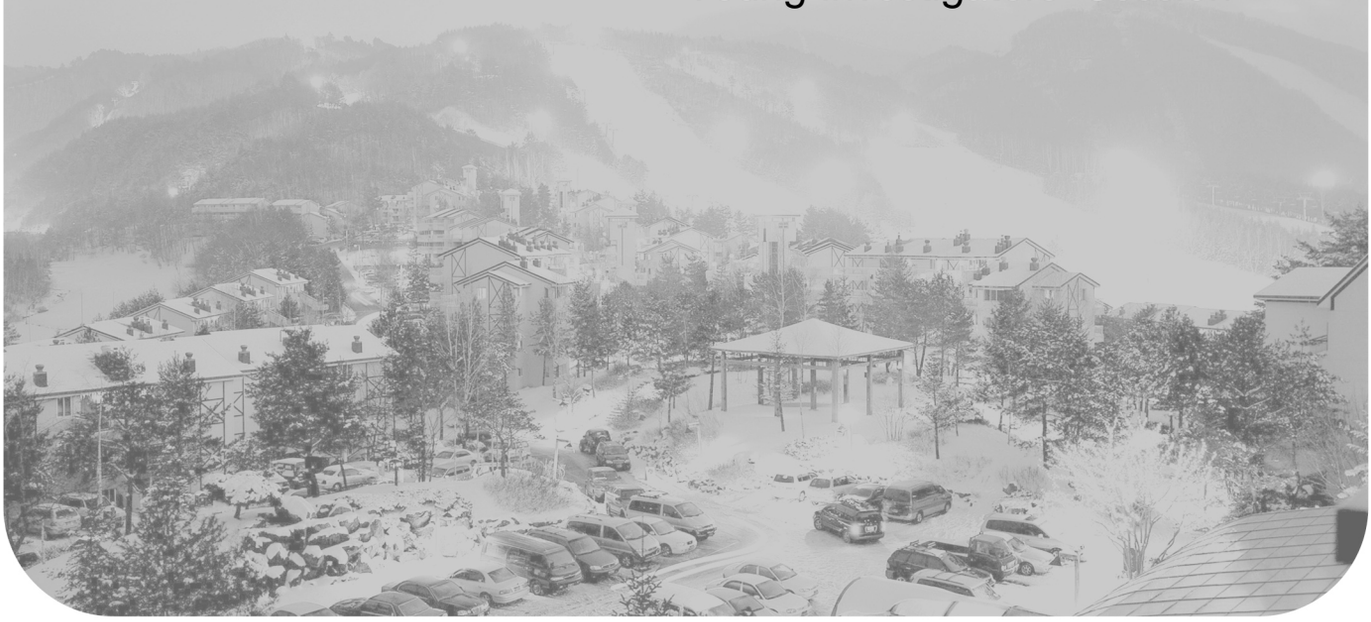
Abstracts



GL

TGF-β Journey of Discovery and Promise

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Growth factors are proteins that bind to receptors on cell surfaces to activate cellular proliferation and differentiation. Many growth factors are quite versatile, stimulating cellular division in numerous different cell types, while others are specific to a particular cell-type. In the nearly 30 years since its discovery and initial characterization, transforming growth factor-β (TGF-β) has emerged as the paradigmatic growth factor, defining the cell- and context-specific actions now attributed to many growth factors. TGF-β1 was the first of what is now known to be a large family of over 40 structurally related growth factors. TGF-β is involved in wound healing and in the pathogenesis of diseases such as autoimmune disease, fibrosis, and cancer. New insights into the growth factor's role in these disease processes are now leading to the development of novel therapies based on interference with TGF-β, its receptor, or its downstream signaling partners. I will discuss TGF-β, some of the roles it plays in cancer, and several therapeutic strategies based on the growth factor.

BL-1

The Role of Cyp4a in Type 2 Diabetes

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Endoplasmic reticulum (ER) stress has been known to be implicated in the development of type 2 diabetes mellitus. ER stress activates the unfolded protein response pathway, which is responsible for insulin resistance and apoptosis. However, the underpinnings of mechanisms that regulate ER stress and T2DM are poorly understood. Here we show the biochemical and physiological characterizations of cytochrome P450 4A (CYP4A) as a novel regulator of ER stress-induced hepatic insulin resistance and apoptosis. We found that CYP4A proteins are up-regulated in livers of mice with genetically induced and diet-induced diabetes. Inhibition of CYP4A in mice reduces hepatic ER stress, apoptosis, insulin resistance, and steatosis. Strategies to reduce levels or activity of CYP4A proteins in liver might be developed for treatment of patients with type 2 diabetes.

