第6回 東京医科歯科大学 駿河台シンポジウム

6TH SURUGADAI SYMPOSIUM

Molecular, Cellular & Integrative Mechanisms of Intractable Diseases

難治疾患克服への挑戦

Date

November 27 (Tue), 2007 9:00 a.m 〜 4:50 p.m

Venue

Tokyo Medical and Dental University
東京医科歯科大学　歯学部特別講堂

9:00-9:05 ***Introduction*** 野田研究所長

Symposium I 座長:山梨、田中

9:05-9:35 Dr. Yoshihiro Ogawa *(Tokyo Medical & Dental University)*
Molecular mechanisms of obesity-induced adipose tissue inflammation

9:35-10:25 Dr. Philipp E. Scherer *(The University of Texas Southwestern Medical Center)*
Adipose tissue: Contribution to insulin sensitivity and metabolic syndrome

10:25-10:35 *coffee break*

10:35-11:05 Dr. Tetsushi Furukawa *(Tokyo Medical & Dental University)*
Non-genomic regulation of cardiac ion channels by sex hormones

11:05-11:55 Dr. Colleen E. Clancy *(Cornell University)*
Mutations and electric disease: Insight from model studies

Symposium II 座長:小川、古川

13:10-13:40 Dr. Kohichi Tanaka *(Tokyo Medical & Dental University)*
A new animal model of autism: Glutamatergic hyperactivity in key neural systems

13:40-14:30 Dr. Akira Sawa *(The Johns Hopkins University)*
Translational Neuroscience for Major Mental Illnesses

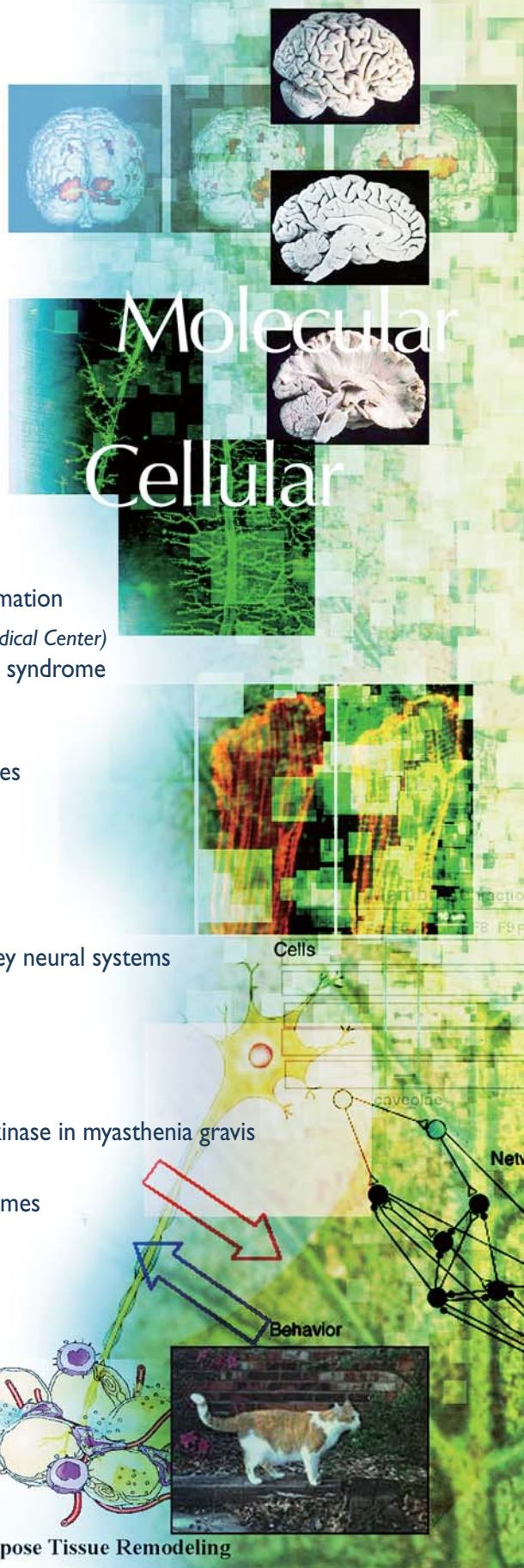
14:30-14:45 *coffee break*

14:45-15:35 Dr. Angela Vincent *(University of Oxford)*
Autoantibodies to acetylcholine receptors and muscle specific kinase in myasthenia gravis

15:35-16:15 Dr. David Beeson *(University of Oxford)*
Molecular mechanisms underlying congenital myasthenic syndromes

