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研究課題名	Inflammation, hematopoietic aging, and clonal drift: deciphering the role of the transcription factor PLZF	
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## IMSUT International Joint Usage/Research Center Project &lt;International&gt;

## Joint Research Report (Annual/Project Completion)

## Annual Report

## Report Development of novel therapeutics targeting hematopoietic stem cell

Aging leads to a deterioration of the hematopoietic system. It is now well established that age-related dysfunction of the hematopoietic system arises from the hematopoietic stem cells (HSCs), which lose their fitness over time. Remarkable work has been achieved in this field with the identification of the hallmarks driving HSC aging that are closely interconnected, forming an integrated network making HSC aging a very complex mechanism.

Recently, we identified a new regulator of HSC aging: the transcription factor PLZF (*Zbtb16*). We showed that its inactivation (loss-of-function mouse model *Zbtb16<sup>lu/lu</sup>*) resulted in a more pronounced aging phenotype in middle-age mice or after regenerative stress characterized by a myeloid skewing potential, an increase in the long-term HSC pool, and a decreased repopulation capacity along with cell cycle defects. Although PLZF expression is not decreased upon aging, we noticed transcriptional and chromatin changes in PLZF target genes. Interestingly these genes were associated with biological processes related to cell cycle, metabolism and inflammation that are known hallmarks of HSC aging. To better understand HSC aging in the absence of functional PLZF, we have performed in collaboration with Pr. Iwama's laboratory, single cell RNA sequencing on HSCs purified from young and old *Zbtb16<sup>lu/lu</sup>* mice. Preliminary results show that *Zbtb16<sup>lu/lu</sup>* remodels HSC compartment by increasing specific subpopulations involved in inflammation signaling and which were identified as Tgf $\beta$ , Interferon, and Notch HSCs (unpublished data). We are now investigating the role of PLZF in aging induced by chronic inflammation (serial injection of Poly-IC) at the functional (clonogenic assay) and transcriptional levels (single cell RNA sequencing).

Altogether, our results suggest that PLZF may control HSC aging by limiting the inflammatory signals that HSCs perceive over time and we are currently studying the effect of inflammatory stress on PLZF transcriptional and epigenetic activities.