別紙様式第４

学　位　論　文　要　旨

博士課程 (甲)・乙	第 4 号	氏　名	Yadav Gnaneshwar Varadaraju

[論文題名]

Ribosomal protein deficiency causes Tp53-independent erythropoiesis failure in zebrafish
リボソームタンパク質の欠損はゼブラフィッシュにおいてTp53非依存的に赤血球形成不全を引き起こす

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[要　旨]

Diamond-Blackfan anemia (DBA) is an inherited genetic disease caused by mutations in ribosomal protein (RP) genes. The disease is characterized by bone marrow failure that mainly results in a severe anemia. Haploinsufficiency of the RPs leads to a defective ribosome biogenesis in DBA, but it is unclear how the mutations in ubiquitously expressed RP genes specifically affect the erythrocyte maturation. It is known that a disruption of the ribosome biogenesis evokes a nucleolar stress response, which activates the TP53 signaling pathway. Studies in a variety of cell line models have highlighted a critical role for TP53 in the clinical manifestation of DBA. While this pathway plays a role in the morphological defects that associate with RP loss-of-function in animal models, its role in the erythroid defects has not been clearly established.

To understand the specificity of erythroid defects in DBA, we knocked down five RP genes (two DBA-associated and three non-DBA-associated) in zebrafish and analyzed the effects on the developmental and erythroid phenotypes in the presence and absence of Tp53. We chose to study the *rpl35a* and *rps24* deficiencies for the DBA-associated genes because the loss-of-function analyses of these genes have not yet been performed in animal models. As for the non-DBA-associated genes, we studied the loss of *rps3, rpl35* and *rplp1* because no mutations have been identified in these genes in DBA patients. A deficiency of these RP genes caused morphological defects and a severe erythroid failure in the presence of Tp53. The co-inhibition of Tp53 activity rescued the morphological deformities but did not alleviate the erythroid aplasia. These results indicate that any RP deficiency, regardless of its role in DBA, led to erythropoietic failure in zebrafish in a Tp53-independent manner. Interestingly, treatment with L-Leucine or L- Arginine, amino acids that augment mRNA translation via mTOR pathway, rescued the morphological defects and resulted in a substantial recovery of erythroid cells. A simultaneous treatment with rapamycin, a specific inhibitor of mTORC1, reversed the

rescue achieved through amino acid treatments indicating that mTORC1 activation caused the recovery in RP-deficient zebrafish. Therefore, we suggest that enhancing the translational efficiency through the mTORC1 activation could rescue the anomalies in DBA. Taken together our results suggest that altered translation because of impaired ribosome function could be responsible for the morphological defects and erythroid failure in RP-deficient zebrafish.

備考　論文要旨は、和文にあっては 2，000 字程度、英文にあっては 1，200 語程度とする。