*Dr. Chiranjeeb Dey, Assistant Professor, Dept. of Zoology*

# T CELL RECEPTORS – STRUCTURE AND SIGNALLING

T lymphocytes have a dual specificity: they recognize polymorphic residues of self major histocompatibility complex (MHC) molecules, which accounts for their MHC restriction, and they also recognize residues of peptide antigens displayed by these MHC molecules, which is responsible for their specificity. MHC molecules and peptides form complexes on the surface of APCs. The receptor that recognizes these peptide-MHC complexes is called the T cell receptor (TCR).

The TCR is a clonally distributed receptor. The biochemical signals that are triggered in T cells by antigen recognition are transduced not by the TCR itself but by invariant proteins called CD3 andξ, which are noncovalently linked to the antigen receptor to form the TCR complex. Thus, in T cells antigen recognition and signaling are iegregated among two sets of molecules-a highly variable antigen receptor (the TCR in T cells and membrane) and invariant signaling proteins (CD3 and ξ chains in T cells).

The physiologic role of some accessory molecules is to deliver signals to the T cell that function in concert with signals from the TCR complex to fully activate the cells.

## Structure of TCR

The TCR is a disulfide-linked membrane-anchored heterodimeric protein normally consisting of the highly variable alpha (α) and beta (β) chains expressed as part of a complex with the invariant CD3 chain molecules. T cells expressing this receptor are referred to as α:β (or αβ) T cells, though a minority of T cells express an alternate receptor, formed by variable gamma (γ) and delta (δ) chains, referred as γδ T cells. A typical T cell may have as many as 20,000 receptor molecules on its membrane surface, all of either the alpha-beta or gamma-delta type.

Each chain is composed of two extracellular domains: Variable (V) region and a Constant (C) region, both of Immunoglobulin superfamily (IgSF) domain. The Constant region is proximal to the cell membrane, followed by a transmembrane region and a short cytoplasmic tail, while the Variable region binds to the peptide/MHC complex.

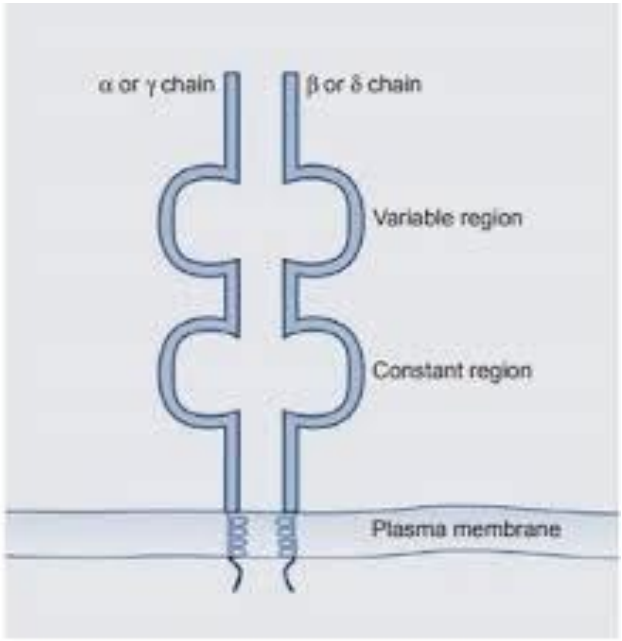
The variable domain of both the TCR α-chain and β-chain each have three hypervariable or complementarity-determining regions (CDRs). There is also an additional area of hypervariability on the β-chain (HV4) that does not normally contact antigen and, therefore, is not considered a CDR.

