LABORATORY OF NUCLEAR DYNAMICS

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A fundamental question in biology is to understand the mechanisms underlying cell-fate decision. Genomic reprogramming after mammalian fertilization reverts terminally differentiated gametes into toti- or pluri-potent states to start a new developmental program. Cell lineage allocation in the reprogramming process is accompanied by drastic changes in the pattern of gene expression, epigenetic configurations, and nuclear organization. We aim to reveal the roles of chromatin dynamics in cell lineage-allocation by deciphering the molecular mechanisms underlying remodeling of nuclear organization and their effects on developmental gene expression, using mouse embryos and embryonic stem (ES) cells as model systems.

I. Epigenetic reprogramming in early mouse embryos.

Genomic reprogramming reverts fully differentiated cells to a totipotent state to start a new developmental program. In the early mouse embryo, terminally differentiated gametes are reprogrammed after fertilization thereby acquiring a totipotent state. Upon the fourth cleavage, 8-cell stage embryos, which have undergone the process of compaction, will give rise to the morula (Figure 1). The outer cells of the morula will differentiate into the epithelial trophectoderm (TE) of the blastocyst. The inner cells of the morula will become the inner cell mass (ICM) of the blastocyst. The ICM subsequently leads to the formation of two lineages, epiblast (EPI) and primitive endoderm (PE), with the former representing pluripotency as it gives rise to the embryo itself. The reprogramming event is accompanied by epigenetic modifications and changes in chromatin structures throughout the embryo, which are essential for regulation of gene expression involved in differentiation, and reprogramming of the EPI.
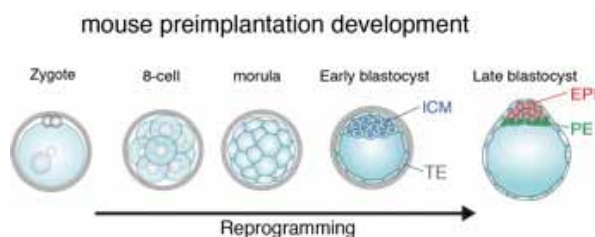

Figure 1. Lineage allocation in mouse preimplantation development

II. Remodeling of nuclear architecture in development

Chromatin is organized in a non-random fashion within three-dimensional nuclear space. During developmental processes, nuclear architecture is dramatically reconstructed, resulting in establishment of cell-type specific nuclear organization. Defects in structural components of the nucleus are responsible for developmental aberrations and several human diseases. Remodeling of nuclear architecture leads to spatial arrangement of genes, which could affect genome functions including gene expression. However, regulatory mechanisms underlying nuclear reorganization during cell-fate decision remains largely unknown.

III. Chromatin structure

Spatiotemporal organization of genomic DNA within the nucleus is suggested as an emerging key player to regulate gene expression. The developmental program accompanies nuclear remodeling, resulting in construction of cell-type specific nuclear architecture. Firstly, chromosomes are confined in discrete nuclear spaces, "chromosome territories" (Figure 2). Within them, further levels of 3D organization, "topologically associating domains" (TADs), are observed. TADs can be defined as linear units of chromatin containing several gene loci, and fold as discrete 3D structures in which gene loci frequently interact with each other. Recent works have revealed that folding of "local" chromatin structures such as enhancer-promoter looping is associated with genome functions. Despite the drastic changes of these hierarchical chromatin structures, their role in cell-fate decision remains largely unexplored.

Figure 2. Hierarchical chromatin structure

IV. Approach

We have developed a powerful imaging technology termed TALE-mediated Genome Visualization (TGV), which allows us to track specific genomic sequences in living cells (Miyanari Y, Nature Structural & Molecular Biology, 2013). Importantly, this technique is versatile and can be extended to allow many robust applications, which will be integrated into our study to manipulate several genome functions. Based on new technological development, we aim to understand biological roles of chromatin dynamics in cell-fate decision.

Publication List

〔**Original paper**〕

● Miyanari, Y. (2014). TAL effector-mediated genome visualization (TGV). Methods 69. 198-204.