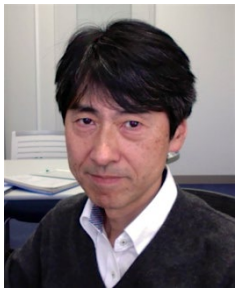
【Grant-in-Aid for Scientific Research (S)】

Broad Section I



Title of Project： Deciphering of the epigenetic machinery that determines the hallmarks of hematopoietic stem cell aging

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Research Project Number：19H05653　Researcher Number：70244126
Keyword：Hematopoietic stem cell, aging, epigenetics

【Purpose and Background of the Research】

Hematopoietic cells represent the cell type with the greatest numbers in the body. They circulate throughout the body or stay in the organs and exert various functions such as supply of oxygen, hemostasis, and immune reactions. Hematopoietic stem cells (HSCs) are exposed to various stresses and show functional decline during aging.

Dysfunction of hematopoietic stem cells results in disorganized hematopoietic system, including anemia and immune dysfunction, thereby causing functional decline in various organs, eventually leading to the individual's functional impairment. Aged HSCs are also predisposed to transformation (Figure 1). Therefore, functional impairment of HSCs is tightly associated with individual's functional impairment. Understanding of the mechanisms regulating HSC function over the entire life course thus promotes understanding of the mechanisms underlying individual's functional impairment.

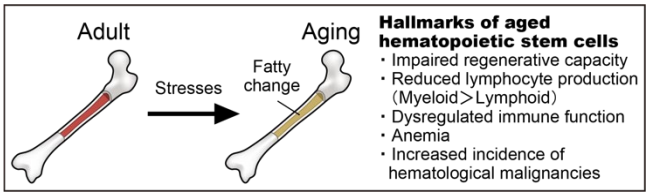


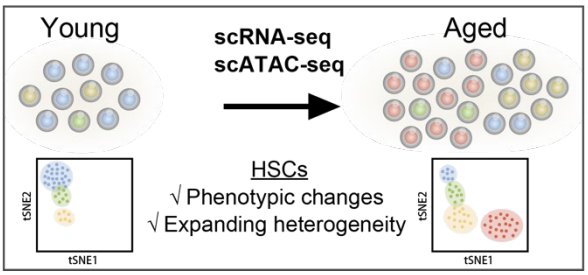
Figure 1. Hallmarks of aged hematopoietic stem cells

【Research Methods】

We will take bioinformatic comprehensive approaches to decipher the changes in epigenetic properties of HSCs over the entire life course: (1) maintenance phase in adult bone marrow and (2) functional impairment phase during aging. We will clarify how various stresses to which mice are exposed alter epigenetic patterns in HSCs and impair individual's function over the entire life course. We have already obtained a part of the epigenetic data of HSCs and identified unique chromatin properties that may account for functional impairment of HSCs with aging. We also take an advantage of single HSC profiling by RNA-seq and ATAC-seq analysis to decipher the alterations in heterogeneities in HSC populations with age (Figure 2).

Because the quality of bone marrow niche holds key to the functional maintenance of HSCs, we will also analyze the alterations in the quality of niche over the entire life course. Furthermore, we will clarify the epigenetic abnormalities responsible for the impaired differentiation of HSCs, which leads to abnormal production of differentiated progenies and transformation into age-associated hematological malignancies.

Figure 2. Single cell assays of HSCs



【Expected Research Achievements and Scientific Significance】

Through a series of analyses, we hope to identify factors responsible for the functional impairment of HSCs and their niche, which eventually affect individual's function over the entire life course. By manipulating those factors, we will develop the modalities to control the individual's functional impairment through reactivating HSCs

【Publications Relevant to the Project】

・Tara S, Isshiki Y, Nakajima-Takagi Y, Oshima M, Aoyama K, Tanaka T, Shinoda D, Koide S, Saraya A, Miyagi S, Manabe I, Matsui H, Koseki H, Bardwell VJ, Iwama A. *Bcor* insufficiency promotes initiation and progression of myelodysplastic syndrome. ***Blood*** 132(23):2470-2483, 2018.

・Sashida G, Harada H, Matsui H, Oshima M, Yui M, Harada Y, Tanaka S, Mochizuki-Kashio M, Wang C, Saraya A, Muto T, Inaba T, Koseki H, Huang G, Kitamura T, and Iwama A. Ezh2 loss promotes development of myelodysplastic syndrome but attenuates its predisposition to leukemic transformation. ***Nat Commun*** 5:4177, 2014.

【Term of Project】 FY2019-2023

【Budget Allocation】 153,800 Thousand Yen

【Homepage Address and Other Contact Information】

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