【Grant-in-Aid for Scientific Research(S)】
Biological Sciences (Medicine, dentistry, and pharmacy Ⅱ)

Title of Project : Niche Regulation for Stem Cell Fate

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Research Area : Medicine, dentistry, and pharmacy

Keyword : hematopoietic stem cells, niche, self-renewal, radical oxygen, hypoxia

【Purpose and Background of the Research】

Stem cells have a capacity for differenciating to multilineage and sustaining the undifferentiate state. Proliferation and differentiation of stem cells are determined not only by intrinsic program but by their microenvironment (niche) such as niche cells and niche factors.

To develop the technology for the regulation of stem cells, it is critical to understand how niche is involved in the determination of stem cell fate. In this project, we will re-analyze the histological structure for hematopoietic stem cell (HSC) niche in the bone marrow and clarify which molecules control the stem cell behavior in the niche.
We will analyze how stem cells block the cell division and sustain the quiescence in the hypoxic niche. Moreover, we will study the cell division mode of stem cells by examining the gene expression of paired daughter cells from single stem cells. Through these studies, we will clarify the self-renewal process of stem cells. We will search for novel self-renewal factors from pluripotent stem (iPS/ES) cells and examine the function and regulation of candidate genes in HSCs. In these studies, we will reveal the regulation mechanism of stem cell fate.

【Research Methods】

A) Analyses for HSC niche
We analyze the structure for HSCs niche in the bone marrow by immunohistochemistry and electronmicroscopy. Especially we focus our study on perivascular cells and osteoblast-osteoclast interaction and identify the niche factors acting on HSCs.
We analyze the metabolic state of HSCs which are located in the hypoxic niche in order to clarify the mechanism how HSCs sustain the undifferentiated state.

B) Niche reconstruction and regulation
Based on the studies described above, we try to control the cell cycle of HSCs and enhance the efficiency of bone marrow transplantation. We will study the self-renewal events of stem cells by examining the gene expression of single stem cells using microfluidics.

【Expected Research Achievements and Scientific Significance】

We will identify the niche structure and function for HSCs to manipulate stem cells ex vivo and in vivo. Through this project,

1) We understand the niche structure for HSCs.
2) We control the cell cycle state by analyzing the niche signaling.
3) We understand the characteristics of HSC metabolism in the hypoxic niche.
4) We recapture self-renewal of HSCs in vitro.
5) We identify the transcriptional regulation of self-renew in HSCs.

We can clarify the regulation of fate decision in HSCs, which will be influential to the other stem cell systems including cancer stem cells.

These studies, we will clarify the self-renewal process of stem cells.

【Publications Relevant to the Project】

Arai F, Hirao A, Ohmura M, Sato H, Matsuoka S, Takubo K, Ito K, Koh GY, Suda T: Tie2/Angiopoietin-1 signaling regulates hematopoietic stem cell quiescence in the bone marrow niche. ***Cell***, 118: 149-161, 2004

Ito K, Hirao A, Arai F, Matsuoka S, Takubo K, Nakagata N, Ikeda Y, Tak W. Mak, Suda T: Regulation of oxidative stress by ATM is required for self-renewal of haematopoietic stem cells. ***Nature***, 431: 997-1002, 2004

【Term of Project】 FY2010-2014

【Budget Allocation】 167,400 Thousand Yen

【 Homepage Address and Other Contact Information】

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