【Grant-in-Aid for Transformative Research Areas（B）】

Understanding Early Embryonic Developmental Strategies: Risk management in early embryonic development

Principal Investigator	Kobe University, Graduate School of Agricultural science, Associated Professor KYOGOKU Hirohisa　Researcher Number : 20726038
Project Information	Project Number : 25B307　Project Period (FY) : 2025-2027 Keywords : Risk management, Early embryo, DNA replication, Chromosome abnormalities, Cell competition

Purpose and Background of the Research

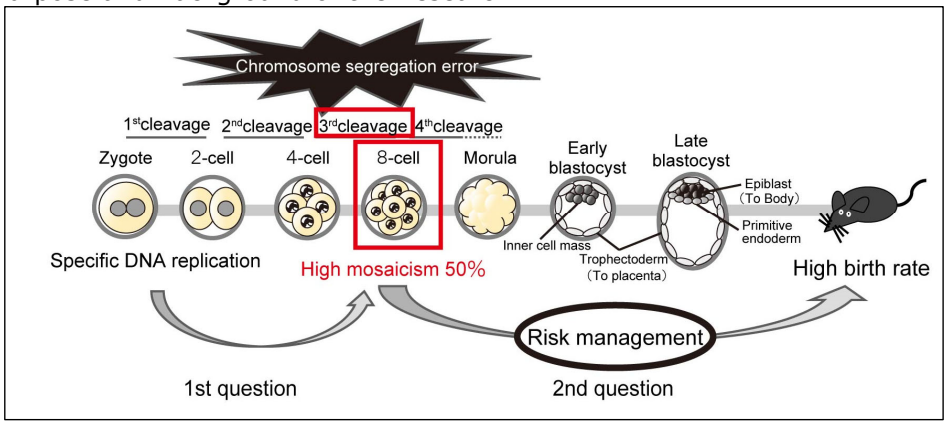

Figure 1. Conceptual diagram of the research to be conducted in this area of research

●How did we come up with the concept of the “Early Embryo Developmental Strategy” area?

We have recently worked with researchers Kyogoku and Takahashi to catalogue chromosome distribution abnormalities in early embryos at the gene sequence level. They found out lots of information from the catalogue, like how often abnormalities happened, when they happened, and what pattern they followed. They also found out which chromosomes were more likely to cause problems. The results showed that there are a lot of abnormalities between the 4-cell and 8-cell stages in early embryos. It was found that "mosaic embryos" are formed in about half of the embryos during this period. These embryos contain cells with the correct chromosomes and cells with the wrong chromosomes. The search for the cause revealed that in one- and two-cell stage embryos, there is no control of 'replication timing', which determines the order in which DNA is replicated. It also became clear that the rate of replication was abnormally slow. In other words, the entire genome was replicating slowly and uniformly, with no fixed order. On the other hand, at the 4-cell stage, a temporal control of replication similar to that in somatic cells suddenly appeared, but the replication rate remained slow. This indicated that DNA replication was temporally incomplete, resulting in abnormal chromosome distribution. These findings have important implications for the study of early embryonic development and chromosome aberrations, and are expected to attract the attention of researchers around the world in the future. Based on these findings, Kyokoku decided that it was necessary to establish a team-based research system and came up with the concept of a new research area, "Developmental Strategies of Early Embryos", which focuses on the two major questions raised by these findings.

Expected Research Achievements

The goal of this research area is to understand the risks behind the dynamic changes that occur during early embryonic development. Rather than looking at individual phenomena in isolation, we seek to elucidate the "strategies" by which early embryos evolve throughout the developmental process. In doing so, we aim to rethink the conventional concept of early embryonic development and evolve it into a new way of thinking that includes a mechanism for overcoming risk (risk management). By focusing on the risk management capabilities of early embryos, a new scientific foundation for developmental mechanisms can be established. These results are of great scientific and societal importance, as they may lead to improvements in fertility treatment and solutions to the problem of declining fertility in the future.

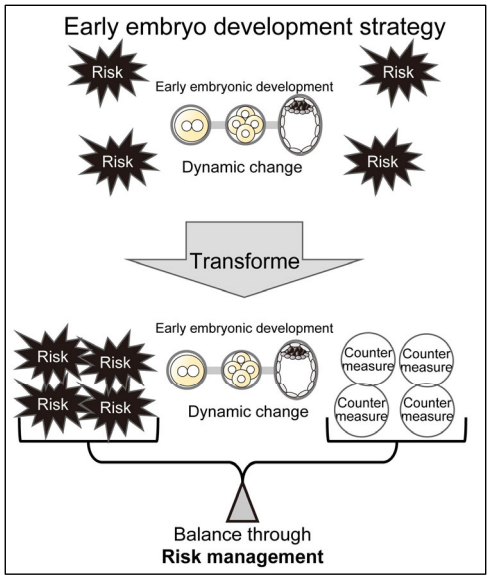

Figure 2. Overview of Research

●Causes and Implications of Risk in Early Embryonic Development Strategies

The first question that arose was: "Why do embryos at the 1- to 2-cell stage go to the trouble and risk of choosing a special way of DNA replication (embryonic replication mode)? The first question that arose was, "Why do embryos at the 1- to 2-cell stage take the risk of choosing a special method of DNA replication (embryonic replication mode)? To answer this question, Takahashi's group focused on the "somatic DNA replication timing control that suddenly appears in 4-cell stage embryos" and continued their research. Specifically, they are trying to determine which of several major changes that occur simultaneously in the early embryo - changes in the three-dimensional structure of the genome, activation of the embryonic genome, and changes in the balance between the nucleus and the cytoplasm - is responsible for the emergence of this replication timing. The early embryo deliberately acquires this mechanism of replication control, despite the high risk of chromosome misdistribution. The purpose of this study is to elucidate the reasons for this and to answer the question.

●Risk Management in Early Embryo Development Strategies

Another question is, "How do early embryos overcome the risk of "mosaic embryos," a mixture of cells with chromosomal abnormalities, and recover to normal development?" This is the question the Kyokoku team asked. To answer this question, the Kyogoku group focuses on how cell fate is determined during differentiation into inner cell mass and trophic ectoderm. The Hashimoto group, on the other hand, focuses on the mechanism of "elimination of abnormal cells" during epiblast formation.

Homepage Address, etc.	https://www.group.kobe-u.ac.jp/emb-dev-strategies/index.html