【Grant-in-Aid for Scientific Research (S)】

Broad Section G

Title of Project：Regime shifts in coastal marine ecosystems: an empirical approach based on advanced monitoring and nonlinear dynamical theory

KONDOH Michio
(Tohoku University, Graduate School of Science, Professor)

Research Project Number：19H05641　Researcher Number：30388160
Keyword：environmental DNA, biodiversity, resilience, coastal ecosystem, data-driven science

【Purpose and Background of the Research】

Anthropogenic disturbances and global changes may cause a dramatic shift in species composition and degradation of ecosystem services. Such an abrupt change in ecosystems is called “regime shift”, which is, according to theory, caused by a change in dynamical property of ecosystems. However, there are few direct empirical evidences from real nature. How to forecast a regime shift is another question that has not been fully answered.

There are two major difficulties to overcome to advance the empirical study of regime shift. First, we are lacking of good monitoring data of regime shift happening in nature. Ecological monitoring is usually effort-demanding and therefore it is not straight forward to capture a regime shift of many-species communities in the field. Second, we are lacking of effective methods that enable evaluating the dynamical property of ecological systems. Consequently, the link between regime shift and dynamical properties is left unanswered.

In the present project we are to give a better empirical understanding of, and to develop a method to forecast, ecological regime shifts by combining the advanced ecological monitoring method and data analytical tools, which allow us overcoming the two abovementioned difficulties.

【Research Methods】

Environmental DNA, the recently monitoring method for biodiversity, forms the basis of present project. The eDNA technique allows one to make a list of biological species from the DNA fragments organisms shed into the environmental water (Fig. 1). We conduct weekly to monthly eDNA monitoring at dozens of monitoring sites located along Japanese coast and obtain a highly-resolved monitoring data that captures the spatio-temporal dynamics of several hundreds to thousands of fish species. Using this massive data, we are to depict when and where ecological regime shifts take place along Japanese coast.

The eDNA monitoring data would be further analyzed by using a modeling tool based on non-linear dynamical theory to test the hypothesis that an ecological regime shift is caused by a change in dynamical property of ecological systems. Furthermore, by using the modeling technique to evaluate system’s stability from time-series data, we are to develop a method with which one can forecast the ecological regime shift either earlier, more correctly or more sensitively.

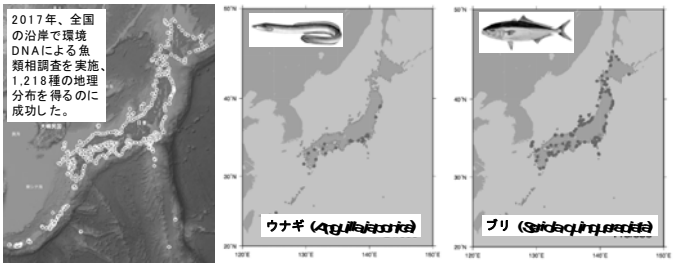

Fig. 1 One can get an advanced data of fish community along Japanese coast by using eDNA.

【Expected Research Achievements and Scientific Significance】

There are four expected achievements from the present project. We would (1) identify the spatio-temporal patterns of ecological regime along Japanese coast and (2) demonstrate if ecological regime shifts are related to changes in dynamical properties of ecological systems. We also develop methods (3) to judge if there is an on-going regime shift or (4) to forecast the future regime shift by using ecological monitoring data,

【Publications Relevant to the Project】

Miya et al. (2015) MiFish, a set of universal primers for metabarcoding environmental DNA from fishes: detection of > 230 species from aquarium tanks and coral reefs in the subtropical western North Pacific. Roy Soc Open Sci 2: 150088.
Ushio et al. (2018) Fluctuating interaction network and time-varying stability of a natural fish community. Nature 554: 360-363.

