論文の内容の要旨

論文題目　Pathogenesis of EVI-1 Overexpressing Acute Myeloid Leukemia
（EVI-1 高発現白血病の病態解明）

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Acute myeloid leukemia (AML) is a heterogeneous disease with variable prognosis depending on genetic abnormalities. AML with Evi1 (ecotoropic viral integration site 1) overexpression ($Evi1^{high}$ leukemia) due to chromosomal abnormalities or other transcriptional dysregulations is one of the subgroups with the poorest prognosis in the disease. Although a variety of mechanisms of how Evi1 contributes to leukemia progression have been reported, effective therapeutic targets of Evi^{high} leukemia have not been identified. In this study, I thoroughly explored gene expression profiles in Evi1-overexpressing leukemia cells. I identified two novel targets regulated by Evi1, $p57^{KIP2}$ and Fbp1 through analyzing RNA-seq data of an Evi1-overexpressing mouse leukemia model. First, $p57^{KIP2}$ expression was spontaneously upregulated and later downregulated upon leukemic transformation. Ectopic expression of $p57^{KIP2}$ in Evi1-overexpressing KSL (Lin^{neg}, c-kit^{pos}, Sca-1^{pos}) cells decreased colony-forming cell capacity of Evi1-overexpressing KSL cells. This suggests that downregulation of $p57^{KIP2}$ contributes to leukemic transformation of $Evi1^{high}$ leukemia. Second, Fbp1 expression was also quickly upregulated by Evi1 overexpression and further increased at later time points. Moreover, we observed an enrichment of Evi1 in the promoter and enhancer region of Fbp1 by chromatin immunoprecipitation followed by qPCR analysis in murine hematopoietic cells, suggesting that Fbp1 expression is directly regulated by Evi1. Furthermore, pharmacological inhibition of Fbp1 and knockdown of Fbp1 in Evi1-overexpressing leukemia cells decreased leukemia burden of $Evi1^{high}$ leukemia mouse model. Through investigating a role of Fbp1 in Evi1 leukemia cells, I showed the importance of altered glucose metabolism in Evi1 leukemia cells *in vivo*. Collectively, these findings provide insights on molecular pathogenesis and new promising therapeutic targets for $Evi1^{high}$ leukemia.