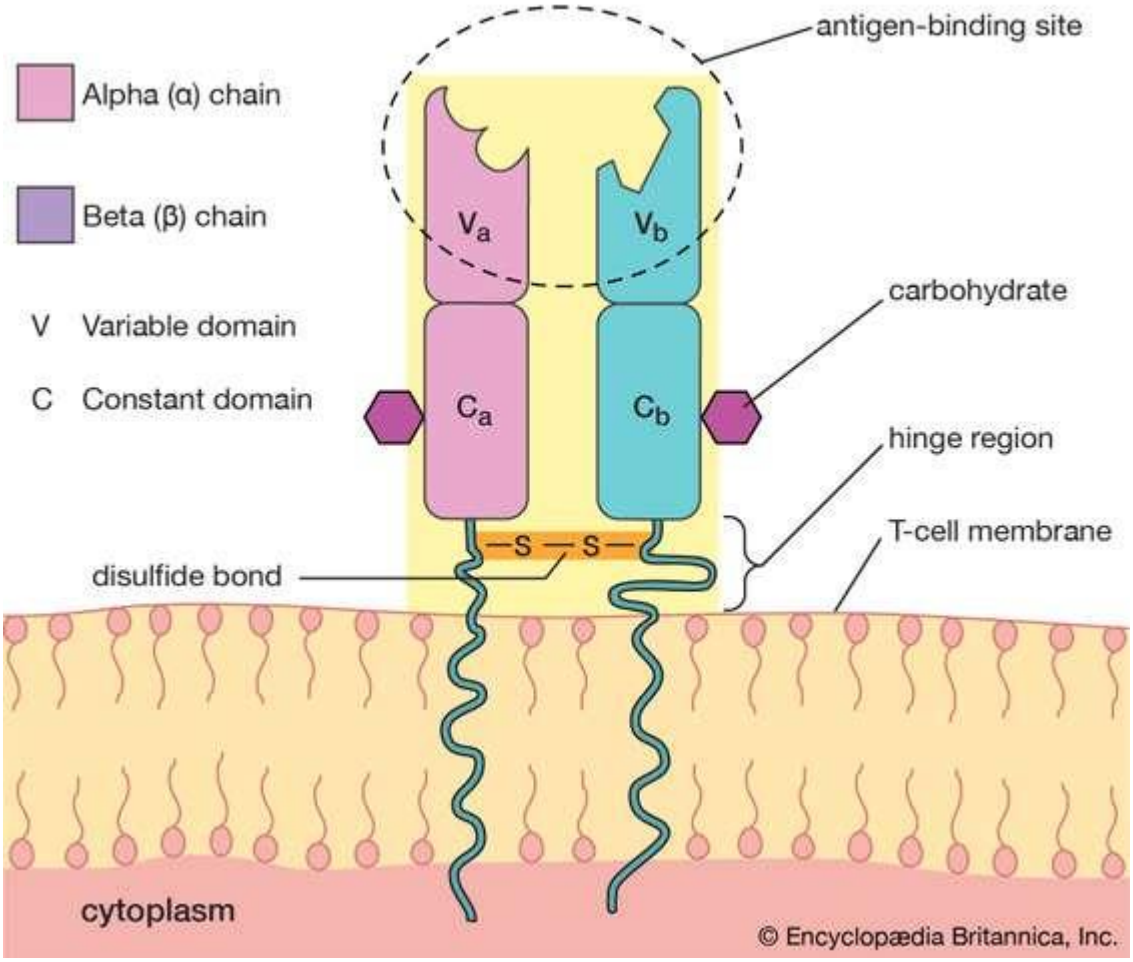
The residues in these variable domains are located in two regions of the TCR, at the interface of the α- and β-chains and in the β-chain framework region that is thought to be in proximity to the CD3 signal-transduction complex. CDR3 is the main CDR responsible for recognizing processed antigen, although CDR1 of the alpha chain has also been shown to interact with the N-terminal part of the antigenic peptide, whereas CDR1 of the β-chain interacts with the C-terminal part of the peptide.

CDR2 is thought to recognize the MHC. CDR4 of the β-chain is not thought to participate in antigen recognition, but has been shown to interact with superantigens.

The constant domain of the TCR consists of short connecting sequences in which a cysteine residue forms disulfide bonds, which form a link between the two chains.

The TCR is a member of the immunoglobulin superfamily, a large group of proteins involved in binding, recognition, and adhesion; the family is named after antibodies (also called immunoglobulins). The TCR is similar to a half-antibody consisting of a single heavy and single light chain, except the heavy chain is without its crystallisable fraction (Fc). The two subunits of TCR are twisted together. Whereas the antibody uses its Fc region to bind to Fc Receptors on leukocytes, TCR is already docked onto the cell membrane. However, it is not able to mediate signal transduction itself due to its short cytoplasmic tail, so TCR still requires CD3 and zeta ξ to carry out the signal transduction in its place. In this way the MHC-TCR-CD3 interaction for T cells is functionally similar to the antigen(Ag) - immunoglobulin(Ig) - FcR interaction for myeloid leukocytes.