BL-2

Intersection of Genetics and Epigenetics across the Human Genome

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Epigenetics is the study of changes in gene expression or cellular phenotype caused by mechanisms other than changes in the underlying DNA sequence. Therefore, epigenetics and genetics cannot conceptually overlap. However, in biology, the interaction of genetic and epigenetic elements and mechanisms plays a critical role in transcription control. Humans vary according to a plethora of traits, such as height, hair color, behavior, and susceptibility to disease. Recent large-scale genetic studies have identified thousands of specific DNA variations in the human population that are associated with different traits. However, these studies do not answer a key question: By what means do most DNA variants alter cellular behavior and contribute to differences in specific traits? Recent studies exploring the mechanistic link between genetic and trait variation in the human population find that DNA variants influence a layer of gene regulation, that is, epigenetics, through the sequence-specific activity of transcription factors. In this talk, I will introduce one of our ongoing research projects that utilize genome-scale epigenetics data in order to better understand genetic mechanisms. Specifically, how genetic changes associated with epigenetic gene regulation have shaped the evolution of human intelligence and behavior during the past 10,000 years will be discussed.

BL-3

Seeing the Unseen with Single-Molecule Perspective

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Handling molecules one at a time and measuring signals from the single molecules provides a unique opportunity to address fundamental biological problems as well as technical challenges at bay. In this seminar, I will talk about our two recent experiments that cannot be paralleled in conventional bulk measurements. First, by combining two orthogonal techniques of single-molecule FRET and magnetic tweezers, we reveal how the 20S particle consisting of NSF and a-SNAP disassembles single SNARE complexes. We observed that NSF exploits only one round of ATP binding and hydrolysis to disassemble the SNARE complex, one of the most stable protein complexes, suggesting a tight coupling between ATP hydrolysis and unfolding of protein substrates. Second, by employing real-time single-molecule fluorescence imaging as a detection scheme, we have recently demonstrated a single-molecule version of the co-immunoprecipitation (co-IP) analysis, which provides an improvement of five orders of magnitude in the time resolution. With the single-molecule sensitivity and millisecond time resolution, it is possible to detect changes in the protein-protein interactions in a given tumour tissue. This suggests a path forward toward molecular diagnostics of cancers at the level of protein-protein interactions. I will close the talk with brief outlook for future researches.

BL-4

The Molecular Basis of Inactivating Germ Cell Abscission

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Intercellular bridges are a distinct feature of mammalian germ cells and its loss disrupts spermatogenesis and causes sterility. Although the observations of intercellular bridges were reported more than 100 years ago, their molecular function is largely unknown and we have recently begun to learn how the intercellular bridges form at the molecular level. To inactivate cell abscission, TEX14 (a testis-expressed gene) is recruited to the midbody and it is essential for intercellular bridges. To gain insights into the structural organization of TEX14 at the midbody, we determined the crystal structures of CEP55-EABR bound to the TEX14 peptide (or its chimera peptides) and performed functional analysis of the CEP55/TEX14 interaction by multi-experiment analysis, suggesting that germ cells inherently possess the ability to inactivate cell abscission through TEX14.

OB-1

Finding Partners: Deubiquitinating Enzymes and Their Substrates

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Protein homeostasis is required for maintaining key proteins in an optimal concentration and also necessary for degradation of regulatory proteins as the way to control signaling pathways. Ubiquitin dependent proteosomal degradation is a protein dumping process affecting many proteins. Since undesired protein degradation may cause severe cellular damages, ubiquitin-proteosome system (UPS) should be tightly regulated and highly specific to the target proteins. For these reasons, three enzymes, E1, E2 and E3, work sequentially for the target specific attachment of ubiquitin chains. Among them, E3 ligases are the key players for defining substrate specificity, and almost 1000 E3 ligases are considered to be present in human cells. Enzymes that function to remove UB from substrate proteins should be present in cells, thereby rescuing them from destruction by preventing indiscriminate degradation. This negative regulator of UPS is referred to as deubiquitinase or deubiquotinating enzyme (DUB). So far, about 100 DUBs have been identified, though the function of many DUBs is not known yet. In these regards, the intriguing questions are what the substrates of each DUB are and how the protein homeostasis can be maintained regardless of inequality between the numbers of ligases and hydrolase. We have been seeking for an answer to these questions, and in this talk, the results of our initial efforts will be presented.

