CDB SEMINAR

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10:00~11:00 A7F Seminar Room

Developmental Regulation of Nuclear Genome Organization

Summary

How the genome is organized in the 3D space of the nucleus is widely assumed to be fundamentally important for developmental gene regulation. However, this is still largely unexplored, owing to the difficulty of measuring such organization quantitatively. DNA replication is spatio-temporally regulated and provides an excellent entry point into exploring 3D genome organization. Indeed, microscopic studies have suggested that chromosomal DNA is composed of megabase-sized domains that replicate at different times during S-phase, with early- and late-replicating domains preferentially occupying the nuclear interior and periphery, respectively. However, a molecular definition of these replication domains and their plasticity were unclear. Several years ago, we addressed this issue by establishing a genome-wide replication timing profiling assay. This allowed us to reveal the megabase-sized replication domain structure of the mammalian genome, with their boundaries precisely mapped throughout the genome. What was even more striking, however, was that we could observe extensive changes during differentiation of mouse embryonic stem cells. In every case examined, replication timing changes were accompanied by subnuclear repositioning, leading us to propose that changes in replication profiles reveal chromosome segments that undergo large changes in organization during differentiation. Later, we found a remarkably high correlation between replication timing and Hi-C maps, further corroborating the idea that replication timing profiles reflect cell-type specific 3D genome organization. Intriguingly, analysis of a series of in vitro models of mouse embryogenesis revealed that the most dramatic change took place at a stage equivalent to the post-implantation epiblast in mice. During this period, extensive early-to-late (EtoL) replication timing changes were observed throughout the genome, accompanied by repositioning of these 'EtoL domains' toward the nuclear periphery as well as their chromatin compaction. The timing and the mode of regulation was reminiscent of the inactive X chromosome in females, leading me to hypothesize a global facultative heterochromatinization event in the post-implantation epiblast. What could be the mechanism and significance of this global facultative heterochromatin formation at the epiblast stage? Is there really an overlap in the mechanisms that regulate the autosomal EtoL domains and the inactive X? As a first step toward this goal, I am taking a multi-step siRNA screening approach to identify putative regulators of this facultative heterochromatin formation. Several potential regulators are beginning to emerge.

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