NOTCH1 signaling promotes human T-cell acute lymphoblastic leukemia initiating cell regeneration in supportive niches.

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Public Summary:
Leukemia initiating cells (LIC) contribute to therapeutic resistance through acquisition of mutations in signaling pathways, such as NOTCH1, that promote self-renewal and survival within supportive niches. Activating mutations in NOTCH1 occur commonly in T cell acute lymphoblastic leukemia (T-ALL) and have been implicated in therapeutic resistance. However, the cell type and context specific consequences of NOTCH1 activation, its role in human LIC regeneration, and sensitivity to NOTCH1 inhibition in hematopoietic microenvironments had not been elucidated. We established humanized bioluminescent T-ALL LIC mouse models transplanted with pediatric T-ALL samples that were sequenced for NOTCH1 and other common T-ALL mutations. In this study, CD34(+) cells from NOTCH1(Mutated) T-ALL samples had higher leukemic engraftment and serial transplantation capacity than NOTCH1(Wild-type) CD34(+) cells in hematopoietic niches, suggesting that self-renewing LIC were enriched within the NOTCH1(Mutated) CD34(+) fraction. Humanized NOTCH1 monoclonal antibody treatment reduced LIC survival and self-renewal in NOTCH1(Mutated) T-ALL LIC-engrafted mice and resulted in depletion of CD34(+)CD2(+)CD7(+) cells that harbor serial transplantation capacity. These results reveal a functional hierarchy within the LIC population based on NOTCH1 activation, which renders LIC susceptible to targeted NOTCH1 inhibition and highlights the utility of NOTCH1 antibody targeting as a key component of malignant stem cell eradication strategies.

Scientific Abstract:
BACKGROUND: Leukemia initiating cells (LIC) contribute to therapeutic resistance through acquisition of mutations in signaling pathways, such as NOTCH1, that promote self-renewal and survival within supportive niches. Activating mutations in NOTCH1 occur commonly in T cell acute lymphoblastic leukemia (T-ALL) and have been implicated in therapeutic resistance. However, the cell type and context specific consequences of NOTCH1 activation, its role in human LIC regeneration, and sensitivity to NOTCH1 inhibition in hematopoietic microenvironments had not been elucidated. METHODOLOGY AND PRINCIPAL FINDINGS: We established humanized bioluminescent T-ALL LIC mouse models transplanted with pediatric T-ALL samples that were sequenced for NOTCH1 and other common T-ALL mutations. In this study, CD34(+) cells from NOTCH1(Mutated) T-ALL samples had higher leukemic engraftment and serial transplantation capacity than NOTCH1(Wild-type) CD34(+) cells in hematopoietic niches, suggesting that self-renewing LIC were enriched within the NOTCH1(Mutated) CD34(+) fraction. Humanized NOTCH1 monoclonal antibody treatment reduced LIC survival and self-renewal in NOTCH1(Mutated) T-ALL LIC-engrafted mice and resulted in depletion of CD34(+)CD2(+)CD7(+) cells that harbor serial transplantation capacity. CONCLUSIONS: These results reveal a functional hierarchy within the LIC population based on NOTCH1 activation, which renders LIC susceptible to targeted NOTCH1 inhibition and highlights the utility of NOTCH1 antibody targeting as a key component of malignant stem cell eradication strategies.