis, expression of NeuN, CNP and MBP showed a significant decrease in the contralateral subventricular zone of hypoxic-ischemic rats compared to control, but these expressions were recovered by treatment with treadmill and EA stimulation. In the immunohistochemical analyses, thickness of the corpus callosum and its IOD of MBP were significantly increased by treatment with treadmill and EA compared to hypoxic-ischemic rats. Synergistic effects by co-treatment with treadmill and EA were also shown in protein

level and IOD of MBP. Marked increase in the number of BrdU and Brdu/NeuN positive cells of this region was also observed in treadmill and EA treated rats, and that of BrdU showed a synergistic effect by co-treatment with treadmill and EA. These results suggest that treadmill and EA stimulation may contribute to enhancement of behavior recovery following hypoxic–ischemia via upregulation of myelin components and neurogenesis, thus treatment with EA stimulation as well as treadmill training offer another treatment option for functional recovery in cerebral palsy.

Keywords: Treadmill, Electroacupuncture, Cerebral Palsy, Functional Recovery

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Low-Level Light Therapy Limits Post-ischemic Brain Injury via Suppression of Inflammasome-mediated Neuroinflammation and Neuronal Cell Death

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Objectives: Transcranial low-level light therapy (LLLT) with light emitting diodes (LED) has responded favorably to inflammatory response modulation. Recently, inflammasome has gained interest as a key mediator of inflammation that contributes to tissue injury in cerebral ischemia. Therefore, the therapeutic interventions that target inflammasome signaling may offer new opportunities for the treatment of ischemic stroke. Here, we show the effects of LLLT on inflammasome signaling in ischemic brain injury for cases in which treatment started after stroke in a clinically relevant setting. **Methods:** Light stimulation was applied transcranially by placing the skin-adhesive light-emitting probes onto the skin at two locations on the head (the right midpoint of the parietal bone and the posterior midline of the seventh cervical vertebra). The mice received LLLT (20 min) twice a day for 3 days commencing at 4 hours post ischemia. Focal cerebral ischemia was induced in C57BL/6J mice using a photothrombotic cortical ischemia model. **Results:** LLLT resulted in a significantly smaller infarct size and improvements in neurological score. LLLT suppressed TLR-2 triggering MAPK signaling pathways and NF-kB activation and attenuated the expression levels of NLRP3 inflammasome proteins, together with a corresponding down-regulation of pro-inflammatory cytokines such as IL-1β and IL-18 in ischemic brain tissue. In addition, LLLT profoundly reduced cleaved caspase-3 and Bax expression and apoptosis, as well as neutrophil infiltration and microglia activation in the ischemic cortex. **Conclusions:** These findings demonstrate that LLLT can attenuate neuroinflammatory response and tissue damage following ischemic stroke by a mechanism involving suppression of priming signaling and NLRP3 inflammasome components and cytokines. Therapeutic interventions targeting the inflammasome via LLLT may be a novel approach to ameliorate of brain injury following ischemic stroke.

Keywords: Low-level light therapy, Focal cerebral ischemia, Inflammasome, Neuroinflammation, Neuroprotection

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P57

N- acetyl-D-glucosamine kinase upregulates axonal growth in developing neurons

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N-acetylglucosamine kinase (GlcNAc kinase or NAGK) is a ubiquitously expressed enzyme which phosphorylates GlcNAc to GlcNAc-6-phosphate in amino sugar metabolism. Recently, it was reported that NAGK has a non-enzymatic, structural role in neuronal dendritogenesis. In this study, we found that NAGK was distributed throughout the whole neuron until developmental stage 3 (axonal

outgrowth) and Its axonal expression remarkably decreased in stage 4 (dendritic outgrowth) and became negligible in stage 5 (mature). Immunocytochemistry (ICC) on hippocampal neurons showed colocalization of NAGK with tubulin, and with Golgi in soma, dendrites, and in nascent axons. A proximity ligation assay (PLA) of NAGK and Golgi marker protein followed by ICC for tubulin or dynein light chain roadblock type 1 (DYNLRB1) in stage 3 neurons showed NAGK-Golgi complex colocalized with DYNLRB1 at the tip of microtubule (MT) in axonal growth cone, and in somatodendritic areas. Subsequently, NAGK-dynein PLA combined with tubulin or Golgi ICC showed a similar pattern of PLA signals, indicating a three way interaction between NAGK, dynein and Golgi in growing axons. Moreover, overexpression of the NAGK gene as well as the kinase mutant NAGK genes increased axonal length, and knockdown of NAGK by small hairpin (sh) RNA reduced axonal growth, which suggests a structural role for NAGK in axonal growth. Finally, transfection of 'DYNLRB1 (74-96)', a small peptide derived from DYNLRB1's C-terminal part which binds with NAGK, resulted neurons with shorter axons in culture. Our data suggest that NAGK-dynein-Golgi tripartite interaction in growing axons is instrumental during early axonal development.

Keywords: Axon, Dynein, Golgi, Microtubule, NAGK, Neuron.

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Text mining of Dongeuibogam and its evaluation for Effectiveness on the Medicinal herbs of Cognitive Enhancement

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In literature on Korean medicine, Dongeuibogam, published in 1613, represents the overall results of the traditional medicines of North-East Asia based on prior medicinal literature. We utilized this medicinal literature by text mining to establish a list of candidate herbs for cognitive enhancement in the elderly and then performed an evaluation of their effects. Text mining was performed for selection of candidate herbs. Cell viability was determined in HT22 hippocampal cells and immunohistochemistry analysis was performed in the hippocampus of a kainic acid (KA) mice model in order to observe alterations of hippocampal cells. Twenty four herbs for cognitive enhancement in the elderly were selected by text mining of Dongeuibogam. In HT22 cells, pretreatment with three candidate herbs resulted in significantly reduced glutamate-induced cell death. In the hippocampus of a KA mice model, pretreatment with eleven candidate herbs resulted in suppression of caspase-3 expression. Treatment with seven candidate herbs resulted in significantly enhanced expression levels of phosphorylated CREB. Number of proliferated cells indicated by BrdU labeling was increased by treatment with ten candidate herbs. *Panax schinseng* was the most neuroprotective herb against cell death in HT22 cells. *Schizandra chinensis* was the most effective herb against cell death and proliferation of progenitor cells and Rehmannia glutinosa in neuroprotection in the hippocampus of a KA mice model. Morris water maze test and passive avoidance test were performed to evaluate the cognitive function by three candidates, P. schinseng, S. chinensis and R. glutinosa. Treatments with three candidates improved learning and cognitive function. These established herbs and their combinations identified by text-mining technique and evaluation for effectiveness may have value in further experimental and clinical applications for cognitive enhancement in the elderly.

Keywords: Neuroprotection, Neurogenesis, Kanic acid, HT22, CREB

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P59

CCR5-CCL Axis in PDL during Orthodontic Biophysical Force Application

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Tooth movement by application of orthodontic biophysical force (OBF) primarily reflects the role of soluble molecules released from the periodontal ligament (PDL). Thus far, many factors have been reported to be involved in orthodontic tooth movement (OTM), but key molecules that orchestrate responses of periodontal tissues to biophysical force are still enigmatic. In this in vivo study, in which the upper 1st molars in rats were moved, differential display-PCR revealed that CC motif chemokine receptor type 5 (CCR5) level was differentially increased during OTM. Strong immunoreactivity for CCR5 was found in the PDL undergoing force application. Moreover, the in vitro compression or tension force application to primary cultured human PDL cells increased the expression of CCR5 and CCR5 ligands. In vitro tension force on human PDL cells did not induce RANKL, an osteoclastogenesis-inducing factor, but induced the upregulation of IL12, an osteoclast inhibitory factor and osteoblast differentiation factors including Runx2 which was attenuated under tension by CCR5 gene silencing, whereas augmented with CCR5 ligands. In contrast, in vitro compression force did not induce the expression of OPG, a decoy receptor for RANKL and Runx2, but induced the upregulation of RANKL which was attenuated under compression by CCR5 gene silencing. These results suggest that the CCR5-CCR5 ligands axis in PDL cells may play a crucial role in the remodeling of periodontal tissues and can be a therapeutic target for achieving efficient OTM.

Keywords: Key words: biophysics, chemokine receptor, orthodontic tooth movement, periodontal ligament, Bone

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P60

The Role of Lhx2 in RANKL-induced Osteoclastogenesis

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The LIM homeobox 2 (Lhx2) transcription factor Lhx2 has a variety of functions, including neural induction, morphogenesis, and hematopoiesis. Here we show the involvement of Lhx2 in osteoclast differentiation. Lhx2 was strongly expressed in osteoclast precursor cells but its expression was significantly reduced during receptor activator of nuclear factor-κB ligand (RANKL)-mediated osteoclastogenesis. Overexpression of Lhx2 in bone marrow-derived monocyte/macrophage lineage cells (BMMs), which are osteoclast precursor cells, attenuated RANKL-induced osteoclast differentiation by inhibiting the induction of nuclear factor of activated T cells c1 (NFATc1). Interestingly, interaction of Lhx2 proteins with c-Fos attenuated the DNA-binding ability of c-Fos and thereby inhibited the transactivation of NFATc1. Furthermore, Lhx2 conditional knockout mice exhibited an osteoporotic bone phenotype, which was related with increased osteoclast formation in vivo. Taken together, our results suggest that Lhx2 acts as a negative regulator of osteoclast formation in vitro and in vivo. The anti-osteoclastogenic effect of Lhx2 may be useful for developing a therapeutic strategy for bone disease.

Keywords: LIM homeobox 2 (Lhx2), Osteoclast, RANKL, NFATc1, Osteoporosis

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NFIC is Required for Chondrocyte Proliferation in Growth Plate during Postnatal Cartilage Development

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The nuclear factor I (NFI) gene family encodes site-specific transcription factors essential for the development of a number of organ systems. Our previous studies indicate that NFI-C is required for tooth root development and bone formation, but the exact function of NFI-C in cartilage development remains unknown. In this study, *Nfic*$^{-/-}$ mice revealed decreased growth-plate lengths compared to

WT. In particular, the width of the proliferating and hypertrophic zone in the growth plate was dramatically reduced in *Nfic*$^{-/-}$ mice compared to WT. However, NFI-C disruption has no influence on prenatal cartilage development. In addition, cell proliferation rates of *Nfic*$^{-/-}$ chondrocytes were decreased approximately 40% at 3 days and 70% at 5 days compared to WT, respectively. PCNA-positive cells were significantly diminished in the proliferating zone of *Nfic*$^{-/-}$ mice compared to WT. In contrast, chondrocyte apoptosis was increased in the hypertrophic zone of *Nfic*$^{-/-}$ mice compared to WT. *Nfic*$^{-/-}$ chondrocytes exhibited increased p21 expression but decreased cyclin D1 expression, strongly suggesting cell growth arrest due to the lack of *Nfic* activity. Further, *Nfic*$^{-/-}$ chondrocytes exhibited increased caspase-3 activation. These results indicate that NFI-C disruption results in decreased femur length caused by reduction in the width of the growth plate, decreased chondrocyte proliferation, and increased chondrocyte apoptosis.

Keywords: NFI-C, Chondrocyte, Proliferation

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Protocatechuic acid attenuates osteoclastogenesis through JNK/c-Fos/NFATc1 signaling and prevents inflammatory bone loss in mice

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Protocatechuic acid (PCA) plays a critical role in nutritional metabolism; it is a major metabolite of anthocyanins, which are flavonoids with a range of health benefits. PCA has a variety of biological activities including anti-oxidant, anti-inflammatory, anti-apoptosis, and anti-microbial activities. However, the pharmacological effect of PCA, especially on osteoclastogenesis, remains unknown. We examined the effect of PCA on receptor activator of NF-κB ligand (RANKL)-induced osteoclast differentiation and bone resorption. PCA dose-dependently inhibited RANKL-induced osteoclast differentiation in mouse bone marrow macrophages (BMMs) and suppressed the bone-resorbing activity of mature osteoclasts. At the molecular level, PCA suppressed RANKL-induced phosphorylation of JNK among MAPKs only, without significantly affecting the early signaling pathway. PCA also suppressed RANKL-stimulated expression of c-Fos and nuclear factor of activated T cells c1 (NFATc1) at the mRNA and protein levels, without altering c-Fos mRNA expression. Additionally, PCA down-regulated the expression of downstream osteoclastogenesis-related genes including *β3-integrin*, *DC-STAMP*, *OC-STAMP*, *Atp6v0d2*, *CTR*, and *CtsK*. Mice treated with PCA efficiently recovered from lipopolysaccharide-induced bone loss *in vivo*. Thus, PCA inhibits RANKL-induced osteoclast differentiation and function by suppressing JNK signaling, c-Fos stability, and expression of osteoclastic marker genes. These results suggest that PCA could be useful in treatment of inflammatory bone disorders.

Keywords: Osteoclast, Protocatechuic acid, RANKL, NFATc1, JNK

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

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The small molecule WHI-131 is a potent therapeutic agent with anti-inflammatory, anti-allergic, and anti-leukemic potential. However, the regulatory effects of WHI-131 on osteoblast and osteoclast

activity are unclear. We examined the effects of WHI-131 on osteoblast and osteoclast differentiation with respect to bone remodeling. The production of receptor activator of nuclear factor kappa-B ligand (RANKL) by osteoblasts in response to interleukin (IL)-1 or IL-6 was decreased approximately 50% in the presence of WHI-131. WHI-131 abrogated the formation of mature osteoclasts by the stimulation of IL-1 or IL-6. Also, WHI-131 treatment decreased RANKL-induced osteoclast differentiation, and reduced the resorbing activity of mature osteoclasts. WHI-131 decreased by almost 2-fold in mRNA expression levels of *c-Fos* and *NFATc1*. Also, statistically significant downregulation of *TRAP*, *OSCAR*, *ATP6v0d2*, and *CtsK* mRNA expressions was induced in response to WHI-131 compared with DMSO-treated control group. Phosphorylation of Akt and degradation of IκB were suppressed by WHI-131; oscillation of Ca^{2+} was also affected as phosphorylation of the c-Src-Btk-PLCγ2 pathway was inhibited. The JAK-STAT signaling pathway was activated by WHI-131, with STAT3 Ser727 phosphorylated and STAT6 dephosphorylated. Moreover, WHI-131 exhibited anti-resorbing effects in an LPS-induced calvaria bone loss model *in vivo*. In osteoblasts, WHI-131 caused about 4-fold increase in alkaline phosphatase activity and Alizarin Red staining. Treatment with WHI-131 increased the mRNA expression levels of genes related to osteoblast differentiation, and induced the phosphorylation of Akt, p38, and Smad1/5/8. In this study, we have shown that WHI-131 plays a dual role, inhibiting osteoclast differentiation and promoting osteoblast differentiation. Thus, WHI-131 could be a useful pharmacological agent that treats osteoporosis through both promoting bone growth and inhibiting resorption.

