Title of Project : Deciphering sugar chain-based signals regulating integrative neuronal functions

Kenji Kadomatsu
(Nagoya University, Graduate School of Medicine, Professor)

【Purpose of the Research Project】

Sugar chains are regarded as the third major biologically active macromolecule, along with nucleic acids and proteins. Japan has led the world in the field of glycobiology by elucidating complex structures and biosynthetic pathways of sugar chains. Nevertheless, how complex sugar chains regulate biological activities has remained largely unclear.

We have recently found that a small stretch of the sugar chain is responsible for the regulation of neuronal functions, and named this region the "functional domain." Furthermore, it has become increasingly clear that sugar chains are involved in various aspects of neuronal functions, such as functional and morphological synaptic plasticity during learning and memory (Fig. 1). Thus, by focusing on these neuronal functions, we expect that we could gain clues to the mechanisms of action of sugar chains.

The goal of this project is to decipher how complex sugar chains are decoded to regulate the integrative neuronal functions. By facilitating interdisciplinary collaboration and communication, we will integrate glycobiology and neurobiology to establish a new research area "neuro-glycoscience."

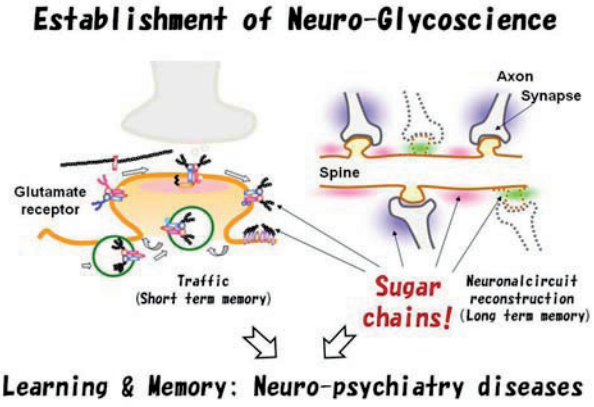


Figure 1. Establishment of neuro-glycoscience

【Content of the Research Project】

To our knowledge, this is the first trial to feature glycoscientists and neuroscientists cooperating together to accomplish collaborative research on such multiple levels. They will discuss many issues using a common platform, and will verify the mechanisms of action of sugar chains through the studies of functional domains of sugar chains, their receptors/interacting molecules, intracellular signaling/molecular interaction, and consequent neuronal functions.

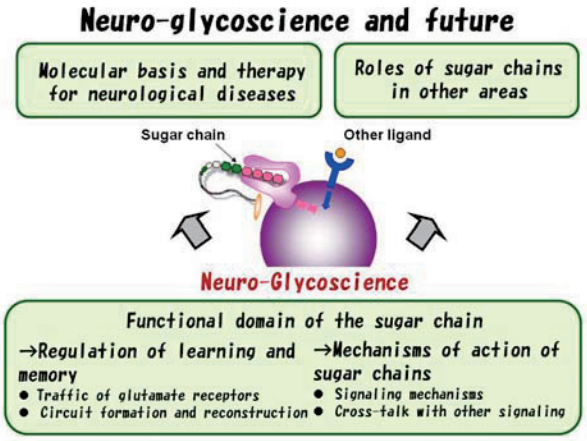


Figure 2. The future and influence of neuro-glycoscience

【Expected Research Achievements and Scientific Significance】

A new concept of the action mechanism of sugar chains will be established. Through an understanding of the relationship between the complexity and accuracy of neuronal functions and the complexity and dynamic changes of sugar chain structures, the novel research area neuro-glycoscience will be established. In addition, the achievements of this project are expected to influence other research areas, and to promote the understanding of diseases and the development of new therapies.

【Key Words】

Functional domain: A small stretch in the sugar chain, which is responsible for the regulation of neuronal functions.

【Term of Project】 FY2011-2015

【Budget Allocation】 1,145,400 Thousand Yen

【Homepage Address and Other Contact Information】

http://shinkei-tosa.net

Title of Project　Brain Environment

Ryosuke Takahashi
(Kyoto University, Graduate school of Medicine, Professor)

【Purpose of the Research Project】

The brain consists of many types of cells, such as neurons, glial cells, vascular cells, and immune cells. Neuronal health is maintained through the maintenance of a healthy environment by cells surrounding neurons. For many years, neurons have been the main focus of neuroscience research. In neurodegenerative disease research, such as in Alzheimer's and Parkinson's diseases, the primary research question was "Why are neurons dying?" To date, many important findings explaining neuronal death were made such as the accumulation of abnormal proteins and organelle dysfunction (mitochondria, endoplasmic reticulum, etc.).

