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Titel des Beitrags: The fusion kinase ITK-SYK mimics a T cell receptor signal and drives oncogenesis in conditional mouse models of peripheral T cell lymphoma.

Abstract: Peripheral T cell lymphomas (PTCLs) are highly aggressive malignancies with poor prognosis. Their molecular pathogenesis is not well understood and small animal models for the disease are lacking. Recently, the chromosomal translocation t(5; 9)(q33; q22) generating the interleukin-2 (IL-2)-inducible T cell kinase (ITK)-spleen tyrosine kinase (SYK) fusion tyrosine kinase was identified as a recurrent event in PTCL. We show that ITK-SYK associates constitutively with lipid rafts in T cells and triggers antigen-independent phosphorylation of T cell receptor (TCR)-proximal proteins. These events lead to activation of downstream pathways and acute cellular outcomes that correspond to regular TCR ligation, including up-regulation of CD69 or production of IL-2 in vitro or deletion of thymocytes and activation of peripheral T cells in vivo. Ultimately, conditional expression of patient-derived ITK-SYK in mice induces highly malignant PTCLs with 100% penetrance that resemble the human disease. Our work demonstrates that constitutively enforced antigen receptor signaling can, in principle, act as a powerful oncogenic driver. Moreover, we establish a robust clinically relevant and genetically tractable model of human PTCL.