Identification of a new T cell regulator

T-cell receptor (TCR) signaling is mediated by the activation of protein-tyrosine kinases such as $p56^{lck}$ and ZAP-70. In mature T-cells, CD4 and CD8 molecules bind to $p56^{lck}$ which then phosphorylates the intracellular immune-receptor tyrosine-based activation motifs (ITAM) in the TCR associated CD3 subunits for ZAP-70 recruitment. ZAP-70 mediated phosphorylation of adaptor protein Src homology 2 domain-containing leukocyte phospho-protein of 76 kDa (SLP-76) tyrosine residues 113, 128, and 145 constitutes a key TCR signaling event. Cells lacking ZAP-70 have diminished phosphorylation of SLP-76 and identity of other potential protein kinases that could phosphorylate SLP-76 remains unknown. SLP-76 plays a crucial role in T-cell activation by linking antigen receptor (TCR) signals to downstream pathways. Beside three key tyrosines (Y113, Y128 and Y145, or “3Y”), SLP-76 at its N-terminus, also has a sterile ? motif (SAM) domain, whose function is unclear.

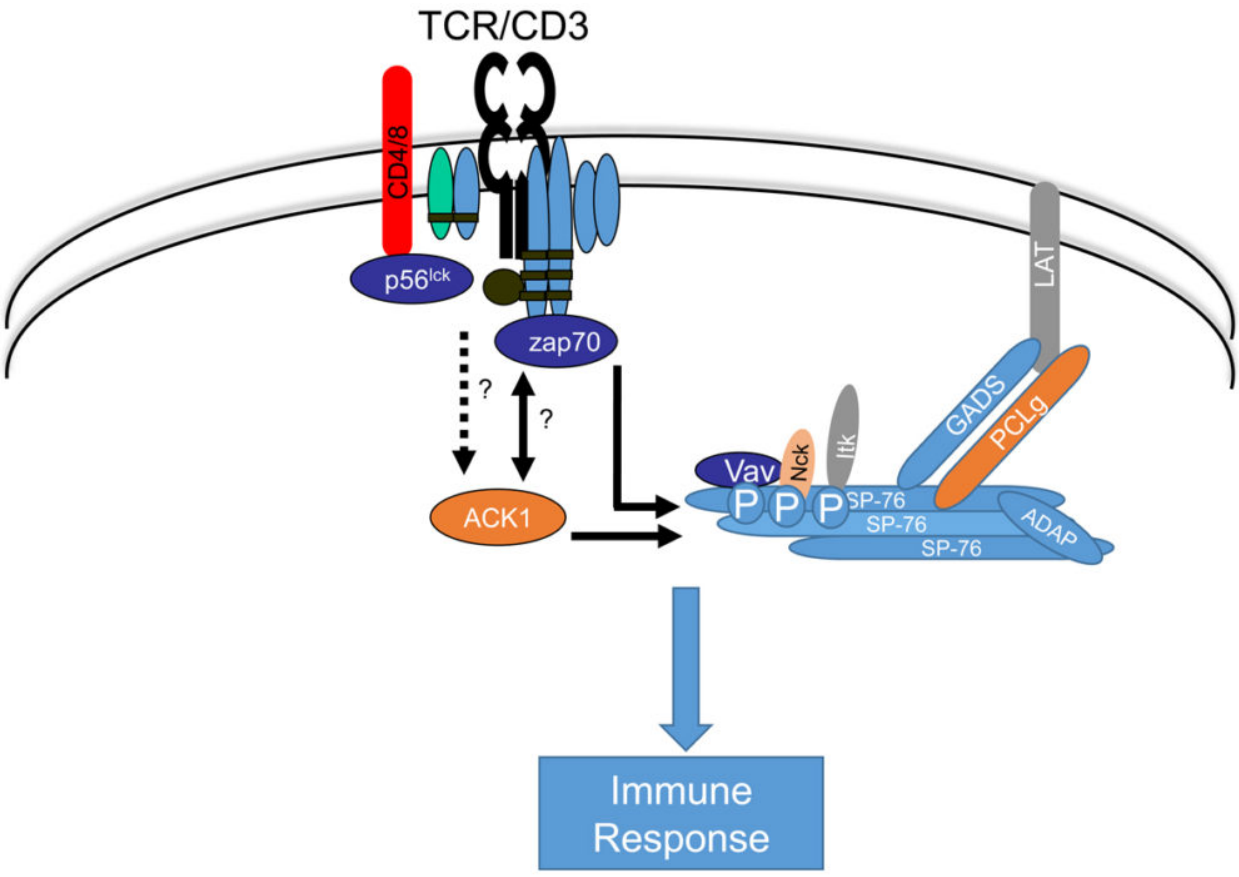

Fig. 1. In response to antigen (TCR/CD3) and CD4/8 surface receptors engagement by cognate MHC-peptide complex on antigen presenting cells, a signaling cascade is initiated at the T cell membrane. p56lck is recruited to CD4/8 resulting in the tyrosine phosphorylation of TCR/CD3 ITAM motifs (black strips) creating recruitment sites for ZAP-70 to TCR/CD3-zeta. ZAP-70 is phosphorylates ITAM motifs as well as SLP-76 proximal tyrosines. In this study, we identified a

new kinase regulator of T cells known as ACK1 (Activated Cdc42-associated kinase 1). ACK1 binds and phosphorylates SLP-76 N-terminus tyrosines resulting in the increased calcium flux and NFAT activity, a hallmark of productive T cell activation. Signaling pathways upstream of ACK1 remains to be explored.

We previously showed that the SAM domain has two binding regions that mediate dimer and oligomer formation of SLP-76 in T cells. The N-terminal SAM domain is essential for optimal thymic differentiation and T cell activation. Despite this progress, mechanisms underlying SAM domain functions remain unclear. In this study, we have examined the capacity of the SLP-76 SAM domain to interact with other SAM domain-carrying proteins. We investigated kinases retrieved from the Sugen/Salk Kinase database (KinBase), present in the human kinome, that contained several SAM kinases with N-terminal SAM domains. We reasoned that the N-terminal domains may have evolved an ability to interact with other N-terminal domains. This led to the identification of activated cell division cycle 42 (Cdc42) associated tyrosine kinase 1 (ACK1; also known as Tnk2, tyrosine kinase non receptor 2) as a kinase that associates with SLP-76 in a SAM-dependent manner and regulates its phosphorylation and aspects of T-cell signaling. Further, the interaction was induced in response to the anti-TCR ligation and abrogated by the deletion of SLP-76 SAM domain (?SAM) or mutation of Y113, Y128 and Y145 to phenylalanine (3Y3F). ACK1 induced phosphorylation of SLP-76 N-terminal tyrosines (3Y) dependent on the SAM domain. ACK1 also promoted calcium flux and NFAT-AP1 promoter activity and decreased the motility of murine $CD4^{+}$ primary T-cells on ICAM-1-coated plates, an event reversed by a small molecule inhibitor of ACK1 (AIM-100). These findings identify ACK1 as a novel SLP-76 associated protein tyrosine kinase that modulates early activation events in T-cells.

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