However, recent unexpected new findings prompted us to recognize the importance of the extra-neural environment in disease. Glial cells are shown to play an important role in disease progression. Further, abnormal proteins released from damaged neurons trigger disease propagation in a spatial manner. These findings led us to explore the 'brain environment' in health and disease.

Therefore, our aim is to understand the 'brain environment' by creating a new innovative research area with a team of researchers from the fields of neurological and psychiatric diseases, basic neuroscience of development, regeneration, glial biology, neuroendocrinology, and molecular neuroimaging. Furthermore, we are promoting research elucidating the mechanisms of neuropsychiatric disease from the viewpoint of brain environment destruction.

【Content of the Research Project】

Our research team consists of three groups; (A01) "Mechanisms of neuronal dysfunction", (A02) "Extra-neural environment", and (A03) "Imaging".

The "Mechanisms of neuronal dysfunction" group aims to uncover the mechanisms of dysfunction within neurons, which leads to the destruction of brain environment, under neurological and psychiatric disease conditions. The "Extra-neural environment" group aims to elucidate the mechanisms of 1) maintenance and destruction of brain environment, and 2) propagation of brain environmental deterioration, focusing on glia-neuron interaction, neuroinflammation, and neuroendocrine systems in health and disease.

The "Imaging" group aims to understand the brain environment by visualizing the elementary processes of maintenance and deterioration of brain environment using cutting-edge molecular imaging techniques including PET (Positron Emission Tomography) on laboratory animals and cell models.

【Expected Research Achievements and Scientific Significance】

A01: Elucidating 1) molecular mechanisms of neuronal death in neurodegenerative and psychiatric diseases, mainly from the viewpoint of intra-neuronal dysfunction, and 2) the mechanisms through which the damaged neurons release "toxic" signals such as abnormal proteins.

A02: Elucidating 1) mechanisms how extra-neuronal cells such as glial cells in the brain environment recognize and respond to toxic signals released from damaged neurons in brain diseases and trauma, and 2) mechanisms of propagation of disease when brain environment is deteriorated.

A03: Understanding brain environment through visualizing each elementary process in pathological disease conditions through the use of cutting-edge molecular imaging techniques (in vivo and cell models). Enhancing research activities of the team, and promoting collaborative research projects through application of imaging techniques.

【Key Words】
Brain Environment, Neurodegenerative Diseases, Glia, Molecular Imaging
【Term of Project】 FY 2011-2015
【Budget Allocation】 1,185,400 Thousand Yen
【Homepage Address and Other Contact Information】
http://www.neurol.med.kyoto-u.ac.jp/brainenvironment/

Title of Project : Regulation of polarity signaling during morphogenesis, remodeling, and breakdown of epithelial tubular structure

Akira Kikuchi
(Osaka University, Graduate school of Medicine, Professor)

【Purpose of the Research Project】

Epithelial tubular structures are essential units for each organ. Epithelial stem cells differentiate into epithelial cells, which form tubule-like structures through assembly and coherent association, and its structures are maintained. Disruption of epithelial tubular structures leads to developmental malformations and various postnatal diseases, including cancer. While understanding of cellular functions at the molecular level has been deepened, the molecular mechanism of the formation and maintenance of epithelial tubules remains to be clarified.

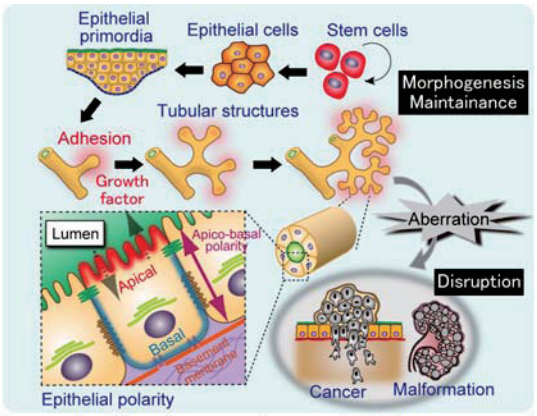


Figure 1 Morphogenesis, maintainance, and disruption of epithelial tubular structure.

