T-cell Receptors (TCR)

The interaction of lymphocytes with antigen takes place through binding to specialized cell surface antigen-specific receptors functioning as recognition units. In the case of B-cells, the situation is straightforward as membrane bound immunoglobulin serves as the receptor for antigen. T-cells use distinct antigen receptors, which are also expressed at the plasma membrane, but T-cell receptors (TCRs) differ from B-cell receptors (BCRs) in a very fundamental way; TCRs cannot recognize free antigen as immunoglobulin can. The majority of T-cells can only recognize antigen when presented within the peptide-binding groove of an MHC molecule.

In response to an appropriate peptide–MHC combination (signal 1) and co-stimulatory B7 molecules (signal 2) presented by the DCs (dendritic cells), T-cells become activated and undergo clonal expansion and differentiation to mature effector cells.

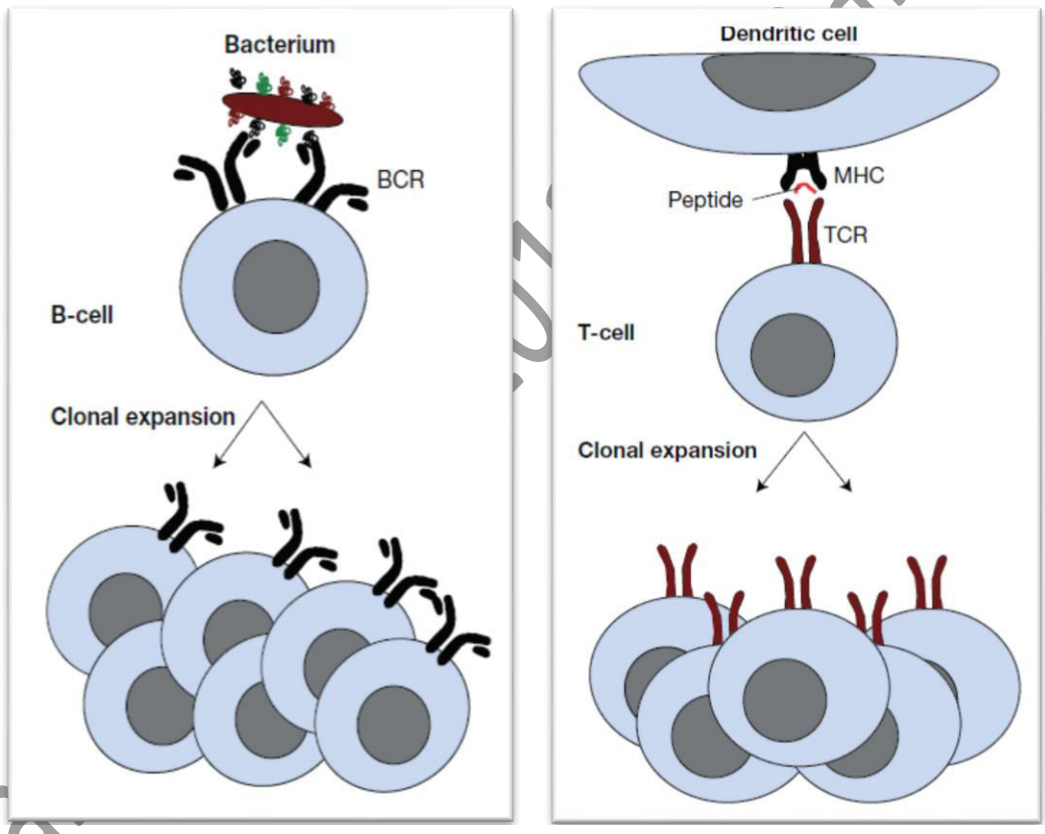

Fig: B-cells and T-cells "see" antigen in fundamentally different ways.