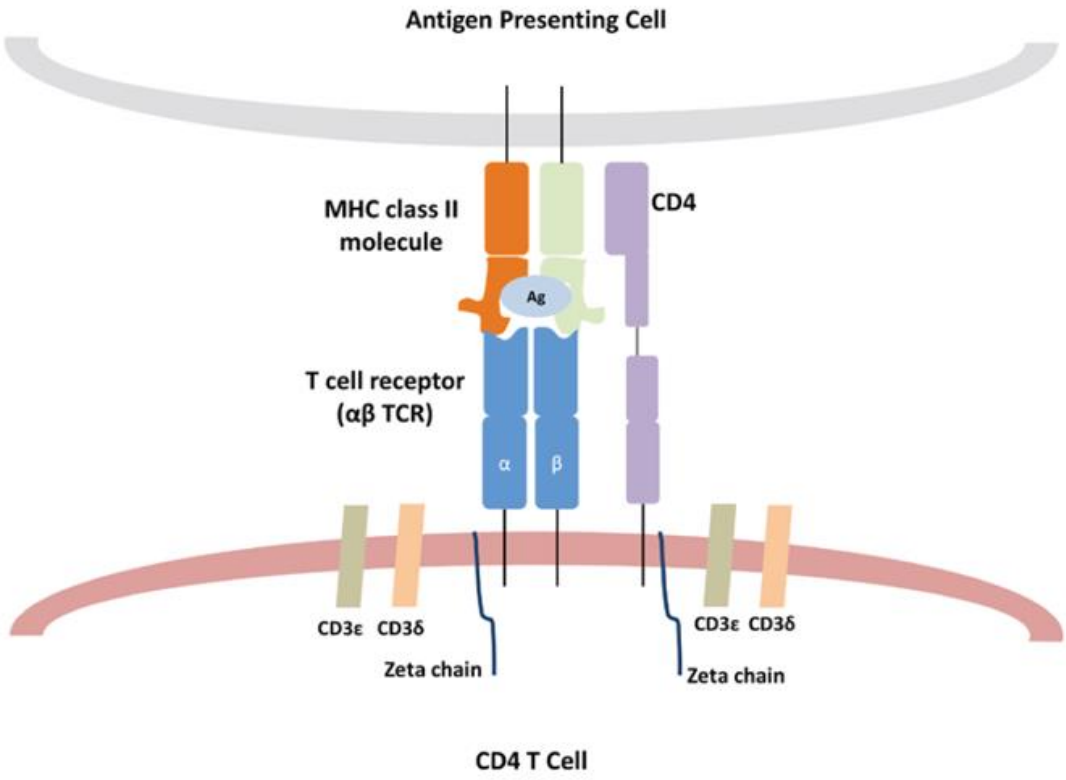





**The TCR- CD 3 complex**

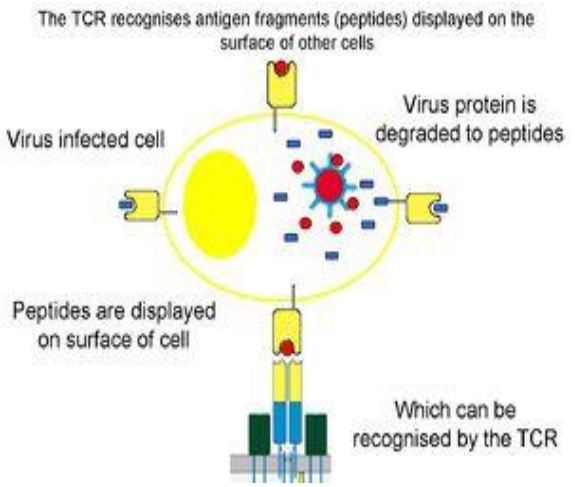
In the plasma membrane the TCR receptor chains α and β associate with six additional adaptor proteins to form an octameric complex. The complex contains both α and β chains, forming the ligand-binding site, and the signaling modules CD3δ, CD3γ, CD3ε and CD3ζ in the stoichiometry TCR α β - CD3εγ - CD3εδ - CD3ζζ. Charged residues in the transmembrane domain of each subunit form polar interactions allowing a correct and stable assembly of the complex.