There are various patterns of epithelial tubular structures, depending on organs. However, we assume that the principle structure of epithelial tubules is regulated by cellular polarization. In this project, we challenge to clarify unresolved issues existed between cell and organ levels: how epithelial cells are polarized to form tubular structures; how disruption of epithelial tubular structures results in diseases.

【Content of the Research Project】

Understanding of the mechanism underlying the formation of epithelial tubular structures and that of its disruption are two side of the same coin. Therefore, simultaneous analyses of both normal and pathological conditions are required to clarify the molecular mechanism of the formation and maintenance of epithelial tubular structures via cell polarity regulation. Thus, this project has two cooperative research groups with different strategies to clarify the mechanism of "formation and maintenance of epithelial tubular structures" and "disruption of epithelial tubular structures".

【Expected Research Achievements and Scientific Significance】

While researches on the formation of central nervous and blood vascular systems, which also show tubular structures, have been progressing, this groundbreaking study on epithelial tubular systems has just begun. Progress in this new research area would contribute to understanding of functional relationship between epithelial tissues and other tissues. It is also expected to contribute to understanding of the formation of central nervous and blood vessel systems. In addition, research achievement in this project would be useful for developing regenerative medicine in next generation, which will be performed on the basis of further understanding of tissue conformation. Finally, we would like to establish new scientific field called "Tubulology (Tubule + biology)" by promoting this new research.

【Key Words】

Polarity signaling: The system that regulates the asymmetric accumulation of mobile components and the oriented organization of polar cytoskeletal components.

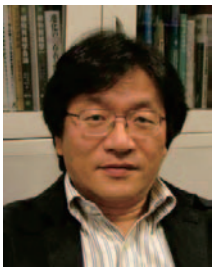
Epithelial tubular structure: Tubule-like structure with epithelial cells having an apical free and a basal surface.

【Term of Project】 FY2011-2015

【Budget Allocation】 1,035,500 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.med.osaka-u.ac.jp/pub/molbiobc/tubulology/

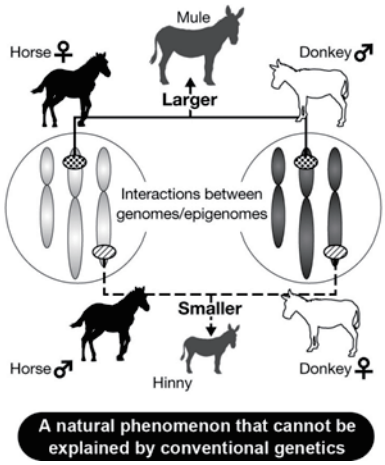


Title of Project : Correlative Gene System: Establishing Next-Generation Genetics

Seiji Takayama
(Nara Institute of Science and Technology University, Graduate School of Biological Sciences, Professor)

【Purpose of the Research Project】

To date, biology has been developed by studying model organisms, which have homogenous genome. Whereas, natural organisms have a highly polymorphic genome and epigenome, in which the complex "correlative gene interaction" determines the actual phenotypes. Conventional genetics cannot always explain such complex natural phenomena. For example, the mule, which is produced by crossing of a female horse and male donkey, is large and suitable for livestock; in contrast, the hinny, which is produced by crossing of a female donkey and male horse, is small and not suitable for livestock. These mechanisms are largely unknown, and such complex genetic phenomena may result from correlative gene interaction between female and male with different genome and/or epigenome. Here, we refer to these as-yet-unknown biological interactions as a "correlative gene system."



In this project, we will uncover molecular mechanisms and the common principle of the "correlative gene system," which drives the diversity and complexity of biological events. Furthermore, by studying the evolutionary process that produces highly polymorphic natural organisms, we will establish a field of next-generation genetics with the concept of "correlative gene system".

【Content of the Research Project】

This research project is primarily intended to dissect common molecular mechanisms of the "correlative gene system" between intra- and inter-individual genomes. Especially, it becomes obvious as the harmonic interaction or conflict between the male and female genomes when they meet each other during reproduction. Therefore, our project includes research themes related to sexual reproduction such as gamete selection, imprinting, hybrid vigor/weakness and speciation. We are also interested in the compatibility or incompatibility of interactions between different species, such as host-parasite interaction and symbiosis.