【Term of Project】 FY2019-2023

【Budget Allocation】 153,700 Thousand Yen

【Homepage Address and Other Contact Information】

https://www.lifesci.tohoku.ac.jp/research/teacher/detail---id-45517.html
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Title of Project：Elucidation of cognitive and learning mechanism of cerebral cortex by multiscale optogenetics

OHKI Kenichi
(The University of Tokyo, Graduate School of Medicine, Professor)

Research Project Number：19H05642　Researcher Number：50332622
Keyword：cerebral cortex, visual cortex, imaging, optogenetics, neural circuits, information processing

【Purpose and Background of the Research】

How does the brain perform complex information processing? How does the brain alter neural circuits through learning and acquire complex functions? Our first goal is to elucidate what kind of information each neuron receives and combines it to output complex information, as an elementary process of information processing in the brain. Our second goal is to elucidate how the information input to each synapse changes, as an elementary process of learning and memory. We will further elucidate the learning rules of synaptic plasticity from the viewpoint of information, and how the learning rules relate to the changes in the function of the cell.

In order to achieve both goals, we will develop a spine level functional imaging method using optogenetics, visualize the information input to each synapse, observe the change continuously, and elucidate the elementary processes of information processing and learning and memory at synapse level. Furthermore, in combination with cell population imaging, we will elucidate how these elementary processes contribute to learning as a whole network. Finally, we will activate the cell population artificially using optogenetics, and examine whether the activity of the cell population has a causal relationship with perception and learning. As described above, in multiscale from the synapse level to the whole brain level, we will elucidate the principles of information processing and learning rules of the brain.

【Research Methods】

(1) Develop functional imaging method of spine level using optogenetics
We will develop a method to comprehensively examine what kind of information is input to thousands of synapses of each neuron.
(2) Elucidate the elementary processes of information processing in the brain
We will develop a method to systematically investigate nonlinear complex receptive fields of neurons in higher visual area using deep learning. By combining the method of item (1), we will elucidate what kind of information each neuron in higher visual cortex receives and combines it to output complex information such as the shape of an object.
(3) Elucidate elementary processes of learning in the brain and learning rules
While the animal learns a new figure over time, we will observe changes in the selectivity of neurons in the higher visual cortex, and observe changes in the information input to the individual spines of the cells over time. We will clarify the learning rules of synapse from the viewpoint of information.
(4) Elucidate changes in information representation by cell population associated with learning and memory
In (3), we will clarify how the information input to individual neurons changes with learning. Here, we will further clarify how it contributes to learning as a whole network.
(5) Develop methods of photo-suppression at the area level and photo-activation of cell populations
In order to examine the causal relationship between the activity of the cell population and perception and learning, we will develop methods of photo-suppression and photo-activation.
(6) Verify causality between cell population activity in higher visual cortex and perception and learning
Using the methods developed in (5), we will examine the causal relationship between cell population activity and perception and learning.

【Expected Research Achievements and Scientific Significance】

We will clarify what kind of information each neural cell in the higher visual area receives and combines it to output complex information, and the learning rules of synaptic plasticity from the view point of information. We expect that the elucidation of the principle of information processing and the learning rule about the information will lead to the development of a new algorithm of artificial intelligence.

【Publications Relevant to the Project】

・Ukita J, Yoshida T, Ohki K. Characterisation of nonlinear receptive fields of visual neurons by convolutional neural network. Sci Rep. 2019 Mar 7;9(1):3791.

【Term of Project】

FY2019-2023

【Budget Allocation】

156,200 Thousand Yen

【Homepage Address and Other Contact Information】

https://physiol1.m.u-tokyo.ac.jp/ern24596/

Title of Project：Understanding the seasonal adaptation mechanism and its application

YOSHIMURA Takashi
(Nagoya University, Graduate School of Bioagricultural Sciences, Professor)

Research Project Number：19H05643　Researcher Number：40291413
Keyword：photoperiodism, seasonal adaptation, medaka, chemical genomics

【Purpose and Background of the Research】

Organisms exposed to seasonal changes in the environment, such as daylength, temperature, and precipitation, are known to adapt their physiology and behavior, including reproduction, hibernation, migration and molting accordingly. How these organisms sense these seasonal changes, remains unknown. In addition, the mechanistic nature that drives the seasonally regulated physiology remains unclear. Furthermore, morbidity in humans, owing to cardiac, cerebrovascular, infectious, and psychiatric diseases, is seasonal, and peaks in winter. At high latitudes, about 10% of population suffer from winter depression, and high suicide rates are a serious social issue. However, the underlying mechanism is yet to be determined.

