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

Understanding the Gene Regulatory Network Ensuring Anisogamy in Mammals

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Purpose and Background of the Research

●Outline of the Research

Sexually different outcomes are often observed during development and growth. Gametogenesis is a typical example: females produce a small number of eggs with large cytoplasm, while males produce a large number of sperm with small heads and motile flagella. This heteromorphic gamete formation, called anisogamy, is thought to be the consequence of coevolution in gametogenesis, in which species with homomorphic gametes produce eggs that store nutrients in the cytoplasm for the next generation and sperm with superior motility to ensure fertilization and subsequent development. Reminiscent of this evolutionary process, during mammalian development, progenitor cells (primordial germ cells) with no sex differences in cell morphology or gene expression differentiate into eggs or sperm in the gonads in a sex-dependent manner (Figure 1). While gonadal somatic cells play an important role in the establishment of such sexual differences in gametogenesis, the fact that sex-converted individuals, e.g. XX males and XY females, do not have sufficient potential to complete gametogenesis indicates that the sex in germ cells per se contributes to gametogenesis. However, compared to the mechanism of sex differentiation of gonadal somatic cells, little is known about the mechanism that establishes the sex difference of germ cells. Therefore, this study aims to understand the gene regulatory network that defines sex differences in mammalian gametogenesis and to examine the effects of these changes on gamete formation and function. For this purpose, we will use an in vitro culture system that induces gametes from pluripotent stem cells (ES/iPS cells). In a previous study, using this in vitro culture system, the principal investigator identified four transcription factors that are sufficient for oocyte formation: forced expression of these transcription factors in mouse ES cells induces gene expression and epigenomic modifications specific to the oogenesis process, resulting in the formation of oocyte-like cells capable of fertilization (Figure 2). Analysis of the target genes of these transcription factors revealed that most of them are required for oogenesis, as expected, and it turned out that a certain group of genes is required for oogenesis. This led to the idea that sex differences in mammalian gametogenesis are ensured by the execution of gene expression programs that promote gametogenesis in each sex as well as by the reciprocal suppression between the sexes (Figure 1). Although previous studies have shown that disruption of genes essential for oogenesis causes ectopic expression of genes required for spermatogenesis, a genome-wide network of such gene repression as well as the functional outcome of the de-repression remain unclear. This study will tackle to clarify these issues.

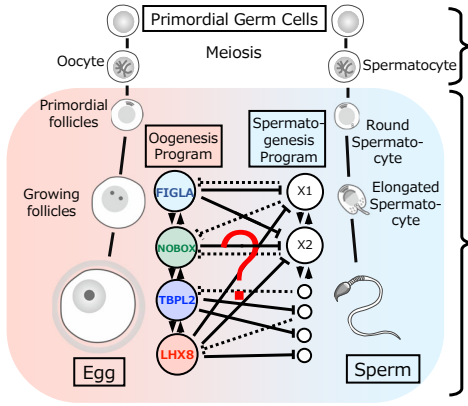

Figure 1. Research summary: Understanding the networks that define sex differences in anisogamy and the effects of their disruption on gamete formation and function.

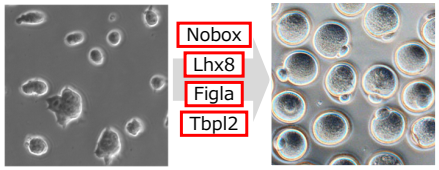

Figure 2. Transdifferentiation into oocyte-like cells upon expression of oocyte-specific transcription factors.

Expected Research Achievements

This study aims to understand the gene regulatory networks that ensure sex differences in gametogenesis and to clarify the effects of their disruption on gamete formation and function. Specifically, focusing on the 'reciprocal repression mechanism in male-female gametogenesis,' we will (1) identify transcription factor networks that are mutually repressed between the sexes, (2) examine the disruptive effects of mutual repression network disruption on gamete formation and function, (3) examine the changes in mutual repression networks due to aging and strain differences, and (4) examine the conservation of the transcription factor network in humans. Through this research, we aim to incorporate a new concept of mutual suppression between males and females into gametogenesis research, which has been conducted separately for males and females. This will provide new insights into the causes of gametogenesis dysfunction and infertility (Figure 3).

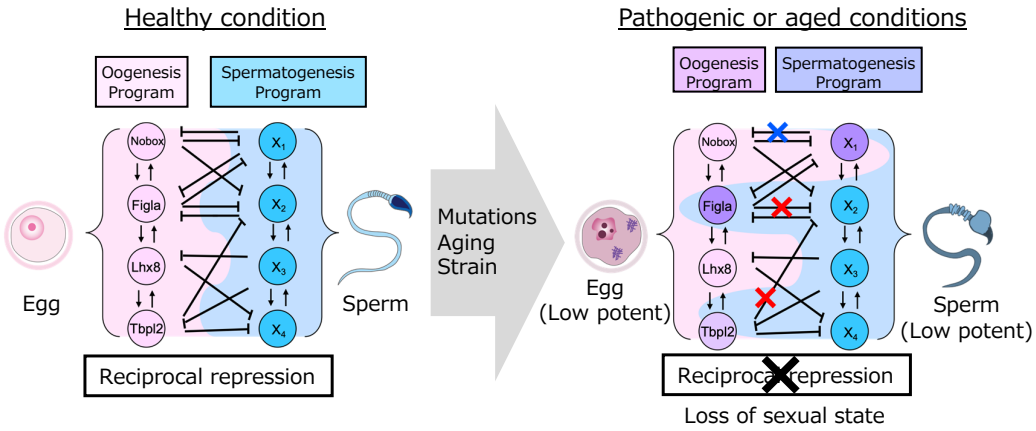

Figure 3. Effect of this research: To understand the mutual inhibitory network between the sexes that ensures sex differences in gametogenesis and to examine the effects of disruptions in this network on gamete formation and function, will establish a new concept of "maintenance and fluctuation of exclusivity between the sexes" in gametogenesis and provide new insights into the causes of gamete dysfunction and infertility.

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