グローバルCOE「生体シグナルを基盤とする統合生命学」

平成23年度大学院講義 新国際基盤生命学特論4 コース 4

12 月 15 日（木）分子細胞生物学研究所 IML 棟 3 階大会議室（担当：竹内 純）

[Session #1: 10:30 - 12:00]

Making a face: What epigenomics can teach us about human development

Dr. Tomek Swigut (Stanford University)

Cell-fate transitions involve the integration of genomic information encoded by regulatory elements, such as enhancers, with the cellular environment. However, identification of genomic sequences that control human embryonic development represents a formidable challenge, as they are embedded within a vast non-coding genomic space. We have recently shown that unique chromatin signatures can be used to annotate two functionally distinct classes of enhancer elements in human embryonic stem cells (hESC): active and poised. We now extended enhancer profiling to other hESC-derived cell types, including the neural crest, anembryonic cell population characterized by its unique developmental plasticity and ability to migrate at long distances. Although ectodermal in origin, neural crest cells can differentiate not only to neuroectodermal cell types from which peripheral nervous system is derived, but also to melanocytes, giving rise to body pigmentation, and to mesenchymal derivatives, which form the majority of craniofacial bones and cartilage and contribute to the heart. We identified over 3400 genomic regions uniquely marked by an active enhancer signature in hNCC and showed that these regions are linked to genes essential for development of NC-derived head structures and are active during distinct spatio-temporal events accompanying NC development. I will discuss broad implication of our results for studies of human craniofacial development, evolution and disease.

[Session #2: 13:00 - 14:15]

MicroRNA-mediated reprogramming of human fibroblasts to neurons

Dr. Andrew Yoo (Washington University)

We recently discovered that small RNA molecules, microRNAs, facilitate changes in the activity of chromatin remodeling complexes during mammalian neural development. Two microRNAs, miR-9* and miR-124 modify the composition of BAF chromatin remodeling complexes by repressing a neural progenitor-specific subunit BAF53a, allowing the incorporation of the neuron-specific BAF53b subunit into the complex (Yoo et al., 2009). Given the propensity of these microRNAs in modulating chromatin states during neural development, we tested the contribution of these microRNAs in the acquisition of neuronal fates. We discovered that miR-9/9* and miR-124 (miR-9/9*-124) could promote the generation of post-mitotic neurons by demonstrating that expression of these microRNAs in non-neuronal cell types converted their cell fates directly into functional neurons (Yoo et al., 2011). Human dermal fibroblasts from neonatal or importantly, adult origin can be directly converted into functional neurons upon ectopic expression of miR-9/9*-124 with as few as one neural transcription factor. miR-9/9*-124 induce the fibroblasts to exit from the cell cycle and start adopting the fates of post-mitotic neurons. The efficiency of this conversion is greatly enhanced by the concurrent expression of additional neural factors, NeuroD2, ASCL1 and Myt1l (DAM), whereas DAM factors alone are inefficient in the absence of miR-9/9*-124 (Yoo et al., 2011). In the same study, we also demonstrated that the neuronal conversion occurs without going through pluripotent/multipotent stages, demonstrating the feasibility of using microRNAs and pro-neural transcription factors to derive post-mitotic neurons directly. Our future goals aim to develop methods to develop tissue culture models of neurological diseases using the skin cells from the patients with neurological disorders.

[Session #3: 14:30 - 15:45]

Regenerate Broken Heart: Possible or Not?

Dr. Li Qian (Cardiovascular Diseases of Gladstone Institute/
UCSF CIRM fellow/researchers, US)

Heart failure affects millions worldwide and is a progressive disease. The human heart has limited endogenous regenerative capacity and is thus a target for novel regenerative medicine approaches. Cardiac fibroblasts comprise approximately 50% of cells in the mammalian heart and contribute to scar formation upon cardiac damage. Our recent report showing direct reprogramming of fibroblasts into cardiomyocyte-like cells by defined factors in vitro raises the possibility that endogenous cardiac fibroblasts could serve as a potential source of new cardiomyocytes for regenerative therapy. Here, we use genetic lineage-tracing to show that resident cardiac fibroblasts can be reprogrammed into cardiomyocyte-like cells in the murine heart by local delivery of Gata4, Mef2c, Tbx5(GMT) after coronary ligation. In vivo induced cardiomyocytes became bi-nucleated and assemble sarcomeres. Analysis of single cells revealed ventricular cardiomyoctye-like action potentials and gap junctions, necessary for electrical coupling. In vivo delivery of GMT attenuated infarct size and rescued cardiac dysfunction up to 3 months after coronary ligation. These results indicate that a significant fraction of endogenous cardiac fibroblasts can be diverted to generate new cardiomyocytes and that introduction of cardiac reprogramming factors into cardiac fibroblasts in vivo can improve cardiac function after myocardial infarction.