Medaka is an excellent model because of its robust responses to seasonal changes in daylength and temperature, as well as the availability of genome-editing techniques. The difficulties in manipulating genes in some species (e.g., quail and sheep) and the unclear seasonal responses in other species (e.g., zebrafish and mouse), presents medaka as an ideal system for these studies (Fig. 1). Furthermore, small teleosts, such as zebrafish and medaka, are emerging models for the study of complex disorders and are becoming powerful models in pharmacogenetic studies.

In this study, we aim to investigate the genetic basis of the seasonal sensing mechanism by using the medaka fish. We will also investigate the molecular basis of seasonally regulated physiology by assessing gene expression on a genome-wide scale in tissue samples collected every month over a period of two years. Furthermore, compounds that rescue the winter phenotype will be developed using a chemical genomics approach.

【Research Methods】

Medaka populations captured at higher latitudes show more robust responses to daylength and temperature alterations than do the populations found at lower latitudes. Our genetic analysis of this fish has already detected significant quantitative trait loci. The candidate genes will be evaluated to understand the genetic basis of the seasonal sensing mechanism.

The RNA-seq analysis of the two-year time-series samples identified seasonally oscillating genes in the medaka fish. We plan to elucidate the molecular basis of the seasonally regulated physiology and behavior.

A multi-omics analyses, together with a chemical screening of the winter medaka to understand and rescue the winter phenotype, will also be performed.

【Expected Research Achievements and Scientific Significance】

Living organisms adapt to seasonal alterations on earth. Although this phenomenon has attracted great interest, the underlying mechanism remains unknown and this is a fundamental question in biology. This study is expected to uncover the genetic and molecular bases of these mechanisms in vertebrates and develop compounds that could regulate the seasonal adaptation mechanisms in animals.

【Publications Relevant to the Project】

- Shimmura T, et al., Dynamic plasticity in phototransduction regulates seasonal changes in color perception. *Nature Communications* 8, 412 (2017)
- Tamai TK, et al., Identification of circadian clock modulators from existing drugs. *EMBO Molecular Medicine* 10, e8724 (2018)
- Nakayama T et al., Seasonal regulation of the lncRNA *LDAIR* modulates self-protective behaviors during the breeding season. *Nature Ecology & Evolution* 3, 845-852 (2019)

【Term of Project】

FY2019-2023

【Budget Allocation】

153,500 Thousand Yen

【Homepage Address and Other Contact Information】

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Figure 1 Medaka shows clear seasonality.

Title of Project：Dissecting the mechanism underlying behavioral regulation through real-time spatiotemporal manipulation of neural circuits

MORI Ikue
(Nagoya University, Graduate School of Science, Professor)

Research Project Number：19H05644　Researcher Number：90219999
Keyword：Neurobiology, Variability, Information Processing, Behavior

【Purpose and Background of the Research】

In contrast to computers, brain computation seems far more variable and complex. Intriguingly, the brain enables to generate variable yet distinct behavioral outputs even when the same sensory stimuli are presented to the animal. Such probabilistic feature of animal behaviors is thought to be important for the survival and reproduction of the animal in ever-changing environments. Despite how brain generates variable behavioral outputs is a fundamental question in neuroscience, the logics behind such variable feature are still elusive. The compact nervous system of *C. elegans* provides an excellent opportunity to dissect the neural mechanisms underlying variability in brain function.

