Decision of self-renewal and differentiation in tissue stem cells

Stem cell are defined as cells having a self-renewal activity and multi-differentiation capacity. Both are tightly controlled to maintain hematopoietic stem cell (HSC) homeostasis in the adult bone marrow. Expansion technology of HSCs have recently shown the significant progress and it is promising for the transplantation after severe chemotherapy in cancer patients.

During fetal development, both HSC expansion (self-renewal) and differentiated hematopoietic cell production (differentiation) are required to sustain the hematopoietic system for body growth. However, it remains unclear how these two seemingly opposite tasks are accomplished within the short embryonic period. Here, we used in vivo genetic tracing to analyze the formation of HSCs and progenitors from intra-arterial hematopoietic clusters, which contain HSC precursors and express the Hlf transcription factor. Through kinetic study, we find the simultaneous formation of HSCs and defined progenitors—previously regarded as HSC descendants—from the Hlf-positive precursor population, followed by prompt hierarchical hematopoietic structure formation in the fetal liver in a HSC-independent manner. The transcription factor Evi1 is heterogeneously expressed within the precursor population, with $Evi1^{hi}$ cells predominantly localized to intraembryonic arteries and preferentially giving rise to HSCs. By genetically manipulating Evi1 expression, we can alter HSC and progenitor output from precursors in vivo (*Nature* in press). These data suggest that HSCs minimally contribute to the generation of progenitors and functional blood cells. Intensive utilization of stem cell-independent pathway during development may be a rational strategy for rapid growth of tissues and stem cell pools. On the basis of this study, I would like to present our ongoing project of HSC expansion ex vivo.