【Grant-in-Aid for Specially Promoted Research】

Understanding of embryonic development by fathoming multi-copy genetic elements

Principal Investigator	Chiba University, Center for Next Generation In vivo Research (cNIVR), Project Professor SIOMI Haruhiko　　Researcher Number : 60202107
Project Information	Project Number : 25H00008　　Project Period (FY) : 2025-2029 Keywords : transposable elements, clustered genes, zygotic genome activation, totipotency

Purpose and Background of the Research

●Outline of the Research

During early embryogenesis, transposable element (TE) burst occurs, which accompanies burst of an abundant set of genes, mostly clustered genes. They are collectively referred to as 2C genes in the mouse (Fig. 1). Here, I propose a multi-faceted approach towards a systematic understanding of the role of these TEs and clustered genes in zygotic genome activation (ZGA) which is a critical post-fertilization step that promotes totipotency and allows different cell fates to emerge in the developing embryo, cell potency, and the normal embryonic development.

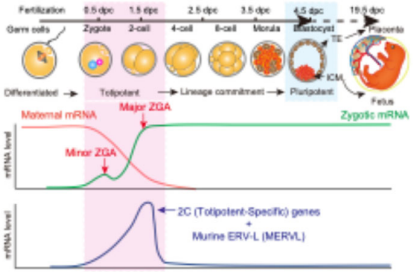

Figure 1. Gene expression during mouse early embryos

Recently, we developed a method which allows us to efficiently repress multi-copy genetic elements and demonstrated that embryonic development requires TE (MERVL) expression.

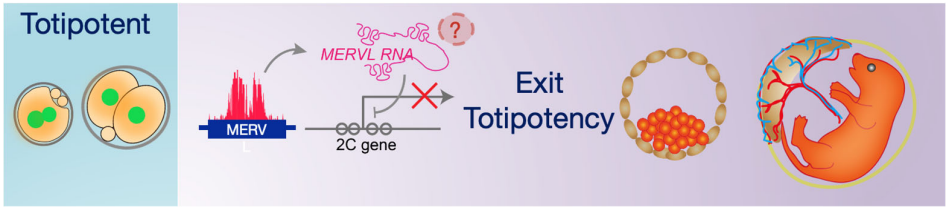

Figure 2. A model in which TE (MERVL) expression promotes the transition from totipotent to pluripotent state

TEs have been thought to be endogenous mutagens to alter sequences and structures of the genome, thereby sometimes causing disease in humans. However, our findings have changed our view of the field - that goes along with the classical view – “Embryonic development requires the expression of TEs”. This proposal will attempt at revealing how functions of TEs and clustered gene are integrated to give rise to emergent properties that regulate development. Conceptual advances in the model animals will strongly impact our understanding of this fascinating regulatory pathway in humans. In addition, cell culture systems that induce mESCs into 2-cell embryo-like cells with totipotency will be developed. To accelerate the understanding of previously hidden roles of TEs and clustered genes, we will develop and implement new algorithms to overcome the multi-mapping challenge in NGS reads so that we can genome-widely quantify the expression of each TE/clustered gene across diverse mammalian species (i.e., mouse, hamster, human).

●Questions & Purposes

Our aim is to elucidate the principles of the molecular communication networks among TEs and clustered genes that burst in mammalian early embryos. We will explore modes and consequences of TE burst, interactions between TEs and clustered genes and their interactions with other cellular genes. I propose the following four specific aims. Experiments are designed with mostly mice and mES cells.

1. To systematically understand the role of TEs and clustered genes in embryonic development.
2. To create a new comparative genomics that reveals conservation and diversity of TEs and clustered genes in mammalian embryonic development.
3. To generate genomics & bioinformatics tools that facilitate characterizations of individual TEs and clustered genes in mammalian early embryos.
4. To develop cell culture systems to induce mESCs into blastocyst-like structure (blastoid) that can be implanted (Fig. 3).

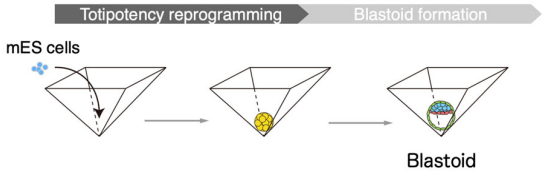

Figure 3. Generation of blastoid from mESCs

Expected Research Achievements

Our approach will allow us to discover novel aspects of TEs and clustered genes in ZGA and in the transition between totipotent and pluripotent states. This proposal aims to explain how TEs including MERVL and clustered genes regulate chromatin structure and expression of other genes to achieve their burst and quick degradation. This will be achieved by means of exploring how interactions between TEs and individual clustered genes and among individual clustered genes contribute to the organization of embryonic gene networks that ensure embryonic development. The particular emphasis is on alterations of epigenetic modifications and chromatin structures as consequences of burst of TEs and clustered genes.

TEs and clustered genes have been studied en masse but not as individual entities within their genomic ecosystem. The most challenging part in this proposal is, therefore, to elucidate how each TE element and clustered gene behaves differently during ZGA and embryonic development and how such behaviors affect gene regulatory networks of totipotent state and the transition from totipotent to pluripotent. To reveal the role of individual TEs/clustered genes and facilitate experiments described above, we will develop state-of-the art bioinformatics platform to analyze them. This will open up a new field of comparative genomics across mammalian species to elucidate the evolutionary impacts of TEs and clustered genes on diversification and convergence of embryonic development.

In Japan, world-class research has been developed to reconstruct the process of gametogenesis (egg and sperm) in vitro. The next step is to turn our attention to ontogenesis, where implantation is the major problem to be solved. The pregnancy success rate of modern reproductive medicine in Japan is also around 30%, and the main reason for this is that the majority of embryos are lost during the implantation period. This research is expected to serve as a bridge between gametogenesis research and life science research that is broadly concerned with ontogenesis. As a social ripple effect, it will contribute to solving the problem of declining birth rates.

Homepage Address, etc.	http://siomilab.med.keio.ac.jp