We recently observed that optogenetic activation of a single *C. elegans* sensory neuron evoked multiple behavioral responses. A brain-wide single neuron ablation coupled with high-throughput behavioral analysis revealed that distinct behavioral responses induced by this single neuron activation required recruiting different neural circuits, each of which is composed of unique combination of neurons. Further, some neurons among the components of these neural circuits showed apparent spontaneous activities even when the sensory neurons were silent.

These observations suggested the possible basis of variability in brain function, where the changes in the activity of the sensory neuron can be interpreted differently depending on the internal state of the nervous system, and hence generate distinct behavioral outputs. In this study, we aim to investigate this possibility and identify the neural principle of variability in brain function.

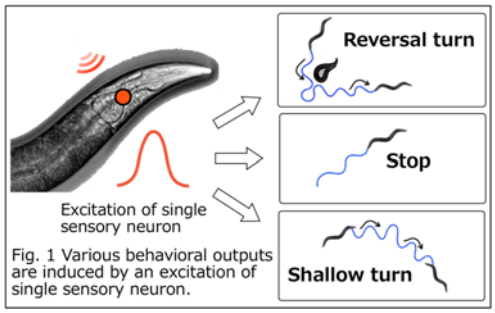


Fig. 1 Various behavioral outputs are induced by an excitation of single sensory neuron.

【Research Methods】

We will develop a new custom microscope system with real-time feedback system, in which timing of optogenetic manipulation of the sensory neuron can be determined by real-time monitoring of neural states of freely-moving animals. With this system, we plan to perform real-time analysis of the following components: 1) tracking the animal movement; 2) identifying neurons in the moving animals; 3) detecting the calcium signals from the neurons; and 4) analyzing the neural activity and determine the timing of optogenetic manipulation of the sensory neuron.

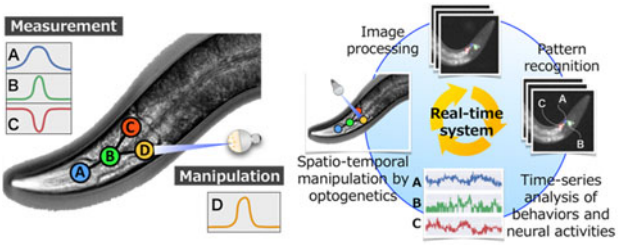


Fig. 2 Real-time optogenetic system to be established

【Expected Research Achievements and Scientific Significance】

Variability in behaviors is a unique feature of living organisms that distinguish them from computers. This study aims to understand the neural logics of information processing that confers variability in brain function. Understanding the principle of variability will be a milestone of neuroscience and also provide a platform for the development of new algorithms for soft computing.

【Publications Relevant to the Project】

Ikeda M., Nakano S., Giles A.C., Costa W.S., Gottschalk A., and Mori I.
Circuit Degeneracy Facilitates Robustness and Flexibility of Navigation Behavior in *C. elegans*. bioRxiv (2018)
https://doi.org/10.1101/385468

【Term of Project】

FY2019-2023

【Budget Allocation】

121,700 Thousand Yen

【Homepage Address and Other Contact Information】

https://nsi.bio.nagoya-u.ac.jp/en/
http://elegans.bio.nagoya-u.ac.jp/~lab/index.html

【Grant-in-Aid for Scientific Research (S)】

Broad Section G

Title of Project：Multi-scale molecular dynamics simulation on biomolecular dynamics in crowded cellular environments

SUGITA Yuji
(RIKEN, Cluster for Pioneering Research, Chief Scientist)

Research Project Number：19H05645　Researcher Number：80311190
Keyword：Multi-scale simulation, crowded cellular environment, liquid-liquid phase separation, protein conformational flexibility, enzyme reaction

【Purpose and Background of the Research】

Proteins or other biomacromolecules are crowded at high concentration in a living cell. Recently, the role of non-specific molecular interaction in the environments is found to be essential for various cellular functions.

