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

Biological Sciences (Medicine, Dentistry, and Pharmacy)

Title of Project : Regulation of self-renewal vs. quiescence status in human myeloid leukemia stem cells

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Research Project Number : 16H06391 Researcher Number : 80380385
Research Area : Biological Sciences
Keyword : Hematology

【Purpose and Background of the Research】

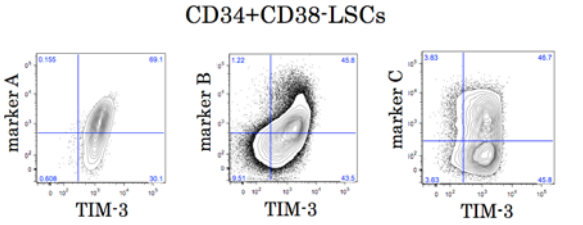
Acute myeloid leukemia (AML) originates from self-renewing leukemic stem cells (LSCs). Purified human LSCs can repopulate human AML in immunodeficient mice, and therefore, LSCs should be an ultimate therapeutic target for treatment of AML. LSCs can self-renew to expand, but can also stop cell cycle to escape chemo-radiotherapy. However, the molecular mechanisms regarding how LSCs dramatically change their cellular status are still unknown. In this project, we will clarify the molecular mechanisms of the plasticity of LSCs.

【Research Methods】

The T-cell immunoglobulin mucin-3 (TIM-3) is expressed on the surface of LSCs in the majority of AML patients (Kikushige et al., Cell Stem Cell 2010). TIM-3 and its ligand, galectin-9 formed an autocrine loop critical for LSC maintenance. TIM-3+ LSCs of human myeloid malignancies secrete galectin-9 into sera, and it binds to TIM-3 to induce self-renewal signaling (Kikushige et al., Cell Stem Cell 2015). The TIM-3/galectin-9 autocrine loop is universally used in LSCs of a variety of myeloid malignancies including AML, myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN) to achieve the clonal dominancy during their disease progression process.

We have identified novel LSCs-specific surface molecules based on the transcriptome analysis of human $CD34^{+}CD38^{-}$ LSCs (Figure 1), and some of these molecules are specifically expressed in quiescent LSCs. By using combination of antibodies against TIM-3 and new surface antigens, we will try to isolate new subpopulations of LSCs with different functions, and will analyze biological characteristics of these subpopulations. We will test the LSC activity of these subpopulations by utilizing a new immuno-deficient xenograft model, and by using high throughput omics analyses including exome sequencing, RNA sequencing and metabolome analysis. We will try to reveal the molecular mechanisms of heterogeneity in human myeloid LSCs, and the role of microenvironment in maintenance of their heterogeneity.

figure 1



These markers enables us to prospectively isolate new sub-fraction of TIM-3+ LSCs

【Expected Research Achievements and Scientific Significance】

We will establish the method for purification of LSC subpopulation with distinct stem cell activities to understand regulation of self-renewal vs. quiescence status in human myeloid malignant stem cells. The result will help understand how LSCs become resistant to chemo-radiotherapy, and to develop new treatment strategies targeting LSCs.

【Publications Relevant to the Project】

1. Y. Kikushige *et al.*, TIM-3 is a promising target to selectively kill acute myeloid leukemia stem cells. *Cell Stem Cell* **7**, 708 (Dec 3, 2010).
2. Y. Kikushige *et al.*, A TIM-3/Gal-9 Autocrine Stimulatory Loop Drives Self-Renewal of Human Myeloid Leukemia Stem Cells and Leukemic Progression. *Cell Stem Cell* **17**, 341 (Sep 3, 2015).

【Term of Project】 FY2016-2020

【Budget Allocation】 118,500 Thousand Yen

【Homepage Address and Other Contact Information】

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