The unraveling of each "correlative gene system"-related phenomenon will lead to overall understanding of the common mechanisms. Gene duplication and epigenetic regulation are possibly involved in the "correlative gene system," as basic molecular mechanisms. Moreover, we will establish a new research field of genetics by examining the evolutionary history of this system.

【Expected Research Achievements and Scientific Significance】

Because the relationship between gene(s) and phenotype(s) is not linear, we still do not have an entire biological view of the complex living organism, although the genomes of many plants and animals have been sequenced. It is also difficult to understand lifestyle diseases and agricultural traits, which are controlled by several loci. This might be partly due to the lack of our understanding of the "correlative gene system." When we systematically elucidate what the "correlative gene system" is, our results are expected to contribute to not only fundamental biology but also to applied areas such as breeding and ecosystem integrity.

【Key Words】

Correlative gene system: A concept of genetic systems producing the phenotypic diversity of living organisms via interaction among various alleles, genes and epigenetic mechanisms.
Epigenome: Overall epigenetic status of a genome, which is determined by DNA and/or histone modification.

【Term of Project】 FY2011-2015

【Budget Allocation】 1,217,000 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.ige.tohoku.ac.jp/prg/genetics/
takayama@bs.naist.jp

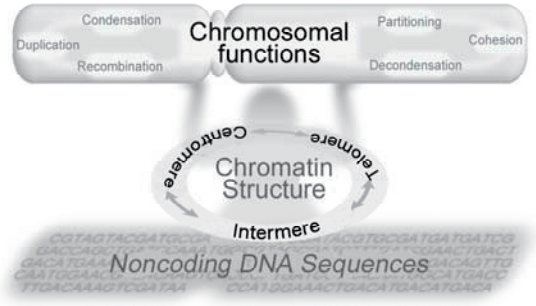
Title of Project : Functions of Non-coding DNA Region for GenomeIntegrity

Takehiko Kobayashi
(National Institute of Genetics / SOKENDAI, Professor)

【Purpose of the Research Project】

Most part of the eukaryotic genome is occupied by noncoding DNA regions that do not encode proteins. Those regions have functions to control all of the chromosomal events (gene expression, initiation of DNA replication, recombination hotspot that causes gene amplification and rearrangement, chromosomal fragile site, chromosome condensation, chromosome segregation, etc.). However, those noncoding DNA regions are so to speak "unexplored regions of the genome" because most part of the regions is occupied by repetitive sequences such as transposons, repeated ribosomal RNA genes, and microsatellites.

By means of experimental and informatical methods in this research project, we will comprehensively identify the functional noncoding DNA sequences we name “intermeres” that scatter in the genome in large numbers. Furthermore we aim to clarify the mechanisms in regulation of chromosomes by noncoding DNA by focusing on the chromatin structure of the intermeres and their network with telomeres and centromeres (three-mere network). Also we will analyze the mechanisms in occurrence of abnormal cellular functions such as oncogenesis and aging caused by malfunctioning regulatory system.



(Fig.) The functional sequences (three-meres: centromere, intermere, and telomere) present in the noncoding DNA regions support the chromosomal functions by forming a network. We will clarify the whole mechanisms in this research project.

【Content of the Research Project】

The following four teams in cooperation will analyze the entity of intermeres that are noncoding functional sequences, and factors related with the three-mere network.

1) The Sequence Team will identify the various DNA sequences in noncoding DNA regions that function in maintaining the chromosomal functions and clarify the role of the associated proteins, RNAs, etc. 2) The Structure Team will identify and analyze arrangement of local nucleosomes regulating chromosomal functions in the hierarchy above intermeres, epigenome modifications such as histone modifications, and change of chromatin structure. The team will also clarify the roles of the factors in maintenance of chromosomes. 3) The Network Team will clarify the entity of network that connects the three-meres through the characteristic chromatin structure. 4) The Pathological Analysis Team will clarify how the failure of chromosome-maintenance system influences the cellular functions and causes oncogenesis and aging.