In this research, we study both specific and non-specific molecular interactions and biomolecular dynamics in crowded cellular environments. For this purpose, we develop multi-scale molecular dynamics simulation methods combining coarse-grained models, atomistic models, and hybrid quantum mechanics/molecular mechanics (QM/MM) models. Simulations using different molecular models are connected by informatics approach.

【Research Methods】

The multi-scale simulation methods are developed and implemented into GENESIS molecular dynamics software. This software has been developed in RIKEN for large-scale atomistic simulations on K computer or post-K (Fugaku) computer.

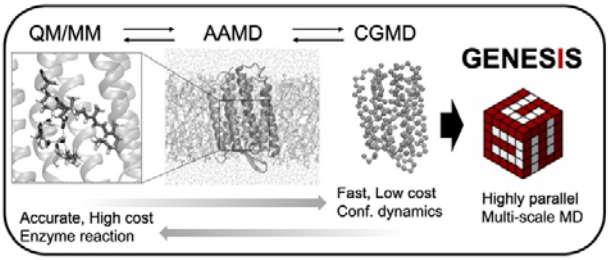


Figure 1　Multi-scale simulation method

In this research, we mainly develop coarse-grained simulations as well as QM/MM calculations. We also develop new methods to connect simulations with different molecular models by using informatics approaches, such as machine learning or Bayesian theory.

The developed methods are applied to two biological phenomena. One is liquid-liquid phase separation caused by proteins in signal transduction pathways. We examine the role of protein conformational flexibility and stability on the formation of liquid-liquid phase separation by performing multi-scale molecular dynamics simulations, solution NMR, and in-cell NMR spectroscopy. Simulation results are, thus, examined experimentally for improving the reliability of computational models and methods.

Second one is the role of cellular environments in enzymatic reactions. Enzymes can catalyze chemical reactions in a living cell. Before conducting the enzyme catalysis, substrate binding is required for enzyme, which can be affected by the surrounding environments. We study the substrate channeling in tryptophan synthase by computer simulations, such as atomistic molecular dynamics and hybrid QM/MM simulations. The simulation results are compared to the existing experimental results.

【Expected Research Achievements and Scientific Significance】

We can develop unique and useful multi-scale simulation modules in GENESIS. Since GENESIS is freeware under GPLv2 license, the developed methodologies will be released in future version of GENESIS. The multi-scale simulation will be available on Fugaku computer as well as PC-clusters with/without GPUs.

To understand molecular function in crowded cellular environments, substrate binding, protein-protein or protein-substrate interaction, and enzyme catalysis are the essential components. In this research, we will study molecular mechanisms underlying these essential functions and propose new insights as well as research strategies combining simulations with experiments.

【Publications Relevant to the Project】

・Yu, I. et al., Biomolecular interactions modulate macromolecular structure and dynamics in atomistic model of a bacterial cytoplasm. *eLife* **5**, e19274 (2016).
・Sakakibara, D. et al., Protein structure determination in living cells by in-cell NMR spectroscopy. *Nature* **458**, 102-105 (2009).

【Term of Project】

FY2019-2023

【Budget Allocation】

152,400 Thousand Yen

【Homepage Address and Other Contact Information】

http://www2.riken.jp/TMS2012/tms/ja/index.html
sugita@riken.jp

Title of Project：Elucidating the Dynamics of Memory

Thomas McHugh
(RIKEN, Center for Brain Science, Team Leader)

Research Project Number：19H05646　Researcher Number：50553731
Keyword：hippocampus, cortex, memory, oscillations

【Purpose and Background of the Research】

Information in the brain is conveyed by the spiking of neurons and the computations underlying memory require these spikes be organized, both spatially and temporally. This is achieved through rhythmic oscillations, a fundamental mechanism of communication and organization throughout the brain. Here we will build on our work in the control and decoding of the physiology of memory to investigate how oscillations in hippocampal/cortical circuits organize the information required for memory and how temporally organized information is altered by dysfunction and disease. Combining novel optogenetic techniques with *in vivo* physiology and computational and analytical approaches we will address several fundamental questions:

•What determines which of a brain's millions of neurons contribute to a given memory trace?
•How are those neurons interconnected, and how does that trace evolve with time and experience?
•How are those neurons engaged during memory consolidation and recall?
•Can memory loss due to aging and disease be treated by intervention to improve synchronous activity?