Structure of TCR:

There are two types of T-cell receptors, both of which are heterodimers. The majority of recirculating T cells bears αβ heterodimers, which bind to ligands made up of an antigenic peptide presented in a molecular groove on the surface of a type I or type II MHC molecule. A second subset of T cells instead expresses a heterodimeric T-cell receptor composed of a different pair of protein chains, termed γ and δ. T cells bearing γδ receptors have particular localization patterns (often in mucosal tissues) and some γδ T cells recognize different types of antigens from those bound by αβ T cells. As it appears earlier in thymic ontogeny, the γδ receptor is sometimes referred to as ***TCR1*** and the αβ receptor as ***TCR2***.

1. TCR proteins are members of the immunoglobulin superfamily of proteins and therefore the domain structures of αβ and γδ TCR heterodimers are strikingly similar to those of the immunoglobulins.
2. The α chain has a molecular weight of 40–50 kDa, and the β chain's is 40–45 kDa. Like the antibody light chains, the TCR chains have two immunoglobulin-like domains, each of which contains an intrachain disulfide bond spanning 60 to 75 amino acids.
3. The Cα domain of the TCR differs from most immunoglobulin domains in that it possesses only a single β sheet, rather than a pair, and the remainder of the sequence is more variably folded.
4. The amino-terminal (variable) domain in both chains exhibits marked sequence variation, but the sequences of the remainder of each chain are conserved (constant).
5. Each of the TCR variable domains has three hypervariable regions, which appear to be equivalent to the complementarity-determining regions (CDRs) in immunoglobulin light and heavy chains. A fourth hypervariable region on the TCRβ chain does not appear to contact antigen, and its functional significance is therefore uncertain.
6. At the C-terminal end of the constant domain, each TCR chain contains a short connecting sequence, in which a cysteine residue forms a disulfide link with the other chain of the heterodimer.
7. C-terminal to this disulfide is a transmembrane region of 21 or 22 amino acids, which anchors each chain in the plasma membrane.
8. The transmembrane domains of the TCR α and β chains are unusual in that they each contain positively charged amino acid residues that promote interaction with corresponding negatively charged residues on the chains of the signal transducing CD3 complex.
9. Finally, like BCRs, each TCR chain contains only a very short cytoplasmic tail at the carboxyl-terminal end.

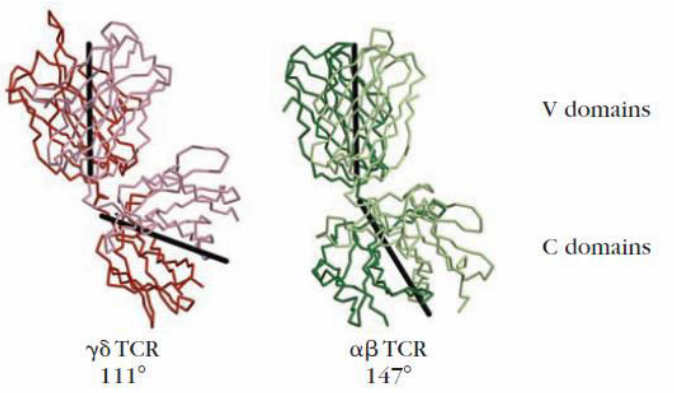

Fig: The crystal structures of γδ and αβ TCRs.

The T-Cell Signal Transduction Complex includes CD3:

Signaling through the TCR depends on a complex of proteins referred to collectively as CD3. The CD3 complex is made up of three dimers: a δε (delta epsilon) pair, a γε (gamma epsilon) pair, and a third pair that is made up either of two CD3 ζ (zeta) molecules or a ζη (zeta, eta) heterodimer. (Note that the CD3 γ and δ chains are different from the chains that make up the γδ TCR.) Like Ig α and Ig β, the cytoplasmic tails of the CD3 molecules are studded with ITAM sequences that serve as docking sites for adapter proteins following activation induced tyrosine phosphorylation. Each of the CD3 dimers contains negatively charged amino acids in its transmembrane domain that form ionic bonds with the positively charged residues on the intramembrane regions of the T-cell receptor.

