学位論文抄録

The acidic domain of Hmga2 and the domain's linker region are critical for driving self-renewal of hematopoietic stem cell

(Hmga2 の酸性ドメインとそのリンカー領域は造血幹細胞の自己複製を促進する)

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Abstract of the Thesis

Background and Purpose: High mobility group AT-hook 2 (HMGA2) is a chromatin modifier protein that plays a critical role in fetal development and leukemia propagation by binding to chromatin and DNA via its AT-hook domains. However, the molecular mechanisms by which Hmga2 activates the expression of target genes to drive the self-renewal capacity of hematopoietic stem cells (HSCs) remain unclear. In this study, we will identify the phenotype of Hmga2 over expression and the molecular mechanism of how the expression of Hmga2 activates the transcription of target genes.

Methods: To identify the phenotype of Hmga2 over expression. We herein generated a Rosa26 locus Hmga2 conditional knock-in mice. By assessing the cellular functions of Hmga2 mutants lacking functional domains, we constructed Hmga2 mutants by retro virus vector to infect mouse HSC. Furthermore, we examined the function of Hmga2 mutants through the assessing expression levels of Hmga2 to identify the expression of target gene by q-PCR.

Results: Over-expression of Hmga2 promoted expansion of HSCs in the BM and competed wild-type HSCs, but maintained the fitness of HSC in the BM, resulting in normal blood cells production in mice. The immunofluorescence assay revealed that all mutants of and wild-type Hmga2 and Hmga1 were dominantly expressed in nucleus, while Hmga2 1-45 mutant lacking the first AT-hook domain showed very lower expression in cells, presumably due to its impaired affinity to chromatin and DNA. Furthermore, we found that the Hmga2 requires At-hook domains and acidic domains with its linker region to activate the expression of target gene and promote the expansion of HSCs.

Conclusions: The AT hook and acidic domain with its linker region of Hmga2 is critical for driving the self-renewal of hematopoietic stem cell