

Development, Expansion and Maturation of Hematopoietic Stem Cells in Mouse Embryo

Atsushi Miyajima, Ken-ichi Minehata, Masaki Takeuchi

Institute of Molecular and Cellular Biosciences, The University of Tokyo, Tokyo, Japan

Abstract

During embryonic development, hematopoiesis occurs in different tissues. Primitive hematopoiesis first occurs in the yolk sac and definitive hematopoietic stem cells (HSCs) arise in the aorta/gonad/mesonephros (AGM) region. Fetal liver then functions as the major hematopoietic organ from the mid to late gestation, before hematopoiesis starts in the bone marrow. We have developed a primary culture system of mouse AGM cells which produces both hematopoietic cells and endothelial cells and found that hemangioblasts, the common precursor of hematopoietic and endothelial cells, are enriched in the cell population which express podocalyxin like protein 1, a CD34-related molecule, but lacks CD45 in the AGM region. We also developed a culture system of E14.5 fetal hepatic cells which support hematopoiesis. AGM-derived HSCs proliferated most vigorously in the presence of such fetal hepatic cells, however HSCs derived from later stages of development proliferated less efficiently in the same co-culture system, suggesting that the proliferation potential of HSCs declines along with development. While AGM-derived HSCs poorly engrafted in the bone marrow of irradiated adult mice, co-culture of AGM-derived HSCs with fetal hepatic cells dramatically increased the bone marrow engraftment. These results indicate that fetal hepatic cells alter the characteristics of HSCs. Interestingly, Oncostatin M (OSM) strongly induced differentiation of immature hepatocytes to metabolically active mature hepatocytes, but it simultaneously reduced their ability to support hematopoiesis. As OSM is produced by hematopoietic cells in the fetal liver, it is likely that OSM plays a role for coordinating the development of hematopoietic cells and the liver. In conclusion, our in vitro system provides a means to study the molecular basis of development, expansion and maturation of HSCs.
