5th World Congress on
Microbial Biotechnology & Vaccine Design
September 17-18, 2018 Lisbon, Portugal

Regulation of TCR-coupled signaling pathways by Crk adaptor proteins

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Cellular responses to environmental cues are controlled by cell surface receptors that are functionally linked to intracellular networks of signal transduction pathways. A hallmark of these signaling pathways is the temporal and spatial assembly of multi-molecular complexes at the site of the engaged receptors. Formation of these complexes is regulated by conformational changes and posttranslational modification of the activated receptors, as well as scaffold and adaptor proteins, which create docking sites for effector molecules, predominantly enzymes and their substrate proteins. The Crk adaptor proteins constitute an integral part of many receptor-coupled signaling networks, thanks to their Src homology 2 (SH2) and SH3 protein-protein binding domains, which enables the interaction with activated receptors and with effector molecules that recruit to the receptor site. A viral form of Crk (v-Crk) is also involved in oncogenesis, while cellular Crk can serve as preferred targets for a number of cell-invading pathogens. Thus, the Crk proteins contribute to bacterial pathogenesis by promoting their entry into cells, and serve as targets for virulence factors that divert host cell signaling pathways to the benefit of the pathogen. We found that TCR/CD3 crosslinking in Jurkat T cells promotes the association of Crk adaptor proteins with the transiently phosphorylated CD3ζ chain. Binding studies and pull down assays revealed that the Crk-SH2 domain mediates binding of phospho-CD3ζ. Crk-mediated binding of phospho-CD3ζ is selective and is not mediated by other SH2 domain-containing adaptor proteins, including Grb2, GRAP and Nck. Our results support the involvement of Crk adaptor proteins in the early steps of T cell activation and suggest a role for Crk in the recruitment of signaling proteins to the activated TCR where Crk might contribute to the fine-tuning of the TCR/CD3-coupled signal transduction pathways.

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