【Grant-in-Aid for Specially Promoted Research】

Biological Sciences

# Title of Project : Omics approaches towards the elucidation of the molecular network regulating the developmental capacity of the mammalian oocyte

Hiroyuki Sasaki
(Kyushu University, Medical Institute of Bioregulation, Professor)

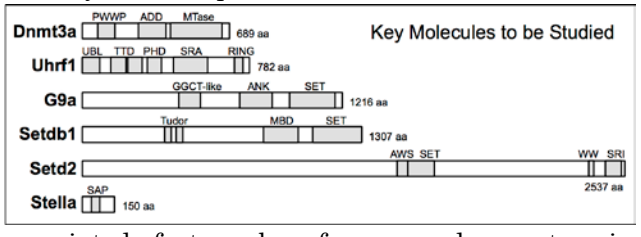
Research Project Number : 18H05214　Researcher Number : 30183825
Keyword : Oocyte, Omics, Epigenome, Genome editing, Machine learning

## 【Purpose and Background of the Research】

The oocyte is a female gametocyte essential for animal reproduction. It possesses essentially all information necessary to support development of an entire animal body (developmental program), but the molecular networks involved in the establishment and/or maintenance of the program are poorly understood. In this project, we study the roles of putative components of the networks in mouse oocyte and identify new components and associated factors using genome editing and multi-omics analyses. We focus on the repressive epigenetic program that is established in the oocyte and involved in silencing of tissue-specific genes, retrotransposons, and non-expressed alleles of imprinted genes in early embryo. Furthermore, we develop models to predict the heritability/reprogrammability of the program and of errors that occur to it. Our study provides the basis for better understanding of mammalian development and epigenetic inheritance.

## 【Research Methods】

Six key epigenetic factors that are potentially involved in the networks are studied: a DNA methyltransferase (Dnmt3a), a hemimethylated CG biding E3 ubiquitin ligase (Uhrf1), histone methyltransferases (G9a, Setdb1, Setd2), and a factor protecting 5mC from oxidation (Stella). We generate mice mutated for the respective genes by genome editing, perform micro-scale multi-omics analyses, and infer the regulatory networks responsible for the repressive program. If necessary, we introduce amino acid changes in specific protein domains of these factors. Embryological and cytological techniques are used to dissect the developmental phenotypes of the mutants. We also identify new components of the networks and their




associated factors by, for example, proteomics approaches. Machine learning is performed to train models to predict the methylated/unmethylated state of a DNA region of interest in oocyte and early embryo and heritability/reprogrammability of the modifications. By integrating the results from all studies, we will try to resolve the regulatory networks involving histone modifications and DNA methylation and understand how epigenetic inheritance occurs.

## 【Expected Research Achievements and Scientific Significance】

We expect that this research project will reveal both expected and unexpected functions of the factors potentially involved in the establishment and/or maintenance of the repressive program and resolve the regulatory networks. The outcome of this study will have impact on the studies of infertility, assisted reproduction technology, pluripotent stem cells, livestock breeding, and inheritance of environmentally induced epigenetic changes.

## 【Publications Relevant to the Project】

・Kaneda, M. et al. Essential role for *de novo* DNA methyltransferase Dnmt3a in paternal and maternal imprinting. *Nature* 429, 900-903 (2004).
・Watanabe, T. et al. Endogenous siRNAs from naturally formed dsRNAs regulate transcripts in mouse oocytes. *Nature* 453, 539-543 (2008).
・Maenohara, S. et al. Role of UHRF1 in de novo DNA methylation in oocytes and maintenance methylation in preimplantation embryos. *PLoS Genet.* 13, e1007042 (2017).

## 【Term of Project】 FY2018-2022

## 【Budget Allocation】 391,200 Thousand Yen

## 【Homepage Address and Other Contact Information】

http://www.bioreg.kyushu-u.ac.jp/labo/epigenome/