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TCR Cross linking Promotes Crk Adaptor Protein Binding to Tyrosine-Phosphorylated CD3ζ Chain

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Tcell antigen receptor (TCR) binding of a peptide antigen presented by antigen-presenting cells (APCs) in the context of surface MHC molecules initiates signaling events that regulate T cell activation, proliferation and differentiation. A key event in the activation process is the phosphorylation of the conserved tyrosine residues within the CD3 chain immune receptor tyrosine-based activation motifs (ITAMs), which operate as docking sites for SH2 domain-containing effecter proteins. Phosphorylation of the CD3ζ ITAMs renders the CD3 chain capable of binding the ζ-chain associated protein 70 kDa (ZAP70), a protein tyrosine kinase that is essential for T cell activation.

We found that TCR/CD3 cross linking in Jurkat T cells promotes the association of Crk adaptor proteins with the transiently phosphorylated CD3ζ chain. Pull down assays using bead-immobilized GST fusion proteins revealed that the Crk-SH2 domain mediates binding of phospho-CD3ζ. Phospho-CD3ζ binding is selective and is mediated by the three types of Crk, including CrkI, CrkII, and CrkL, but not by other SH2 domain-containing adaptor proteins, such as Grb2, GRAP and Nck.

Crk interaction with phospho-CD3ζ is rapid and transient, peaking one minute post TCR/CD3 cross linking. The results suggest the involvement of Crk adaptor proteins in the early stages of T cell activation in which Crk might help recruiting effector proteins to the vicinity of the phospho-CD3ζ and contribute to the fine-tuning of the TCR/CD3-coupled signal transduction pathways.