Title of Project : Biomimetic stem cell niche: Reconstruction of hematopoietic niche complex for the expansion of stem cells.

Fumio Arai
(Keio University, School of Medicine, Associate Professor)

Research Area : Biological Sciences (Medicine, dentistry, and pharmacy)
Keyword : Hematology

【Purpose and Background of the Research】

The interaction of hematopoietic stem cells (HSCs) with their specialized niches is crucial for the maintenance of the balance among self-renewal, differentiation, and quiescent status of HSCs. We identified that multiple types of osteoblast and mesenchymal progenitor cell (MPC), which we hypothesized to form "niche complex" in endosteum and support HSCs. We also found that the cell cycle of HSCs shifts from active to quiescent state with the postnatal BM development. These finding suggest that the mechanisms of HSC regulation by the niche vary between neonatal and adult bone marrow (BM). In this research, we aim to clarify developmental changes of the function of niche cells and niche factors, and to establish the techniques of the manipulation of HSC's characteristics. In addition, based on the analysis of the niche cells and niche factors in endosteal niche complex, we would like to develop the methodology for the construction of biomimetic scaffold. Ultimately, we would like to establish optimized culture system for ex vivo expansion of HSCs in the artificial niche.

【Research Methods】

1. Functional analysis of the niche complex
-To analyze the developmental changes of niche complex, endosteal cell fractions (MPC, immature and mature osteoblast) from 2, 4, 6, and 8 week-old mice will be isolated and analyzed for the gene expression at the single cell level by high-throughput real-time PCR analysis using novel nanofluidic chip.
-Identification of the molecular signalings that are commonly induced by Angiopoietin-1 and Thrombopoietin and maintain the quiescence of HSCs
-Establishment of the manipulation techniques of HSC-niche interaction by the inhibition/activation of niche signaling pathways.

2. Establishment of artificial biomimetic niche
-Development a biomimetic system for *ex vivo* expansion of HSCs.
-Real-time imaging of the HSC-niche interaction in the biomimetic scaffold by the labeling of HSCs.
-Analysis of the signaling pathway of niche factors in HSCs during the culture in biomimetic scaffold.

【Expected Research Achievements and Scientific Significance】

The clarification of the functional difference of the BM niche regulation between neonatal and adult enable us to identify the detailed molecular mechanism of the regulation of self-renewal and quiescence of HSCs. Results of this study should contribute to establish the new strategy of regenerative medicine involving manipulation of stem cell niches, and are critical for the development of the artificial biomimetic niche.
Artificial niche applied to the *ex vivo* expansion of HSCs and live imaging of HSCs should also enhance the research of the niche regulation of normal and leukemic stem cells.

【Publications Relevant to the Project】

Arai F, Hirao A, Ohmura M, Sato H, Matsuoka S, Ito K, Takubo K, Koh GY and Suda T. Tie2/Angiopoietin-1 signaling regulates hematopoietic stem cell quiescence in the bone marrow niche. Cell 118: 149-161, 2004.
Yoshihara H, Arai F, Hosokawa K, et al. Thrombopoietin/Mpl signaling regulates hematopoietic stem cell quiescence and interaction with the osteoblastic niche. Cell Stem Cell. 1: 685-697, 2007.

【Term of Project】 FY2009-2013

【Budget Allocation】 80,200 Thousand Yen

【 Homepage Address and Other Contact Information】

http://web.sc.itc.keio.ac.jp/celldiff/