【Expected Research Achievements and Significance】

In this research project, we will construct a Japanese cooperative research system based on strong relationships of mutual trust. By this, discovery of the third functional sequences following centromere and telomere, and clarification of novel mechanisms that regulate those sequences in an integrated manner are expected, which would let us take the global initiative in this field. The intermere and its network that this research project provokes are definitely essential factors for the chromosome maintenance system. Failure of the system would result in not only chromosomal inversion, translocation and abnormality such as gene amplification, but also increase of cancer incidence through the occurrence of extremely fragile sites of chromosome, inactivation of tumor-suppressor genes, activation of oncogenes, and furthermore association with progressive diseases caused by cell death, aging, etc. Identification of intermere and its network will lead to constructing a basic research for the mechanisms of those diseases, and following development of novel diagnostic methods and treatment techniques.

【Key Words】

Noncoding DNA region: DNA region that is not translated into protein. Repetitive sequences: Sequences repetitively present in the genome such as transposons, ribosomal RNA genes, and microsatellites. They account for approximately half of the human genome. Intermere: Neology. Noncoding functional sequences present in the main body of chromosome except for telomere and centromere. Chromatin: Consisted of a nucleosome structure in which histones are wrapped by DNA. Modification of histones such as acetylation and methylation alters the local chromatin structure.

【Term of Project】 FY2011–2015

【Budget Allocation】 1,189,100 Thousand Yen

【Homepage Address and Other Contact Information】

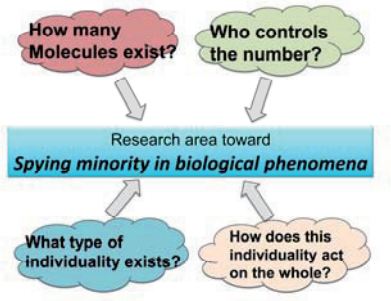
http://www.cdb.riken.jp/cmd/ncDNA.html
takobaya@lab.nig.ac.jp

Title of Project : Spying minority in biological phenomena -Toward bridging dynamics between individuals and ensemble precesses-

Takeharu Nagai
(Hokkaido University, Research Institute for Electronic Science, Professor)

【Purpose of the Research Project】

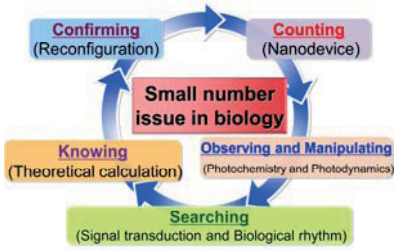
The "cooperative" functioning of a nanosystem composed of a small number of elemental molecules can be considered as a vital phenomenon in living system. However, no previous study has analyzed the elementary process of cooperation among small groups of molecules (minority molecules) in live cells. As a result, there is no information on the approaches to induce extremely high levels of cooperation among these molecules. Cooperative reactions among these small groups of molecules contribute to output stabilization; conversely, the output can also lose stability because of a lack of cooperation between these molecules. The equivocal nature of these reactions may be responsible for the operating stability of macroscopic life systems across hierarchies and may also be indirectly responsible for partial operating instability. Therefore, this equivocal behavior is considered to be extremely important in understanding the operating principles of living systems. However, there are no theories describing the reactions of these minority molecules in cells, and no techniques have been developed to manipulate and measure the intracellular behaviors of these minority molecules. In this research area, we have prepared a biological system composed of minority molecules, and conducted research to construct a theory that can describe the reactions among minority molecules.



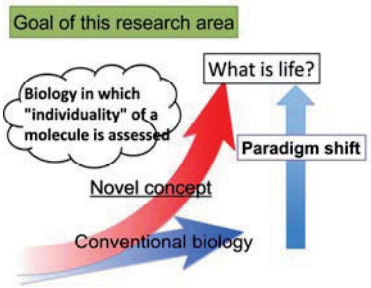
【Content of the Research Project】

In this research area, we study chemical reaction systems composed of a small number of elemental molecules that function neither as individual molecules nor as a part of a majority group. By combining the principles of optical microscopy, microelectromechanical systems (MEMS) technology, fluorescent physical chemistry, synthetic organic chemistry, protein engineering, cell biology, systems biology, and mathematical science, we developed a new field of research called "minority biology."

