ORIGINAL ARTICLE

Therapeutic antibody targeting of Notch1 in T-acute lymphoblastic leukemia xenografts

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T-acute lymphoblastic leukemia (T-ALL) is characterized by several genetic alterations and poor prognosis in about 20–25% of patients. Notably, about 60% of T-ALL shows increased Notch1 activity, due to activating *NOTCH1* mutations or alterations in the *FBW7* gene, which confer to the cell a strong growth advantage. Therapeutic targeting of Notch signaling could be clinically relevant, especially for chemotherapy refractory patients. This study investigated the therapeutic efficacy of a novel anti-Notch1 monoclonal antibody by taking advantage of a collection of pediatric T-ALL engrafted systemically in NOD/SCID mice and genetically characterized with respect to *NOTCH1/FBW7* mutations. Anti-Notch1 treatment greatly delayed engraftment of T-ALL cells bearing Notch1 mutations, including samples derived from poor responders or relapsed patients. Notably, the therapeutic efficacy of anti-Notch1 therapy was significantly enhanced in combination with dexamethasone. Anti-Notch1 treatment increased T-ALL cell apoptosis, decreased proliferation and caused strong inhibitory effects on Notch-target genes expression along with complex modulations of gene expression profiles involving cell metabolism. Serial transplantation experiments suggested that anti-Notch1 therapy could compromise leukemia-initiating cell functions. These results show therapeutic efficacy of Notch1 blockade for T-ALL, highlight the potential of combination with dexamethasone and identify surrogate biomarkers of the therapeutic response.