Title of Project : Constructive understanding of multi-scale dynamism of neuropsychiatric disorders

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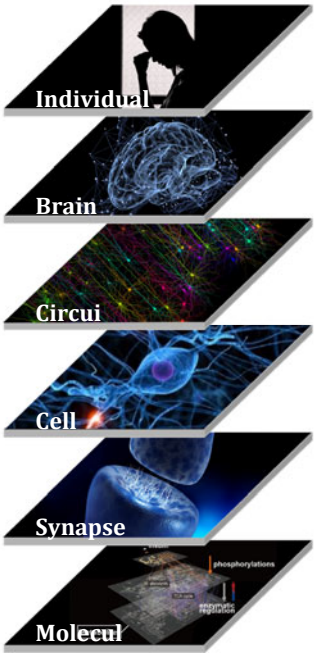
Research Project Number : 18H05428 Researcher Number : 60415271

【Purpose of the Research Project】

Despite extensive recent efforts, the pathogenesis of psychiatric disorders remains poorly understood, mainly because their pathophysiology is a synergistic interaction between multiple genes variants and environmental factors. Thus, what we recently know as contributory factors for the diseases is the susceptible gene variants (Molecular layer), synaptopathy (Subcellular and Cell layer), alteration in neuronal circuits (Circuit layer), conceivably resulting in the behavioral manifestations (Individual layer). However, the understanding of each layer has been limited within a single layer, which hinders the integrative and causal mechanistic understanding of behaviors. Probably, each layer can affect one another, macroscale to the mesoscale and then to the microscale layer or vice versa. Thus, we deal with phenomena of intricate complexity of psychiatric disorders that are governed by various mechanisms integrated across multiscale layers.



【Content of the Research Project】

In this study, we aim at a constructive understanding of multiscale hierarchical nature of psychiatric disorders with use of recently available state-of-art techniques: hypothesis-free and comprehensive omics technologies and powerful simulation/analysis tools generate new types of heterogeneous data with a density and depth previously unimaginable, which can handle big data from multiscale layers ranging from molecules/ synapses/neurons/circuit (and ideally, all the way to behavior).

For instance, the role of genes identified by genetic analysis of families of psychiatric disorders as well as molecules identified by omics analysis of postmortem brain samples will be analyzed and subject to the construction of mathematical models. Using animal models of the candidate genes, a responsible neural circuit will be identified by behavioral and anatomical analyses. Within that neural circuit, responsible cell types will be identified using omics analysis and the mechanism for the emergence of behavioral changes will be pursued by manipulation of a specific neural circuit and by employing mathematical modeling of the responsible neural circuit. By using induced pluripotent stem (iPS) cells derived from patients with psychiatric disorders, neural cells and cerebral organoids will be generated and cellular pathology underlying mental disorders will be studied using omics analyses.

【Expected Research Achievements and Scientific Significance】

Through the series of studies as described above, a mathematical model of psychiatric disorders that incorporate multiple layer facets including molecular, cellular, circuit and behavioral levels, will be constructed and thereby we will aim at a constructive understanding of the multiscale phenomena of psychiatric disorders. One of the goals of neuroscience research is to elucidate how specific neuronal populations form functional neuronal circuits are altered in the disease state. Findings based on our strategy that would causally identify the contributory factors for the disease will provide the knowledge necessary to establish circuit-centric therapeutics as well as the rationale molecular (and chemistry) based drug designs.

【Key Words】 Psychiatric disorders, Multiscale, Constructive understanding, Optical manipulation, Modeling, Transomics

【Term of Project】 FY2018-2022

【Budget Allocation】 1,212,900 Thousand Yen

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Title of Project : Ensuring integrity in gametogenesis

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Research Project Number : 18H05544 Researcher Number : 20287486

【Purpose of the Research Project】

Gametes are highly specialized cells for the creation of new individuals. To finally become functional gametes, the germ cell lineage including the precursors undergoes a unique series of differentiation processes. Quality of germ cell lineage closely relate to viability of embryos and individuals. The aim of this project is to understand how the functionality of gametes, named "gamete integrity", is established during gametogenesis *in vivo*. Based on this knowledge, the project also aims to reconstitute the process *in vitro*.

Recently, the research members in this project succeeded in production of functional gametes *in vitro* (*in vitro* gametogenesis) by culturing reproductive organs or inducing differentiation of pluripotent stem cells. However, the developmental potential of the gametes from *in vitro* gametogenesis was extremely limited, suggesting that gamete integrity was not properly reconstituted in culture. Therefore, this project will try to understand the molecular mechanisms and biological processes for construction of gamete integrity *in vivo*. The project includes the technological development of a non-invasive system to evaluate gametes. Based on this knowledge, we try to establish *in vitro* gametogenesis that can firmly and stably reconstitute gamete integrity.

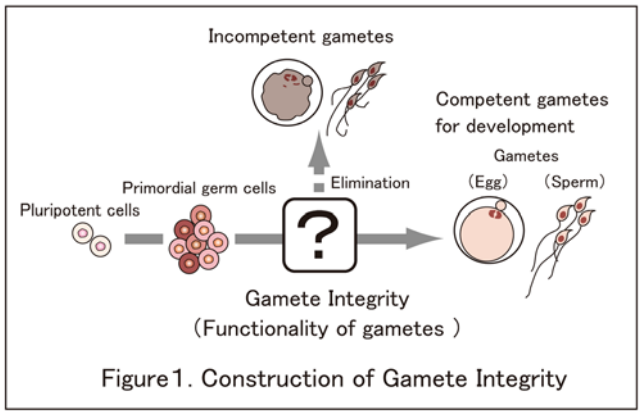

Figure 1. Construction of Gamete Integrity

【Content of the Research Project】

This project is composed of three subjects (A01-A03) to achieve the aim. In A01, we focus on the development of the culture system to reconstitute gamete integrity. In A02, we plan to identify the molecules regulating gamete integrity, which includes development of the non-invasive system. In A03, we want to understand the biological process needed for selection of competent gametes (and eliminate incompetent gametes).