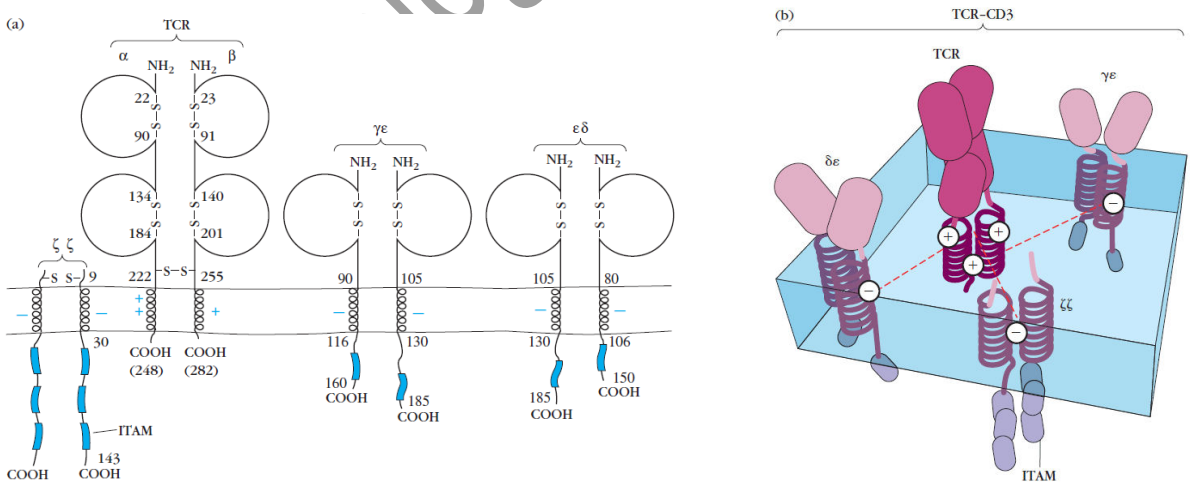

Fig: Schematic diagram of the TCR-CD3 complex, which constitutes the T-cell antigen-binding receptor

CD4 and CD8 molecules act as co-receptors for TCRs:

In addition to the TCR, the majority of peripheral T-cells also express one or other of the membrane proteins **CD4** or **CD8** that act as co-receptors for MHC molecules. CD4 and CD8 molecules play important roles in antigen recognition by T-cells as these molecules dictate whether a T cell can recognize antigen presented by MHC molecules that obtain their peptide antigens primarily from intracellular (**MHC class I**), or extracellular (**MHC class II**), sources. This has major functional implications for the T-cell, as those lymphocytes that become activated upon encounter with antigen presented within MHC class I molecules (CD8+ T-cells) invariably become cytotoxic T-cells, and those that are activated by peptides presented by MHC class II molecules (CD4+ T-cells) become helper T-cells.

CD4 is a 55 kDa monomeric membrane glycoprotein that is extended like a rod and projects from the T-cell surface. It contains four extracellular immunoglobulin-like domains (D1–D4), a hydrophobic transmembrane region, and a long cytoplasmic tail containing three serine residues that can be phosphorylated. The cytoplasmic tail of the CD4 molecule is important for TCR signaling as this region is constitutively bound by a protein tyrosine kinase, ***Lck***, that initiates the signal transduction cascade that follows upon encounter of a T-cell with antigen.

CD8 takes the form of a disulfide-linked αβ heterodimer or αα homodimer. Both the α and β chains of CD8 are small glycoproteins of approximately 30 to 38 kDa. Each chain consists of a single, extracellular, immunoglobulin-like domain connected to an extended and heavily glycosylated polypeptide projecting from the T-cell surface, a stalk region, a hydrophobic transmembrane region, and a cytoplasmic tail containing 25 to 27 residues, several of which can be phosphorylated. CD8 plays a similar role to CD4, as it also binds Lck and recruits this kinase to the TCR complex.

