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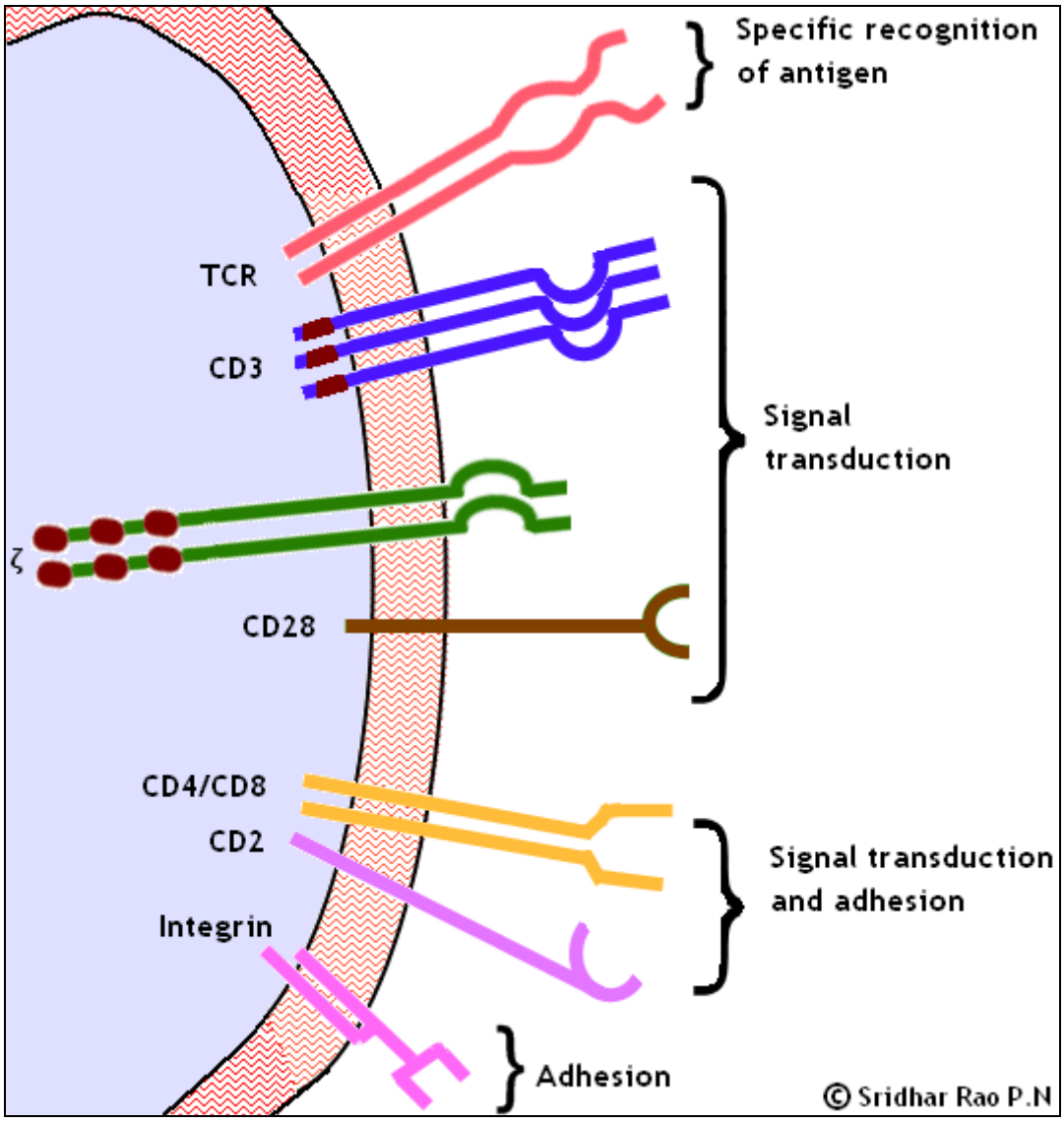
ANTIGEN RECEPTORS & ACCESSORY MOLECULES

T cells respond to peptide antigens that are displayed by the antigen presenting cells along with self-MHC molecules. The initiation of this response requires specific antigen recognition, stable adhesion of T cells to APC and transduction of the activating signals to the T cell. Each of these events is mediated by distinct set of molecules on the T cell. T lymphocytes have dual specificity; they are specific to self-MHC molecule and specific to peptide antigen displayed by the MHC molecules. The receptor that recognizes the peptide-MHC complex is T cell receptor (TCR). Clones of different T cells express different TCRs.