16:15-16:45 Dr. Yuji Yamanashi *(Tokyo Medical & Dental University)*
Dok-7/MuSK signaling and a congenital myasthenic syndrome

16:45-16:50 ***Closing Remarks*** 鍔田研究部長



主催：東京医科歯科大学　難治疾患研究所
大学院疾患生命科学研究部・生命情報科学教育部

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Molecular mechanism of obesity-induced adipose tissue inflammation

Dr. Yoshihiro Ogawa
Professor
Department of Molecular Medicine and Metabolism
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Tokyo Medical & Dental University

Recent studies demonstrated that obese adipose tissue is characterized by adipocyte hypertrophy, followed by increases in angiogenesis, macrophage infiltration, and pro-inflammatory adipocytokine production, suggesting the previously unrecognized dynamic changes in function and morphology, which may be referred to as “adipose tissue remodeling”. Using an *in vitro* co-culture system composed of 3T3-L1 adipocytes and RAW264 macrophages, we have provided evidence that a paracrine loop involving saturated fatty acids and tumor necrosis factor a (TNFa) derived from adipocytes and macrophages, respectively, establishes a vicious cycle that aggravates inflammatory changes in obese adipose tissue. Interestingly, saturated fatty acids, which are released in large quantities from hypertrophied adipocytes via the macrophage-induced adipocyte lipolysis, serve as a naturally occurring ligand for toll-like receptor 4 (TLR4), thereby inducing the inflammatory changes in obese adipose tissue. We also found that highly purified eicosapentaenoic acid (EPA), the only class of n-3 polyunsaturated fatty acids that has been used clinically to treat hyperlipidemia, is capable of antagonizing the saturated fatty acid-induced inflammatory changes in macrophages, thereby highlighting the anti-inflammatory effect of EPA.

Monocyte chemoattractant protein-1 (MCP-1), an important chemokine whose expression is increased during the course of obesity, plays a role in macrophage infiltration into obese adipose tissue. We have recently found that MCP-1 production is induced, which is followed by extracellular signal-regulated kinase (ERK) activation and mitogen-activated protein kinase (MAPK) phosphatase-1 (MKP-1) down-regulation in obese adipose tissue prior to macrophage infiltration. *In vitro* studies with 3T3-L1 adipocytes have demonstrated that ERK activation through MKP-1 down-regulation is involved in increased production of MCP-1 during the course of adipocyte hypertrophy, suggesting that MKP-1 down-regulation is critical for the inflammatory changes in hypertrophied adipocytes at the early stage of obesity.

Our data help unveil the molecular mechanism underlying “adipose tissue remodeling” and identify a novel therapeutic target that may reduce obesity-induced adipose tissue inflammation.

Adipose tissue: Contributions to Insulin Sensitivity and Metabolic syndrome

Dr. Philipp E. Scherer
Director, Touchstone Diabetes Center
Department of Internal Medicine
The University of Texas Southwestern Medical Center

Until recently, adipose tissue has been considered to be a mere storage compartment of triglycerides. It is now clear that adipocytes are highly active endocrine cells that play a central role in overall energy homeostasis and are important contributors to some aspects of the immune system. They do so by influencing systemic lipid homeostasis, but also through the production and release of a host of adipocyte-specific and adipocyte-enriched hormonal factors, cytokines and extracellular matrix components (commonly referred to as "adipokines").

The characterization of adipocyte-specific secretory proteins involved in energy homeostasis has proven to be a very productive approach. In particular, two of these proteins have caught our attention: 1) Adiponectin/Acrp30 and 2) Resistin. Adiponectin is an adipocyte secretory protein whose circulating levels are decreased in obese and diabetic states. Adiponectin has been shown to play a role in liver insulin sensitivity and whole-body metabolism. It has also been implicated in cardiovascular health as well, at the very least as a highly sensitive serum marker for the prediction of future cardiovascular events even when controlling for conventional risk factors. Animal models also corroborate these observations, showing that adiponectin is particularly important for preventing diet-induced progression of atherosclerosis.

The exact mechanism of adiponectin's anti-atherosclerotic activity has not been completely elucidated. The association between adiponectin levels and cardiovascular risk *independent* of other variables suggests that adiponectin mediates direct effects on vascular health, as opposed to indirect effects through insulin sensitivity and diabetes.

