学位論文要旨

Analyses of zebrafish Ddx46 function in the tissue and organ formation.
(組織・器官形成におけるゼブラフィッシュ Ddx46 の機能解析)

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It is well known that RNA helicases of the DExD/H-box protein family are involved in gene expression processes, including transcription, pre-mRNA splicing, and rRNA biogenesis. Although one DExD/H-box protein, Prp5, a homologue of vertebrate Ddx46, has been shown to play important roles in pre-mRNA splicing in yeast, the in vivo function of Ddx46 remains to be fully elucidated in metazoans. In our previous study, we isolated the zebrafish *mor* mutant had a mutation in *Ddx46*. Then we analyzed and revealed Ddx46 is required for the development of the digestive organs and brain by specific pre-mRNA splicing.

The Ddx46 transcript is maternally supplied, and as development proceeds in zebrafish larvae, its ubiquitous expression gradually becomes restricted to specific organs, including digestive organs and brain. It had been implicated that *Ddx46* expression sites showed defects in *Ddx46* mutants. In this study, we found the novel *Ddx46* expression site and defects in *Ddx46* mutants.

Balanced and precisely controlled processes between self-renewal and differentiation of HSCs into all blood lineages are critical for vertebrate definitive hematopoiesis. The molecular mechanisms underlying the maintenance and differentiation of HSCs have not been fully elucidated, however. Here, we show that zebrafish *Ddx46*, encoding a DEAD-box RNA helicase, is expressed in HSCs of the CHT. The number of HSCs expressing the molecular markers *cmyb* or *T-cell acute lymphocytic leukemia 1* (*tal1*) was markedly reduced in *Ddx46* mutants. However, massive cell death of HSCs was not detected, and proliferation of HSCs was normal in the CHT of the mutants at 48 hpf. We found that myelopoiesis occurred, but erythropoiesis and lymphopoiesis were suppressed, in *Ddx46* mutants. Consistent with these results, the expression of *spi1*, encoding a regulator of myeloid development, was mai-

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tained, but the expression of *gata1a*, encoding a regulator of erythrocyte development, was downregulated in the mutants.

Taken together, our results provide the first genetic evidence that zebrafish Ddx46 is required for the multi-lineage differentiation of HSCs during development, through the regulation of specific gene expressions.