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The NOTCH1 signaling pathway is tightly controlled by a number of physiologic mechanisms. Anomalous NOTCH1 signaling can occur through abnormal expression of NICD, mutations in the NOTCH1 receptor, an abundance of membrane-anchored ligands, or overproduction of endogenous antagonists such as NOG and ARSM1. NICD often resides in the nucleus and results in activation of target genes and down-stream signaling through regulation of the proapoptotic transcription factor NF-κB. In T-ALL, oncogenic signaling is frequently initiated by mutations in NOTCH1. Deregulated NOTCH1 signaling is most commonly due to the absence of the transcriptional activator RBPJ, causing constitutive NICD nuclear localization and oncogene-driven T-cell transformation. However, a number of mutations in NOTCH1 or its ligands have been identified in T-ALL patients, indicating that this pathway may be dysregulated in some cases of human T-ALL. For example, mutations in NOTCH2A, ligands and transcriptional effectors, and alterations in the downstream targets of the NOTCH1 pathway may occur in a subset of T-ALL cases. NOTCH1 has been identified as an oncogene that promotes the growth and survival of transformed T cells (73). However, pharmacologic inhibition of NOTCH1 has shown inconsistent effects in preclinical studies 19 and has also been associated with reduced T-ALL latency (290, 291). Genetic inhibition of NOTCH1 was investigated in a mouse model of T-ALL. In this model, Notch activation in multipotent hematopoietic cells predisposes these precursors to develop leukemia with a high frequency of immature and malignant CD4-CD8- T cells (49, 55). Mice lacking Notch1 in T cells with a hematopoietic compartment that contains bone marrow precursors and that is reconstituted with fetal liver hematopoietic progenitors develop an aggressive form of T-ALL with enhanced proliferation, abnormal pattern of differentiation, and dysfunction of the T-cell immune response (55, 290, 291). In the Notch1 -mutant mice, the malignant cells die with a mechanism that involves CD8 and CD4 T cells and uses perforin-granzyme and FasL for their elimination. Resistance to apoptosis may also be related to enhanced resistance to oxidative stress (291).

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Recently, the collaboration of a large international consortium, the GEMMs of NOTCH1, has unveiled the indispensable role of NOTCH1-mediated MYC activation in the induction of T-ALL in mice as a consequence of Notch1 activation in the context of the inherited TAL1-V□16A rearrangement. 103 Notably, the widespread activation of the Notch1-associated partner genes, such as Gata3 and Tcl1 in these animals, shows that the pronounced functional overlap between NOTCH1 and MYC in immature T cells is maintained in vivo in the context of the germline modification of target genes, thus making them a potentially powerful tool to model human NOTCH1-mediated T-ALL transformation. 30, 103 By using a Cre-dependent system for the conditional inactivation of the NMe enhancer in vivo, the conditional inactivation of NMe directly downstream of the V□16 promoter (specifically engineered to delete the NMe enhancer upon mutagenesis and T-ALL development) in mice led to the identification of critical target genes, including noncoding sequences of the Gata3 and Tcl1 locus, which are not targeted by NMe in the absence of Notch1. 30 These data identify a comprehensive set of target genes of the MYC oncogene in the context of a T-ALL-initiating Notch1 mutation and demonstrate that these target genes are preserved in vivo during the T-ALL development process. Fig. 10. T-ALL induction and maintenance pathways in immature T cells and in thymic precursors. This mouse model of T-ALL characteristically shows high expression of TAL1, TAL1-V□16A, and MYC in immature T cells and thymic precursors; albeit steady expression in mature T cells, as well as in thymocytes, following its deletion, aster v7 activation□154 p.27aster v7 activation 154 5ec8ef588b