Keywords: WHI-131; Osteoclasts; Osteoblasts; Osteoporosis

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Ebselen is a potential anti-osteoporosis agent by suppressing RANKL-induced osteoclast differentiation *in vitro* and LPS-induced inflammatory bone destruction *in vivo*

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Ebselen is a non-toxic seleno-organic drug with anti-inflammatory and anti-oxidant properties that is currently being examined in clinical trials to prevent and treat various diseases, including atherosclerosis, stroke, and cancer. However, no reports are available for verifying the pharmacological effects of ebselen on major metabolic bone diseases such as osteoporosis. In this study, we observed that ebselen suppressed the formation of tartrate-resistant acid phosphatase (TRAP)-positive multinucleated cells in an osteoblast/osteoclast co-culture by regulating the ratio of receptor activator of nuclear factor kappa-B ligand (RANKL)/osteoprotegerin (OPG) secreted by osteoblasts. In addition, ebselen treatment in the early stage of osteoclast differentiation inhibited RANKL-dependent osteoclastogenesis by decreasing the phosphorylation of IκB and Akt in early signaling pathways and subsequent expressions of c-Fos and nuclear factor of activated T-cells c1 (NFATc1). Further, ebselen induced the cleavage (activation) of caspase-3 and caspase-9, which mediate the induction of apoptosis, in the late stage of osteoclast differentiation. In addition, ebselen treatment suppressed filamentous actin (F-actin) ring formation and bone resorption activity of mature osteoclasts. Reflecting these *in vitro* effects of ebselen on osteoclast differentiation and function, administration of ebselen recovered bone loss and its μ-CT parameters in lipopolysaccharide (LPS)-mediated mice model. Histological analysis confirmed that ebselen prevented trabecular bone matrix degradation and osteoclast formation in the bone tissues. These results indicate that ebselen is a potentially safe drug for treating metabolic bone diseases such as osteoporosis.

Keywords: Ebselen,Osteoclast,Osteoporosis

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CTRP3 Acts as a Negative Regulator of Osteoclastogenesis through AMPK-c-Fos-NFATc1 Signaling *In Vitro* and RANKL-Induced Calvarial Bone Destruction *In Vivo*

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Adipokines derived from adipocytes are important factors that act as circulating regulators of bone metabolism. C1q/tumor necrosis factor (TNF)-related Protein-3 (CTRP3) is a novel adipokine with multiple effects such as lowering glucose levels, inhibiting gluconeogenesis in the liver, and increasing angiogenesis and anti-inflammation. However, the effects and the mechanisms of CTRP3 on bone metabolism, which is regulated by osteoblasts and osteoclasts, have not been investigated. Here, we also found that CTRP3 inhibited osteoclast differentiation from mouse bone marrow macrophages (BMMs) induced by RANKL in a dose-dependent manner without cytotoxicity. Functionally, CTRP3 inhibited the F-actin formation and bone resorbing activity of mature osteoclasts. Pretreatment with CTRP3 significantly inhibited RANKL-induced expression of c-Fos and nuclear factor of activated T-cells (NFATc1), essential transcription factors for osteoclast development. Surprisingly, the activation of AMP-activated protein kinase (AMPK) was considerably increased by pretreatment with CTRP3. The CTRP3-stimulated AMPK activation was also maintained during RANKL-induced osteoclastogenesis. CTRP3 did not affect RANKL-induced p38, ERK, JNK, Akt, IκB, CREB, and calcium signaling. These results suggest that CTRP3 plays an important role as a negative regulator of RANKL-mediated osteoclast differentiation by acting as an inhibitor of NFATc1 activation through the AMPK signaling pathway. Furthermore, CTRP3 treatment reduced RANKL-induced osteoclast formation and bone destruction in mouse calvarial bone *in vivo* based on micro-CT and histologic analysis. In conclusion, these findings strongly suggest that CTRP3 deserves new evaluation as a potential treatment target in various bone diseases associated with excessive osteoclast differentiation and bone destruction.

Keywords: Adipokine, AMPK, Bone resorption, CTRP3, Osteoclast differentiation

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Dendrobium moniliforme Exerts Inhibitory Effects on Receptor Activator of Nuclear Factor Kappa-B Ligand-Mediated Osteoclast Differentiation *in Vitro* and Lipopolysac charide-Induced Bone Erosion *in Vivo*

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Dendrobium moniliforme (DM) is a well known plant-derived extract that has been widely used in oriental medicine. Although a variety of pharmacological effects of DM and its chemical constituents, including anti-oxidation, anti-inflammation, and anti-tumor have been disclosed, there are no reports to verify the beneficial effects of DM on bone diseases, such as osteoporosis. Thus, we investigated the relationship between DM and osteoclasts, well characterized cells whose function is bone resorption. In this study, we figured out that DM significantly reduced receptor activator of nuclear factor kappa-B ligand (RANKL)-induced tartrate-resistant acid phosphatase (TRAP)-positive osteoclasts formation. In this anti-osteoclastogenic activity, DM directly induced down-regulation of c-Fos and nuclear factor of activated T cells c1 (NFATc1) without affecting RANKL-dependent various transduction pathways. In the late stage of osteoclast maturation, DM negatively regulated organization of filamentous actin (F-actin) structure, resulting in impaired bone-resorbing activity of mature osteoclasts. Furthermore, micro-computed tomography (μ-CT) analysis exhibited that DM exerted beneficial effect on lipopolysaccharide (LPS)-mediated bone erosion mice model and histological analysis showed that DM recovered degradation of trabecular bone matrix and formation of TRAP-

positive osteoclast in bone tissues. These results suggest that DM is a potential candidate for improving metabolic bone disorders, such as osteoporosis.

Keywords: Dendrobium Moniliforme (DM); Osteoclast; Bone Resorption; Osteoporosis

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Smad4-Osx Signaling Axis Is Required For Odontoblast Differentiation

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Dentin is formed by odontoblasts that have differentiated from dental mesenchymal cells. Research indicates that Smad4-mediated Wnt signaling plays a crucial role in the fate of dental mesenchymal cells, and that Osx is essential for osteoblast differentiation. To understand the molecular mechanisms that control odontoblast differentiation and dentin formation, we investigated the functional significance of Smad4 and Osx in the regulation of odontoblast differentiation through tissue-specific inactivation of *Smad4* and *Osx* in osteocalcin-Cre (*OC-Cre*)-expressing cells. Simultaneous ablation of *Smad4* and *Osx* results in more severe defects in odontoblast differentiation and dentin formation compared to single-gene-disrupted mice. In *OC-Cre*;*Smad4*$^{fl/fl}$:*Osx*$^{fl/fl}$ mice, crown dentin was extremely thin and was accompanied by loss of polarity in odontoblasts. Furthermore, a lack of molar roots was caused by severe impairment of root odontoblast differentiation. Although Hertwig's epithelial root sheath (HERS) was extended apically after crown formation, root odontoblast differentiation was disrupted. Immunohistochemistry analysis revealed that Lef-1, a Wnt target protein, and Ki67, a cell proliferation marker, demonstrated increased immunoreactivity in the dental papilla adjacent to HERS in *OC-Cre;Smad4*$^{fl/fl}$:*Osx*$^{fl/fl}$ mice. These results indicate that simultaneous disruption of *Smad4* and *Osx* leads to increased cell proliferation through upregulation of Wnt activity and impaired odontoblast differentiation. Thus, Smad4 and Osx are essential for maintaining odontogenic fate in dental mesenchyme and odontoblast differentiation, respectively. Furthermore, the Wnt-Smad4-Osx signaling axis is required for proliferation, odontoblast differentiation, and dentin formation during tooth development. [This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MEST) (No. 2013R1A2A1A01007642)]

Keywords: Odontogenic Fate, Dental Mesenchyme, Differentiation, Dentin, Root

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Aberrant Dentin Formation In Hutchinson-Gilford Progeria Mutation

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Hutchinson-Gilford progeria syndrome (HGPS) is a rare accelerated senescence disease, manifesting dental abnormalities. Although irregular secondary dentin formation in HGPS patients has been reported, pathological mechanisms underlying aberrant dentin formation remains undefined. Here, we analyzed the mandibular molars of tissue-specific mouse model that overexpresses the most common HGPS mutation (LMNA, c.1824C>T, p.G208G) by histology, immunohistochemistry, scanning electron microscopy (SEM), and micro-computed tomography. In the molars of HGPS mutant at postnatal week 3, numbers and height of odontoblasts decreased. In addition, dentin thickness was remarkably thinner than those of wild-type (WT) littermates. Irregular circumpulpal dentin was deposited beneath the mantle dentin from postnatal week 5 and gradually obliterated almost of pulp cavity until postnatal week 20. In SEM analysis, irregular circumpulpal dentin of HGPS mutant showed porous bone-like structures, different from regular tubular structure in circumpulpal dentin of WT and mantle dentin in HGPS mutant. In immunohistochemistry, Dsp was localized in mantle dentin and circumpulpal dentin both of HGPS and WT molars. However, Dmp-1 was strongly localized in irregular circumpulpal dentin of HGPS mutant in contrast to its weak expression in mantle dentin both of HGPS and WT mice. No Bsp localization was observed in the dentin of HGPS and WT molars. These results indicate

that expression of HGPS mutation in odontoblasts disturbs physiologic circumpulpal dentin formation but promotes irregular tertiary dentin formation. In HGPS mutant, aberrant circumpulpal dentin may be formed by reactionary response following HGPS expression in odontoblasts. [This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MEST) (No. 2013R1A2A1A01007642)]

Keywords: HGPS, Premature Senescence, Circumpulpal Dentin, Tertiary Dentin, Mice

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Expression of Amelogenin and Effects of Cyclosporine A in Developing Hair Follicles

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Amelogenin, an enamel matrix protein has been considered to be exclusively expressed by ameloblasts during odontogenesis. However, burgeoning evidence indicates that amelogenin is also expressed in non-mineralizing tissues. Under the hypothesis that amelogenin may be a functional molecule in developing hair follicles which share developmental features with odontogenesis, this study for the first time elucidated the presence and functional changes of amelogenin and its receptors during rat hair follicle development. Amelogenin was specifically localized in the outer epithelial root sheath of hair follicles. Its expression appeared in the deeper portion of hair follicles i.e. the bulbar and suprabulbar regions rather than the superficial region. Lamp-1, an amelogenin receptor was localized in either follicular cells or outer epithelial sheath cells, reflecting functional changes during development. The expression of amelogenin splicing variants increased in a time-dependent manner during postnatal development of hair follicles. Amelogenin expression was increased by treatment with cyclosporin A, which is an inducer of anagen in the hair follicle, whereas the level of Lamp-1 and -2 was decreased by cyclosporin A treatment. These results suggest that amelogenin may be a functional molecule involved in the development of the hair follicle rather than an inert hair shaft matrix protein.

Keywords: Key words amelogenin, lamp-1, hair follicle, Cyclosporine A, development

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Regulation of ADAM10 and ADAM17 by Sorafenib Inhibits Epithelial-to-Mesenchymal Transition in Epstein-Barr Virus–Infected Retinal Pigment Epithelial Cells

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Purpose: The a-disintegrin-and-metalloprotease (ADAM) family proteins are widely expressed in the different layers of the retina throughout development. The effect of ADAM proteins on the epithelial-to-mesenchymal transition (EMT) in proliferative vitreoretinopathy (PVR) or AMD is yet to be elucidated. In this study we used Epstein-Barr virus (EBV)-transformed adult retinal pigment epithelial (ARPE) cells to investigate how sorafenib, a multikinase inhibitor, modulates ADAM proteins to control EMT.
Methods: Epithelial to mesenchymal transition and related mechanisms in EBV-infected ARPE cells were determined by RT-PCR, Western blot, invasion assay, ELISA assay, and gene silencing with siRNA.
Results: Mesenchymal-like ARPE/EBV cells exhibited considerably increased cellular migration and invasion compared with ARPE cells and produced EMT-related cytokines. Sorafenib significantly inhibited production of TGF-β1, VEGF, IL-6, IL-8, MCP-1, and TNF-α and blocked the activation of migration-related signaling molecules, such as HIF-1α, p-STAT3, MMP2, and Ang-1. The expression of mature ADAM10, ADAM17, and cleaved Notch 1 proteins in ARPE/EBV cells was downregulated after treatment with sorafenib through the regulatory activity of nardilysin (NRD-1). Gene silencing of NRD-1 in ARPE/EBV cells attenuated secretion

of EMT-related cytokines and expression of ADAM10 and 17 and upregulated epithelial markers.

Conclusions: Sorafenib controls the mesenchymal characteristics of EBV-infected ARPE cells. Nardilysin and ADAM family proteins might be new targets for the prevention or control of EMT in retinal diseases.

Keywords: RPE cells, Epstein-Barr virus, Sorafenib, Epithelial-mesenchymal transition, ADAM, Nardilysin

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Roles of O-GlcNAcylation in lung metastasis from cervical cancer cells

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Background: High-risk human papillomaviruses (HPV) are largely implicated in the carcinogenesis of cervical cancer. However, recent study showed that HPV DNAs were found in lung metastasis from cervical cancer. O-GlcNAcylation plays important roles in tumor formation, maintenance, dissemination and metastasis in many cancers including lung cancer, while O-GlcNAcylation in lung metastasis from cervical cancer remains unknown. Therefore, we examined whether O-GlcNAcylation of several proteins in cervical cancer cells affects lung metastasis from cervical cancer.

Method: E6, E7, O-GlcNAc, OGT, and HCF-1 levels were measured by Western Blotting in lung tissues from HeLa or sh-OGT treated HeLa cells. Further, O-GlcNAcylation of HCF-1, E6 and E7 expression levels were measured in HeLa cells after OGT overexpression or deletion. Moreover, chemokine receptor CXCR4 levels were examined in the xenograft model after OGT-specific shRNA treatment of cervical cancer cells.

Results: E6 and E7 oncoproteins were found in lung tissues of nude mice injected with HeLa (HPV-18-positive) cells. The expression levels of E6, E7, O-GlcNAc, HCF-1 were decreased in HeLa cells after OGT-specific shRNA treatment. In addition, OGT deletion significantly decreased expression of CXCR4 in HeLa cells as well as in the xenograft model. These results suggest that OGT increases E6 and E7 expression not only in primary cancer but also in lung metastasis from cervical cancer.

Conclusion: Our study shows that inhibition of O-GlcNAcylation decreases levels of E6, E7 and CXCR-4, resulting in lowering lung metastasis from cervical cancer.

Keywords: O-GlcNAcylation , Lung cancer, E6/E7, CRCR4

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Epigenetic therapeutic activity of hinokitiol as a novel DNA methylation inhibitor in human colorectal cancer cells

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Hinokitiol, a tropolone-related natural compound that induces apoptosis and has anti-inflammatory, anti-oxidant, and anti-tumor activities. However, the function of hinokitiol as DNA methylation inhibitor in tumor cells is unknown. We investigated whether a hinokitiol can affect DNA methylation and gene expression in colorectal cancer (CRC) cell line. The sensitivity of CRC cells (HCT-116 and SW480) to hinokitiol was higher than that of normal colon cells (CCD18Co) at >10 μM concentrations. DNMT1 and DNMT3B mRNA levels were higher in HCT-116 cells than in CCD-18Co and other CRC cells at basal state. Following hinokitiol (<10 μM) treatment, the expression of DNMT1 mRNA as well as protein was reduced in HCT-116 cells. To clarify the mechanism of hinokitiol-induced demethylation, the levels of 5-mC and 5-hmC were also examined by ELISA or FACS analysis. Hinokitiol led to an increase of 5-hmC with concomitant the decrease of 5-mC in HCT-116 cells. Using MethyLight and qRT-PCR, methylation and silenced states of 12 genes including 5 CIMP markers were determined in HCT-116 cells but not in CCD18Co cells. The methylation levels of MGMT, ELOVL4, and BTG4 were decreased and mRNA expression of them

was recovered in HCT-116 cells after hinokitiol treatment. These results suggest that hinokitiol may exert DNA demethylation effect through the mechanism of DNA methyltransferase inhibition. Therefore, hinokitiol may be a potential DNA methylation inhibitor and may contribute to epigenetic therapeutic activity for CRC treatment.

