ABSTRACT

Special Lectures
SL1  Modeling Psychiatric/Neurological disorders using iPS cell technologies and transgenic non-human primates

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What makes the investigation of human psychiatric/psychiatric disorders so difficult? In order to overcome these difficulties, we took advantage of iPS cell technologies and transgenic non-human primates for modeling human psychiatric/psychiatric disorders. So far, we have established iPS cells from the patients of about 30 human psychiatric/psychiatric disorders and characterized their pathophysiology. For faithfully modeling the human psychiatric/psychiatric disorders in vivo, we developed transgenic non-human primates (common marmosets) with germline transmission (Sasaki et al., Nature, 2009). In the present talk, we also wish to mention our recent data of generation of common marmoset transgenic models of neurodegenerative diseases, including Parkinson disease, Alzheimer disease and ALS. Furthermore, we could generate knock-out technologies of common marmoset using genome editing technologies for the generation of transgenic marmoset model of autism and psychiatric disorders. At the end, I will mention about Brain Mapping Projects in Japan, in which investigation of common marmoset brains plays key roles.

SL2  Inflammation and immune mechanisms of brain damage after stroke

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Stroke accounts for more than 10% of deaths worldwide, and over a third of survivors are left with major neurological impairment. The need for new and effective therapies for stroke is therefore clear and urgent. While some advances have been made toward understanding its mechanisms, still only one intervention has been found to reduce brain injury following clinical stroke - the ‘clot-buster’ recombinant tissue plasminogen activator. Unfortunately however, with a short time window of only 4.5 h, this therapy is available to less than 10% of stroke patients. For further advances in the clinical treatment of ischemic stroke, the complex mechanisms of cellular injury following cerebral ischemia must be elucidated to provide novel targets for future therapies. The initial ischemic insult is now known to be followed by induction of cytokines and chemokines, which attract numerous inflammatory cell types to the damaged brain region and ultimately contribute to secondary brain injury. Neutrophils, monocytes, T and B lymphocytes may each become activated, infiltrate the brain and modulate the severity of stroke outcome. This presentation will describe some of our recent work targeting various immune cell mechanisms for novel therapies in acute stroke.

SL3  Perspectives of disease-modifying therapy for neurodegenerative disease

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Spinal and bulbar muscular atrophy (SBMA) is an adult-onset motor neuron disease caused by the expansion of a trinucleotide CAG repeat, which encodes the polyglutamine tract, within the first exon of the androgen receptor (AR) gene. The ligand-dependent accumulation of the pathogenic AR, an initial step in the neurodegenerative process in SBMA, is followed by several downstream molecular events such as transcriptional dysregulation and axonal transport disruption. Androgen deprivation through leuprorelin improved the symptoms, histopathological findings, and nuclear accumulation of the pathogenic AR in the male AR-97Q mice. In a large-scale randomized clinical trial, leuprorelin treatment was associated with a greater reduction in barium residue than was placebo. We also identified miR-196a CGRP-1, HSPs, etc, as molecules which regulate disease pathophysiology of SBMA, and thus these are the target for disease-modifying therapy for neurodegenerative diseases.

SL4  Functional analyses of target proteins for drug development by NMR

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Analysis of the mechanism of drug actions as well as comprehension of true nature of drugs are strong points of the pharmacology, which cannot be accomplished with reductionism. The knowledge between molecular level and individual behavior level is still a black box. Broader temporal and spatial analysis of neural activities with concomitant micro-level resolution reveal novel contrivance of brain function. We have found that febrile seizure of neonates induces abnormal location of granule cells in the hippocampus via upregulation of GABA receptors that persists into adulthood. Hippocampal neural activities are modified by intra- and extra-hippocampal active levels. Complex inter-nuclei interactions are important for accomplishment of fear memory in which amygdala plays a crucial role. Brain function is not free from peripheral accomplishment of fear memory in which amygdala plays a crucial role. Brain function is not free from peripheral activities. Activation of vagus afferents bidirectionally affects synaptic activities in the hippocampus as well as formation of memory. Personal view of prospective direction of pharmacology will be addressed.