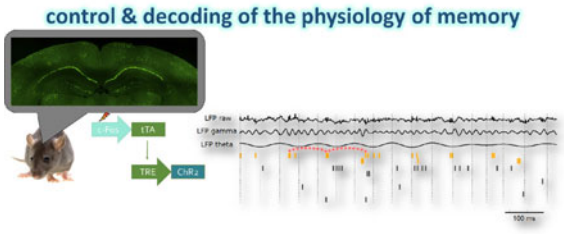


Fig. 1

【Research Methods】

We have recently combined our expertise in physiology with the emerging technology of memory engram labeling, based on the combination of immediate early gene expression and optogenetics, to functionally tag, identify & manipulate neurons involved in the encoding of a specific memory (Fig. 1). Building on this we will collect and analyze high-density recording of neuronal activity in the other regions of the hippocampus and cortex, allowing us to examine the interactions of neurons across brain regions during memory consolidation and recall. Further, the identification of a general signature of neurons engaged by memory will allow us to train algorithms with data from the high density recording to permit the identification of engram neurons based on physiology alone, without the need for optogenetic identification. These efforts will allow us to create models to classify memory age and quality based on physiology (Fig. 2) and better understand how temporal and spatial organization of activity can improve memory and brain health in cases of disease.

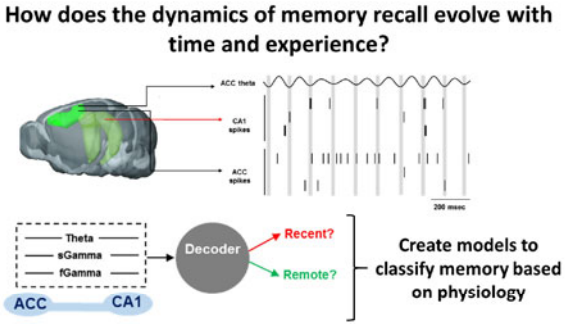


Fig. 2

【Expected Research Achievements and Scientific Significance】

This research will build on our ability to disambiguate information (spiking) and oscillations in the encoding, consolidation and recall of a specific memory. These advances leave us in a unique positon to investigate the mechanisms of integration of information and oscillations across regions of the brain and reveal their individual roles in memory, as well as yield insight to treatments of disorders involving aberrant neural dynamics.

【Publications Relevant to the Project】

Tanaka et al (2018) The hippocampal engram maps experience but not place. Science, 361(6400):392-397.
Middleton et al (2018) Altered hippocampal replay is associated with memory impairment in mice heterozygous for the SCN2A gene. Nature Neuroscience, 21(7):996-1003.
Middleton and McHugh (2016) Silencing CA3 disrupts temporal coding in the CA1 Ensemble. Nature Neuroscience, 19(7): 945-951.

【Term of Project】 FY2019-2023

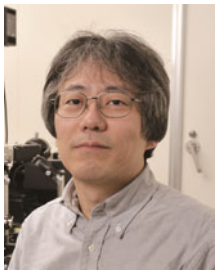
【Budget Allocation】 127,900 Thousand Yen

【Homepage Address and Other Contact Information】

http://cbs.riken.jp/en/faculty/t.mchugh/

【Grant-in-Aid for Scientific Research (S)】

Broad Section G



Title of Project：Comprehensive approach toward understanding cell surface receptor functions coupled with membrane structure and lipid composition

SAKO Yasushi
(RIKEN, Cluster for Pioneering Research, Chief Scientist)

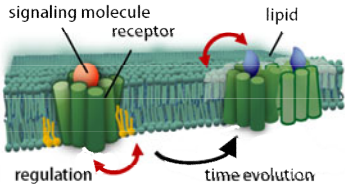
Research Project Number：19H05647　Researcher Number：20215700
Keyword：Receptor, Cell membrane, Cell signaling, Single-molecule measurement

【Purpose and Background of the Research】

The cell membrane, which is the boundary of cells and environment, has the fundamental structure of lipid bilayer. Receptor proteins embedded in the cell membrane are responsible for the acceptance, processing and transduction of extracellular information into the cells.

