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The Tec kinase, Itk, in T cell activation and development

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The Tec family tyrosine kinase, Itk, plays an important role in TCR signaling. Studies of T cells from Itk-deficient mice have demonstrated that Itk is critical for the activation of phospholipase-Cg1, leading to calcium mobilization and Map-kinase activation in response to TCR stimulation. This biochemical defect leads to reduced IL-2 production by Itk-deficient T cells. Using a retroviral reconstitution system to express Itk mutants in primary Itk-deficient T cells, we have shown that the Itk PH, SH2, and SH3 domains, as well as Itk kinase activity and Itk transphosphorylation by a Src-kinase are all required for Itk function. Further studies on downstream effects of the Itk-deficiency have demonstrated that Itk is required for maximal activation of Egr2, Egr3, and Fas-ligand transcription after TCR stimulation. These transcriptional defects lead to reduced activation-induced cell death of stimulated $Itk^{-/-}$ T cells. Finally, we have examined thymic selection in $Itk^{-/-}$ mice crossed to an array of different TCR transgenic lines. These studies indicate that Itk is required for robust positive selection of MHC class II-specific TCRs, but has no apparent role in CD4/CD8 lineage commitment. Together these studies have defined an important role for Itk in TCR signaling leading to thymic development, cytokine gene expression, and activation-induced cell death.

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