急性白血病の治療標的としてのNOTCHシグナル

NOTCH signaling as a therapeutic target for acute leukemia

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NOTCH signaling is a crucial regulator of normal hematopoietic stem cells (HSC). It also plays roles in the pathophysiology of various hematological malignancies. Therefore, NOTCH can be a therapeutic target. It was reported that half of acute T-lymphoblastic leukemia (T-ALL) cases have activating *NOTCH1* mutations and that NOTCH activation plays oncogenic roles in T-ALL. However, whether NOTCH is oncogenic or tumor suppressive in acute myeloid leukemia (AML) is still controversial. We found that AML cells express NOTCH1 and NOTCH ligand JAGGED1 and that *NOTCH1* mutations are rare in AML. Stimulation with recombinant NOTCH ligands generally suppressed *in vitro* growth of AML cells, which suggests NOTCH works as a tumor suppressor in AML. Treatment with .-secretase inhibitors (GSI), which suppress NOTCH activation, suppressed *in vitro* growth of T-ALL cells and induced erythroid differentiation of some erythroleukemia cell lines. Knockdown of *NOTCH* by small interfering RNA also suppressed *in vitro* growth of T-ALL cells, but not that of AML cells. Successful clinical trials of GSI for T-ALL have not been reported. HSC and leukemia cells are regulated by various stemness-related signaling pathways other than NOTCH, such as WNT, HEDGEHOG, HIF, and mTOR. We reported that these pathways were related with NOTCH signaling and that the combinatorial administration of the NOTCH inhibitor and inhibitors for each pathway synergistically suppressed *in vitro* growth in cell-dependent manners.