Keywords: Hinokitiol DNA methylation inhibitor Colorectal cancer Epigenetics Anti-tumor activity

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The cytotoxic effect of SB365 Isolated from Pulsatilla Koreana on Human glioblastoma cells

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Introduction: The anti-cancer effects of SB365, Pulsatilla saponin D isolated from the root of Pulsatilla koreana, has been reported in various cancers. However, it is still unknown the cytotoxicity of SB365 against bran tumors, especially glioblastoma multiforme grade IV.
Purpose: This study was investigated to determine a anti-cancer effect of SB365 on glioblastoma and its related mechanism.
Result: SB365 significantly up-regulated intracellular ROS levels and decreased the viability and proliferation of glioblastoma cell lines such as T98G and U87-MG in a dose-dependent manner. SB365 showed the apoptotic effects including cell shrinkage, DNA condensation and increased expression of cytochrome c and cleaved caspase-3 expression. The elevated populations of apoptotic cells were also examined by flow cytometric analysis with annexin V and 7-AAD staining. Moreover, we investigated the expression of two key molecules for the formation of autophagosomes such as microtubule-associated protein lightchain 3 (LC3) and autophagy-related gene 6 (Beclin-1). SB365 increased LC3-II expression, which was not dependent to Beclin-1 expression. However, SB365 did not induced apoptosis or autophagy in normal mouse brain tissue culture. In addtion, SB365 suppressed the phosphorylation of Akt and induced the phosphorylation of p38 MAPK and ERK in U87-MG glioblastoma cells.
Conclusion: These findings suggest that SB365 induces autophagy and apoptosis via ROS production through the regulation of p38 MAPK, ERK and AKT signaling. Therefore, SB365 may be a novel anti-cancer drug for human glioblastoma multiforme.

Keywords: glioblastoma, SB365, autophagy, apoptosis, ROS

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ATOH1 Can Regulate the Tumorigenicity of Gastric Cancer Cells by Inducing the Differentiation of Cancer Stem Cells

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Cancer stem cells (CSCs) have been shown to mediate tumorigenicity, chemo-resistance, radio-resistance and metastasis, which suggest they be considered therapeutic targets. Because their differentiated daughter cells are no longer tumorigenic, to induce the Differentiation of CSCs can be one of strategies which can eradicate CSCs. Here we show that ATOH1 can induce the differentiation of gastric cancer stem cells (GCSCs). Real time PCR and western blot analysis showed that ATOH1 was induced during the differentiation of GCSCs. Furthermore, the lentivirus-induced overexpression of ATOH1 in GCSCs and in gastric cancer cell lines significantly induced differentiation, reduced proliferation and sphere formation, and reduced in vivo tumor formation in the subcutaneous injection and liver metastasis xenograft models. These results suggest ATOH1 be considered for the development of a differentiation therapy for gastric cancer.

Keywords: ATOH1 Differentiation Gastric Cancer stem cells (GCSCs)

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Three-Dimensional Prostate Cancer Cell Culture using Fish Collagen/ Polycaprolactone Nanofiber Scaffold as a Model to Study Epithelial-Mesenchymal Transition *In Vitro*

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Cells in three-dimensional (3D) culture can represent *in vivo*-like original state more than cells in two-dimensional (2D) culture. In the present study, we established a 3D cell culture model of human prostate cancer using fish collagen/polycaprolactone (FC/PCL) nanofibrous scaffold. The cytocompatibility of human prostate cancer cells on FC/PCL scaffolds was evaluated by WST-1 assay, confocal microscopy, western blot, RT-PCR and flow cytometry. It was found that the scaffolds not only facilitated cell proliferation but also stimulated the expression of genes and proteins involved in tumor cell behaviour such as growth and malignant transformation. The expression of pro-angiogenic growth factors and the transcriptions of regulators of malignancy significantly increased in cells cultured in 3D FC/PCL scaffolds. The upregulation of epithelial mesenchymal transition (EMT) markers was observed in cells cultured in FC/PCL scaffolds. In addition, Notch signaling, which is involved in tumorigenesis and induction of EMT, was found to be activated. Therefore, these findings suggest that a novel three-dimensional culture model for human prostate cancer cells using a nanofibrous scaffold was fabricated. Furthermore, our data may provide a useful platform technology to develop functional, biocompatible, three-dimensional scaffolds for 3D culture of various cancer cells.

Keywords: 3D culture, nanofiber scaffold, cell viability, prostate cancer

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Characterization of Human Prostate Cancer Lines in a Hydrogel-based 3-Dimensional *in vitro* Model of Prostate Cancer

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In recent years, three-dimensional (3D) cell culture draws increasing attention since cells cultured in 3D represent *in vivo*-like original state of cells more than cells cultured in two-dimensional (2D) in various aspects of cell behaviors such as gene and protein expression, signaling events and other biological activities. In this context, conventional 2D prostate cancer cell culture models do not reflect the true biological activities of prostate cancer cells *in vivo*, and thus drug screening and testing in 3D prostate cancer cell culture models are more effective than conventional 2D monolayer culture system. In the present study, we established a hydrogel-based 3D prostate cancer culture system using various human prostate cancer cell lines (LNCaP, DU145 and PC3). The cells were encapsulated homogeneously in the hydrogel matrix during hydrogelation. It was found that cells residing in the hydrogel matrix grow as tumor-like clusters in 3D formation when compared to cells cultured in 2D monolayer culture. Histological examination of all the three types of prostate cancer cells demonstrated the formation of spheroids, whereas none of the cell types in 2D formed any spheroids. RT-PCR, Western blot, drug resistance and immunofluorescence staining analyses also revealed that the expression of various genes related with prostate cancer malignancy was significantly up-regulated in all the three types of cells in 3D cell culture when compared to 2D cell culture. Therefore, this study provides a novel hydrogel-based three-dimensional culture technique for human prostate cancer cells. Furthermore, our data may provide a useful platform technology to develop functional, biocompatible, three-dimensional scaffolds for 3D culture of various cancer cells.

Keywords: 3D culture, hydrogel, tumor spheroid, prostate cancer

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P77

A Heptamethine Cyanine Dye Is a Potential Diagnostic Marker for Myeloid-Derived Suppressor Cells

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Myeloid-derived suppressor cells (MDSC) are immature myeloid cells with inhibitory effects on T cell-mediated antitumor reactivity. MDSC are amplified in various conditions including cancers or inflammation. In fact, it has been well known that MDSC are over amplified in most cancer patients for cancer cells to avoid anticancer immunity. However, specific surface marker for MDSC is yet to be identified. In this study, we investigate the potentiality of heptamethine cyanine dye as a MDSC diagnostic marker. 4T1 breast cancer cells-bearing mice were created in female BALB/c mice. Splenocytes were isolated from 4T1-bearing mice at 21 days after injection or healthy mice. FACS scan analysis was applied to these splenocytes to verify the specificity of dye. MDSCs were magnetically selected from mice spleen using Gr1 antibodies. Splenocytes were also stained with heptamethine cyanine dye followed by isolating dye-positive cells with cell sorter. To determine whether dye-positive cells possess inhibitory effect on T-cell proliferation, CFSE-based T cell proliferation assay was performed. Compared to normal mice, tumor-bearing mice showed tremendous increase of MDSC (CD11b+/LY6G+). Over 90% of these CD11b+/LY6G+ cells were also reactive to heptamethine cyanine dye. Notably, other cell populations including lymphocytes and monocytes were not reactive to this dye. In addition, heptamethine cyanine dye-positive cells significantly reduced T cell proliferation, suggesting that dyes react to the cells possessing similar function of MDSC.

Our study demonstrates that heptamethine cyanine dyes react to the cells with characteristic MDSC markers and MDSC function. With extensive study with human specimen, this dye can be a novel tool to detect MDSC and further utilized to predict cancer patient prognosis.

Keywords: MDSC, Heptamethine Cyanine Dye, T Cell

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Cinnamic Aldehyde Suppresses Hypoxia-Induced Angiogenesis via Inhibition of Hypoxia-Inducible Factor-1α Expression During Tumor Progression

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During tumor progression, hypoxia-inducible factor 1 (HIF-1) plays a critical role in tumor angiogenesis and tumor growth by regulating the transcription of several genes in response to a hypoxic environment and changes in growth factors. This study was designed to investigate the effects of cinnamic aldehyde (CA) on tumor growth and angiogenesis and the mechanisms underlying CA's anti-angiogenic activities. We found that CA administration inhibits tumor growth and blocks tumor angiogenesis in BALB/c mice. In addition, CA treatment decreased HIF-1α protein expression and vascular endothelial growth factor (VEGF) expression in mouse tumors and Renca cells exposed to hypoxia in vitro. Interestingly, CA treatment did not affect the stability of von Hippel-Lindau protein (pVHL)-associated HIF-1α and CA attenuated the activation of mammalian target of rapamycin (mTOR) pathway. Collectively, these findings strongly indicate that the anti-angiogenic activity of CA is, at least in part, regulated by the mTOR pathway-mediated suppression of HIF-1α protein expression and these findings suggest that CA may be a potential drug for human cancer therapy.

Keywords: Angiogenesis; Tumor; Cinnamic aldehyde; Hypoxia-inducible factor-1α

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CD46 is Overexpressed in Colorectal Cancers and Mediates Enhanced Tumor Transduction Efficacy of Ad5/35 Chimeric Adenovirus

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CD46 is a complement inhibitor membrane cofactor protein and also acts as a receptor for certain pathogenic microbes, including group B adenovirus (Ad). Whereas many Ads infect cells through coxsackie-adenovirus receptor (CAR), CAR expression is down-regulated in many cancers preventing effective therapeutics of Ad-based therapies. There have been increasing numbers of studies in cancer gene therapy by modification of Ad fiber knobs to utilize more ubiquitously expressed CD46. However, very limited information is available on expression status of CD46 in many cancers.

To seek the evidence whether colorectal cancers are good target for adenovirus-mediated gene therapy, chimeric Ad5 vectors that are capable of targeting CD46 were employed. Compared to mock-BHK and CAR-overexpressing BHK cells, CD46-ovrexpressing BHK cells showed significantly higher response not only to Ad5/35-GFP but to Ad5/35-TK/GCV suicide therapy. While CRC cells express variable levels of CD46, CD46 expression was positively correlated with Ad5/35-mediated GFP fluorescence and cell killing, demonstrating that HCT-116, DLD-1, and Caco-2 cells are highly responsive. Furthermore, injection of Ad5/35-TK/GCV caused higher anti-cancer effects in CD46-overexpressed M010119 melanoma cells bearing nude mice compared to mock cell bearing mice. CRC patient samples showed that there is inverted correlation between CD46 expression and clinico-pathological parameters in terms of differentiation, invasion, metastasis, T stage, and survival, suggesting that adenoviral gene therapy may not be as effective to the patients with highly advanced colorectal cancers. Taken altogether, our study demonstrated that CD46 is generally overexpressed in colorectal cancers in which group B-based adenoviral gene therapy seems to be suitable approach but careful consideration needs to be given to select cancer types and cancer status for effective cancer gene therapies.

Keywords: CD46, Adenovirus, Gene therapy, Colorectal cancer

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HOXB13-mediated Suppression of $p21^{WAF1/CIP1}$ Regulates JNK/c-Jun Signaling In Prostate Cancer Cells

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Many prostate cancer (PCa) patients die of recurrent disease due to the emergence of hormone-independent cancer cells of which mechanism is not fully understood. Our previous studies demonstrated that most castration resistant prostate cancers (CRPC) overexpress the HOXB13 transcription factor to confer positive growth signals. Since HOXB13 also suppresses $p21^{WAF1/CIP1}$ (p21) expression, we studied the correlation between HOXB13 and p21 in selected samples of PCa. While there was no statistically significant correlation between expression of HOXB13 and p21, HOXB13-deficient tumors had 3 times higher odds for expressing p21than HOXB13-positive tumors. Moreover, CRPC showed more negative correlation than hormone-dependent PCa (HDPC). Further *in vitro* proliferation assay demonstrated that androgen did not affect the growth-suppressive function of p21 in androgen-dependent PCa cells, suggesting that p21 seems to override the growth-promoting function of androgen and suppression of p21 expression by HOXB13 is an important step in PCa cell survival under no androgen influence. HOXB13 also inhibited AP-1 signals via suppressed expression of JNK/c-Jun. While HOXB13 suppressed p21 expression via regulation of JNK signals, alteration of p21 expression also affected c-Jun and AP-1 activity. Taken together, overexpression of HOXB13 in CRPC is an important step in avoiding the growth-suppressive effect of p21 in a harsh condition such as an androgen-deprived environment.

Keywords: HOXB13, p21WAF1/CIP1, JNK, c-Jun, Prostate Cancer

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PIK3CA Amplification is Common in Left Side-tubular Adenomas but Uncommon Sessile Serrated Adenomas Exclusively with KRAS Mutation

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Colorectal cancer is a heterogeneous disorder than arises via multiple distinct pathways, from tubular adenomas (TAs) and sessile serrated adenomas (SSAs), which are clinically, morphologically, and molecularly different. We examined PIK3CA amplification in colorectal precancerous legions, including TAs and SSAs. DNA was isolated from paired normal and tumoral tissues in 64 TAs and 32 SSAs. PIK3CA amplification, *KRAS* mutation, and *BRAF* mutation were analyzed by real-time PCR and pyrosequencing. PIK3CA amplification was found in 25% of TAs and 9.4% of SSAs, respectively. *KRAS* and *BRAF* mutations were mutually exclusive in both TAs and SSAs. In TAs, PIK3CA amplification was associated with left side and it was mutually exclusive with *KRAS* mutation. These results suggest that PIK3CA amplification may be early and important event in colorectal carcinogenesis and may drive the development of left-side TAs independently with *KRAS* mutation.

Keywords: Colorectal cancer; Mitochondria; Polymorphism; Sessile serrated adenomas; Tubular adenomas

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Absence of GNAS Mutation in Colorectal Carcinogenesis

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Purpose: The incidence rate of colorectal cancer (CRC) has increased seriously every year in Korean populations. However, association between the GNAS mutation and colorectal precancerous lesions has not been studied in in Korean populations. To contribute to better understanding on colorectal carcinogenesis, we have analyzed GNAS mutation in 100 cancerous and 96 precancerous colorectal lesions.
Methods: The records of colonoscopic polypectomy performed at Dongsan Medical Center between 1999 and 2003 were reviewed retrospectively. According to the records, precancerous lesions were comprised of 7 villous adenomas, 59 tubular adenomas, and 18 sessile serrated adenomas, and 12 hyperplastic polyps. Keimyung Human Bio-Resource Bank at Dongsan Medical Center provided 100 CRC samples.
Results: GNAS mutation was not found in any colorectal cancer and any precancerous colorectal lesions including villous adenoma which is thought to harbor the mutation.
Conclusions: Summing up our data and previous animal data, therefore, we suggest that the role of GNAS mutation might be limited in colorectal neoplasm of Korean population.