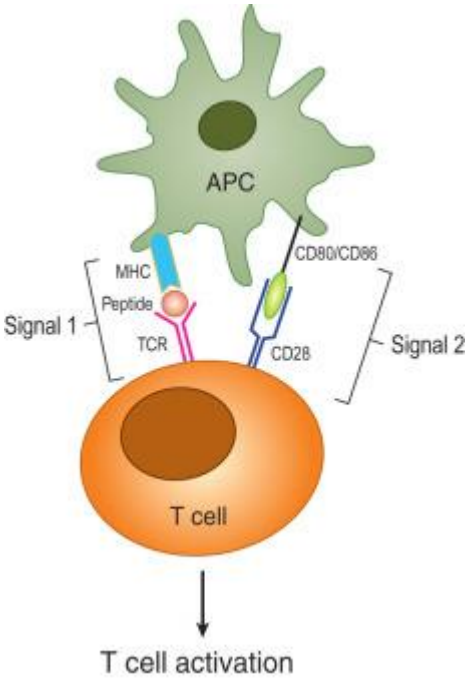
The cytoplasmic tail of the TCR is extremely short, hence the CD3 adaptor proteins contain the signalling motifs needed for propagating the signal from the triggered TCR into the cell. The signalling motifs involved in TCR signalling are tyrosine residues in the cytoplasmic tail of these adaptor proteins that can be phosphorylated in the event of TCR-MHC binding. This motif is very common in activator receptors of the non-catalytic tyrosine-phosphorylated receptor (NTR) family and is referred to as immunoreceptor tyrosine-based activation motif (ITAM). CD3δ, CD3γ and CD3ε each contain a single ITAM, while CD3ζ contains three ITAMs. In total the TCR complex contains 10 ITAMs. Phosphorylated ITAMs act as binding site for SH2-domains of additionally recruited proteins.

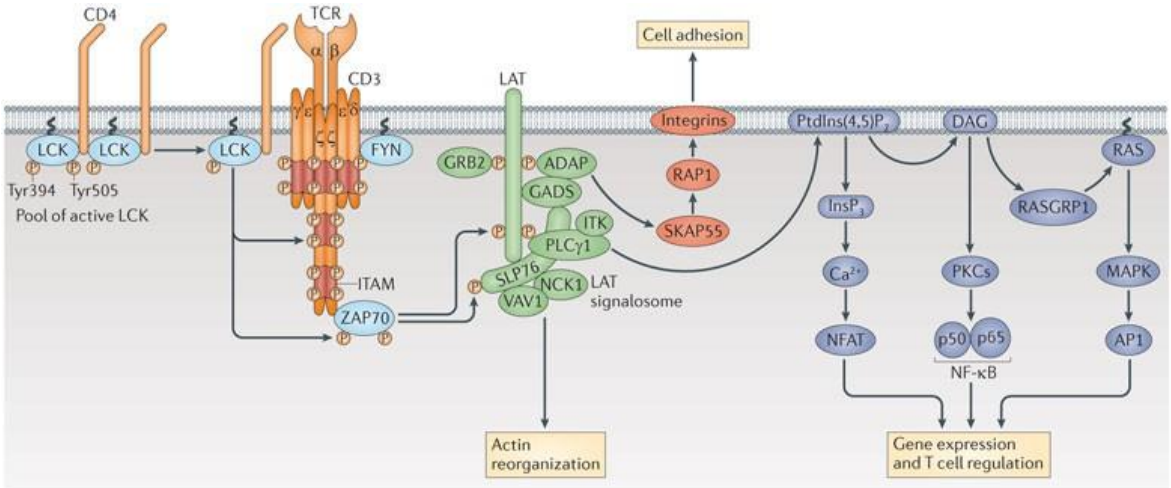



## TCR Signalling

The essential function of the TCR complex is to identify specific bound antigen derived from a potentially harmful pathogen and elicit a distinct and critical response. At the same time it has to ignore any self-antigen and tolerate harmless antigens such as food antigens. The signal transduction mechanism by which a T cell elicits this response upon contact with its unique antigen is termed T-cell activation. Upon binding to MHC, the TCR initiates a signalling cascade, involving transcription factor activation and cytoskeletal remodelling resulting in T cell activation. Active T cells secrete cytokines, undergo rapid proliferation, have cytotoxic activity and differentiate into effector and memory cells. When the TCR is triggered, T cells form an immunological synapse allowing them to stay in contact with the antigen presenting cell for several hours. T cell activation signalling requires TCR complex, which consists of TCR, CD3 complex, and also the coreceptors CD4 or CD8. T cells can adopt two signalling pathways- Phosphotidylinositol and MAPK.




Nature Reviews | Immunology

---