第４０回 プロテオーム医療創薬研究会

【実施日】　2012 年 8 月 30 日(木)　15:00～17:05

【会　場】　横浜市立大学　附属病院 10 階 臨床講堂

【来場者】　約 50 名

【内　容】

演題：　Neonatal stress disrupts cortical circuit formation

講師：Takuya Takahashi
Dept. of Physiology, Yokohama City University School of Medicine, Yokohama, Japan

発表要旨：

Stressful events during early childhood can have a profound lifelong influence on emotional and cognitive behaviors. However, the mechanisms by which stress affects neonatal brain circuit formation are poorly understood. Here, we find that neonatal social isolation disrupts molecular, cellular and circuit developmental processes leading to behavioral dysfunction. Neonatal isolation prevents long-term potentiation and experience-dependent synaptic trafficking of α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors normally occurring during circuit formation in the rodent barrel cortex. This is mediated by an increase of the stress glucocorticoid hormone, associated with reduced Calcium/calmodulin-dependent protein kinase type II (CaMKII) signaling, and results in the attenuation of the whisker-sensitivity at the cortex.
These effects lead to defects in whisker-dependent behavior in juvenile animals. These results indicate that neonatal social isolation alters neuronal plasticity mechanisms and perturbs the initial establishment of a normal cortical circuit, potentially explaining the long lasting behavioral effects of neonatal stress.

演 題 ： Screening for new proteins required for cellular function by Chromophore Assisted Light Inactivation

講師：Daniel G. Jay
Dept. of Physiology, Tufts University School of Medicine, Boston, USA

発表要旨：

Chromophore Assisted Light Inactivation (CALI) targets light energy via localized photosensitizers to damage specific proteins in cells and tissue leading to the acute and localized knock down of protein function. It has long been a means for ascribing *in situ* function and of testing mechanistic hypotheses. The combination of CALI-based methods with antibody libraries and high throughput assays has provided an opportunity to using light-based inactivation as a discovery engine. In the last several years, CALIhas been increasingly applied as a screening tool to identify new proteins implicated in cellular processes. This talk will describe efforts to identify proteins required for cancer invasion, apoptosis and drug resistance and describe complementary studies tovalidate these findings. The talk will conclude with a discussion of the future ofCALI-based screens using molecularly encoded photosensitizers and their potential applications.

演題：Expanding the optogenetic tool box: red-light activator and synaptic inhibitor

講師：John Y. Lin
Dept. of Pharmacology, HHMI – University of California, San Diego, USA

発表要旨：

The utilization of 'optogenetic' tools has been an important development in the field of neuroscience. These tools enable the researchers to manipulate the activities of specific neurons with light. Although some of these optogenetic tools have been widely used, the properties of some of tools are not ideal as research tools. In addition, we yet to have a suitable technique that can be used to inhibit synaptic release. In this talk, I will discuss our efforts to improve the spectral and biophysical properties of
light-activated channel, channelrhodopsins, and the development of a novel optogenetic approach that can be used to inhibit synaptic release directly based on Chromophore-assisted light inactivation.

演題：Imaging analysis of synapse dynamics

講師：Shigeo Okabe
Dept. of Cellular Neurobiology, The University of Tokyo Graduate School of Medicine, Tokyo, Japan）

発表要旨：

Development of neural circuit is regulated by a proper balance between synapse formation and elimination. In the early phase of neural circuit development, redundant connections between neurons may exist, but they are eliminated by the extrinsic instructive signals such as sensory inputs. Previously we monitored single synapse behavior by using GFP-labeled synaptic proteins in cultured hippocampal neurons.
Time-lapse imaging of GFP-labeled synaptic proteins revealed highly motile behavior of synapses. Within one day, 10-20% of total synapses were eliminated and a roughly equal number of synapses were newly generated. Quantitative analysis indicated a slight bias toward synapse formation,

which underlay gradual increase of the total number of synapses in culture. Two-photon imaging of GFP-labeled synaptic proteins invivo confirmed the existence of counterbalance between synapse formation and eliminationin the developing neocortex. The higher rate of synapse turnover in the early postnatal period contrasted with the scarcity of dynamic synapses in the mature neocortex. It is likely that the rapid down-regulation of synapse turnover is associated with developmental switch in the neocortical functions, such as visual perception and motor skills.

To further understand the mechanisms of neural network formation in the brain, synapse formation in different types of neurons and in different brain regions should be compared. For this purpose, we performed imaging analyses of excitatory synapse formaton between neocortical pyramidal neuron axons and inhibitory neuron dendrites, and also between cerebellar granule cell axons and Purkinje cell dendrites. We found unique synapse translocation along the dendrites of cortical interneurons, which plays an essential role in synapse maturation. Furthermore, we found that dynamic structural changes of the cerebellar granule cell axons facilitated the maturation of both pre- and postsynaptic structures in the early postnatal cerebellum.

The presence of multiple mechanisms of synapse development should be important in the establishment of complex neural network with individual connections variable and tunable.

演題：Closing remark

講師：Shigeo Ohno

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