Keywords: Colorectal cancer; GNAS; Villous adenoma; Tubular adenoma; Sessile serrated adenomas

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HOXC9 Induces Phenotypic Switching Between Proliferation and Invasion in Breast Cancer Cells

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HOX genes encode a family of transcriptional regulator that are involved in pattern formation and organogenesis during embryo development. In addition, it has been revealed that HOX genes play important roles in adult tissues and some of the dysregulated HOX genes are associated with cancer development and metastasis. Like many other HOX genes, HOXC9 is aberrantly expressed in certain breast cancer cell lines and tissues, however, its specific functions in breast cancer progression are not investigated. In the present study, we demonstrated that HOXC9 overexpression in MDA-MB-231 cell line increases invasive potential and suppresses cell proliferation. Inhibition of HOXC9 expression by siRNA increased cell proliferation in MCF7 cell line. The clinical impact of HOXC9 in breast cancer was interpreted from the data of survival analysis, in which high HOXC9 expression had significantly poorer disease free survival and distant metastasis free survival, especially in lymph node positive patients. Together with its prognostic relevance, HOXC9-derived phenotypic switch between proliferative and invasive states in breast cancer cell lines suggest that HOXC9 could be a possible prognostic marker in breast cancer patients having lymph node metastasis, and possible target for a therapeutic intervention in malignant breast cancer.

Keywords: HOXC9 in breast cancer

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Induction of Apoptosis by Bamboo Salt in Human Mouth Carcinoma Cells through the Mitochondria/ Caspase Pathway

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Bamboo salt (BS) is a medicinal food originating from Korea and widely used in East Asia. BS is made by placing the solar salt into bamboo joint case produced by plants that grow for 3 years, sealing the case with natural red clay at ends, and bake 9 times by pine. In the present study, the BS exhibited significant cytotoxicity in human mouth epidermal carcinoma cells (KB cell). Herein, we investigated cytotoxicity mechanism of BS in KB cells. Based on DAPI staining, BS-treated cells manifested nuclear shrinkage, condensation, and fragmentation. Treatment of BS to KB cells resulted in activation of the caspase-3 and cleavage of poly ADP-ribose polymerase (PARP). In the upstream, BS decreased the expression of BCL-2. BS-induced, dose-dependent induction of apoptosis was accompanied by phosphorylation of ERK and p38 MAPK. These results suggest that BS induced apoptosis in KB cells through Bcl-2 family protein-mediated mitochondria/ caspase-3-dependent pathway.

Keywords: Bamboo salt, Caspase-3, BCL-2, Apoptosis, MAPK

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The redox-signal pathway study of the tumor suppressor GPx3

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Glutathione peroxidase 3 (GPx3) belongs to a panel of selenocysteine-containing redox enzymes, which plays a pivotal role in preventing from deleterious effects of hydrogen peroxide (H_2O_2). Our and other previous reports suggested that GPx3 has a tumor suppression function; however, its mechanism is to be revealed. To this end, we initially looked into GPx3 expression levels in 7 lung cancer cell lines. Out of them, H157, H934, A549 and H460 exhibited high expression levels of GPx3, whereas H1650, H1299 and H1975 did the low expression levels. To investigate the influence of GPX3 on the proliferation, migration and invasion of cancer cells, we changed the GPx3 expression levels into the cell. Over-expression of GPx3 by secis vector in H1975 suppressed cell proliferation, migration and invasion, whereas down-regulated GPx3 in A549 cells (by GPx3 siRNA) increased cell proliferation, migration and invasion. Then, we focused on the enzymatic function (peroxidase) of GPx3 which could protect target proteins from oxidation by H_2O_2. To identify the target proteins of GPx3 that contains redox-sensitive cysteines,

we employed the oxidized-cysteine capturing system. The target proteins were isolated from H1975 GPx3 (-/+) cell after exposure to 100 μM H_2O_2/10 min. Proteomic analysis enabled a total of 97 proteins to be identified. Furthermore, we performed a comparative transcriptome analysis between H1975 GPx3 (-/+) cells. Overall, 188 genes were over-expressed and 139 genes down-expressed >2-fold. Taken together, it suggested a new signal pathway of GPx3 in the tumor suppression.

Keywords: Glutathione peroxidase 3, Reactive oxygen species, Disulfide bonded proteins, Redox signal pathway

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Different Association between Telomere Length and Mitochondrial Copy Number in Colorectal Carcinogenesis

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Positive association between telomere length and mitochondrial DNA copy number were introduced in healthy and patients with psychiatric disorder. Based on frequent genetic changes of telomere and mitochondria in colorectal carcinomas (CRC), we studied this association in colorectal carcinogenesis. DNA was extracted from 109 CRC, 64 colorectal tubular adenoma (TA), and 28 serrated polyps (SPs), and their telomere length and mitochondrial DNA copy number were analyzed by using a real-time PCR assay. mtDNA copy number and telomere length (mean ± S.D) in CRCs was 1.61 ± 1.37 and 1.87 ± 1.52, respectively. In TAs, relative mtDNA copy number and telomere length (mean ± S.D) was 0.92 ± 0.71 and 1.18 ± 0.94, respectively. In SP, they were 1.84 ± 1.06 and 1.37 ± 1.13, respectively, and mtCN was statistically different in TA and SP ($p = 0.017$). They did not show a clinical and prognostic value in CRCs, however, positive correlation between telomere length and mitochondrial DNA copy number were found in CRC ($r = 0.408$, $p < 0.001$). However, this association was not shown in precancerous lesions ($r = -0.031$, $p = 0.765$). This result suggests that loss of co-regulation of telomeres and mitochondrial function may induce the initiation or play a role as trigger factor of colorectal carcinogenesis.

Keywords: Colorectal cancer; Mitochondria copy number; Telomere

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HOXB gene upregualtion is epigenetically regulated in tamoxifen-resistant MCF7 breast cancer cells

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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 human breast cancer samples as well as breast cancer cell lines. 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 up-regulation of *HOXB* including *HOXB2, HOXB3, HOXB4*, and *HOXB6*. ChIP analysis of histone modification revealed that the activation of *HOXB* cluster in MCF7-TamR cells is associated with the loss of H3K27me3 and

gain of H3K9ac. Meanwhile, Kaplan-Meier analysis of the overall survival for all patients treated with only endocrine therapy showed the correlation of high *HOXB* expression with a poor response to endocrine therapy. These results suggest a functional role of epigenetically regulated *HOXB* in the development of aquired tamoxifen resistance in breast cancer.

Keywords: Breast cancer, Tamoxifen resistance, HOX genes

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Cyclooxygenase-2 is induced on celecoxib-trated lung cancer cells and transferred to THP-1 through exosomes

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Cyclooxygenase-2 (COX-2) is an enzyme that is inducible by various stimuli such as inflammation. COX-2 expression is increased in a variety of cancers. Celecoxib is a selective inhibitor of COX-2 that have been shown to affect cell growth and apoptosis on various cancer cell lines. We investigated that celecoxib induces apoptosis on H460 and A549, lung cancer cell lines. ER-stress, stress-induced kinase and some cytokines were also increased after celecoxib treatment. Interestingly, celecoxib increase COX-2 transcription and protein level on lung cancer cells in time- and dose-dependent manners. As well as cytoplasmic COX-2, celecoxib triggered COX-2 loading on exosomes. Exosomes are small vesicles composed by bilayer membrane and finded in most biological fluid such as blood breast milk, urine. We isolated exosomes from celecoxib-treated lung cancer cell culture supernatant, and incubated with several types of cells. THP-1, monocytic leukemia cell line effectively uptake COX-2 by lung cancer cell-derived exosomes. After incubation with exosomes, COX-2 protein level was increased on THP-1, but COX-2 mRNA was not changed. Taken together, we suggested that celecoxib induces COX-2 expression and apoptosis on lung cancer cells, and highly-expressed COX-2 on exosomes can be transferred to other cells.

Keywords: Cyclooxyganase-2, Celecoxib, Lung cancer, Exosome

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The Anti-inflammatory Effect of Cysteamine on Experimental Autoimmune Uveitis through the Down-regulation of Interleukin-22 and Its Receptor Expression

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Interleukin (IL)-22 has both of pro-anti-inflammatory role. It is recently reported that IL-22 is increased in patients with autoimmune noninfectious uveitis, but its specific mechanism is unclear. Cysteamine has anti-inflammatory activity, but its regulatory role in the pathogenesis of uveitis is also to be clarified. In this study, we investigated whether cysteamine has therapeutic effects on experimental autoimmune uveitis (EAU) via the regulation of IL-22 and its receptor expression. As results, serum IL-22 levels in uveitis patients were increased compared to those in healthy donors. The production of MCP-1 remarkably was increased by IL-22 treatment. Moreover, IL-22 stimulation was definitely increase the proliferation of retinal pigment epithelial cell line, ARPE-19 via the activation of p38MAPK and NK-κB. Cysteamine was daily administered by intraperitoneal injection at one day before the IRBP inoculation, and then EAU was induced by a footpad injection of human $IRBP_{1-20}$ (250 μg/mouse). We found 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+ T cells and the production of IL-22. Interestingly, we also confirmed that RORγt expression and the production of IL-22 were inhibited by cysteamine in uveitis patients *in vitro*. In addition, IL-22Rα expression on ARPE-19 is increased in a PI3K/Akt dependent pathway, but its expression is inhibited by cysteamine treatment. 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.

Keywords: Experimental Autoimmune Uveitis, IRBP, Cysteamine, IL-22, IL-22 receptor

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P90

Preventive Effect of GV1001 on Gemcitabine-induced Pancreatic Cancer Cachexia

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GV1001 derived from the human telomerase reverse transcriptase (hTERT) sequence is a peptide vaccine for the treatment of pancreatic cancer. The preclinical data clearly showed immunogenicity of GV1001 in patients with pancreatic cancer supported by the synergy of gemcitabine with cancer vaccines and the other positive immunomodulatory effects of gemcitabine. Even though it is reported that GV1001 may block weight loss of cancer patients and improve general condition after treatment of gemcitabine, but there are insufficient evidences so far. For this reason, we evaluate the preventive effect of GV1001 on gemcitabine-induced weigh loss in xenograft animal model. There was definite weight loss of tumor-bearing mice by the treatment of gemcitabine. However, it was recovered by the treatment of gemcitabine with GV1001. Interestingly, we found that leptin, the satiety hormone, is decreased in tumor-bearing mice by treatment of GV1001, but ghrelin, the hunger hormone, is increased. In addition, we compared skeletal muscle integrity between tumor-bearing mice upon the treatment of gemcitabine with or without GV1001. When tumor-bearing mice were treated with gemcitabine only, the decrease of skeletal muscle integrity was observed. The decrease is ameliorated by the co-treatment of GV1001. Taken together, GV1001 effectively prevents the loss of weight and skeletal muscle integrity by gemcitabine.

Keywords: GV1001, Pancreatic cancer, Gemcitabine, Cachexia

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The anti-inflammatory effect of GV1001 through down-regulation of ENO1-induced pro-inflammatory cytokines production

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GV1001 is a peptide derived from the human telomerase reverse transcriptase (hTERT) sequence and reported to have anti-cancer and anti-inflammatory effects. Enolase1 (ENO1) is a glycolytic enzyme, and its stimulation induces the production of a large amount of pro-inflammatory cytokines from concanavalin A (Con A)-activated peripheral blood mononuclear cells (PBMCs) and from ENO1-expressing monocytes and macrophages in rheumatoid arthritis (RA) patients. Therefore, this study investigated whether GV1001 down-regulates ENO1-induced production of pro-inflammatory cytokines as an anti-inflammatory peptide. From the results, it was observed that GV1001 does not affect the expression of ENO1 in both Con A-activated PBMCs and RA PBMCs. However, ENO1 stimulation increased the production of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6 which was down-regulated by pre-treatment with GV1001. Moreover, p38 mitogen-activated protein kinase (MAPK) and nuclear factor (NF)-κB were activated when ENO1 on the surface of Con A-activated PBMCs and RA PBMCs was stimulated, and they were successfully suppressed by pre-treatment with GV1001. These results suggest that GV1001 could be an effective anti-inflammatory peptide that down-regulates the production of pro-inflammatory cytokines through the suppression of p38 MAPK and NF-κB activation by ENO1 stimulation.

Keywords: Inflammation, GV1001, Enolase1, Rheumatoid arthritis, p38 mitogen-activated protein kinase, Nuclear factor -κB

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Effects of Soluble Common Gamma Chain to Collagen-Induced Arthritis: A Novel Treatment of Autoimmune Diseases by Blockading on sγc Functions

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IL-2Rγ (γc) is generally known as an essential subunit in γc cytokine signaling which is very important in development and homeostasis of immune cells. Recently, we showed that the soluble form of γc (sγc) is generated by alternative splicing and their production is enhanced in activated T cells. Moreover, we found that sγc inhibits γc cytokine signaling and enhances Th17 differentiation, consequently exacerbates an inflammation. Since Th17 cells are known to play pivotal roles in the pathogenesis of autoimmune rheumatoid arthritis (RA) disease, we have questioned whether sγc affects RA pathogenesis. Consistent with EAE model, we found that sγc overexpressing mice induced with chicken type II collagen (CIA) displayed accelerated clinical score of arthritis compared to WT with CIA. In addition, serum level of sγc was significantly increased in CIA mice compared to WT. These results indicate that sγc may contribute to exacerbate the pathogenesis of RA. It is conceivable that a blockade of sγc function potentially improves autoimmune diseases such as RA and EAE. Although sγc dimerization is more functional than monomer, the dimerization mechanism of sγc is not fully understood. To address it, we generated a mutant sγc form which cysteine (Cys) of new C-terminal residue is replaced to alanine (Ala) to confirm whether the generation of sγc homodimer is elicited by disulfide bond. Interestingly, the mutant sγc form failed to generate homodimer without DTT, while WT sγc form successfully generates dimer. This result suggests that Cys is a clearly critical factor to form the dimer structure. To further study, we are designing sγc inhibitor to block sγc functions with peptides and aptamers and then testing inhibitory effect in RA animal model. Collectively, it is expectable that new development of sγc inhibitor relieves other autoimmune diseases.

Keywords: Common gamma chain, Autoimmune disease, Collagen-induced arthritis

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Mis-Acylation of tRNAs Induces Atopic Dermatitis with Modulation of T Cell Responses

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The mouse sticky mutation which is a missense mutation in editing domain of the alanyl-tRNA synthetase gene impairs the proofreading activity during aminoacylation of tRNAs. An editing-defective tRNA synthetase induces the accumulation of misfolded proteins in the neuron which is associated with Neuro-degenerative disorder. Although the sticky mice were characterized by the rough, unkempt, sticky appearance, it is not clear whether the sticky mutation is associated with inflammatory skin disease, such as atopic dermatitis. It has been known that atopic dermatitis is elicited by orchestration with T, B and myeloid cells in which cytokine environment generated by Th2 polarization induces Ig isotype switching to IgE and interaction with activated mast cell and basophils. First of all, we thus tested the effect of tRNA aberrancies in immune cells using sticky mice. Interestingly, the LN T cell number of sticky mice was significantly reduced compared to *Sti*/+ and WT mice, while LN profiles of sticky mice were not big different from control groups. Reduced cellularity by sticky mutant results from impaired proliferation, not by impaired IL-7Rα expression and IL-7 signaling which is critical in T cell development and homeostasis. In addtion, the mutations in tRNA processing enhanced Th2 polarization, whereas inhibited Th1 and Th17 polarization, indicating that the dermatitis of sticky mice emerges in induction of skewed Th2 differentiation. Since the IgE level is important in dermitatis onset, we will examine whether the IgE level is increased in sticky mice and Th2 polarization induces Ig Isotype switching as further study. These findings indicate that disruption of translational fidelity regulates cytokine production in T cells and then mediates the acute and chronic inflammation by disrupting the Th1/Th2 balance. And this provides a novel mechanism which the alteration of tRNA pool affects Th differentiation and may cause atopic dermatitis by Th2-skewing of CD4 T cells.