It has been well established that NF-κB activation must be kept temporally and spatially in check by well-orchestrated negative feedback loops to protect excessive activation. However, in cancer cells, these feedback loops are overridden through unclear mechanisms to sustain a constitutive activation of NF-κB signaling. The topic will be present and discuss how we made a novel discovery that toddler domain containing protein, PHF20 is a key protein to maintain NF-κB in a default active state. Here, we show that, in PHF20 overexpressing cells, the termination of TNF-induced p65 phosphorylation is impaired while the upstream signaling events triggered by TNF are not affected. More importantly, the involvement of PHF20 in this process is specifically and highly contingent upon its interaction with Lys methylated-p65 which interrupts the recruitment of protein phosphatase PP2A to p65 and thus leads to a prolonged p65 phosphorylation. Thus, here we propose a new molecular mechanism of constitutive NF-κB activation by PHF20 recognizes the methylation status of p65 in the context of pathologic conditions such as inflammation-linked cancer development.

Calcium is important not only for the structure of bone but also for signaling in every cell of the body. There is a huge concentration gradient into cells and multiple mechanisms exist to regulate its entry. Once in the cell calcium profoundly influences many process depending on amplitude, space and time. Entry via voltage-gated calcium channels often leads to excitation, for example in the form of muscle contraction and neurotransmitter release. These channels are inhibited by drugs such as amlodipine and pregabalin, used to treat hypertension and neurological conditions such as neuropathic pain in diabetes. But many other types of calcium channel have been discovered over the past 20 years, gated not by voltage but other factors. They exist also in non-excitable cells and many are up-regulated in common diseases. We are investigating these other channels which include Piezo channels, identified 5 years ago as mechanical impact sensors in nociceptive neurones. Recently we identified importance of Piezo1 as a frictional force sensor of endothelial cells, showing its critical role in development (Li et al 2014 Nature doi: 10.1038/nature13701). We are now developing small-molecule modulators of non-voltage-gated calcium-permeable channels to facilitate studies of their biology and explore their potential for drug discovery.

DNA damage responses (DDR) are important surveillance systems to maintain genomic integrity. Once genomic stresses such as DNA damage, oxidative stress, and activation of oncogenes are sensed, DDR execute transient cell cycle arrest through inhibition of the activity of cell cycle regulators. DDR also trigger apoptosis and cellular senescence when cells sense severe and extensive chromosomal abnormalities. Numerous key players have been identified in terms of damage sensor proteins, transducer kinases and effectors, but their coordination, interconnectedness, and the mechanisms by which they regulate important anti-tumor protective responses have become evident only recently. Under genomic stresses, cell survival is completely dependent on these mechanisms. However, most cancer cells defect a part of DDR, leading to gross genomic instability and malignant transformation. These observations also indicate that survival of cancer cells depends on the residual DDR. Thus, inhibitors for the residual DDR might be effective and specific drugs for most cancers through inducing synthetic lethality. In this talk, I would like to introduce details of DDR and discuss about their potential use as therapeutic targets for malignant tumors.
Renin angiotensin system and cardiovascular diseases

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Tigerstedt and Bergmann discovered renin in 1898. Recent 40 years renin-angiotensin research has been rapidly promoted in fields of protein chemistry, molecular biology, genetically-modified animals, and drug discovery. The inhibitors of renin-angiotensin system contribute to the therapy in cardiovascular diseases. Short review of these findings and ongoing topics will be made comments. Cardiovascular diseases have cross interactions with chronic inflammation. In these circumstances exosome play a role on cell to cell communications. Exosome contains many intracellular components such as DNAs, RNAs, proteins, and cytokines. Heat shock proteins and tetraspanin containing exosome react with endothelial cell receptors such as toll-like receptor. The relationships between exosome derived from macrophage and vascular endothelial cells in hypertensive animals may play an important role on tissue remodeling in chronic hypertension.

Store-operated Ca\(^{2+}\) entry

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The concept of capacitative or store-operated calcium entry, a process by which the depletion of stored calcium signals the opening of plasma membrane calcium channels, has its roots in the late 1970's, and was formalized in 1986. The first part of this lecture will attempt to summarize some of the early experimental work that led to the idea of store-operated calcium entry, some of the initial proofs for it, and major advances and distractions leading ultimately to the discovery of the major molecular players, STIM1 and Orai1. The second part of the lecture will present findings from current research in my laboratory focusing on the cell biology of store-operated channels, and on the physiological roles of these channels by use of genetically modified mice. We discovered that the major pore-forming subunit of the store-operated channel, Orai1, exists in two forms due to alternative translation initiation. We have examined the function of these two forms of Orai1 in forming classical CRAC channels, and in more complex channels involving TRPC subunits, and in channels that are not store-operated but respond to arachidonic acid. Studies with mice lacking Orai1 or with conditional deletion of STIM1 reveal multiple roles of store-operated channels including: innate immunity, exocrine gland function, bone formation, the differentiation and wound-healing function of skin, lactation, and male fertility.