【Expected Research Achievements and Scientific Significance】



"What is life" is fundamental question in bioscience, and are difficult to explain using conventional scientific approaches. From our studies, we expect a paradigm shift to occur not only in biology but also in other scientific fields such as physics and c hemistry. The new concepts derived from our study may provide important information and facilitate the development of the basic technology necessary for artificially synthesizing biological nanomachines with extremely high energy-utilization efficiency, which will be required worldwide in the future.



【Key Words】

System of minority molecules: A reaction system composed of a few tens of molecules with significant levels of discreteness.

【Term of Project】 FY2011-2015

【Budget Allocation】 1,191,800 Thousand Yen

【Homepage Address and Other Contact Information】

http://paradigm-innovation.jp

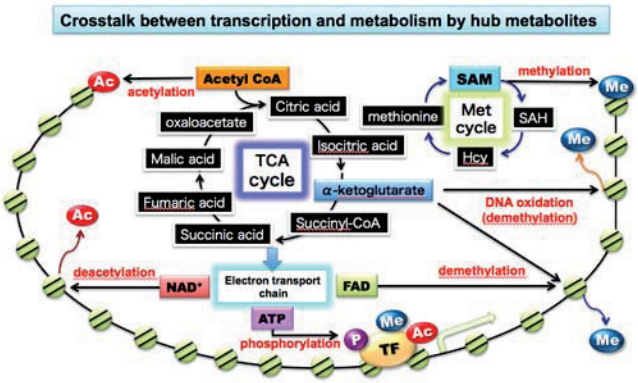
Title of Project : Crosstalk of transcriptional control and energy pathways by hub metabolites

Akiyoshi Fukamizu
(Grad. School Life Environ. Sci. Univ. of Tsukuba, Professor)

【Purpose of the Research Project】

Gene expression is controlled by transcriptional environments that are formed by the genomic information encoded by DNA; DNA methylation; epigenomic information regulated by chromatin modifications such as phosphorylation, acetylation, and methylation of histones; and the effect of transcription factors. These transcriptional environments are deeply involved in a variety of cell functions such as the establishment of cell specific identity, cell proliferation, and differentiation coupled with signal pathways and intranuclear complexes. On the other hand, cell metabolism is dynamically regulated by cell proliferation conditions and differentiation steps; thus, it enables the maintenance of homeostasis and the transition into a new steady state. In this case, some metabolites (hub metabolites; ATP, SAM, and so on) such as those generated by glycolysis, the TCA cycle, and the methionine cycle, are utilized in the formation of transcriptional environments.

Therefore, we aim to understand the effect of transcriptional environments on metabolism or the effect of metabolic changes induced by the stimulation of cells as well as internal and external stimulation of individuals on the construction of transcriptional environments.



【Content of the Research Project】

Research in transcription and metabolism has greatly progressed independently; however, a research field that encompasses transcription and metabolism fields and links them to a vital function has not been established. Complex network and transcription-metabolism systems relating to the expression of target genes are investigated by focusing on mechanisms such as "writing" by modification transferase, "reading" of modifications by adaptor factors, "erasing" by demodification enzymes, and "rewriting" by chromatin repair, in order to understand the crosstalk control between the formation of transcriptional environments and energy metabolism.

【Expected Research Achievements and Scientific Significance】

It has been shown the analyses of genomic predisposition (genetic alteration) contribute greatly to resolving of the pathogenic mechanism of diseases depending on gene mutations. Recently, a new concept has been proposed wherein a change in the transcriptional environment, not accompanied by DNA mutation, widely associates with the onset of diseases involved in nutrition and energy metabolism as well as functions as an epigenomic predisposition (epimutation). Thus, focusing on the crosstalk between transcriptional environments and energy metabolism may elucidate a new molecular mechanism in the maintenance of homeostasis, stress response, and signaling. Furthermore, it will contribute to the understanding of the cause of diseases such as metabolic diseases and cancer and validation of therapeutic targets.

【Key Words】

Hub metabolites: Functional small molecules produced from a variety of metabolic pathways.
Epigenome: The state of chromatin modification in specified cells.