OB-2

Progerin-lamin A/C Binding Inhibitors Show Anti-aging Properties

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Hutchinson-Gilford progeria syndrome (HGPS) is a rare autosomal dominant genetic disease, caused by a silent mutation of the LMNA gene encoding lamin A/C. This mutation (G608G) generates a new splicing donor site and produces an alternative splicing product of LMNA, termed progerin, which is also expressed in normal aged cells. In this study, we first show that progerin binds directly to lamin A/C and induces profound nuclear aberrations. Based on this observation, we have performed a random screening of a chemical library and found three novel compounds (JH1, JH4, and JH13) which efficiently block progerin-lamin A/C binding. These three chemicals, in particular JH4, alleviate nuclear deformation and reverse senescence markers characteristic of HGPS cells, including growth arrest and senescence-associated β-galactosidase (SA-β-gal) activity. Moreover, by using microarray-based analysis, we show that JH4 is able to rescue defects of cell cycle progression in both HGPS and aged cells. Furthermore, administration of JH4 to $Lmna^{G609G/G609G}$ mutant mice which phenocopy human HGPS, results in a marked improvement of several progeria phenotypes and extends lifespan. Accordingly, we propose that specific inhibitors with ability to block the progerin-lamin A/C binding may represent a promising new strategy to improve lifespan and healthspan in both HGPS and normal aging.

SI-1

Molecular Imaging for Cancer Microenvironments

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Herein, we propose that future cancer molecular imaging and cancer therapy must account for cancer microenvironments to become effective. We suggest new concept that 'cancer microenvironment-responsible theranostic nanotechnology'. That is reprograming heterogeneous cancer cells to homogeneous cancer cells with foreign stimulus (metabolic engineering, ultrasound, radiation, temperature), not by genetic engineering. These reprogramed homogeneous cancer cells can be efficiently targeted using 'bio-orthogonal click chemistry, 'echogenic nanoparticles, 'thermo-sensitive nanoparticles', 'apoptosis-activatable nanoparticles', etc. Therefore, we will overcome the lower tumor targeting efficacy of present nanotechnology and molecular imaging in cancer imaging and therapy.

SI-2

Sphingolipid & Neurodegeneration

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Sphingosine is a major storage compound in Niemann-Pick type C disease (NP-C), although the pathological role(s) of this accumulation have not been fully characterized. Here we found that sphingosine kinase (SphK) activity is reduced in NP-C patient fibroblasts and NP-C mouse Purkinje neurons (PNs) due to defective vascular endothelial growth factor (VEGF) levels. Sphingosine accumulation due to inactivation of VEGF/SphK pathway led to PNs loss via inhibition of autophagosome-lysosome fusion in NP-C mice. VEGF activates SphK by binding to VEGFR2, resulting in decreased sphingosine storage as well as improved PNs survival and clinical outcomes in NP-C cells and mice. We also show that induced pluripotent stem cell (iPSC)-derived human NP-C neurons are generated and the abnormalities caused by VEGF/SphK inactivity in these cells are corrected by replenishment of VEGF. Overall, these results reveal a pathogenic mechanism in NP-C neurons where defective SphK activity is due to impaired VEGF levels.

SI-3

Plant Communications

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The form and function of plants is mainly determined by efficient communication among cells, tissues and organs, and cross-talkswith environmental stimuli. In higher plants, phytohormones regulate growth and morphogenesis by coordinating distribution of carbon source. We have been elucidating signaling networks of various phytohormones such as cytokinin, auxin, brassinosteroid, abscisic acid, and salicylic acid.We have constructed our own 'interactome' database and molecular networks as a platform to explore the cross-talks among different phytohormones and environmental conditions. We are also investigating epigenetic regulations of the induced resistance(e.g. priming) against various pathogen attacks at genome level. Recently, we are prompting to understand how secondary organs such as lateral roots, cambia, and nodules in legume plants are initiated and developed in accordance to environmental changes. To this end, we are taking 'systems biology' approaches, which provides a comprehensive research tool to understand these complex developmental processes viewed as the keys to understanding life at least in plants.