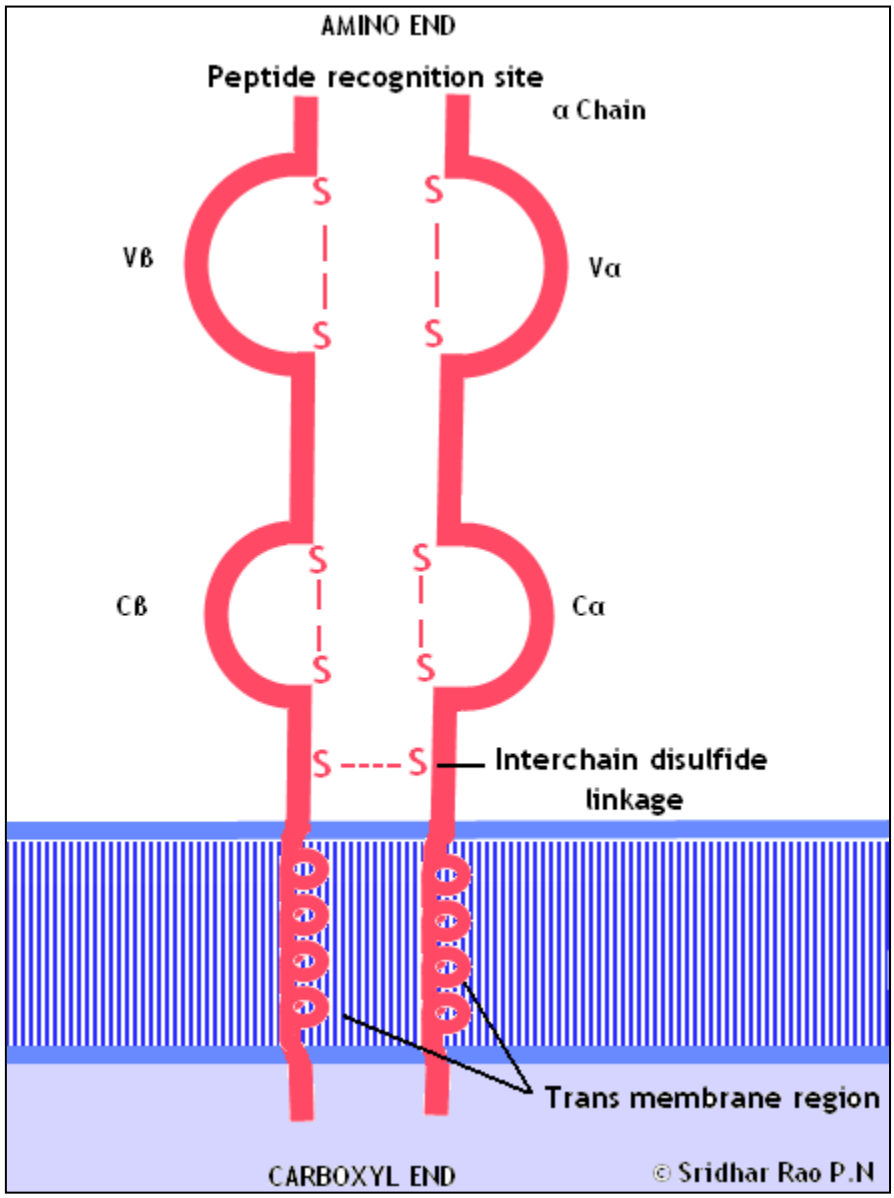


The biochemical signals that are triggered in the T cells following antigen recognition are transduced by invariant proteins called CD3 and ζ, which are non covalently linked to TCR forming TCR complex. T cells also express other membrane receptors called accessory molecules, which do not recognize antigen but

participate in response to antigens. These accessory molecules have varied role, they may act as adhesion molecule helping the T cell bind to the APC during antigen presentation for duration that is sufficient for antigen recognition or act as signal transducers. Adhesion molecules also regulate the migration of T cells to the sites where they locate and respond to antigens. Once activated the T cells also express some membrane and secreted molecules, which bring about various effector functions of the T cells.