Keywords: Atopic Dermatitis, IgE, Th2-Skewing, Sticky Mice

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Nrf2 Induced in Tumor Hypoxic Condition Suppresses Anti-Tumor Responses of T Cells

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The transcription factor nuclear factor-erythroid 2-related-2 (Nrf2) controls cellular redox homeostasis and displays immunomodulatory properties. Nrf2 is usually activated to protect cells from harmful conditions such as oxidative stress. Hypoxic microenvironment in solid tumors generated by their outgrowth activates Nrf2 which induces the expression of cytoprotective genes and supports continuous growth and proliferation via metabolic reprogramming. It is easy to imagine that hypoxic situation may affect function of immune cells infiltrated into tumor mass. We have thus questioned how hypoxic condition affect T cell immune response against tumor and the role of Nrf2 is involved. First, tumor infiltrating T cells were sorted from tumor mass to investigate the alteration of Nrf2 expression. Interestingly, we found that mRNA levels of Nrf2 are significantly increased in T cell of TILs compared to draining LN T cells and T cells from non-tumor WT mice. In order to test whether T cell responses are affected by Nrf2 levels, we stimulated T cells and measured Nrf2 expression. Nrf2 mRNA and protein levels are significantly downregulated by TCR activation, indicating that Nrf2 may negatively regulate T cell responsiveness. To further confirm the role of Nrf2 in T cell responses, we used Nrf2 deficient mice which have normal T cell development and homeostasis. Expectedly, IFN-γ production in activated T cells was dramatically enhanced in the absence of Nrf2, indicating that Nrf2 can modulate various functions of T cells, specifically their ability to express cytokine. There has been mounting evidence exhibiting the positive role of Nrf2 in cancer protection and how it is an essential transcription factor in protecting from oxidative stress-related diseases such as cancer. Our findings offer novel insights into how immune response and oxidative stress is integrated in tumor cells, and we highlight Nrf2 as candidate of molecular target to control tumor in hypoxic condition.

Keywords: NF-E2-related factor 2, Hypoxic condition, Anti-tumor responses, T cell respones

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Studies on A Novel Regulatory Mechanism of γc Expression in Activated T Cells

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The common γ chain (γc) is necessary to signal γc cytokines, including interleukin (IL)-2, -4, -7, -9, -15, and –21. The signals of these cytokines phosphorylate Janus Kinase (JAK) and subsequently signal transducer of activator of transcription (STAT) proteins. Activated STAT proteins are involved in development, proliferation and survival of immune cells as a transcription factor. γc deficiency leads to X-linked severe combined immunodeficiency (X-SCID). Although γc is an indispensable receptor in immune system, its regulatory mechanism is still not unveiled. We found that the level of γc expression on EL4 cells, T cell lymphoma cell lines, is increased upon stimulation with PMA and ionomycin that mimic T-cell receptor (TCR) signaling. It suggested γc expression might be regulated by TCR signaling. The up-regulation of γc mRNA expression was inhibited in the presence of cyclosporin A (CsA). These results implied that γc expression was transcriptionally regulated. Transcription factor mainly related with TCR signaling is a nuclear factor of activated T cells (NFAT). By measuring γc promoter activity with luciferase assay, we identified critical NFAT binding sites on γc promoter with different combinations of γc promoter region by serially deleted construct. In order to further directly confirm, we will test whether NFAT actually binds on γc promoter regions using ChIP assay. We will additionally investigate the level of γc expression with NFAT deficient T cell stimulated by anti-CD3 antibody. Because γc family cytokines are related to many autoimmune diseases and cancers, our studies about regulatory mechanism of γc provide therapeutic benefits on these fatal diseases.

Keywords: Common γ-chain, NFAT, EL4 cell lines, TCR signaling

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Paradoxical Effects of human Adipose Tissue-derived Mesenchymal Stem Cells on Progression of Experimental Arthritis in SKG mic

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We evaluated the therapeutic effect of human adipose tissue-derived mesenchymal stem cells (hAd-MSCs) in a SKG arthritis model, a relevant animal model for human rheumatoid arthritis. hAd-MSCs were administered intraperitoneally into the mice for five consecutive days from on day 12 or 34 after arthritis induction, when the average clinical score was 0.5 or 5, respectively. They remarkably suppressed arthritis when administered on day 12. Disease suppression was correlated with reduction of proinflammatory cytokines and with increased levels of TGF-β and IL-10 from splenocytes. However, when hAd-MSCs were administered on day 34, the clinical scores were not improved, the histopathological scores were aggravated, and cytokine profiles were differed. Thus, hAd-MSCs showed paradoxical effects, according to the disease phase when they were administered. These suggest that the same cells acted differently depending on the disease progress, and cautions should be paid for safe and effective use of MSCs.

Keywords: Human Mesenchymal Stem Cell, Arthritis, SKG mouse, Immunosuppression, Immunostimulation

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Protective Effects of Rice Prolamin Extract Against DNCB-induced Atopic Dermatitis in Mice

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Rice prolamin has been reported to exert antioxidative, anti-inflammatory and immune-promoting activities. This study is aimed to examine the protective effects of dietary rice prolamin extract (RPE) against dinitrochlorobenzene (DNCB)-induced atopic dermatitis (AD)-like skin lesions in mice. BALB/c mice were fed diet supplemented with 0-0.1% RPE for 6 weeks. For the last 2 weeks the back skin of mice was applied repeatedly with 1 or 0.2% DNCB to induce AD-like lesions. Following AD induction, the severity of skin lesions was examined macroscopically and histologically. Also, the serum levels of IgE, IgG1 and IgG2a were determined by ELISA, and the skin IL-4 and IFN-γ mRNA expressions were determined by real-time PCR. Dietary RPE suppressed the clinical symptoms of DNCB-induced dermatitis as well as its histopathological changes such as epidermal hyperplasia and infiltration of mast cells and eosinophils in the dermis. RPE treatment also suppressed the DNCB-induced increase in transepidermal water loss. Dietary RPE was shown to inhibit the DNCB-induced enhancement of serum IgE and IgG1 levels, whereas it raised the serum IgG2a level in DNCB-treated mice. In addition, dietary RPE upregulated the INF-γ mRNA expression and downregulated the IL-4 mRNA expression in the DNCB-treated mouse skin. The above results suggest that dietary RPE exerts a protective effect against DNCB-induced AD in mice via upregulation of Th1 immunity and that RPE may be useful for treatment of AD patients.

Keywords: Dietary rice prolamin extract, Atopic dermatitis, Interferon-gamma

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Indole-3-carbinol inhibits renal fibrosis via attenuation of interstitial proliferation

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Renal fibrosis is the ultimate feature of chronic kidney disease and the common cause of renal failure. Because interstitial proliferation play a crucial role during the pathogenesis, the developments of strategies that inhibits this process is therefore important. We evaluated the effects of Indole-3-carbinol (I3C), a nutritional component derived from cruciferous vegetables, on mouse model of renal fibrosis, which were administrated with Unilateral ureteral obstruction(UUO), and on fibroblast proliferation in vivo. C57/BL6 mice were randomly divided into 3 groups: sham operation, UUO and UUO/I3C(200mg/kg/day intraorally for 7 days after operation). The mice were sacrificed on postoperative day 7, and kidney weight, kidney injury score, and interstitial fibrosis index were determined. To confirm whether the I3C exerted its activity on myofibroblast, which is the main source of interstitial collage deposition, double immunofluoscence study using antibodies against Ki-67 (proliferation marker) and alpha-smooth muscle actin(myofibroblast marker) was performed. Finally we evaluated whether the anti-fibrotic effects of I3C were occured by inhibition of AKT-GSK3-CREB pathway and subsequent cell cycle arrest in mouse embryonic fibroblast cells, 3T3, which were further differentiated into myofibroblast type by TGF-beta. Kidney size and weight was not altered, the extent of kidney injury and interstitial fibrosis in histological study were significantly attenuated by I3C treatment. By double immunofluorescence study, we demonstrated that fibroblast-myofibroblast differentiation and proliferation were suppressed by I3C. Mechanistically, I3C significantly inhibited the AKT-GSK3-CREB pathway thereby induced the cell-cycle arrest at G0/G1 phase of the differentiated into myofibroblast type. Collectively, we concluded that I3C treatment attenuated interstital fibrosis in animal model induced by UUO at least in part, through inhibition of myofibroblast proliferation.

Keywords: Indole-3-carbinol, Renal fibrosis, Unilateral ureteral obstruction, Anti-proliferation

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Osr1 interacts synergistically with Wt1 to regulate metanephric mesenchyme specification and nephron endowment

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Renal hypoplasia is a common cause of pediatric renal failure and several adult-onset diseases. Recent studies have associated a variant of the *OSR1* gene with reduction of newborn kidney size and function in heterozygotes and neonatal ethality with kidney defects in homozygotes. How OSR1 regulates kidney development and nephron endowment is not well understood, however. Here we show that, while *Osr1* heterozygous mice exhibit normal kidneys, most mice heterozygous for both *Osr1* and *Wt1* null alleles exhibit defects in metanephric kidney development, including unilateral or bilateral kidney agenesis or hypoplasia. The developmental defects in the $Osr1^{+/-}Wt1^{+/-}$ mouse embryos were detected as early as E10.5, during specification of the metanephric mesenchyme, with the $Osr1^{+/-}Wt1^{+/-}$ mouse embryos exhibiting significantly reduced $Pax2^{+}$ nephron progenitor cells. Moreover, expression of Gdnf, the major nephrogenic signal for inducing ureteric bud outgrowth, was significantly reduced in the metanephric mesenchyme in $Osr1^{+/-}$ $Wt1^{+/-}$ embryos in comparison with the $Osr1^{+/-}$ or $Wt1^{+/-}$ littermates. By E11.5, as the ureteric buds invade the metanephric mesenchyme and initiate branching morphogenesis, kidney morphogenesis was histomorphologically impaired in the $Osr1^{+/-}Wt1^{+/-}$ embryos in comparison with the $Osr1^{+/-}$ or $Wt1^{+/-}$ embryos. These results indicate that Osr1 and Wt1 act synergistically to regulate nephron endowment by controlling metanephric mesenchyme specification during early nephrogenesis.
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Keywords: kidney, nephron endowment, renal agenesis, renal hy-

poplasia, Osr1, Wt1

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Methionine sulfoxide reductases (Msrs) play an important role on ischemia/reperfusion injury in mouse kidney

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Renal ischemia/reperfusion is a major cause of acute kidney injury (AKI). I/R induces disruptions of tubular epithelial cells, resulting in renal functional impairments and progressive fibrotic changes in the kidney. Kidney tubular segments present different susceptibility to ischemia/reperfusion (I/R) injury which is associated with oxidative stress. Methionine sulfoxide reductases (Msrs) play antioxidant scavengers by reversing the oxidation of S-form or R-form methionine and protects kidneys against I/R injury. In the present study we investigated the role of Msrs on kidney I/R injury. In normal kidney, MsrA expressed in the cytosol, nucleus and mitochondria. MsrA expression levels were the cortex, the outer medulla (OM), the inner medulla (IM) in the order. The expression of MsrA in proximal tubules (PTs) was greater than in the distal tubules (DTs). However MsrB1 expression levels were highest in OM, modest in cortex and lowest in IM. The expression of MsrB1 in collecting ducts (CDs) and DTs was greater than PTs. I/R induced decreases of MsrA and MsrB1, B2 and B3 expressions. In consistency with the decreases of Msrs expression, MsrA and MsrBs activities also decreased 24 h after 30 min of ischemia. MsrA gene deletion worsened kidney I/R injury, but, MsrB1 gene deletion did not. These results indicate that renal I/R injury decreases Msrs activity and expression in the kidney, suggesting that the MsrA plays a critical role on kidney I/R injury.

Keywords: Acute kidney injury, Ischemia/reperfusion, Methionine sulfoxide reductases

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P101

Hydration status affects osteopontin expression in the rat kidney

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Purpose: Osteopontin (OPN) is a secretory protein that plays an important role in urinary stone formation. Hydration status is associated with the development of urolithiasis. The purpose of this study was to examine the effect of dehydration and hydration on OPN expression in the rat kidney. **Methods:** Animals were divided into three groups: control, dehydrated, and hydrated. Kidney tissues were processed for light and electron microscope immunocytochemistry, *in situ* hybridization, and immunoblot analysis. **Results:** Dehydration induced a significant increase in OPN protein expression whereas increased fluid intake induced a decrease in protein expression. Under control conditions, OPN protein and mRNA expression was detectable only in the descending thin limb (DTL). Dehydration induced increased expression in the DTL and the development of detectable expression in the thick ascending limb (TAL). In contrast, after hydration, OPN expression levels declined to less than the controls in the DTL; no expression of either protein or mRNA was detectable in the TAL. Immunoelectron microscopy demonstrated that hydration status altered tubular ultrastructure and intracellular OPN expression in the Golgi apparatus and secretory cytoplasmic vesicles. **Conclusions:** These data identify that changes in oral fluid intake can regulate renal tubular epithelial cell OPN expression.

Keywords: Osteopontin, Tubular epithelial cells, Renal stone, Hydration

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Autophagy Deficiency in Tubular Epithelial Cells Deteriorate Renal Fibrosis Through Epithelial-Mesenchymal Transition

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Aim: Epithelial-mesenchymal transition (EMT) is a process by which injured renal tubular epithelial cell undergo a phenotypic conversion into mesenchymal cell and an important pathway to generation fibroblast in renal fibrosis. Autophagy is a cellular process of degradation of damaged cytoplasmic components and regulates cell death or proliferation. It is unclear whether autophagy plays a role in TGF-β induced tubular EMT. In this study, we investigated the role of autophagyin TGF-β induced tubular EMT and renal fibrosis induced by UUO by using conditional knockout mice in which Atg7 is genetically ablated specifically in tubular epithelial cell. **Methods:** Atg7-floxed mice were crossed with Ksp-Cre mice to generate tubular-epithelial cell-specific Atg7 knockout mice ($Atg7^{flox/flox}$;$Ksp\text{-}Cre^{+}$). Unilateral ureteral obstruction (UUO) was performed and mice were sacrificed 3, 7 and 14 days after UUO. **Results:** In vitro, TGF-β treatmentinduced autophagy. In vivo, after UUO, tubular cell apoptosis and renal fibrosis were markedly more induced in $Atg7^{flox/flox}$;$Ksp\text{-}Cre^{+}$ than in wild-type mice. The expression of TGF-β was more increased in $Atg7^{flox/flox}$;$Ksp\text{-}Cre^{+}$ than in wild-type mice. The expression of E-cadherin was more decreased and the expression of α-smooth muscle antibody and vimentin were more increased in Atg7flox/flox;Ksp-Cre+ than in wild-type mice. **Conclusions:** Our data suggest that tubular-epithelial cell specific deletion of Atg7 increased apoptosis of tubular epithelial cells and expression of TGF-β and enhanced renal fibrosis via tubular EMT after UUO.