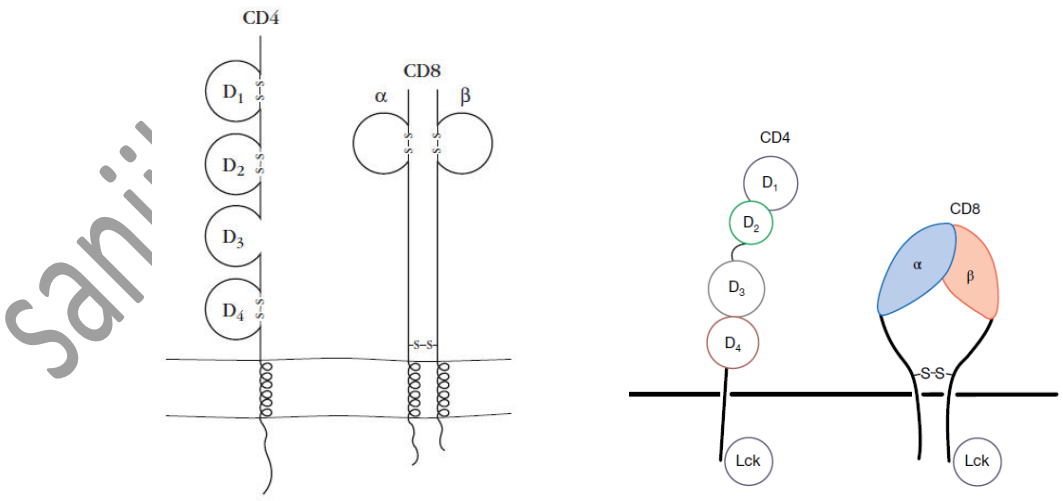

Fig: General structure of the CD4 and CD8 coreceptors; the Ig-like domains are shown as circles

TCR Signalling:

TCR-antigen binding leads to a multitude of consequences including transcription factor upregulation, reorganization of the cytoskeleton, and cytokine secretion. T-cell signaling also affects the expression of adhesion molecules such as integrins on the cell surface, and chemokines, which has subsequent effects on cell localization.

Steps:

1. The Src-family tyrosine kinase Lck is normally found associated with CD4 and CD8, and the association between Lck and CD4 is particularly close.
2. Antigen-induced clustering of the receptor–co-receptor complex brings Lck into the vicinity of the membrane-associated tyrosine phosphatase, CD45, which removes the inhibitory phosphate group on Lck.
3. Reciprocal phosphorylation by nearby Lck molecules at their activating tyrosine sites then induces Lck to phosphorylate CD3 ITAM residues.
4. Once the CD3 ITAMs are phosphorylated, a second tyrosine kinase, ZAP-70, docks at the phosphorylated tyrosine residues of the CD3ζ chains.
5. ZAP-70 is activated by Lck mediated phosphorylation and goes on to phosphorylate many adapter molecules including SLP-76 and LAT (*L*inker protein of *A*ctivated *T* cells), a transmembrane protein associated with lipid rafts in the plasma membrane.
6. Following TCR ligation, LAT is phosphorylated on multiple residues by ZAP-70, and these phosphorylated residues now provide docking sites for several important enzymes bearing SH2 domains, including PLCγ1, important in T-cell activation.
7. Phosphorylated LAT also binds to the adapter protein GADS, which is constitutively associated with the adapter SLP-76. This combination of adapter proteins is critical to T-cell receptor signaling, providing the structural framework for most downstream signaling events.
8. PLCγ1, localized to the plasma membrane by binding to LAT, is further activated by tyrosine phosphorylation, mediated by the kinase Itk.
9. PLCγ1breaks down PIP2, releasing IP3, which induces the release of calcium and the activation of NFAT via calcineurin activation. The DAG created by PIP2 hydrolysis binds, in T cells, to a specialized form of PKC called PKCθ (theta).
10. This part of the signaling cascade similarly culminates in the degradation of the inhibitors of NF-κB and the translocation of the active transcription factor into the nucleus
11. Phosphorylated LAT also associates with the SH2 domain of Grb2 that binds constitutively to SOS, the GEF that facilitates activation of the Ras pathway
12. In T cells, the Ras pathway is important both to the activation of the transcription factor AP-1, which functions to signal cytokine secretion, and to the passage of the signals that reorganize the actin cytoskeleton for directed cytokine release.