STRUCTURE OF TCR

TCR on a $CD4^+$ and $CD8^+$ T cells is a heterodimer, consisting of two transmembrane polypeptides namely α chain and β chain. The two chains are covalently linked to each other by disulphide bonds. There are two types of TCR, depending on the type of polypeptide chains. While α and β chains are encountered on most subsets of T cells, there are a few subsets with γ and δ polypeptide chains. Both α and β chains have three regions, an extracellular portion with immunoglobulin like domains, a transmembrane segment and a cytoplasmic tail. The extracellular amino ends of the both polypeptides have a variable and a constant domain. The antigen binding site of TCR is identical to the antigen binding site of the immunoglobulin.



The variable regions of α and β chains contain short stretches with maximum variation, which form the hypervariable or the complementarity determining regions (CDRs). There are three CDRs in α and β chains each, which together form the peptide recognizing unit of the TCR. The variable domain of the β chain contains an additional CDR, to which no peptide binds but is a binding site for superantigens.

Just like the variable regions of light and heavy chains of immunoglobulins, both α and β chains are encoded by multiple gene segments, which undergo somatic rearrangements during the maturation of T lymphocytes. The CDR3 region of the α chain is composed of sequences coded by the V and J gene segments while the CDR3 region of the β chain is composed of sequences coded by V, D and J gene segments. The CDR3 region also contains sequences that are not encoded in genome but are coded by random nucleotide additions. Therefore, most of the sequence variability in TCRs is in CDR3.

The constant region of α and β chains are covalently linked together by disulfide bonds. The residues of the transmembrane portion interact with the residues of transmembrane portions of CD3 and ζ polypeptides, which form the TCR complex. The cytoplasmic tails don't participate in signal transduction.

Even though TCR and immunoglobulin are structurally similar, there are many differences.

	Immunoglobulin	**T cell receptor**
Polypeptide chains	Heavy & light chains	α and β chains
Number of Ig domains	1 V domain & 3-4 C domains in Heavy chain 1 V and 1 C domain in Light chain	1 V and 1 C domain in each chain
Number of CDRs	3 in each chain	3 in each chain, 4th CDR in β chain binds to superantigen
Associated signaling molecule	Igα and Igβ	CD3 and ζ
Production of secreted form	Yes	No
Isotype switching	Yes	No
Somatic mutation	Yes	No

The antigen binding site of the TCR is formed by CDRs of α and β chains. In most cases, CDR1 and CDR2 recognize self-MHC and CDR3 recognizes peptide antigen. The affinity of TCR for peptide-MHC complex is lower than that of immunoglobulins for antigen. The half life of TCR-peptide-MHC complex is 1-10 seconds, which is why the T cells must utilize the services of adhesin molecules to prolong the duration of antigenic stimulation of T cells.

γδ TCR is another type of T cell receptor that is present in a small number of T cells. It is also a heterodimer and is structurally similar to αβ TCR. The γδ heterodimer associates with CD3 and ζ proteins like αβ TCR. The majority of γδ T cells don't express either CD4 or CD8. These T cells are known to produce cytokines and lyses target cells. Approximately 10% of human intraepithelial lymphocytes are γδ expressing T cells.

OTHER PROTEINS OF TCR COMPLEX:

CD3 and ζ proteins are non covalently associated with TCR αβ dimer. When the TCR recognizes the antigen, these associated proteins transduce the signals that lead to T cell activation. The CD3 molecule actually consists of three proteins CD3α, δ and ε. Protein ζ is a disulfide linked homodimer. CD3 and ζ, which form part of TCR complex is identical on all T cells. Expression of TCR complex requires synthesis of all its components. Although CD3 and ζ are synthesized in maturing T cells in thymus much earlier than TCR α and β chain, they are expressed only when the T cell matures. During maturation the TCR complex is synthesized in the endoplasmic reticulum and transported to the surface for expression.