SI-4

Anti-Tumoral Effect of the Mitochondrial Target Domain of Noxa Delivered by an Engineered Salmonella typhimurium (Bacterial Cancer Therapy)

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Bacterial cancer therapy relies on the fact that several bacterial species are capable of targeting tumor tissue and that bacteria can be genetically engineered to selectively deliver therapeutic proteins of interest to the targeted tumors. However, the challenge of bacterial cancer therapy is the release of the therapeutic proteins from the bacteria and entry of the proteins into tumor cells. This study employed an attenuated Salmonella typhimurium to selectively deliver the mitochondrial targeting domain of Noxa (MTD) as a potential therapeutic cargo protein, and examined its anti-cancer effect. To release MTD from the bacteria, a novel bacterial lysis system of phage origin was deployed. To facilitate the entry of MTD into the tumor cells, the MTD was fused to DS4.3, a novel cell-penetrating peptide (CPP) derived from a voltage-gated potassium channel (K_v2.1). The gene encoding DS4.3-MTD and the phage lysis genes were placed under the control of P_{BAD}, a promoter activated by L-arabinose. We demonstrated that DS4.3-MTD chimeric molecules expressed by the Salmonellae were anti-tumoral in cultured tumor cells and in mice with CT26 colon carcinoma.

SI-5

Targeting Phospholipase D1 Attenuates Intestinal Tumorigenesis by Controlling E2F1/miRNA-4496/β-catenin Signaling Circuits

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Expression of the Wnt target gene phospholipase D1 (PLD1) is upregulated in various carcinoma, including colorectal cancer (CRC). However, mechanistic significance of its elevated expression in intestinal tumorigenesis remains unknown. Here, we show that genetic and pharmacological targeting of PLD1 disrupt spontaneous and colitis-associated intestinal tumorigenesis in $Apc^{Min/+}$ and AOM/DSS mice model. Intestinal epithelial cells-specific PLD1 overexpression in $Apc^{Min/+}$ mice accelerated tumorigenesis with increased proliferation and nuclear β-catenin level, compared with $Apc^{Min/+}$ mice. PLD1 inactivation suppressed the self-renewal capacity of colon cancer-initiating cell (C-IC) by decreasing expression of b-catenin via E2F1-induced miRNA-4496. Ultimately, low expression of PLD1 coupled with high level of E2F1 apoptotic targets and low level of C-IC markers was predictive of good prognosis in CRC patients, suggesting in vivo relevance. Collectively, our data reveal that intestinal PLD1 expression has a crucial role in modulation of functional interaction of a variety of cancer-relevant pathways. Modulation of PLD1 expression and activity represents a promising therapeutic strategy for the treatment of intestinal tumorigenesis.

SI-6

Multi-Faced Hedgehog Signaling in Auditory Neurosensory Organ Development

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Hearing ability is crucial for daily activities throughout the animal kingdom. Sound perception begins at the auditory neurosensory organ known as the cochlea, which is composed of numerous specialized cell types to receive, process, and transmit sound signals to the brain. How this complex organ is built during vertebrate development has been intensively studied during the past decade. Several signaling pathways have been identified to be involved in the formation of functional cochlea. Among many of them, I have been focusing on Sonic Hedgehog (Shh) signaling. In this symposium, I will summarize our studies demonstrating that Shh signaling plays multiple roles during cochlear development, which include 1) early specification of cochlear fate, 2) elongation of the cochlear duct, and 3) differentiation of sensory hair cells. In addition, I will also discuss on our recent results that Shh signaling gradient is important for providing a positional identity along the cochlear duct, which is crucial for sound frequency discrimination.

SI-7

Disctinct Role of Adenylate Dinase 2 in Cell Death and Cell Growth: Is It a Tumor Suppressor?

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Adenylate kinase 2 (AK2), which balances adenine nucleotide pool, is known as a multi-functional protein. We have previously shown that AK2 plays a role in the intrinsic cell death of tumour cells by forming AK2-FADD-caspase-10 protein complexes. Here we show that AK2 negatively regulates tumor cell growth. AK2 forms a complex with DUSP26 phosphatase, and stimulates DUSP26 activity independently of its adenylate kinase activity. AK2/DUSP26 phosphatase protein complex dephosphorylates phospho-FADDSer194 to regulate cell growth. AK2 deficiency enhances cell proliferation with cell cycle alteration and induces tumor formation in xenograft assay. Down-regulation of AK2 expression is frequently found in tumor cells and human cancer tissues showing high level of phospho-FADD. Reconstitution of AK2 in AK2-deficient tumor cells retards cell proliferation. Further, AK2 knockout mouse embryo fibroblasts exhibit enhanced cell proliferation with significant alteration in phospho-FADDSer191. These results suggest that AK2 is an associated activator of DUSP26 and suppresses cell proliferation via FADD dephosphorylation, postulating AK2 as a suppressor of tumor growth.

