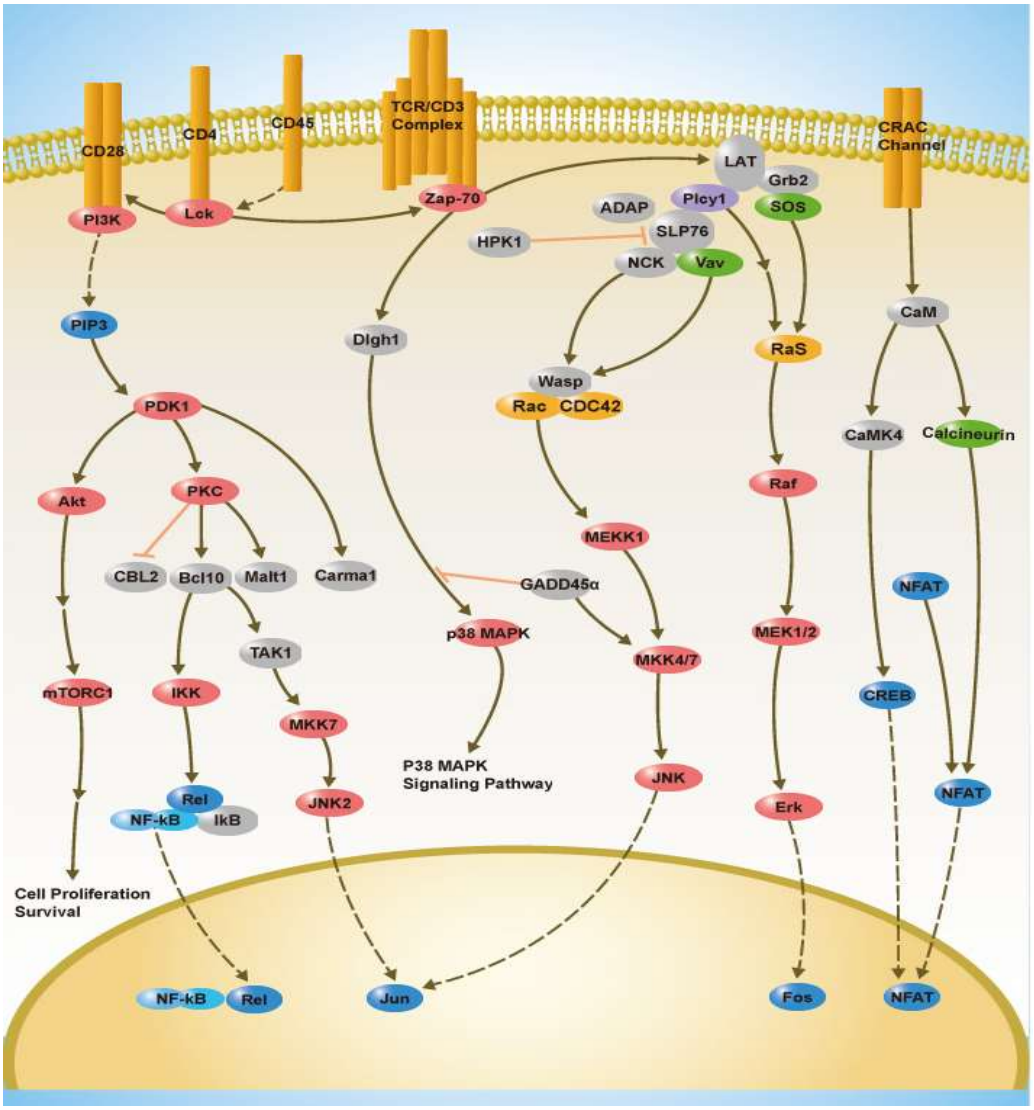

T Cell Receptor Signaling Pathway Background

T cell receptors (TCR) play a key role in functioning of T cells and formation of the **immunological synapse.** It provides connection between T cell and the antigen-presenting cell (APC). TCRs activation promotes a number of signaling cascades that ultimately determine cell fate through regulating cytokine production, cell survival, proliferation, and differentiation. Activation of T lymphocytes is a key event for an efficient response of the immune system.TCR activation is regulated by various co-stimulatory receptors. **CD28** provides an essential co-stimulatory signal during T-cell activation, which augments the production of IL-2 (Interleukin-2), increases T-cell proliferation and prevents the induction of anergy and cell death. CD28 ligation by B7-1 or B7-2 helps in bringing the T-Cell and Antigen Presenting Cell membranes into close proximity. Besides CD28, many other transmembrane receptors also modulate specific elements of TCR signaling,such as CD45 and CD4. An early event in TCR activation is phosphorylation of immunoreceptor tyrosine-based activation motifs (ITAMs) on the cytosolic side of the TCR/CD3 complex by lymphocyte protein tyrosine kinase (Lck). The CD45 receptor tyrosine phosphatase modulates the phosphorylation and activation of Lck and other Src family tyrosine kinases. TCR activation also leads to cytoskeletal rearrangements through the

activation of GTP-binding proteins Rac and PAK, downstream of ZAP70.

Negative regulation of TCR signaling is also significant, in order to keep a check on the hyperactivation of immune response associated with the pathway. SIT (SHP2-interacting transmembrane adaptor protein) is a recently identified transmembrane adaptor protein, which interacts with the SHP2 (SH2-containing protein tyrosine phosphatase-2) via an ITIM (immunoreceptor tyrosine-based inhibition motif), and the complex acts as a critical negative regulator of TCR-mediated signaling.

In addition, CTLA4 (cytotoxic T-lymphocyte antigen-4) also negatively regulates T-cell activation. The transmembrane protein CTLA4 also serves as a natural inhibitor. Once T-cells become activated, by whatever disease process is turning them on, the body has a natural process to turn down the T-cell pathways so that it does not get out of control.