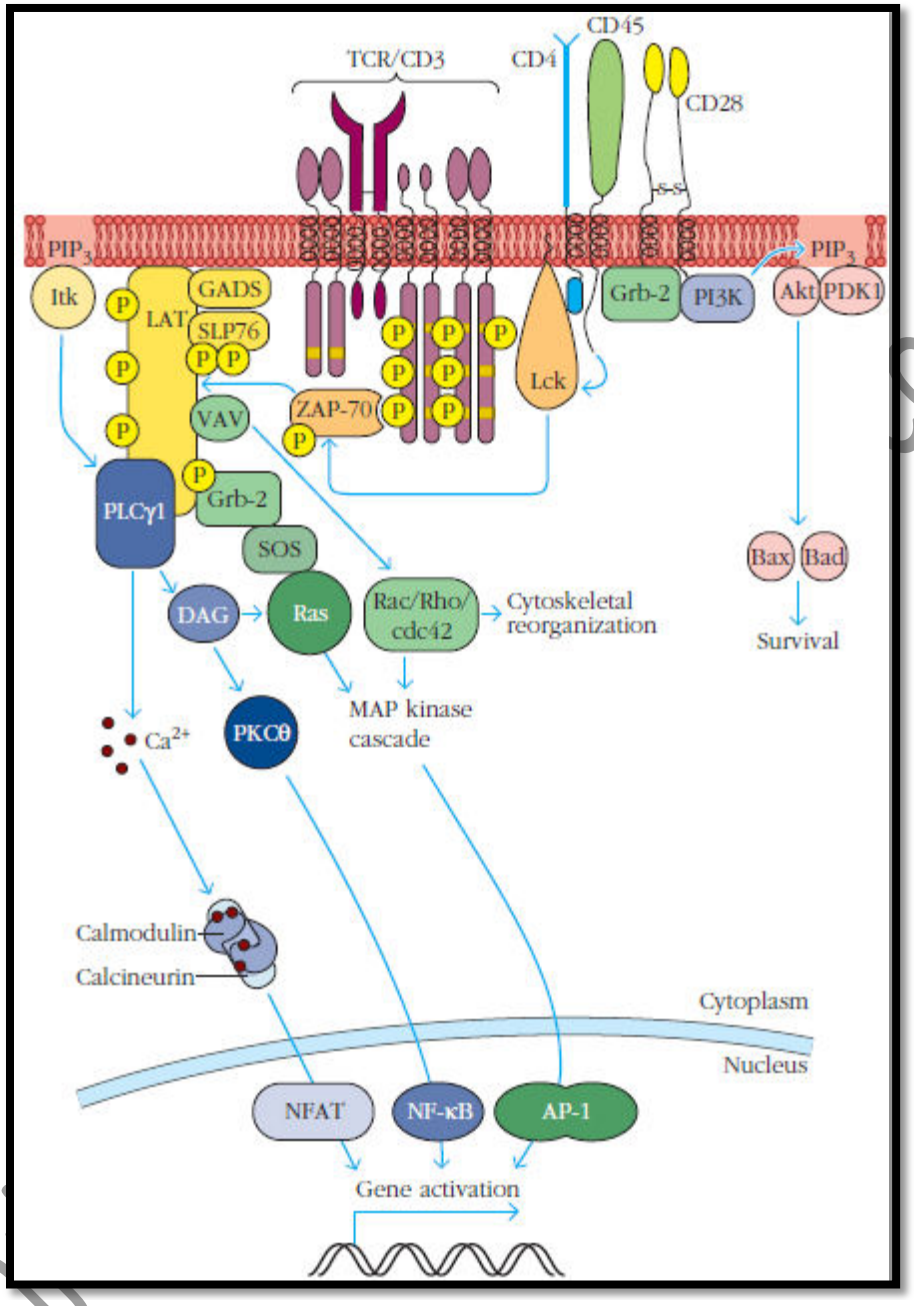

Fig: **Signal transduction pathways emanating from the TCR**

T cell antigen binding activates the src-family kinase Lck, which phosphorylates the kinase ZAP-70. ZAP-70 in turn phosphorylates the adapter molecules LAT, SLP76, and GADS which form a scaffold enabling the phosphorylation and activation of PLCγ1 and PKCθ with the consequent effects on transcription factor activation described in the text. The GEF proteins Vav and SOS are also activated on binding to LAT, leading to activation of the Ras/MAP kinase transcription factor pathway and the Rac/Rho/cdc42 pathway, leading to changes in cell shape and motility. PI3 kinase, translocated to the cytoplasmic side of CD28, forms PIP3, inducing localization of the enzymes PDK1 and Akt to the membrane. This leads to further NF-κB activation and increased cell survival as described.