SII-1

Disturbance of ER Homeostasis and Oxidative Stress Synergizes to Cause Cell Death

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Upon ER stress, activated PERK phosphorylates eIF2α at Ser51 leading to rapid and transient attenuation of protein synthesis. Paradoxically, under these conditions translation of Atf4 mRNA is selectively enhanced, which induces the proapoptotic transcription factor CAAT-enhancer binding protein (C/EBP) homologous protein (CHOP). Although it has been known for a long time that ATF4 and CHOP play key roles in ER stress-mediated cell death, the detailed mechanisms underlying apoptotic process are not clear yet. Through ChIP-Seq and mRNA-Seq, we found that ATF4 and CHOP bind to a common set of genes that encode the mRNA translational machinery to increase protein synthesis. Surprisingly, the increased translation rate by ATF4 and CHOP induced cell death through increased levels of oxidative stress. The correlation of ER stress with oxidative stress was further demonstrated, in which we showed that mice defective for protein folding in β cells display hyperglycemia, and their β cells recapitulate all the properties, including oxidative stress, of β cell failure observed in humans with type 2 diabetes. When these diabetic mice were fed with an antioxidant-supplemented diet, glucose homeostasis was restored and there was an increase in β cell mass and function. In conclusion, these results suggest that eIF2α phosphorylation and subsequent induction of ATF4/CHOP causes increased protein synthesis and oxidative stress, which contribute the ER stress-mediated cell death.

SII-2

Explore Synaptic Communication by Opto-Physiology (The Role of CDK5 and Calcineurin at CNS Synapses)

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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 show 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 Ca2influx 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, CNA α and CDK5 enzymatic activities are key determinants of release probability.

SII-3

The Advent of Soluble Common Gamma Chain Rocks the T Cell World; A Novel Therapeutic Target for Autoimmune Diseases

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The common γ-chain (γc) plays a central role in signaling by IL-2 and other γc–dependent cytokines. Here we report that activated T cells produce an alternatively spliced form of γc 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 IL-2Rβ and IL-7Rα proteins on T cells to inhibit cytokine signaling and promote inflammation. Soluble γc impaired naive 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. Thus, sγc expression is a new mechanism for regulating cytokine signaling and controlling T cell activation and differentiation. Furthermore, these data may lead to the generation of novel therapeutic targets for the treatment of inflammatory autoimmune diseases, as sγc is genetically conserved in human and circulating levels of sγc have been linked to autoimmune diseases patients.

SII-4

Development of a Risk Prediction Model for Late-Onset Alzheimer's Disease

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Recent advances in neuroimaging and genetics allow acquisition of both highly detailed structural brain scans and genome-wide genetic variations across a large cohort. Combined analysis of these huge datasets are providing novel opportunities not only to find novel genetic variations influencing both brain structure and neurodegenerative disease but also to predict the onset of neurodegenerative diseases including Alzheimer's disease (AD). Here we show that effects of AD progression and aging on gray matter decay across the cerebral cortex. From 282 brain MRIs of normal subjects and AD patients, gray matter thickness was analyzed at 327,684 surface points on the whole cortex using Freesurfer. Massive statistical analysis revealed that AD patients showed severe atrophy of gray matter concentrated in the temporal cortex while normal subjects showed age-related decline of cortical gray matter across brain. These results suggested that structural analysis of cortical gray matter provide a possible explanation of dementia symptoms without biochemical hallmarks.

