The Role of Notch Signaling in T-Cell Acute Lymphoblastic Leukemia

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T-cell acute lymphoblastic leukemia (T-ALL) is a quickly progressing cancer of the hematopoietic system that is caused by the malignant transformation of T-cell progenitors. Researchers have identified activating mutations in a gene called Notch1 in more than 50% of T-ALL cases. Subsequently, there have been two major attempts at inhibiting Notch1 in T-ALL: gamma secretase inhibitors (GSIs), which inhibit signaling through all four Notch family member receptors, and Notch1 blocking antibodies, which target only Notch1. GSIs exhibited strong anti-proliferative effects in vitro, yet caused serious side effects when moved into clinical studies. Notch1 blocking antibodies, by contrast, were less potent than GSIs but also avoided many of the toxicities associated with GSI use. Since blocking the Notch pathway as a whole showed strong anti-proliferative effects, but blocking only Notch1 did not, it suggests that Notch signaling pathways other than Notch1 may be involved in the progression of T-ALL. Here, we show that inhibiting Notch3 has anti-proliferative effects in some T-ALL cell lines. This anti-proliferative effect of Notch3 blockade seems to stem from the inhibition of downstream c-Myc signaling. We also link the sensitivity of different leukemic cell lines to Notch pathway inhibitors to their underlying genetics.

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