CDB SEMINAR

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16:00-18:00 Seminar Room A7F

Engineering hematopoietic stem cells from human pluripotent stem cells

Summary

Hematopoietic stem cell (HSC) transplantation is an important curative source for malignant and non-malignant blood diseases. However, HSC transplantation has limitations, including donor availability and immunologic mismatch. To resolve these issues, researchers have been mounting considerable efforts to induce HSCs from autologous sources, such as induced-pluripotent stem cells, hematopoietic precursors, and fibroblasts.

Human pluripotent stem cells (hPSCs) are an intriguing platform that allows for large-scale expansion culture and correction of mutations. Achieving the formation of HSCs from hPSCs would transform our ability to model and treat hematologic disease from autologous stem cells. Desired cell types have been generated from hPSCs by two approaches, one is directed differentiation by supplementing signaling factors; the other is synthetic biology by exogenously expressing transcription factors (TFs). Either approach has not achieved fully functional HSCs from hPSCs so far. Thus combination of these two, directed differentiation to hematopoietic precursors followed by exogenous expression of TFs, was taken in this study.

hPSCs can be differentiated to bi-potent hemogenic endothelium (HE) that commits to both vessels and blood in vitro. HE has been considered as a platform to engineer HSCs because of its consistency and robustness to be induced from hPSCs. However, HE lacks both multipotent hematopoiesis in vitro and robust hematopoietic capacity (e.g. engraftment upon transplantation) in vivo. To characterize HE at molecular level, its gene expression profile was categorized using the computer algorithm CellNet (established in Daley lab) to compare HE with reference cell populations. This revealed that HE shared features of endothelial cells strongly rather than that of hematopoietic cells, which is consistent with the observation that transplanted HE exclusively contributes to vessels. A considerable number of TFs specifying HSCs was downregulated in HE. By adding a library of these TFs using lentiviral vectors, HE conferred robust multipotent colonies in vitro, and reconstituted hematopoiesis in vivo. Integrated viral transgenes are detected by genomic PCR to define TFs that specify HSCs. Ongoing analysis is aimed at identifying if and how defined TFs convey self-renewal capacity to HE-derived HSCs, and molecular dissection of the process of HSC specification.

The future direction of this work is gene-correction of hPSC-derived hematopoietic cells, for example, Cas9-mediated genome editing of congenital anemia. This work will provide a significant platform to produce human HSCs for potential clinical applications as well as better understanding of hematopoiesis.

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