SII-5

Anthracnose Resistance in Chili Pepper: From Genetics to Commercialization

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Chili pepper (Capsicum annuum L.) is one of the most important and inevitable vegetable crop in Korea. It is the second income earner of Korean farmers after rice. In seed industry, it is the first rank in domestic as well as in worldwide for last decade. However, it's yield loss and quality deterioration have been severely occurred by several pests and diseases during almost whole cultivation period. Especially, the anthracnose (Colletotrichum spp.) has been known that the most destructive disease in direct yield loss, because it attacks mainly pepper fruits and severely spread out during monsoon season. Resistance breeding is the most effective and environmental friendly control ways to the disease, but there is no single resistant variety developed worldwide. Our breeding program for anthracnose resistance in chili pepper was started in 1996 and we have finally developed the good F_1 variety in 2012. During that period ① we have developed the reliable inoculation systems for anthracnose resistance, ② we have identified good genetic resources resistant to anthracnose, ③ we carried out interspecific hybridization between Capsicum annuum and C. baccatum to introgress the resistance gene(s), ④ we have done the genetic analysis and developed molecular markers associated anthracnose resistance by using QTL mapping, ⑤ we have developed the breeding lines and F_1 variety resistant to anthracnose by using male sterile system. This is the world-first commercialization for breeding chili resistant to anthracnose.

YI-1

PTPσ Is Required for Excitatory Synapse Development as a Presynaptic Receptor for the Glypican-4/LRRTM4 Complex

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Leukocyte common antigen-related receptor protein tyrosine phosphatases (LAR-RPTPs), comprising LAR, PTPδ and PTPσ, are synaptic adhesion molecules that organize synapse development. Here, we identify glypican-4 (GPC-4) as a ligand for PTPσ. GPC-4 showed strong (nanomolar) affinity and heparan sulfate (HS)-dependent interaction with the immunoglobulin domains of PTPσ. PTPσ bound only to proteolytically cleaved GPC-4 and formed additional complex with LRRTM4 in rat brains. Moreover, single knockdown (KD) of PTPσ, but not LAR, in cultured neurons significantly reduced the synaptogenic activity of LRRTM4, a postsynaptic ligand of GPC-4, in heterologous synapse-formation assays. Finally, PTPσ KD dramatically decreased both the frequency and amplitude of excitatory synaptic transmission. This effect was reversed by wild-type PTPσ, but not by a HS-binding-defective PTPσ mutant. Our results collectively suggest that presynaptic PTP σ, together with GPC-4, acts in a HS-dependent manner to maintain excitatory synapse development and function.

YI-2

Runx3 Inactivation Is an Initial Event for Lung Tumorigenesis

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In lung tumorigenesis, it has been postulated that bronchioalveolar stem cells (BASCs), which normally contribute for the renewal of lung epithelial cells, are the origin of lung adenocarcinoma. In this study, we show that postnatal disruption of Runx3 in mouse lung results in retro-differentiation of bronchiolar epithelial cells (Clara cells or ciliated cells) to BASC-like cells (BASC-Ls). The BASC-Ls proliferate and differentiate to alveolar epithelial cells and form two distinct types of adenomas depend on their origins. Therefore, overall process of lung adenocarcinoma development is a trans-differentiation of bronchiolar epithelial cell to alveolar epithelial cell and inactivation of Runx3 initiates this process. In addition, inactivation of Runx3 destroyed cellular defense mechanism against oncogene insult. BASC-Ls acquired K-Ras activation progressed to corresponding types of adenocarcinomas. We also show that the combination of Runx3 inactivation and Ras activation is not limited to multi-step tumorigenesis of lung, but also associated with that of other types of tumors.

YI-3

SREBP/MDT-15 Moderates Toxic Effects of Glucose on Lifespan via Regulating Lipogenic Genes in C. elegans

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Glucose-rich diet shortens lifespan in model organisms, including C. elegans. Glucose is metabolized to various nutrients including lipids. However, it remains unknown how glucose and lipid metabolisms are linked to influence lifespan. Here, we show that sterol regulatory element-binding protein (SREBP) and mediator 15 (MDT-15) transcription factors prevent life-shortening effects of dietary glucose by promoting fat synthesis in C. elegans. We find that dietary glucose activates SREBP and MDT-15, which in turn increases the levels of key enzymes for lipid synthesis. Activation of SREBP/MDT-15 is necessary and sufficient for alleviating the toxic effect of high glucose diet. We further show that metabolic flow from glucose to glycolysis and de novo fatty acid synthesis modulates the effects of glucose on lifespan. Thus, accelerated glucose-to-fat metabolic flow by the activation of SREBP/MDT-15 appears to moderate the glucose toxicity. Our study will help designing strategies against metabolic diseases including diabetes. This research is supported by Korean Health Technology R&D Project (HI14C2337) to S-J.L, by NRF-2013H1A8A-1003751 to D-E.J, and by NRF-2012H1A2A1049108 to H.S.