

T cell receptor signalling

Joseph Lin and Arthur Weiss

Department of Medicine and The Howard Hughes Medical Institute, University of California, San Francisco, CA 94143-0795, USA

T cell receptor (TCR) signalling has been an area of intense study for many years. New proteins are being continually discovered each year, making the task of understanding the various pathways evermore challenging. Depicted here are only some of the many TCR-responsive proteins and the mechanisms by which they lead to production of the cytokine interleukin 2 (IL-2).

Upon engagement of the TCR by antigen presented on major histocompatibility complex (MHC) molecules, the Src family kinase Lck is activated and proceeds to phosphorylate immunoreceptor tyrosine-based activation motifs (ITAMs) on the ϵ , δ , γ and ζ subunits of the TCR. Phosphorylated ITAMs promote the recruitment and subsequent activation of another tyrosine kinase ZAP-70. Two known substrates of ZAP-

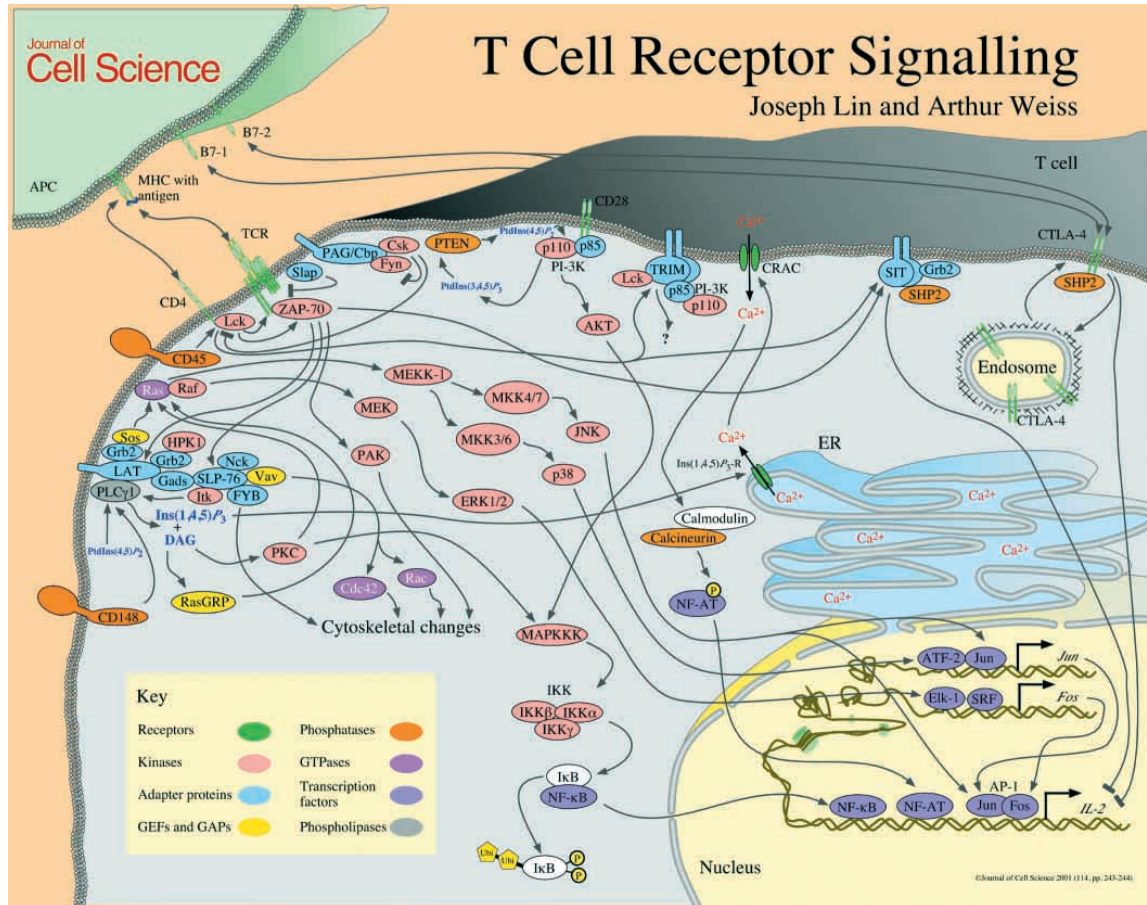
70 are the adapter molecules LAT and SLP-76. Phosphorylation of tyrosine residues on LAT and SLP-76 results in recruitment of a number of other proteins involved in activation of the Ras pathway, calcium mobilization and cytoskeletal reorganization.