Keywords: Autophagy, Fibrosis, EMT, TGF-β

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Notch Pathway Regulate Renal Fibrosis Through TGF- β Induced Epithelial-Mesenchymal Transition

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Aim: Notch signaling pathway is involved in cell fate specification and plays critical role in kidney development and development of renal fibrosis. Mind bomb-1 (Mib1) encodes an E3 ubiquitin ligase required for theinitiation of Notch signaling. Recent study showed that the renal collecting duct plays an important role in renal fibrosis. In this study, we investigated the role of E3 ubiquitin ligase in renal fibrosisby using conditional knockout mice in which Mib1 is genetically ablated specifically in renal collecting duct epithelial cell. **Methods:** Mib1-floxed mice were crossed with aquaporin (AQP) 2-Cre mice to generate principal cell-specific Mib1 knockout mice ($Mib^{flox/flox}$;$AQP2\text{-}Cre^{+}$). Unilateral ureteral obstruction (UUO) was performed and mice were sacrificed 3, 7 and 14 days after UUO. **Results:** After UUO, we observed the decreased expression of AQP2 in wild-type (WT) mice, which was substantially decreased in the $Mib^{flox/flox}$;$AQP2\text{-}Cre^{+}$ mice compared to those of UUO-kidneys of WT mice. Renal fibrosis were markedly more induced in $Mib^{flox/flox}$;$AQP2\text{-}Cre^{+}$ than in WT control mice. The expression of TGF-β was more increased in $Mib^{flox/flox}$;$AQP2\text{-}Cre^{+}$ than in WT control mice. The expression of E-cadherin was more decreased and the expression of α-smooth muscle antibody and vimentin were more increased in $Mib^{flox/flox}$;$AQP2\text{-}Cre^{+}$ than in WT control mice. **Conclusions:** Our data suggest that renal collecting duct principal cell specific deletion of E3 ubiquitin ligase increased expression of TGF-β and enhanced renal fibrosis via epithelial-mesenchymal transition after UUO.

Keywords: Notch, Fibrosis, EMT, TGF-β

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연령에 따른 사구체경화의 증가: 사체 콩팥을 이용한 연구

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여러 요인으로 인하여 사구체경화의 증가는 콩팥의 기능저하와 직접적인 연관을 갖는다. 정상적으로도 연령의 증가에 따라 경화되는 사구체의 수가 증가하는 것으로 몇몇 인종에서 보고된 바 있다. 그러나 한국인을 대상으로는 보고된 바 없기에 본 연구에서 가톨릭의과대학에 기증된 시신을 대상으로 콩팥에서 사구체 경화의 양상을 조사하였다. 연구에 사용한 시신은 선행사인 및 직접사인에서 당뇨병, 고혈압, 만성신부전 등으로 기재된 시신을 제외한 총 57구로서, 남성 37구 (54세~92세) 여성 20구 (67세~93세)였다. 콩팥의 일부를 절취하여 파라핀 조직을 작성한 후, H-E 염색, PAS 염색 및 Masson's trichome 염색을 시행하여 광학현미경으로 관찰하여, 사구체가 거의 유리화 또는 섬유화된 것을 경화된 것으로 판정하였다. 57개의 시료에서 총 8636개의 사구체를 관찰하였다. 통계처리는 MS사의 Excel 프로그램에서 선형회귀분석법을 사용하였다. 사구체의 크기(혈관극~요세관극)는 연령에 따른 차이는 없었으며 평균 206.88um 이었고, 경화된 사구체의 경우 191.86um 이었으나 통계적으로 유의한 차이는 없었다. 사구체경화의 빈도는 여성의 경우 60대 6.4%, 70대 14.7%, 80대 25.5%, 남성의 경우 50대 3.6%, 60대 8.5%, 70대 14.9%, 80대 23.5%, 90대 27.9% 이었다. 성별에 다른 차이는 없었고, 연령에 따라 사구체의 경화가 유의하게 증가하였다. 경화된 사구체는 겉질바깥층 (outer cortex)에 52.8%, 중간층에 28.3%, 겉질속층 (inner cortex)에 18.9% 의 빈도로 존재하였다. 연령이 증가할수록 사구체경화가 겉질바깥층에서 주로 발생함을 시후하였다.

Keywords: Aging. Kidey. Human. Glomerulosclerosis. Korean

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P105

혼합자기장검출법(Frequency Mixing Magnetic Detection; FMMD)을 이용한 In vivo ROS측정

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활성산소종을 측정하는 방법에는 크게 생화학적 방법을 이용한 접근법과 전자기스핀공명을 이용한 분광법이 있으며, 이들은 현재 가장 널리 이용되고 있는 분석법이다. 이런 방법들은 생체에서 병리 조직을 절취하여 in vitro상에서 측정하는 방법들로, 살아있는 생명체내에서의 발생하는 ROS 발생 여부를 측정할 수 없는 한계를 가지고 있다. ROS는 free radial 형태의 산소를 기본으로 하는 물질로 비공유전자쌍을 갖아 magnetic property를 형성한다. 그리고 혼합전자기장검출법(Frequency Mixing Magnetic Detection; FMMD)은 다른 두 개의 파장에 의해 형성되는 magnetic field에서 특정 물질이 가지고 있는 magnetic material을 측정하는 검출법이다. 따라서 FMMD를 이용하여 특정 물질에서 생성되는 ROS를 측정하는 것이 가능하다. 연구자들은 FMMD를 이용한 ROS 검출법이 가능한지 여부, 그리고 생체 조직에서의 ROS 검출이 가능한 지 여부를 확인함으로써, 앞으로 본 시스템의 생체 적용 가능성을 검토하고자 본 연구를 실시하였다. 소규모 FMMD 장비를 제작하여 superoxide와 hydroxy radical을 생성할 수 있는 화합물로 FMMD를 이용해 free radical 측정이 가능함을 확인하였다. 그리고 생체 조직에서 생성되는 ROS를 FMMD를 이용하여 측정할 수 있는지 확인하기 위해 중추신경계에서 ROS를 생성 분비하는 주요 세포로 잘 알려진 활성 미세아교세포를 쥐 뇌로부터 분리하여 측정해 대조군과 유의한 신호차이를 분석해 낼 수 있었다. 그리고 생체 조직에서의 측정 가능성을 확인하기 위하여 2차원으로 측정 가능한 FMMD 장비를 제작하여 paramagnetic 성질을 지닌 호일을 이용하여 주위 blank와는 비교되는 신호를 얻을 수 있었고, python program을 이용하여 2차원 영상을 얻어 FMMD 장비로 paramagnetic한 성질을 측정 할 수 있다는 사실과 생체 시료를 이용한 실험 또한 가능하다는 것을 생각할 수 있었다. 체내 여러 병리상황에서 활성산소종의 생성은 그 병인과 무관하게 나타나는 매우 일반적은 현상이다. 특히 알츠하이머병이나 파킨슨병과 같은 퇴행성뇌질환에서 역시 병변 부위에서의 ROS 생성이 확인된다. 따라서 FMMD와 같은 장비를 이용하여 현재 MRI를 촬영하듯 비침습적으로 간단히 인체를 촬영하고 ROS 생성 여부 및 부위를 감별할 수 있다면 여러 질환의 조기 진단 및 예방에 유용하게 이용될 수 있으리라 기대된다.

Keywords: 활성산소종, 혼합전자기장

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MDM2 E3 Ligase-mediated Ubiquitination of HDAC 1 in Vascular Calcification

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Vascular calcification (VC) often associates with many cardiovascular and metabolic diseases. Although VC is the cause of high morbidity and mortality, molecular mechanisms have yet to be elucidated. Here we report that MDM2-induced ubiquitination of histone deacetylase 1 (HDAC1) mediates VC. Loss of HDAC1 activity enhanced VC in vivo and in vitro. HDAC1 protein was reduced in cell and animal calcification models and in human calcified coronary artery. Calcification stresses induced MDM2 E3 ligase, which resulted in HDAC1 K74 ubiquitination. Forced expression of MDM2 enhanced VC, whereas loss of MDM2 blunted it. Both a decoy peptide spanning HDAC1 K74 and an MDM2 inhibitor prevented VC. These results demonstrate a previously unknown ubiquitination pathway as well as the involvement of HDAC1 in VC. Our results suggest MDM2-mediated HDAC1 ubiquitination as a new therapeutic target in VC.

Keywords: Vascular calcification, HDAC1, Ubiquitination, MDM2

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Effect of Ethanol Extract of Ceramium kondoi on Hypopigmentation and Antioxidant Activity

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This study was performed to investigate the antioxidant activities and the melanin synthesis inhibitory effects of *Ceramium kondoi* extracts. *Ceramium kondoi* was extracted with 100% ethanol. The anti-oxidative and whitening effects of extracts were determined by in vitro assays using the 1,1-diphenyl-2-picrylhydrazyl(DPPH) method and inhibitory effects of the *Ceramium kondoi* extract against collagenase and tyrosinase in B16F10 melanoma cells. The results have been revealed that *Ceramium kondoi* extract significantly reduced intracellular tyrosinase activity and melanin synthesis in B16F10 cell. Furthermore, decreased the expression of melanogenic enzymes in B16F10 cells. Additionally, *Ceramium kondoi* inhibited the α-melanocyte stimulating hormone(α-MSH)-induced. Also, *Ceramium kondoi* showed high efficacy in DPPH radical scavenging activity and collgenase activity. In conclusion, it was indicated that *Ceramium kondoi* could be utilized as whitening cosmetic ingredients.

Keywords: Ceramium kondoi, tyrosinase, melanin, melanogenesis, anti-oxidative

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P108

YAC tripeptide of EGF iInduces EGFR Clustering Through FAK-mediated Rac1-Wave2-Arp2 and RhoA-Rock2-Ezrin Signaling Axis

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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, regeneration, migration, endocytosis and clustering. Focal adhesion kinase (FAK) is an essential regulator of growth factor receptors that function as actin cytoskeleton-related network of signaling transduction proteins, including Src, cdc42, Rac1 and RhoA. Dimerization and clustering are the most important procedures in receptor tyrosine kinase activation of signaling transduction, which are modulated by actin cytoskeleton remodeling. However, molecular mechanisms underlying dimerization and clustering of receptor molecules are still unclarified. In this study, we investigated how an EGF-derived peptide called YAC tripeptide induces EGFR dimerization. Our study presents that YAC tripeptide induces the physical interaction among EGFR-Grb2-SOS-FAK-cSrc complex, which leads to FAK phosphorylation. Transfection of MCF-7 cells with either dominant negative FAK or FAK siRNA reduced EGFR dimerization and subsequent endocytosis of EGFR. YAC tripeptide enhanced the interaction of RhoA, Rac1 and cdc42 with FAK. Dominant-negative RhoA, Rac1 or cdc42 abrogated YAC tripeptide-induced endocytosis of EGFR. Moreover, it induced FAK-mediated activation of Rac1-Wave2-Arp2 and RhoA-Rock2-Ezrin axis. These results demonstrate that YAC tripeptide enhances EGFR clustering through FAK-mediated Rac1-Wave2-Arp2 and RhoA-Rock2-Ezrin signaling axis.

Keywords: Clustering, Dimerization, EGFR, FAK, YAC tripeptide

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P109

MITF- and SFRP5-derived Peptides Inhibit Melanogenesis via Suppression of MITF and Wnt activity

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Melanin is synthesized by melanocytes in skin epidermis and plays a vital protective role against the ultraviolet radiation of the solar light. UV-exposed keratinocytes secrete α-MSH, which then activates cyclic adenosine monophosphate/protein kinase A (cAMP/PKA) signaling and subsequently upregulates the expression of microphthalmia-associated transcription factor (MITF), the master regulator of melanogenesis, through phosphorylation and activation of the cAMP response element binding protein (CREB) transcription factor. On the other hand, canonical Wnt/β-catenin is activated by Wnt family of secreted glycolipoproteins and causes stabilization of β-catenin by inhibiting GSK-3β through the Wnt signalosome. Upregulated MITF and stabilized β-catenin are translocated into nucleus and bind the target genes for melanogenic enzymes including tyrosinase, tyrosinase related protein-1 (TYRP1), and tyrosinase related protein-2 (TYRP2). In present study, we investigated the effects of MITF and SFRP5 antagonist peptides on melanogenesis and its underling mechanism in vitro and in vivo. Treatment of melanocytes with the MITF and SFRP5 antagonist peptides inhibited α-MSH-induced melanin production and TYR activity. Furthermore, the MITF and SFRP5 antagonist peptides reduced expression of the melanogenic enzyme genes at both mRNA and protein levels in a dose-dependent manner. Moreover, MITF and SFRP5 antagonist peptides decreased the formation of MITF/CREB and MITF/β-catenin complexes, which led to a decrease in melanin synthesis. Collectively, these results suggest that MITF and SFRP5 antagonist peptides might be promising candidates for the treatment of melanogenesis-associated disorders.

Keywords: Peptide, Melanogenesis, MITF, Wnt, Tyrosinase

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ACT-PRESTO: Rapid and consistent tissue clearing and labeling method for 3-dimensional (3D) imaging

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Identification and exploration of detailed organization of organs or whole body at cellular level are fundamental challenges in biology. Conventionally this task has been approached by serial sections, labeling of specific targets, and the reconstitution of 2-dimensional serial images into 3-dimensional structures, processes which are not only labor-intensive and time-consuming but also can limit accuracy. The recent advent of tissue clearing techniques has revolutionized the efficacy of volume imaging mainly by elimination of tissue sectioning and reconstitution steps. However, currently available protocols for organ clearing require long process time. Herein, we present a rapid and highly reproducible ACT-PRESTO (active *c*larity *t*echnique-*p*ressure *r*elated *e*fficient and *s*table *t*ransfer of macromolecules into *o*rgans) that renders tissue or whole-body clearing within a day while preserving tissue architecture and protein-based signals derived from endogenous fluorescent proteins or by conventional immunolabeling procedure. Especially, ACT-PRESTO allows rapid antibody penetration to the dense organs by pressure-assisted delivery. Rapidity and consistency of this method will enable high-content mapping and analysis of normal and pathological elements in intact organs and bodies.

Keywords: Brain clearing, Whole-body clearing , Organ clearing, 3-dimensional structures, Immunolabeling

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Kalirin, GEF for Rac1, is implicated in FSTL-1-mediated role: impacts on myokine in glucose homeostasis

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Follistatin-like 1 (FSTL-1) is an extracellular glycoprotein and is regarded as novel myokine, however very little is known about the metabolic role in skeletal muscles. Here, we reported that FSTL-1 stimulated glucose uptake in an AMP-activated protein kinase (AMPK)-dependent manner in L6 rat skeletal muscle cells. FSTL-1 increased intracellular calcium concentration. Calcium/calmodulin-dependent protein kinase kinase (CaMKK) inhibition blocked FSTL-1-induced AMPK phosphorylation and glucose uptake. In addition, FSTL-1 stimulated the phosphorylation of p21-activated kinase (PAK1), a small GTPase Rac1 downstream protein. PAK1 knockdown or inhibition of Rac1 blocked FSTL-1-induced glucose uptake. Moreover, kalirin, a Rac1 GEF, was induced by FSTL-1. Knock-down of kalirin blocked FSTL-1-induced PAK1 phosphorylation and glucose uptake. There results suggest that kalirin, Rac1 GEF, plays an important role in FSTL-1-mediated Rac1 activation in skeletal muscle cells.