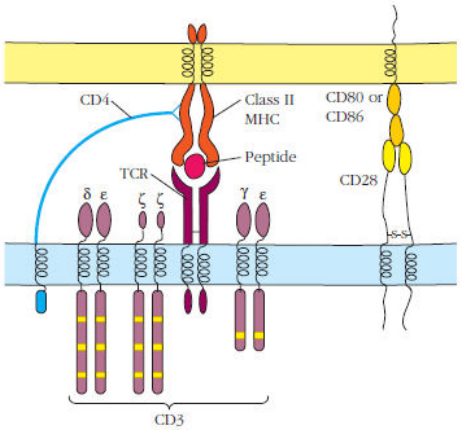

Fig:T-cell receptors require receptor associated molecules and co-receptors for signal transduction

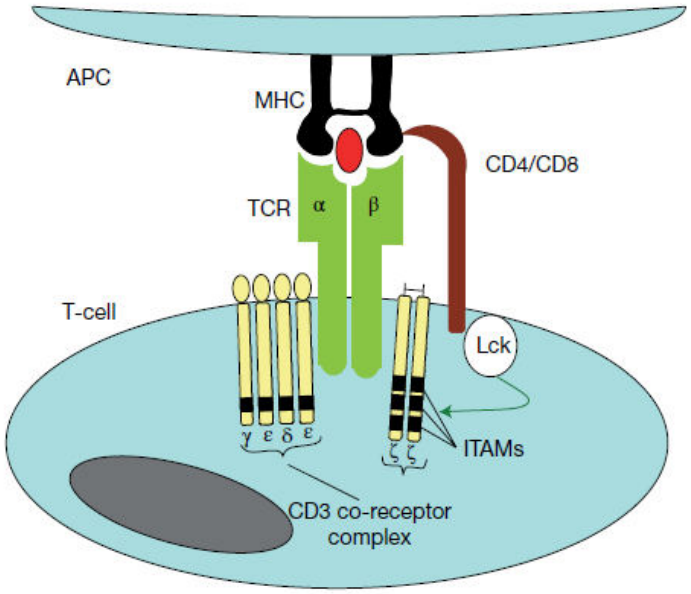

Fig: The T-cell receptor (TCR) complex, assisted by CD4 or CD8 receptors, recognizes peptide antigen in the context of MHC molecules. TCR activation signals are propagated via the CD3 co-receptor complex, which is made up of CD3 γ, ε, δ, and ζ chains. Co-clustering of CD4 or CD8, which are constitutively associated with the Lck kinase, with the TCR complex facilitates Lck-initiated signal propagation through phosphorylation of immunoreceptor tyrosine-based activation motifs (ITAMs) within the CD3 ζ chain.

References:

- **Kuby Immunology Seventh edition.**
- **Roitt's Essential Immunology Thirteenth edition**