【Grant-in-Aid for Scientific Research (S)】

Biological Sciences (Medicine, Dentistry, and Pharmacy)

Title of Project : Homeostasis of Hematopoietic Stem Cell Maintenance

Toshio Suda
(Kumamoto University, Priority Organization for Innovation and Excellence, Visiting Professor)

Research Project Number : 26221309 Researcher Number : 60118453
Research Area : Medicine, dentistry, and pharmacy
Keyword : hematopoietic stem cells, niche, radical oxygen, hypoxia

【Purpose and Background of the Research】

Stem cells have a capacity for differentiating 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.

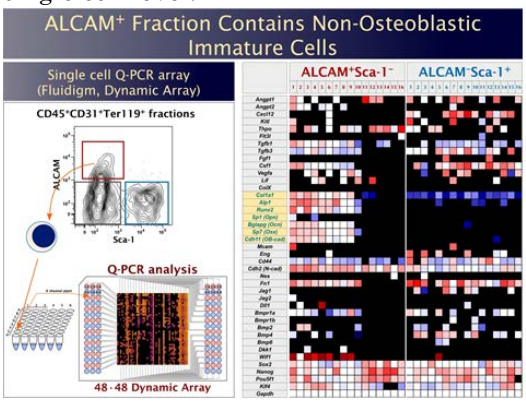
【Research Methods】

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.

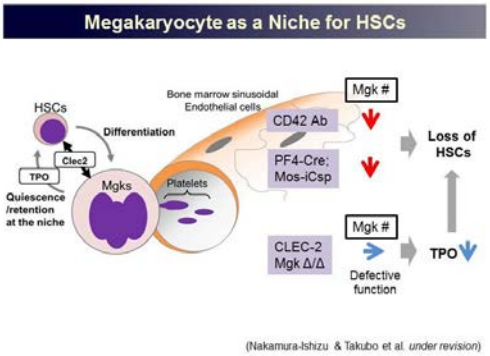
B) Niche reconstruction and regulation

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 at the single cell level.



【Expected Research Achievements and Scientific Significance】

Based on physiological research, we will also clarify whether stem cell aging is related to the pathogenesis of hematological malignancies. We will analyze the aging process in HSCs and their niche and clarify the accumulation of DNA damage. We will focus on the telomere dysfunction in HSCs from the Shelterin function and clarify the pathogenesis of CLL and MDS, which are known to be niche cell-derived and age-dependent. These studies may help to elucidate the pathophysiology of diseases and provide critical clues to develop novel treatment and preemptive measures for the prevention of these diseases.



(Nakamura-Ishizu & Takubo et al. *under revision*)

【Publications Relevant to the Project】

Suda T, Takubo K, Semenza GL: Metabolic regulation of hematopoietic stem cells in the hypoxic niche. ***Cell Stem Cell*** 9: 298-310, 2011

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

【Term of Project】 FY2014-2018

【Budget Allocation】 150,000 Thousand Yen

【Homepage Address and Other Contact Information】

http://web.sc.itc.keio.ac.jp/celldiff/index.html
sudato@z3.keio.jp