【Term of Project】 FY2011-2015

【Budget Allocation】 1,146,200 Thousand Yen

【Homepage Address and Other Contact Information】

http://tmsystem.tara.tsukuba.ac.jp/

Title of Project: Matryoshka-type evolution

Tomoyoshi Nozaki, M.D., Ph.D.
(Department of Parasitology, National Institute of Infectious Diseases, Director
Tsukuba University Graduate School of Life and Environmental Sciences, , Professor)

【Purpose of the Research Project】

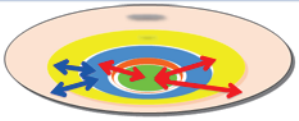
The objective of this project is to understand the role of endosymbiosis in the evolution of eukaryotes and their organelles. The endosymbiotic theory for the origins of the mitochondria and chloroplasts is widely accepted, that is, these organelles originated as free-living bacteria taken inside another cell as endosymbionts. Our understanding, however, of the formation of secondary plastids and other complex structures, through successive rounds of endosymbiosis is incomplete. Similarly, adaptation mechanisms and enslavement in endosymbiont-host associations are poorly understood. The multilayered and multidirectional relationship between the endosymbiont and host cell mimics the Russian nesting doll called *Matryoshka*, and we designate the mechanisms involved in eukaryote evolution under such associations as *Matryoshka*-type evolution.

The objectives of our proposal are: (1) To discover ecosystems that facilitate the formation of endosymbiotic relationships, and understand the mechanisms involved; (2) To determine the diverse functions of endosymbiosis-derived compartments and organelles; (3) To establish the concept of organelle-driven evolution; and (4) To develop basic technologies to create artificial organelle-driven eukaryotic evolution *in vitro*.

Fig. 1. New paradigm "*Matryoshka*-type evolution"
Multilayered and multidirectional relationship in endosymbiont-host associations lead to the evolution of eukaryotes and their organelles.

Multilayered	For example, a bacterium or plastid in a protozoan parasite, living inside a mammalian host.
Multidirectional	For example, from inside to outside and vice versa.

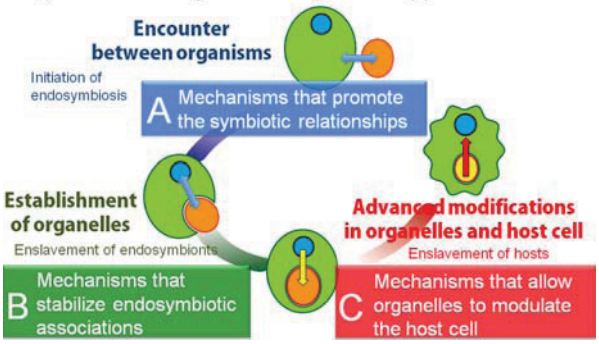

Russian nesting doll or *Matryoshka*


Schematic representation of multilayered and multidirectional relationships

【Content of the Research Project】

The research project is divided into three parts based on the stages involved in the formation of endosymbiosis-derived compartments and organelles: (1) Requirements involved in the establishment of symbiosis and endosymbiosis; (2) Modifications undergone by endosymbionts and host cells during organelle establishment; (3) Advanced modifications in organelle functions that facilitate enslavement of the host cell to the endosymbiont.

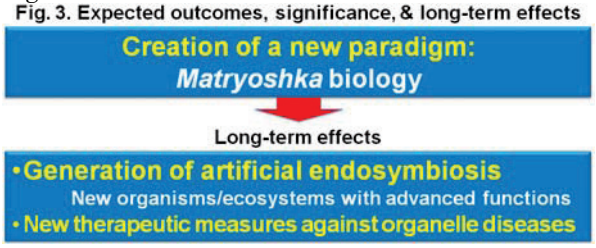
Fig. 2. Three steps in "*Matryoshka*-type evolution"



【Expected Research Achievements and Scientific Significance】

We expect to create and establish a new paradigm: that endosymbiosis is the major driving force in eukaryotic evolution, and that modifications in host cell functions are driven by endosymbiosis-derived organelles.

Fig. 3. Expected outcomes, significance, & long-term effects



【Key Words】

Matryoshka: Russian nesting doll; Endosymbiosis: A type of symbiotic relationship, or intimate and prolonged association between different organisms, in which one organism (endosymbiont) lives inside another organism (host) with the two participants typically behaving as a single organism.

【Term of Project】 FY2011-2015

【Budget Allocation】 1,179,500 Thousand Yen

【Homepage Address and Other Contact Informetion

http://www.nih.go.jp/niid/para/matryoshka-evolution/
nozaki@nih.go.jp