Non-genomic regulation of cardiac ion channels by sex hormones

Dr. Tetsushi Furukawa
Professor
Department of Bio-informational Pharmacology
Medical Research Institute
Tokyo Medical & Dental University

Gender-specific-medicine (GSM) has gained much attention based on the facts that risk for many diseases and response to various therapeutic maneuvers show gender difference. It has long been known that female sex is an independent risk factor for cardiac arrhythmias called torsade de pointes (TdP). Drug-induced TdP is one of the most common causes for withdrawal of drugs from development, pre-clinical trial, and the retail market: drug-induced TdP occurs in females as twice as in males. Within females, TdP risk varies during the menstrual cycle, during pregnancy, and by post-menopausal hormone replacement therapy. These clinical data implicate the presence of acute effects of sex hormones on cardiac ion channels. Despite vigorous efforts by multiple research groups, details remain unknown. Here we show that testosterone, estrogen, and progesterone activates one of the K^+ channel (I_{Ks} channel) and inhibits Ca^{2+} channel ($I_{Ca,L}$ channel) via the non-genomic pathway of sex hormone receptors, which involves activation of eNOS and resultant release of NO. These non-genomic signaling occur in a membrane-limited manner in a specialized membrane domain, caveolae. In addition to the receptor-dependent regulation, estrogen, but not testosterone nor progesterone, regulates other K^+ channel (I_{Kr} channel) and modulates drug-sensitivity of the I_{Kr} channel. In this symposium, I will discuss the molecular mechanism of the non-genomic regulation of cardiac ion channels, and its potential clinical implication.

Mutations and electrical disease: Insights from model studies

Dr. Colleen E. Clancy
Assistant Professor
Department of Physiology and Biophysics
Department of Medicine (Cardiology)
Institute for Computational Biomedicine
Weill Medical College of Cornell University

Electrically based syndromes like arrhythmia and epilepsy are integrative disorders that result in disruption of normal electrical behavior .
Synchrony is abolished during arrhythmia, while epileptic seizures result from pathological synchronization in neuronal networks. However, understanding how these syndromes develop has been extremely difficult.
Approaches to understand system level electrical disorders that focus on one specific part of the system fail to reveal the most valuable information-how protein and cell anomalies affect complex interactions to disrupt the tissue and cause the disease state. To achieve an integrative understanding of such a complex system we are attempting to use mathematics and high performance computing to construct quantitative representations of the heart and hippocampus brain region. Such an approach will allow us to follow perturbations across multiple scales, from the modified proteins to altered cellular states to the propagation of the perturbation in cell networks. By helping us to predict the origin and pathway of pathological triggers, we may be able to improve diagnosis and treatment.

A new animal model of autism: glutamatergic hyperactivity in key neural systems

Dr. Kohichi Tanaka
Professor
Department of Molecular Neuroscience
Medical Research Institute & School of Biomedical Science
Tokyo Medical & Dental University

Autism is a neurodevelopmental disorder characterized by impairments in reciprocal social interaction, communication deficits and repetitive and restricted patterns of behavior and interests. Yet, the etiology of autism is largely unknown, although a joint contribution of genetic and environmental factors is widely acknowledged. L-glutamate, the principle excitatory neurotransmitter, plays an important role in brain development. Aberrant glutamate function is often cited as an important element of risk for autism, but little is known about the underlying molecular determinants and neural mechanisms. In the present study, we generated a genetically manipulated animal in which glutamate receptors are overstimulated by genetic down-regulation of glutamate transporters (GLT1 and GLAST). Resulting mutant mice showed abnormal social interaction and increased anxiety-like behavior. We observed enlarged amygdala and hippocampus, including activated astroglia with enlarged cell bodies and processes. These mutant mice replicate many aspects of the behavioral and neuroanatomical abnormalities seen in autism. Scanning the genomes of the largest cohort of autism spectrum disorder families revealed that GLT1 falls close to one of linkage peaks. Thus, these mutants are new animal models of autism

Dysregulated glutamate signaling is not unique to autism but also can be found in depression, schizophrenia, and several neurological diseases. Our findings open up new possibilities for treating autism and possibly other diseases sharing a common pathophysiology.

Translational Neuroscience for Major Mental Illnesses

Dr. Akira. Sawa
Associate Professor
Department of Psychiatry and Behavioral Sciences
Department of Neuroscience
Director, Program of Molecular Psychiatry
Johns Hopkins University School of Medicine

Identification of susceptibility genes for major mental illnesses, such as schizophrenia and mood disorders, has recently contributed to forward biological studies for the diseases at the mechanistic levels. However, it is still very difficult to link animal phenotypes to human conditions. Obviously, it is insufficient to expect behavioral assays as a strategy to bridge between animals and humans. I am going to overview this problem at present and discuss future perspectives beyond the dilemma.