One critical protein that is recruited to LAT upon TCR stimulation is phospholipase C γ 1 (PLC γ 1). Activated PLC γ 1 is responsible for the production of the second messengers diacylglycerol (DAG) and inositol 1,4,5-triphosphate [Ins(1,4,5)P $_3$] by cleaving phosphatidylinositol 4,5 bisphosphate [PtdIns(4,5)P $_2$] at the plasma membrane. These second messengers are essential for T cell activation. DAG activates a number of proteins, such as the various isoforms of protein kinase C (PKC) and Ras guanyl-nucleotide-releasing protein (RasGRP), whereas Ins(1,4,5)P $_3$ binds to Ins(1,4,5)P $_3$ receptors (Ins(1,4,5)P $_3$ -Rs) on the surface of the endoplasmic reticulum (ER). Upon Ins(1,4,5)P $_3$ receptor binding, Ca $^{2+}$ stores in the ER are released into the cytoplasm. This event triggers the opening of Ca $^{2+}$ -release-activated Ca $^{2+}$ (CRAC) channels

at the plasma membrane, allowing influx of extracellular Ca $^{2+}$. The increased Ca $^{2+}$ levels then activate the protein phosphatase calcineurin by disrupting the inhibitory effects of calmodulin. Calcineurin activation leads to the dephosphorylation of NFAT, allowing it to enter the nucleus, where it cooperates with other transcription factors to bind promoters.

Activation of Ras occurs through recruitment of its exchange factors Sos and RasGRP to the membrane. RasGRP contains a C1 domain, which requires binding to DAG for its function. Other proteins, such as the many isoforms of PKC, may also play a role in Ras activation. GTP-bound Ras leads to the activation of a number of serine/threonine kinases and dual-specificity kinases that are responsible for the eventual activation of the mitogen-activated protein (MAP) kinases Erk1/2, JNK and p38. These MAP kinases directly phosphorylate transcription factors involved in the formation of the heterodimeric transcription factor AP-1.

Another transcription factor important



(See poster insert)

for the generation of IL-2 is NF- κ B. Activation of NF- κ B is dependent on stimulation of the TCR and co-stimulation via CD28. The serine/threonine kinase Akt and the MAP kinase kinase kinases (MAPKKKs) participate in activation of the heterotrimeric I κ B kinase complex. The I κ B kinase (IKK) complex regulates NF- κ B activity by phosphorylating I κ B, which leads to its ubiquitination. Free from its association with I κ B, NF- κ B can move into the nucleus and activate transcription.

Many recent studies have focused on functional and physical interactions between the TCR and cytoskeleton. TCR clustering at the site of antigen-

presenting cell (APC) contact and re-orientation of the microtubule-organizing center (MTOC) are just some examples. Although proteins such as Vav, Cdc42, Rac and Fyb have been implicated in these events, the exact pathways still remain unclear. The cytoskeleton may also play a role in downregulating IL-2 production by promoting the trafficking of CTLA-4 to the plasma membrane from endosomes. At the plasma membrane, CTLA-4 can then bind its ligand B7-1 or B7-2, causing downregulation by an as-yet-undetermined mechanism.

As more research is done, many of the missing pieces are falling into place. Eventually, through the continuing work

of many labs, the complex pathways involved in signalling through the TCR should be fully understood. Since T cells play various critical roles in orchestrating the immune responses, this knowledge should lead to an understanding of how breakdowns in immune regulation lead to autoimmune diseases and of how the immune system could be better manipulated to overcome afflictions such as cancer, infection and autoimmune diseases.

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