Keywords: AMPK, FSTL-1, glucose, kalirin, small GTPase

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BDNF secreted from Macrophages and MSCs Stimulates angiogenesis after Myocardial Infarction

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After myocardial infarction (MI), the heart produces new blood vessels in the infarct area by itself, and macrophages recruited to infarct sites. Recent studies indicate that blood levels of brain-derived neurotrophic factor (BDNF) are markedly elevated after MI. In this study, the authors investigated the relationship between BDNF expression and 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, infiltrating cells including macrophages expressed BDNF progressively in peri-infarct and infarct areas. Interestingly, BDNF expression in macrophages was strong at 5 and 7 days (angiogenesis period) post-ligation in MI hearts. To identify the macrophage responsible for BDNF expression, double immunofluorescence staining for BDNF and macrophage subtype markers (iNOS for M1 and Arg I for M2), and flow cytometry for BDNF and macrophage surface markers (CD 86 for M1 and CD 206 for M2) were conducted, it was found that both M1 and M2 macrophages displayed strong BDNF expression. In addition, activated macrophages were found to be located near new blood vessels during angiogenesis. These findings suggest that both M1 and M2 macrophages are sources of BDNF in MI heart, and that both activated macrophages are associated with angiogenesis in MI hearts. To elucidate the role of BDNF, we made genetically modified mesenchymal stem cells (BDNF-MSC) that specifically express BDNF with high efficiency. Secreted BDNF level in conditioned medium was dramatically increased in BDNF-MSC (5,833 pg/ml) compared with GFP-MSC (404.3 pg/ml) by ELISA. MI rats randomly received injection of 1×10^6 GFP-MSC, BDNF-MSC or PBS alone after ischemia reperfusion injury. BDNF-MSC and GFP-MSC group animals showed increased microvessel densities, smaller scar size than PBS group animals. These results suggest that BDNF secreted from macrophages and MSCs has angiogenic and cardioprotective effects in MI heart.

Keywords: BDNF, myocardial infarction, M1 macrophage, M2 macrophage, mesenchymal stem cells,

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Pre-Pubertal Exposure of High Caffeine Delays Sexual Maturation and the Development of Female Reproductive Organs in the Rats

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Recently, consumption of a lot of dietary caffeine including energy drinks has been increased. We previously showed that peri-pubertal caffeine exposure to the immature male rats interfered sexual maturation and testis growth. In this study, we examined the effects of caffeine on the sexual maturation during puberty in immature female rats. A total of 60 immature female SD rats were divided into 3 groups and received tap water (control) or water containing caffeine 120 and 180mg/kg/day via gavage for 4 and 8 weeks. Body weight and food intake were monitored daily throughout the experiment and body composition was also analyzed at the end of experiment. In order to monitor sexual maturation, vaginal opening and estrus cycle were evaluated. After sacrificed, reproductive organ weights were measured and blood samples were collected for hormone analysis. Caffeine fed groups significantly decreased body weight and amount of total body fat. Food efficiency ratio was significantly decreased in the caffeine-fed groups at the first two weeks of exposure, after then no difference was observed in the control and caffeine-fed groups. Age at vaginal opening was significantly delayed and irregular estrus cycle was more frequently observed in the caffeine-fed groups. In addition, caffeine reduced the weights of the ovary and uterus after 4 weeks of exposure, but not after 8 weeks. Caffeine increased serum estradiol as well as basal secretory activity of granulosa cells ex vivo, but no difference was noted in proportion of follicles according to the developmental stage in the control and caffeine-fed groups. These results demonstrated that pre-pubertal caffeine exposure could negatively affect reproductive organ growth and estradiol production from the ovary in immature female rat. In turn, it may delay sexual maturation by directly interfering with ovarian growth and secretory function [Supported by grants from NRF-2014R1A1A2053601].

Keywords: Caffeine; Sexual Maturation; Ovary; Estrogen; Rat

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허혈/재관류(Ischemia/reperfusion) 후 신장 세뇨관 세포의 손상과 회복 시 미세소관의 아세틸화(microtubule acetylation)의 변화

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미세소관(microtubule)을 구성하는 튜블린(tubulin)의 아세틸화(acetylation)와 같은 번역 후 변형(post-translational modification)은 세포의 분화, 분열 및 이동에 관여하여 미세소관의 역동성에 중요한 역할을 한다. 허혈/재관류(ischemia/reperfusion)는 세포의 미세소관에 손상을 일으켜, 세포의 구조 및 기능적 장애를 유발한다. 하지만 아직까지 허혈/재관류에 의한 콩팥세뇨관세포의 손상과 회복 과정과 튜불린의 아세틸화가 어떠한 관련이 있는지 보고되지 않고 있다. 따라서 본 연구에서는 신장의 허혈/재관류 손상과 회복 과정에 있어서 미세소관의 안정화에 중요한 아세틸화와 이를 조절하는 단백질의 발현 변화를 조사하였다. 8주령 수컷 생쥐의 양쪽 신장의 혈류를 30분 동안 차단하여 허혈을 유도하였고, 대조군은 혈류를 차단하지 않았다. 허혈 후 0시간, 1시간 30분, 4시간, 1, 3, 5, 9일에 신장을 취하여 실험을 진행하였다. 허혈 후 24시간 째에 acetylated-α-tubulin(ac-α-tubuin)의 발현은 가장 많이 감소하였다가 서서히 회복하였다. α-tubulin양은 대조군과 유의한 차이가 없었다. 대조군 콩팥에서 ac-α-tubulin은 근위세뇨관과 원위세뇨관보다 집합관에서 가장 많이 발현하였으며, 사구체의 혈관사이세포와 족세포에서 또한 강하게 발현하였다. 허혈 후 24시간째에서는 대조군에 비해, 근위세뇨관, 원위세뇨관과 족세포에서 ac-α-tubulin 발현이 감소하였다. 신장의 섬유화가 일어나는 허혈 후 9일 째에는 ac-α-tubulin의 발현은 근위세뇨관, 족세포와 간질 세포에서 허혈 후 24시간째 보다 증가하였다. 튜불린을 아세틸화시키는 α-tubulin acetyltransferase-1(α-TAT-1)은 허혈 후 감소하여 9일째 까지도 전혀 회복되지 않았다. 탈아세틸화에 관여하는 HDAC6의 발현은 세뇨관 세포가 손상을 가장 많이 받는 허혈 후 24시간에는 모든 세뇨관에서 현저히 증가하였다가 서서히 9일 째까지 감소하였다. 이 결과들은 tubulin acetylation이 허혈/재관류에 의한 신장 세뇨관 세포의 손상과 회복과정에 중요한 역할을 함을 보여주고 있다.

Keywords: Ischemia/reperfusion, Microtubule, Tubulin, Acetylation

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P115

Oleic acid Induces Chondrocytes Apoptosis Through PKCK2 Down-regulation

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Various stimuli can favor chondrocyte death. We previously reported that PKCK2 downregulation facilitates TNF-α-induced chondrocytes death through apoptosis. Obesity has been traditionally thought of as a local risk factor that contributes to osteoarthritis (OA) through increased load and altered mechanical axis on weight-bearing joints, but obese individuals also have an increased risk of OA in non-weight-bearing joints, suggesting that soluble factors play a role in the onset and progression of OA. Our recent study showed that leptin, which is mostly increased in the blood and synovial fluid of obese patients, plays a local role in articular joint, supporting those previous reports. Free fatty acids are emerging as another risk factors for OA. In obese persons, body fluid level of free fatty acids are higher compared to control persons. Free fatty acids tend to accumulate in various cells of obese persons. A previous study demonstrating that lipid contents increase in articular cartilage as the age and body weight increase. Another recent study elucidating that a free fatty palmitate acid exerts proapoptotic and proinflammatory effects on articular chondrocytes. However, the detailed mechanism underlying chondrocytes death, in which free fatty acids are involved, has not documented yet. In the present study using cultured rat articular chondrocytes, we demonstrated that oleic acid reduced the viability of articular chodnrocytes. Multiple assays indicate that oleic acid induces lipoapotosis in rat articular chondrocytes. We further examined whether cilostazol, which was demonstrated to prevent the TRAIL-induced decrease of PKCK2 activity in articular chondro-

cytes, inhibits oleic-acid induced chondrocytes apoptosis. Importantly, we observed cilostazol completely blocked oleic acid-induced chondrocytes death by inhibiting the subcellular translocation of apoptosis-inducing factor and cytochrome c and the activation of caspases 3 and 7.

Keywords: Osteoarthritis, PKCK2, Oleic acid, Apoptosis

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P116

PCB-138 Confers Adipocytes The Resistance To TNF-α Induced Cell Death

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Polychlorinated biphenyls (PCBs) having a highly lipophilic characteristics are accumulated in adipose tissue, eventually arouse obesity, insulin resistance, diabetes, cardiovascular disease, sexual hormonal imbalance, and cancers. Previous studies showed that PCBs induce increased weight gain in mice and promote adipocytes differentiation. In the present study we tested the effect of PCB-138, which are commonly found around our area, on adipocytes differentiation using 3T3-L1 cell line. We observed that PCB138 exposure accelerated adipocytes differentiation. Notably, lipid droplets in PCB treated adipocytes tend to coalesce in producing mega lipid droplets. Based on these findings, we postulated that PCB exposure during differentiation would confer mature adipocytes the resistance to TNF-α induced cell death, inducing the number of adipocytes *in vivo*. For validating our hypothesis, we examined whether PCB-138 modulates cell death in adipocytes treated with TNF-α. We observed that PCB-138 exposure inhibits the reduction of viability and the cleavage of caspase 3. zVAD-fmk, a pan-caspase inhibitor, abolished the difference in cell viability between control group and PCB-138 exposure group, indicating that PCB-138 blocks cell death through inhibiting caspase 3 activation. Annexin V and PI assay showed that PCB-138 blocked apoptosis in particular, not necroptosis. We also observed the decrease of JNK phosphorylation and SOCS3 expression level in PCB-138 exposure group. In contrast, cIAP1 expression level was increased in PCB-138 exposure group. We further examined whether curcumin, a main component of curry powder having an anti-inflammatory, antioxidant and anticancer properties, exerts apoptosis-inducing activity even in adipocytes exposed to PCB-138. Importantly, curcumin efficiently induced cell death even in in adipocytes exposed to PCB-138, suggesting the possibility of curcumin as a treatment strategy in obesity induced by PCB exposure.

Keywords: Adipocytes, PCBs, Tumor necrosis factor-α

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P117

Resisitn, a novel adiopocytokine, promotes metastasis of MDA-MB-231 human breast cancer cells through ERM activation

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Resistin, an adipocyte-secreted factor, is known to be elevated in breast cancer patients. However, the molecular mechanism by which acts was not fully elucidated. Here, resistin increased the invasion and migration of MDA-MB-231 breast cancer cells. Resistin increased the phosphorylation of a member of the ezrin, radixin, and moesin (ERM) protein family in in Ca^{2+}-dependent manner. Phosphorylation of Src was increased by resistin and BAPTA-chelation of intracellular Ca^{2+} blocked resistin-mediated activation of Src, suggesting that resistin increased the activity of Src by increasing Ca^{2+} release. In addition, resistin induced the phosphorylation of PKCα by inhibiting the activity of PP2A. Inhibition of PKCα decreased the phosphorylation of ERM and the interaction between ERM and PKCα was increased by resistin, suggesting that ERM is downstream target of PKCα. Moreover, knockdown of ERM abrogated resistin-induced invasion and migration. Resistin-induced expression of vimentin, key molecule for invasion, also down-regulated by ERM knocks down. Taken together, our results suggest that activation of ERM by resistin induces cell invasion and migration through the signaling pathway to cytoskeletal dynamics in breast cancer cells.

Keywords: Resistin, Invasion, Breast cancer, ERM, Signal transduction

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P118

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.

Keywords: Development, Vitamin C, Pregnancy, Fetal growth

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거꾸로 학습을 이용한 해부실습

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해부학 교육에서 강의와 실습 시간의 감소로 교육의 효율성을 높이기 위한 다양한 방법들이 고안되고 있다. 특히 해부실습은 학생들이 많은 시간과 노력을 투자하는데 비해 지식을 응용할 수 있는 수준까지 도달하는데 많은 어려움이 있다. 최근에 도입되고 있는 거꾸로 학습 이론을 해부실습에 도입하였다. 1) 먼저 해부실습 동영상과 해부실습 매뉴얼을 이용하여 실습 전 사전학습을 하고, 2) 실습 전에 예 • 복습시험 (퀴즈형태)을 실시하고, 3) 실습과정에서는 조원 별 역할 분담과 지정한 구조물을 표시하게 하였다. 4) 실습 평가는 실습 그 다음날 표시한 구조물이 정확한지를 평가하여 다음 실습시간에 점수를 공지하여 환류 하였다. 해부실습 중간인 10회를 마치고 모든 학생을 대상으로 on-line으로 사전학습과 동료평가에 대하여 설문지 (Likert 5단계 평가, 1: 전혀 아니다, 2: 아니다, 3: 보통이다, 4: 그렇다, 5: 매우 그렇다)로 조사하여 그 내용을 분석하고, 예 • 복습시험 및 조별 평가의 성적과 비교하였다. 실습 전에 동영상과 실습 매뉴얼을 이용한 사전학습에 대한 만족도는 4.2였으며, 사전 학습에 투자한 시간은 72.6%의 학생이 1~3시간이었으며, 동영상 시청 횟수는 64.1%가 1~2회였다. 해부실습 후에 인체의 부위에 대한 이해도 향상은 3.7이였다. 시험 성적은 실습과정의 주도적 참여 정도 및 달성 수준과 유의한 상관관계가 있었으며, 사전 학습과 실습과정의 관련성은 사전학습의 만족도와 실습의 집중도, 흥미도와 이해도 향상, 동영상 시청 횟수와 주도적 실습참여 사이에 유의한 상관관계를 보였다. 요약하면 사전 학습은 학생들이 높은 만족도를 보였으며, 예 • 복습시험, 주도적 실습 참여, 구조물에 대한 이해 수준의 향상, 흥미와 이해도 향상에 기여하였으며, 실습과정에서 변이의 발견 건수가 예년에 비하여 증가하여 학생들이 보다 해부실습에 집중하는 것으로 생각하였다. 따라서 해부실습 전에 해부실습 동영상을 이용한 거꾸로 학습이 실습의 만족도와 효율을 높이는 방안의 하나라고 생각하였으며, 보완해야 할 내용으로는 사전 학습을 할 수 있는 시간의 확보, 해부실습 과정에서 각 부위와 관련된 응용 시험 문제를 제시하여 답안을 제출하게 하는 방안 등을 검토했으면 한다.

Keywords: 의학교육, 해부실습, 거꾸로 학습

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P120

The Effect of Botulinum Neurotoxin Type A on TGF-β1 signaling: Implications for Silicon Implants

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One of the most serious complications of breast implant is the scar and/or capsule formation. Several preventive treatment, including steroids, antibiotics and vitamin have been introduced, but the problem of capsular formation has not yet been completely resolved. We have previously identified effect of Botulinum Neurotoxin Type A (BoNT-A) on capsule contracture but mechanism remains yet. TGF-β1 signaling is one of main contributive to differentiation of fibroblast to myofibroblast, indicator of capsule contraction. Therefore, we investigated that BoNT-A on TGF-β1 signaling in the human fibroblasts. Phosphorylation of Smad2 was inhibited by BoNT-A (5U) treatment. The expression of collagen Type1 α1, 1 α2 and Type 3 were inhibited by treatment of BoNT-A, while MMP2 and MMP9 were enhanced. Gelatin zymography experiments confirmed enhanced MMP2 activity on collagen degradation. Finally, BoNT-A treatment reduce capsule thickness and phosphorylation of Smad2 in silicone-implant to rat hypodermis. Taken together, our data suggest that BoNT-A has the potential to prevent differentiation of fibroblast to myofibroblast through TGF-β1 signaling and BoNT-A has an important role in inhibition of capsule formation after breast implant surgery.

