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

A Study of hematopoietic stem cell aging and its implication in the pathogenesis of hematological malignancies

Principal Investigator	The University of Tokyo, Institute of Medical Science, Professor IWAMA Atsushi　Researcher Number : 70244126
Project Information	Project Number : 24H00066　Project Period (FY) : 2024-2028 Keywords : hematopoietic stem cells, aging, heterogeneity, clonal hematopoiesis, hematological malignancies

Purpose and Background of the Research

●Outline of the Research

√ In the Scientific Research (S) (2019~2023), we identified an hematopoietic stem cell (HSC) aging marker gene *Clusterin* and identified that the reporter mice of *Clusterin*, an aging HSC signature gene, and demonstrated the reporter mice of *Clusterin* identify and prospectively track the two functionally distinct mouse HSC subsets throughout (Figure 1).

√ In this study, using this mouse system, we understand the HSC aging and the heterogeneity of aged HSCs. Furthermore, we identify the stem cell subpopulations, from which clonal hematopoiesis and hematological malignancies originate.

√ We integrate the data from mouse models with the data obtained from human aged HSCs and myeloid malignancies and decipher the role of HSC aging in the pathogenesis of age-associated hematological malignancies.

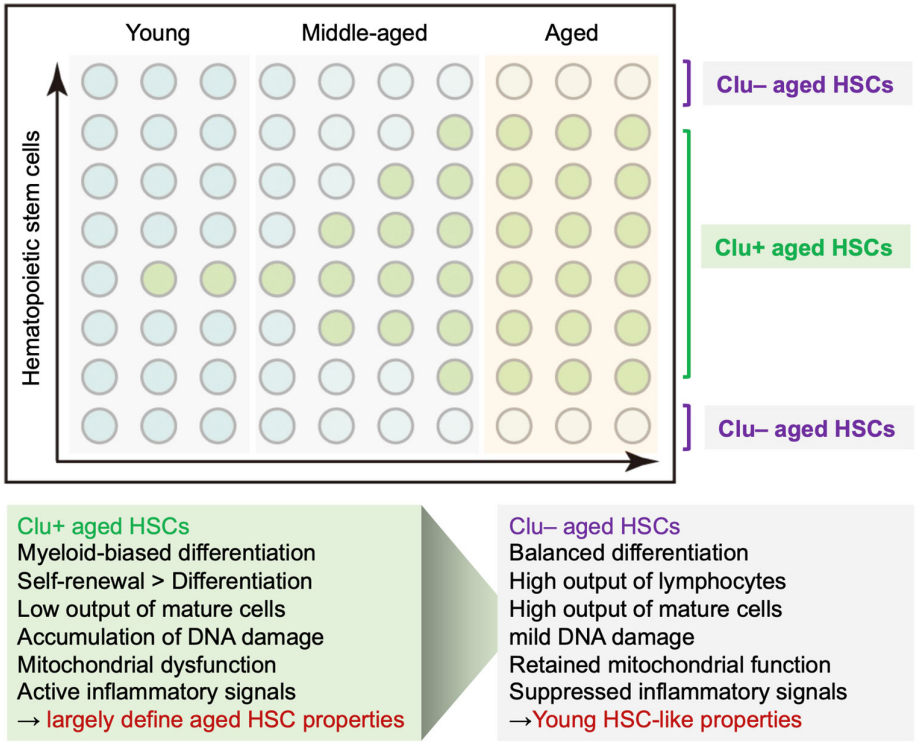
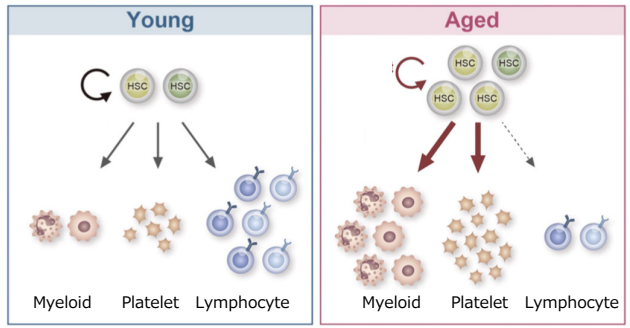


Figure 1. Heterogeneity of aged hematopoietic stem cells



● Aged HSCs

The following issues remain to be clarified (Figure 2);

1. Their differentiation properties
2. Their heterogeneity
3. The relationship between HSC aging and clonal hematopoiesis by HSCs that acquired somatic driver gene mutations

1. Impaired repopulating capacity of hematopoiesis, increase in proportion
2. Myeloid/platelet-biased differentiation, low output of lymphocytes, anemia
3. Dysregulated immune function (Immunosenescence)
4. Clonal hematopoiesis and increased risk of myeloid malignancies

Figure 2. The characteristics of aged HSCs

Expected Research Achievements

●Monitoring of aging process of HSCs

We determine whether Clusterin-negative HSCs become Clusterin-positive HSCs or a small population of Clesterin-positive HSCs expands with aging.

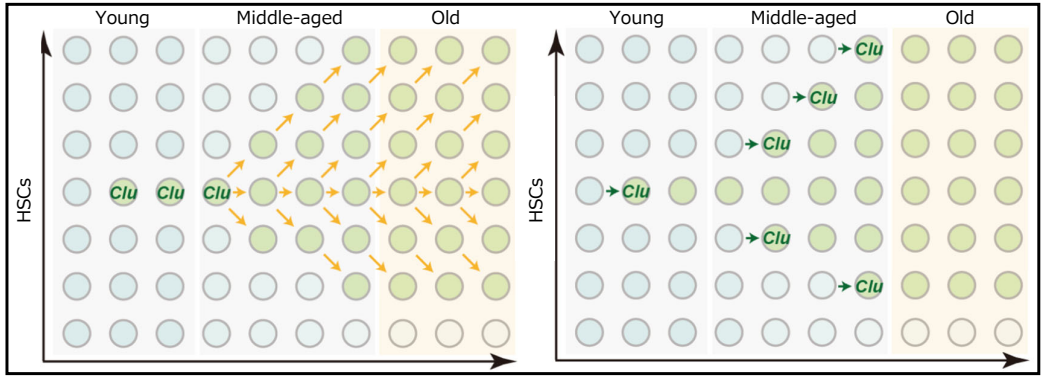


Figure 3. Model of HSC aging process

●Identification of the HSC subpopulations responsible for clonal hematopoiesis

Using *Tet2*-deficient mice, we monitor the process of clonal expansion and transformation of Clusterin-positive and -negative HSCs and determine which HSCs are more prone to transformation.

●Development of intervention approaches to HSC aging

We develop a model mice in which Clu-positive HSCs can be conditionally eliminated (Figure 4). Ablation of Clu-positive HSCs may allow expansion of Clu-negative HSCs, thereby rejuvenating hematopoiesis and preventing the development of clonal hematopoiesis and hematological malignancies.

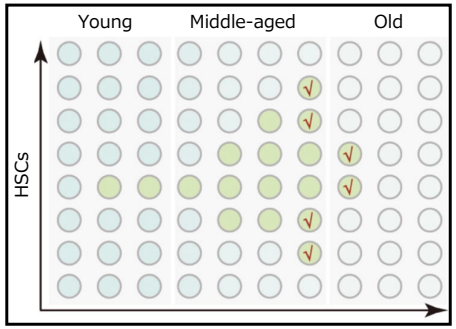


Figure 4. Ablation of Clu-positive HSCs (√)

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