Lipid bilayer is a two-dimensional fluid, in which several hundred species of lipid molecules inhomogeneously distributed dynamically changing their assembly. Interactions with membrane domain structure and specific lipids regulate functions of membrane receptors. Vice versa, activities of membrane receptor affect compositions of boundary lipids and membrane structure. Such interactive communications produce self-organization of cell membrane for signal processing and transduction.

In this research, by applying cutting edge single-molecule technologies, we study behavior-function relationships of the most species of the major human membrane receptors to elucidate general mechanism of regulation of membrane receptor functions by the self-organization of membrane structures.



【Research Methods】

We have developed method of single-fluorescent molecule measurement of membrane proteins. This method allows quantification of molecular movements, dimerization, oligomerization, and interaction with extra- and intra-cellular proteins of membrane proteins on the living cell surface. It also allows measurements of structural dynamics and reactions of purified receptor molecules in artificial membranes. This project will use this method for the study of membrane receptors.

G protein-coupled receptors (GPCRs) and receptor tyrosine kinases (RTKs) are the targets of this study. We will compare the single molecule behaviors and functions about 300 species of GPCRs (excluding odorant receptors) and 60 species of RTKs in human cells to obtain general mechanism of signal processing and transduction of membrane receptors. We will focus on the diversification of the signaling pathways, signal bias, and crosstalk between different species of receptors.

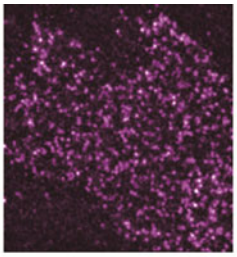
We also study dynamics of membrane domain structure and composition of boundary lipids of receptors. By using protein probe for specific lipid molecules, we can achieve super resolution imaging of 10~100 nm-scale lipid domains. Biochemical analysis of the boundary lipids of membrane receptors will be done in nanodiscs.

Major items of our project are as follows:

1. Comprehensive single-molecule measurement of membrane receptors
2. Super-localization imaging of membrane receptors and lipids
3. Analysis of the boundary lipids of membrane receptors
4. Measurement of molecular dynamics and lipid regulation in artificial membrane

【Expected Research Achievements and Scientific Significance】

In this study, we wish to understand meanings of the transient spatiotemporal dynamics of membrane structure and lipid compositions in the expression of signal processing and transduction functions of membrane receptors. Comprehensive single-molecule measurement is first enabled by our recent development of the automated imaging system. Since GPCRs and RTKs are the major targets medical drugs, this study will contribute to medical science and pharmacology.


Single-molecule imaging of membrane receptors

【Publications Relevant to the Project】

・Yanagawa M, Hiroshima M, Togashi Y, Yamashita T, Shichida Y, Murata M, Ueda M, Sako Y. Single-molecule diffusion-based estimation of GPCR activity. Sci. Sig. 11, eaaao1917 (1-16) (2018)
・Hiroshima M, Pack C-g, Kaizu K, Takahashi K, Ueda M, Sako Y. Transient acceleration of epidermal growth factor receptor dynamics produces higher-order signaling clusters. J. Mol. Biol. 430, 1386-1401 (2018)

【Term of Project】 FY2019-2023

【Budget Allocation】 117,700 Thousand Yen

【Homepage Address and Other Contact Information】

http://www2.riken.jp/cell-info/
sako-lab@riken.jp

Title of Project：Biology of sugar-alcohol modification in glycan

ENDO Tamao
(Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, Senior Fellow)