Autoantibodies to acetylcholine receptors and muscle specific kinase in myasthenia gravis

Dr. Angela Vincent
Professor
Deaprtment of Neuroimmunology and
Head of Department of Clinical Neurology
University of Oxford

Myasthenia gravis is a prototypic acquired disease caused in most cases by antibodies to the acetylcholine receptor. The antibodies lead to loss of acetylcholine receptors at the neuromuscular junction and defective neuromuscular transmission causing muscle weakness and fatigue. The antibodies are usually detected by radio-immunoprecipitation of solubilised acetylcholine receptors that are labelled with radioactive alpha-bungarotoxin and are present in 85% of patients with generalized muscle weakness. We have recently found, using new approaches for antibody detection, that some of the 15% without these high-affinity antibodies have low-affinity acetylcholine receptor antibodies that only bind when the receptors are present at high density on a membrane surface. Interestingly, most of the remaining patients have antibodies, instead, to muscle specific kinase (MuSK) a receptor tyrosine kinase that plays an essential role during muscle development and is highly restricted to the neuromuscular junction. MuSK antibodies define a group of myasthenia gravis patients with more severe disease, lack of thymic pathology, tendency to muscle atrophy and often poor responses to treatment. The mechanisms by which the MuSK antibodies affect neuromuscular transmission and muscle function are still not clear and current concepts and animal models will be discussed.

Molecular mechanisms underlying congenital myasthenic syndromes

Dr. David Beeson
Professor
Department of Molecular Neuroscience,
MRC Senior Non-Clinical Fellow
Honorary University Lecturer,
Weatherall Institute of Molecular Medicine
University of Oxford

Congenital myasthenic syndromes (CMS) stem from genetic defects that affect transmission of information at the neuromuscular junction (NMJ) and result in fatiguable muscle weakness. They comprise a disabling – and sometimes potentially lethal - set of disorders with subtly different clinical features. Molecular genetic analysis of the CMS has defined defects in pre-synaptic, synaptic and post-synaptic proteins, with the majority located in the postsynaptic acetylcholine receptor (AChR), and its associated protein rapsyn. Recently the newly identified NMJ protein, Dok-7, has been found to be another major locus for CMS mutations. Functional analysis demonstrates diverse pathogenic mechanisms. Slow channel and fast channel syndromes are caused by kinetic abnormalities of AChR function that prolong or attenuate activations of the AChR ion channel. In AChR deficiency syndrome, the endplate AChR is reduced in number and density, and distributed over an increased area of the postsynaptic membrane. This condition is most frequently caused by mutations in the AChR e subunit gene, but also is often the result of mutations in the AChR-clustering protein, rapsyn. Dissecting the molecular genetics of these disorders provides a definitive diagnosis, a rational basis for treatment and insights into the underlying mechanisms that govern neuromuscular transmission

Dok-7/MuSK signaling and a congenital myasthenic syndrome

Dr. Yuji Yamanashi
Professor of Cell Regulation
Medical Research Institute
Tokyo Medical & Dental University

Skeletal muscle contraction is controlled by motor neurons, which contact the muscle at the neuromuscular junction (NMJ). Defects of neurotransmission at the NMJ cause muscle weakness, which can be autoimmune (myasthenia gravis) or genetic (congenital myasthenic syndromes (CMSs)). The formation and maintenance of the NMJ requires the muscle-specific receptor tyrosine kinase MuSK to orchestrate postsynaptic differentiation, including the clustering of acetylcholine receptors (AChRs). We identified a MuSK-interacting protein Dok-7, which is localized at the postsynaptic region of the NMJ. Surprisingly, this cytoplasmic adaptor-like protein plays an essential role for MuSK activation and subsequent AChR clustering in myotubes. Similar to MuSK-deficient mice, mice lacking Dok-7 form neither AChR clusters nor NMJs. Thus, Dok-7 is essential for neuromuscular synaptogensis and its interaction with MuSK appears to be crucial for this process. Furthermore, *DOK7* has been found to be a major locus for mutations that underlie CMS. Patients with *DOK7* CMS have small, simplified NMJs but normal AChR function. The most common mutation causes a C-terminal truncation, which greatly impairs Dok-7's ability to activate MuSK. Recently, a series of differing *DOK7* mutations have been identified, and the study of these mutations may help understand the underlying pathogenic mechanism of *DOK7* CMS.