A01 will optimize culture conditions, develop novel culture devices, purify proteins and substances required for gametogenesis, and produce supporting somatic cells from pluripotent stem cells. A02 will identify genes regulating gamete integrity by comparison between competent and incompetent gametes, which are sorted by the non-invasive system. A03 will identify the heterogeneity of the germ cell population, analyze gene expression at the single cell level, and understand the biological significance of the heterogeneity.

By combining all the knowledge, we will gain deep insights into gamete integrity and reconstitute it *in vitro*.

【Expected Research Achievements and Scientific Significance】

We expect to identify molecules (genes, proteins and other substances) that have critical roles on gametogenesis. Understanding of the biological process for gamete selection will provide important information for the field of biology, in particular reproductive biology, developmental biology and evolutionary biology. The establishment of *in vitro* gametogenesis that efficiently produces competent gametes will have many experimental applications. Finally, this project will provide scientific evidence to apply to human *in vitro* gametogenesis.

【Key Words】

Gamete integrity, Developmental potential, *in vitro* gametogenesis, non-invasive system, heterogeneity

【Term of Project】 FY2018-2022

【Budget Allocation】 1,181,700 Thousand Yen

【Homepage Address and Other Contact Information】

https://www.gamete-integrity.com

Title of Project：Chromatin potential for gene regulation

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Research Project Number：18H05526　Researcher Number：30241392

【Purpose of the Research Project】

In multicellular organisms, diverse cell phenotypes arise from identical genetic information in DNA. The diversity in phenotypes is achieved by differential gene expression in different cell types. Therefore, understanding the mechanism of gene regulation is one of the most important subjects in biology.

Genetic information in eukaryotes is packed into the nucleus through the formation of chromatin. Recent studies have revealed that chromatin structure plays an important role in gene regulation. However, the big question of "how chromatin regulates gene expression in living cells" remains unclear. Recent imaging techniques to track particular chromatin structures in living cells have allowed us to link chromatin structure with transcription potency. In this research program, we aim to reveal the factors that determine the "chromatin potential" for gene activation (Fig. 1).

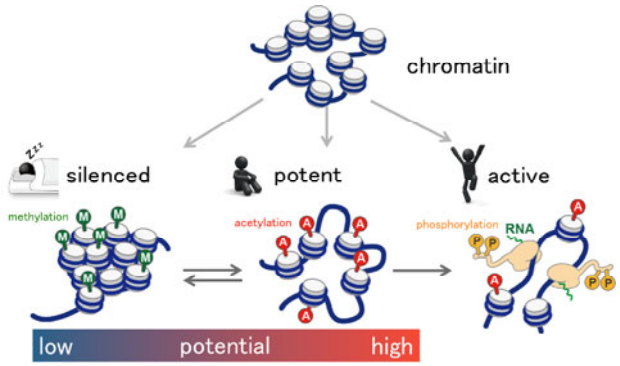

Fig. 1: The concept of "chromatin potential".

【Content of the Research Project】

Genes are regulated at various levels of chromatin, including post-translational histone modifications, histone variant exchange, chromatin condensation, higher-order nuclear compartmentalization, interactions with nuclear domains, and physical forces (Fig. 2). By gathering top researchers with different expertise, this research group will help reveal the nature of chromatin potential through interdisciplinary approaches, including quantitative measurements of chromatin dynamics, acquisition of omics data, reconstitution of functional chromatin *in vitro* and *in vivo*, and theoretical modeling. By integrating the data obtained from different approaches, we will be able to address which factors contribute and to what extent each helps establish transcriptionally competent or incompetent chromatin states. This research group will focus on biological phenomena associated with dynamic changes in chromatin and gene expression, such as development and differentiation in model organisms.

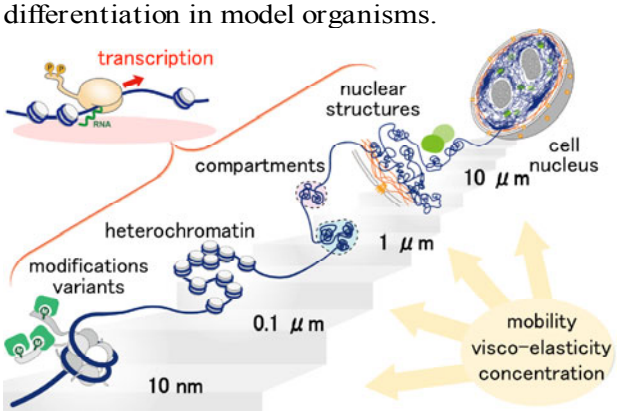

Fig. 2: Various levels that determine chromatin potential.

【Expected Research Achievements and Scientific Significance】

By revealing the factors that control chromatin potential, we expect to predict and control the probability of gene expression through the measurement and manipulation of chromatin states. This study will open up new routes to designing cell properties and fate by artificially controlling gene expression, which in turn will contribute to broad fields of applied biology.

【Key Words】

Chromatin: A complex in the eukaryotic nucleus, consisting of DNA, protein, and RNA. The major components of chromatin are DNA and histone protein.

【Term of Project】

FY2018-2022

【Budget Allocation】

1,181,500 Thousand Yen

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