Research Project Number：19H05648　Researcher Number：30168827
Keyword：glycosylation, sugar-alcohol, post-translational modification

【Purpose and Background of the Research】

Glycosylation is an important post-translational modification of cell surface and intercellular molecules, regulating various physiological processes, such as molecular interactions and intracellular communications. We have found novel glycan modifications by sugar-alcohol phosphates (ribitol-phosphate and glycerol-phosphate) in mammals (Ref. 1,3). We also identified several enzymes involved in the sugar-alcohol phosphate modifications and revealed that a defect in ribitol-phosphate modification causes severe disorders such as congenital muscular dystrophy with brain malformation (Ref. 1,2). In the sugar-alcohol phosphate modification, ribitol or glycerol binds to saccharide through phosphodiester linkage, while typical glycans are formed by glycosidic linkage between monosaccharides. The sugar-alcohol phosphates have long been known as a component of bacterial cell wall, teichoic acid, but they have never been found in mammals. Interestingly, the mammalian sugar-alcohol phosphates are conserved as molecules with a function disinct from that in bacteria and are related to diseases. However, details of the metabolic pathway of mammalian sugar-alcohol phosphates are poorly understood. Additionally, the advantage of the usage of phosphodiester linkage in glycosylation is also unclear. In this study, we aim to elucidate the biological significance of sugar-alcohol phosphates modification in glycan formation.

【Research Methods】

In this study, we will focus on the following subject areas to elucidate the biological significance of sugar-alcohol phosphate modification:

1. Physicochemical characteristics: we will synthesize a series of glycans containing sugar-alcohol phosphate and examine their physicochemical properties.
2. Molecular basis of sugar-alcohol phosphate modification: the mechanism of modification will be elucidated by studies on the structural biology of related enzymes.
3. Metabolic pathway of sugar-alcohol phosphate modification: the enzymes responsible for synthesis and metabolism of sugar-alcohol phosphate will be elucidated by biochemical assays.
4. Target molecules of sugar-alcohol phosphate modification: specific detection methods for the modified glycans will be developed using chemical biology and antibodies or lectin-like molecules.
5. Biological function: the effects of sugar-alcohol phosphate deficiency on biological functions will be examined using genetically modified cells/animals.

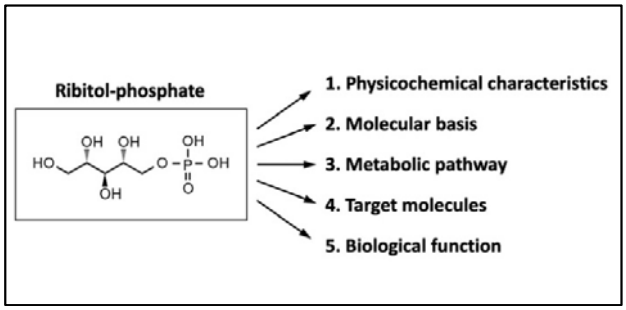


Figure 1. Research methods

【Expected Research Achievements and Scientific Significance】

The underlying molecular mechanism of sugar-alcohol modification and its biological significance will be elucidated by this study. Furthermore, the results will provide a pathomechanism of congenital muscular dystrophy and aid in the development of therapies.

【Publications Relevant to the Project】

1. Kanagawa M. et al. (2016) Identification of a post-translational modification with ribitol-phosphate and its defect in muscular dystrophy. *Cell Rep.*, 14, 2209-2223
2. Kuwabara N. et al. (2016) Carbohydrate-binding domain of the POMGnT1 stem region modulates *O*-mannosylation sites of α-dystroglycan. *Proc. Natl. Acad. Sci. USA*, 113, 9280-9285
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【Term of Project】FY2019-2023

【Budget Allocation】135,000 Thousand Yen

【Homepage Address and Other Contact Information】

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