Keywords: Botulinum Toxin A, Fibroblast, Capsule formation

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P121

Ethanol-extract of Antirrhinum majus Linne improves and prevents menopausal symptoms in preclinical research

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Many natural substances were screened to develope nutraceutical reducing menopause symptoms. Fortunately, Antirrhinum majus Linne extracts exerted significant positive effects. Under low concentration of estrogen representing postmenopausal physiological conditions, the Antirrhinum majus Linne extracts made MCF-7 cells healthy by way of enhancing estrogen activity reversibly. Specially, Antirrhinum majus Linne extracts induced the activation of estrogen receptor-alpha (ERα) by increasing of ERα expression and phosphorylation. Also, in rat models taken ovariectomy, the changes of bone-specific alkaline phosphatase activity and osteocalcin as well as LDL-cholesterol and triglyceride levels were significantly reduced by Antirrhinum majus Linne extracts. These results represent that Antirrhinum majus Linne extracts protected bone health and reduced metabolic disturbance. So, it is plausibly suggested that the Antirrhinum majus Linne extracts is prefer natural substance remedying menopausal symptoms including colpoxerosis with safe.

Keywords: Antirrhinum majus Linne extracts, menopause, MCF-7 cells, ovariectomized rat

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Influence of Thymus vulgaris L. on the proliferation of estrogen receptor-positive MCF-7 cell line

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This study examined the influence of *Thymus vulgaris* L. extract on estrogen-induced proliferation of estrogen receptor-positive breast cancer cells by using the MCF-7 human breast adenocarcinoma cell test system. The influence of *Thymus vulgaris* L. extract on the proliferation of the MCF-7 cells was determined using the alamar blue assay. 17β-estradiol (0.01–100 nM) induced cell proliferation in MCF-7 cells at concentrations of 1, 5 and 10 nM without cytotoxic activity. An ethanol extract of *Thymus vulgaris* L. slightly increased cell proliferation, but the increase in cell proliferation was not statistically significant. However, the *Thymus vulgaris* L. extract significantly increased cell proliferation in combination with 17β-estradiol. These findings suggest that *Thymus vulgaris* L. extracts may provide a safe, natural remedy for menopause by increasing the sensitivity of 17β-estradiol response on estrogen receptor-positive cells.

Keywords: MCF-7 cell, menopause, Thymus vulgaris L., proliferation assay

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Tristetraprolin Suppresses VEGF mRNA Stability Induced by Hypoxia in ARPE-19 Cells

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The anti-neovascular effect of monoclonal anti-VEGF antibodies such as Ranibizumab and bevacizumab has been revealed by many studies. However, multiple treatments were required and some patients did not respond to intravitreal anti-VEGF antibodies injection. There are recently several efforts to overcome these limitations. VEGF transcription is activated by hypoxia factor. VEGF transcripts contain AU-rich elements (AREs) within their 3′ untranslated regions (3′ UTR), which determine mRNA stability. ARE-mediated post-transcriptional regulation is facilitated by trans-acting ARE-binding proteins, which form stable complexes with the 3′ UTR and regulate the stability of VEGF mRNA. Therefore, the relative abundance of these ARE-binding proteins determines the levels of VEGF transcripts. Tristetraprolin (TTP) is a 34kDa member of the CCCH class of tandem zinc finger proteins and one of the ARE-binding proteins. Since TTP was first shown to interact with the ARE of mRNA, and its list of known and likely mRNA targets continues to grow. As far as we know, there is no study about the effects of TTP in a human retinal epithelial cell line (ARPE-19 cells).
The aim of the present study is to investigate the effects of tristetraprolin (TTP) on VEGF mRNA and VEGF protein in ARPE-19 cells under hypoxic condition and to consider the possibility of TTP as a new treatment tool for AMD

Keywords: Tristetraprolin, VEGF, ARPE-19 cells, Hypoxia, Neovascularization

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Fermentation with *Lactobacillus Plantarum* P1201 Increases the Anti-obesity Effect of Soybean in 3T3-L1 Adipocyte

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Obesity has become a global health problem and a source of major metabolic diseases like type-2 diabetes, hypertension, heart disease, nonalcoholic fatty liver and cancer. Synthetic anti-obesity drugs are effective but very costly and with undesirable side effects, so

natural products such as soybean are needed as an alternative for obesity treatment. *Lactobacillus Plantarum P1201* is a probiotic bacterial strain reported to produce conjugated linoleic acid (CLA) and increase the ratio of aglycone-isoflavone of soybean, both of which have anti-obesity effect. In this study, the anti-obesity effect of the fermented soybean extract with P1201 (FSE) will be evaluated compared with that of the soybean extract (SE) by 3T3-L1 cells as an *in vitro* model of adipogenesis. 3T3-L1 cells were treated with SE and FSE during the nine days of the differentiation, lipid accumulation was evaluated by oil-red staining and triglyceride content, and the mRNA expression level of adipogenic or lipogenic genes were analyzed by RT-PCR and qPCR. The results showed that formation of lipid droplets in differentiated 3T3-L1 cells was inhibited and triglyceride content was reduced by 23.1% after treated with 1000 μg/mL of FSE compared with control. For SE-treated groups, no delipidating effect was observed. The effect of FSE on adipogenesis inhibition can be attributed to the down-regulation of mRNA expression of CCAAT/enhancer binding protein (C/EBP-α), lipoprotein lipase (LPL), adiponectin, adipocyte fatty acid-binding protein (aP2), fatty acid synthesis (FAS) and CoA carboxylase (ACC). Our results demonstrated that the anti-obesity effect of soybean can be improved by fermentation with P1201, and P1201can be used as a potential probiotic bacterial strain to produce natural anti-obesity food.

Keywords: Obesity, Lactobacillus Plantarum, Soybean, Fermentation, Adipocyte

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Polychlorinated Biphenyls (PCB-118 and -138) Promotes Adipocyte Differentiation and Induces Insulin Resistance via Lipid Droplet Growth in 3T3-L1 Adipocytes

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Polychlorinated biphenyls (PCBs) are persistent environmental pollutants that are found at elevated concentrations in the adipose tissue of contaminated organisms. Although recent epidemiological studies associate PCBs to the development of obesity and its related metabolic disorders such as diabetes, how these compounds interfere with metabolic regulation remains poorly understood. Adipose tissues, which are preferential sites for PCB accumulation, are characterized by their large lipid droplets (LDs). The LD is an important subcellular organelle responsible for lipid storage. Excess lipid storage in adipose tissue results in the development of obesity and other metabolic disorders such as insulin resistance or diabetes. Thus, LD size correlates with the susceptibility to insulin resistance and diabetes. In this study, we examined effects PCB-118 (*dioxin*-like PCBs) and PCB-138 (Non-*dioxin*-like PCBs) on adipocyte differentiation, LD growth and insulin resistance in 3T3-L1 adipocytes. We found that exposure of preadipocytes to PCBs resulted in significant promotion in their subsequent ability to fully differentiate into mature adipocytes. Also, exposure of both preadipocytes and mature adipocytes to PCBs significantly increased the LD size. Fat-specific protein 27 (Fsp27), which is localized to LD-contact sites and promotes LD fusion and growth, increased in PCBs-treated 3T3-L1 adipocytes. Not only depletion of Fsp27 by siRNA resulted in the inhibition of LD growth and attenuation of insulin resistance in PCBs-treated 3T3-L1 adipocytes, but an antidiabetic drug, metformin reduced not only expression of Fsp27 protein but also LD size and attenuated insulin resistance in PCBs-treated 3T3-L1 adipocytes. These findings indicate that PCBs modulate LD growth through Fsp27. In conclusion, PCB-118 and PCB-138 may contribute to the development of obesity through accelerating adipocyte differentiation and induce insulin resistance via LD growth.

Keywords: Polychlorinated Biphenyls (PCB), Adipocyte Differentiation, Insulin Resistance, Lipid Droplets, Fsp27

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CTCF negatively regulates the retinoic acid induced Hoxa5 in F9 teratocarcinoma cells

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Hox genes are essential for anterior-posterior body patterning at early stage embryonic development. In mammals, 39 *Hox* genes are divided into four cluster called *HoxA, B, C* and *D* on four different chromosomes. The combinatorial expression of *Hox* genes plays important role in the process of mammalian development. Especially, *Hox* genes are expressed spatially and temporally defined order, i.e. the colinearity. However, the precise mechanisms by which signal pathways are stimulated to regulate the collinear expression of *Hox* genes are not clear. In the previous study, retinoic acid (RA) has been identified as important modulator of cell survival, proliferation, differentiation and body axis formation in the developing embryo. Interestingly, RA induces clustered *Hox* gene expression in F9 cells. Furthermore, CCCTC-binding factor (CTCF) was recently reported as a controller of *Hox* gene expression. Here we provide relationship of RA, CTCF and *Hox* genes expression in F9 teratocarcinoma cells. In order to investigate the expression pattern of *Hox* genes in response to the RA, we performed the RT-PCR in the retinoic acid treated F9 teratocarcinoma cells. The result showed that the anterior *Hoxa* genes mRNA level were up-regulated in retinoic acid treated F9 cells. However, RA induced *Hoxa5* gene expression level was decreased in CTCF over-expressed F9 cells. This experiment demonstrated that CTCF negatively associated with up-regulation of *Hoxa5* in response to retinoic acid. In addition, to investigate whether the RA regulates the CTCF binding at *Hoxa5* promoter region, we carried out the chromatin immunoprecipitation (ChIP) assay, using the antibody against mouse CTCF. When RA was present, CTCF was dissociated from the binding site near the *Hoxa5* promoter region. In conclusion, RA might regulate the expression of *Hoxa5* gene by modulating the binding of CTCF at the *Hoxa5* promoter region.

Keywords: Hox genes, Retinoic acid, CTCF

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Expression of Androgen Receptor and its Related Genes in Human Hair Follicle

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The androgen receptor (AR) is a type of nuclear receptor that is activated by binding either of the androgenic hormones, testosterone, or dihydrotestosterone. AR is expressed in the dermal papilla (DP) of the hair follicle. AR expression is known to be increased in the DP of scalp hair in androgenetic alopecia (i.e., hair loss). However, AR expression is also increased paradoxically in the DP of the beard hair growing actively. To resolve the 'androgen paradox', study on the AR isoform and the signal molecules regulating AR action are required. Gene expression of AR and AR45, an isoform of AR, was detected in the human hair bulb including the DP. Gene expression of CTBP1, regulatory genes involving action of AR, CTBP1-AS, a regulatory long non-coding RNA involving AR action, were also detected in the human hair bulb. However, the expression pattern of AR, AR45, CTBP1, and CTBP1-AS was different among the people. This data suggest that AR action may by regulated intricately by AR related genes, such as AR45, CTBP1, and CTBP1-AS in human hair follicle.

Keywords: Androgen receptor, hair follicle, AR45, CTBP1, CTBP1-AS

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Effect of BRN2 Overexpression on the Ec crine Sweat Glands in Mouse Paw

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Eccrine sweat glands regulate body temperature by secreting water including electrolytes. Eccrine sweat glands are presented in whole body skin except lips and external genitals in human. In mice, eccrine sweat glands are presented only in the paw pad. BRN2(N-Oct-3, POU3F2) is a protein belonging to a large family of transcription factors that bind to the octameric DNA sequence ATGCAAA. Aquaporin(AQP) is a water channel protein that exists in plasma membrane and allows passage of water molecule. Aquaporin 5 is located in apical area of secretory coil plasma membrane and known to have important roles in sweat secretion. The aim of this study was to investigate difference of morphology of eccrine sweat glands, expression of AQP5 and perspiration in wild type and BRN2-overexpressed mice paw. Hematoxylin-eosin staining was performed and reconstructed into three-dimensional features with a 3D reconstruction program. Immunohistochemistry for AQP5 was performed and in vivo perspiration experiment were also performed in the hind paw pad. Volume of eccrine sweat glands significantly decreased in the BRN2-overexpressed mouse, compared with wild type mouse. However, the intensity of AQP5 immunoreactivity seems to be higher in the BRN2-overexpressed mouse than wild type mouse. Perspiration in hind paw pad was significantly decreased in the BRN2-overexpressed mouse compared with wild type. Our data suggests that overexpression of BRN2 may cause hypohidrosis by massive reduction in volume of the eccrine sweat glands in mouse paw.

Keywords: BRN2, Eccrine sweat glands, Aquaporin, Perspiration

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Dose- & Time-dependent Effect of Caffeine on the Growth & Maturation of Sexual Organs in Immature Male Rats

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Previously, we showed that pre-pubertal high caffeine exposure adversely affects the development of the testes in immature male rat. This study investigated the dose- and time-dependent effects of caffeine consumption on reproductive organs throughout puberty in pre-pubertal rats. A total of 80 male SD rats were randomly divided into four groups: control (0 mg/kg/day) and caffeine-fed rats (20, 60, or 120 mg/kg/day via gavage) for 10, 20, 30, or 40 days. Preputial separation was daily monitored and total body fat was measured using DXA on the day before sacrificed. Terminal blood samples were collected for hormone assay, and reproductive organs were grossly evaluated and weighed. One of testes was processed for histological analysis and the other was collected for Leydig cells isolation and culture. Caffeine decreased body weight gain and body fat in a dose- and time-dependent manner, accompanied by delayed preputial separation and decreases in reproductive organ weights. In addition, mean height of the germinal epithelium & seminiferous tubule diameter decreased in the caffeine-fed groups after 40 days of exposure. Caffeine intake reduced in vivo and ex vivo testosterone production as well as germ cell proliferation. Our results demonstrate that caffeine exposure during the puberty negatively influences on the development of reproductive organs even after short-term exposure. As consequences, caffeine intake delayed the onset of puberty and sexual maturation in a dose- and time-dependent manner. Furthermore, caffeine may disturb testosterone production and germ cell proliferation by directly acting on the Leydig cells and germinal epithelial cells. Further studies are required to determine the minimal safe dose of caffeine using a larger number of animals as well as in female.[Supported by grants from NRF-2014R1A1A2053601]

Keywords: Caffeine; Puberty; Reproductive organs; Testosterone; Leydig cell

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Identification Of Small GTPase Molecules As A Novel Myogenesis Regulating Factor And Characterizing Its Molecular Mechanism In Skeletal Muscle Cells

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Myogenesis is involved in many kinds of biological situation. However, the mechanism by which regulates myogenesis is unclear. Thus, we aimed at searching for key regulating factor in myogenesis using primary myoblast system. We are focus on small GTPase molecules. Small GTPases are known to involve in process of cell growth, cytoskeleton rearrangement, differentiation, lipid vesicle transport and so on. With screening, we found that several small GTPase regulating factors are dramatically regulated during myogenesis. Some are GEF (guanine nucleotide exchange factor)s, others are GAP (GTPase activating protein)s. Now, we are currently characterizing its molecular mechanism and try to identify biological significance of these candidate genes in myogenesis. We hope to understand the pathophysiological mechanisms of myogenesis-related diseases, such as diabetes, obesity and muscular-dystrophy, and thus hope to provide the molecular target for the development of treatment drug.

Keywords: Myogenesis, small GTPases, Differentiation

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