ACCESSORY MOLECULES OF T CELLS

T cells express many integral membrane proteins, other than TCR complex, which play crucial role in the response of T cells to antigen recognition. These proteins are collectively called accessory molecules. The properties of these molecules are:

1. Accessory molecules on T cells specifically bind to the ligands present on the antigen presenting cells
2. These molecules are nonpolymorphic and invariant
3. Accessory molecules such as CD4 and CD8 transduce signals generated by TCR to the interior of the T cell
4. Binding of these molecules to their ligands on APCs increases the strength of adhesion between T cells and APCs
5. The binding of accessory molecules to endothelial cells and extracellular matrix proteins is responsible for homing of T cells to tissues and the retention of T cells in tissue.
6. These molecules are useful cell surface markers, which makes it useful in their identification in normal tissue or pathological lesions.

CD4 AND CD8 CO-RECEPTORS:

CD4 and CD8 are T cell proteins that bind to non-polymorphic regions of MHC molecules and together with TCR, they transduce the signal generated from antigen recognition to initiate T cell activation. CD4 and CD8 interact with MHC at the time when TCR recognizes peptide-MHC complex on the APCs. Apart from signal transduction, they may also contribute to strength of adhesion between T cells and APCs. Because CD4 and CD8 operate together with TCR in recognition of MHC molecule and in T cell activation, they are also called co-receptors. Both CD4 and CD8 are transmembrane glycoproteins of the Ig superfamily. Both have extracellular portion, transmembrane segment and cytoplasmic tail.

CD4 is expressed as a monomer and has four Ig like domains. It binds to β2 domain of MHC class II molecule by its two N-terminal domains. Most CD8 molecules exist as disulfide-linked heterodimers composed of two related chains called CD8α and CD8β. Both α and β chain have a single extracellular domain, which binds to the α3 domain of MHC class I molecule.

The selective binding of CD4 to class II molecules and of CD8 to class I molecules ensures that CD4+ T cells recognize and respond to class II associated peptide antigens and that CD8+ T cells respond to class I associated peptide antigens.

CD28 AND CTLA-4: RECEPTORS FOR CO-STIMULATORS:

For a lymphocyte to be activated, it needs two signals. The first signal is provided by the recognition of MHC-peptide by TCR and binding of CD4/CD8 to MHC molecules. The second signal for T cell activation is provided by molecules called costimulators. The best known costimulators for T cells are B7-1 and B7-2 that are present on APCs. The T cell receptors for B7 co-stimulators on APC are CD28 and CTLA-4.

CD28 is a homodimer of two chains with Ig domains that is expressed on >90% CD4+ T cells and 50% of CD8+ T cells. Binding of CD28 to B7 of APC delivers signal to T cells that induces the expression of anti-apoptotic proteins, stimulate proliferation of growth factors and cytokines, and promote T cell proliferation and differentiation. CD28 is the principal receptor for delivering second signals for T cell activation.

A second receptor CTLA-4, which is structurally similar to CD28 is expressed only in recently activated T cells. It also binds to B7 molecule on APC, but serves to inhibit T cell activation. By counteracting signals generated from CD28, CTLA-4 is involved in terminating T cell response.

OTHER ACCESSORY MOLECULES WITH SIGNALLING FUNCTIONS:

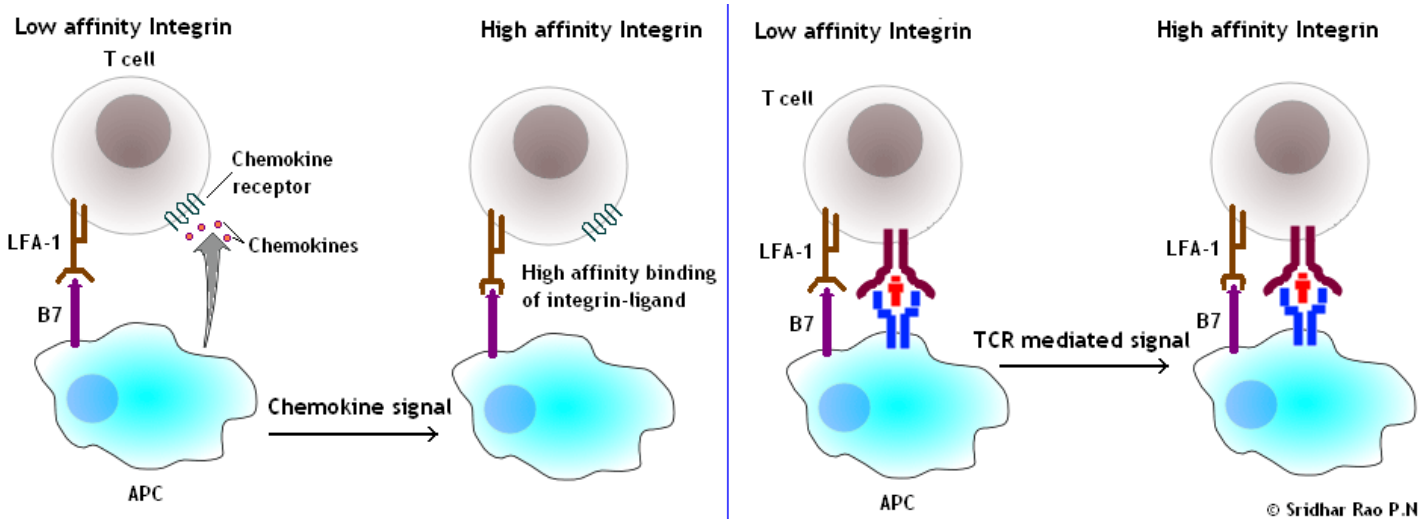
CD45: It is a cell surface glycoprotein that plays a role in T cell activation. Various forms of CD45 are known to occur on T cells, B cells, thymocytes, monocytes, and neutrophils.

CD2: It is a glycoprotein that is present on NK cells and >90% of mature T cells. It contains two extracellular Ig domains, transmembrane segment and a long cytoplasmic tail. CD2 binds to a ligand called leucocyte function antigen-3 (LFA-3), which is expressed on wide variety of cells. CD2 functions both as adhesin molecule as well as a signal transducer.

ADHESION MOLECULES OF T CELLS:

Integrins: These are heterodimeric proteins consisting of α chain and β chain that is expressed on leucocytes, whose cytoplasmic domains bind to cytoskeleton. There are two subfamilies of integrins, β1 and β2. The β chain remain conserved in both subfamilies but the α chain differs. β1 is also called VLA (very late activation) and β2 is called LFA-1. LFA-1 is expressed on most T cells, B cells, granulocytes and monocytes. Specific ligand to LFA-1 is intercellular adhesion molecules-1 (ICAM-1), which is expressed on wide variety of cells including B cells, T cells, fibroblasts, and endothelial cells. Other ligands for LFA-1 are ICAM-2, which is expressed on endothelial cells and ICAM-3, which is expressed on lymphocytes. The major functions of T cell integrins are to mediate adhesion to APCs, endothelial cells, and extracellular matrix proteins. T cell

activation increases the expression of integrins and similarly, exposure of APCs and endothelial cells to inflammatory cytokines increases the expression of ligands for the integrins. Once the T cells are stimulated through TCR or acted upon by chemokines, the avidity of integrins for their ligands increases rapidly. LFA-1 mediated adhesion is very important in activation of T cell, lysis of target cells by cytotoxic cells and lymphocyte adhesion to endothelium. The binding of activated lymphocytes to the endothelium at the site of infection or inflammation is due to the binding of T cell integrins to the endothelial ligands. The ability of integrins to bind to matrix molecules is responsible for retention of antigen-stimulated T cells in lymphoid organs and at peripheral sites of infection.



Selectins: Selectins are carbohydrate-binding proteins present on leucocytes, endothelial cells and platelets. Their principal function is to regulate migration of leucocytes to various tissue. L-selectin, which is present on naïve T lymphocyte but not on activated T cells, binds to carbohydrate moiety of glycoprotein present on endothelium of venules in lymph node. L-selectin, thus mediates the transfer of naïve T cells into lymph node, where captured antigens are concentrated.

CD44: It is a membrane glycoprotein that is expressed on variety of cell types including mature T cells, B cells, granulocytes, monocytes, RBCs, and fibroblasts. Recently activated T cells and memory T cells express high levels of CD44. By binding to hyaluronic acid, CD44 is responsible for retention of T cells in extravascular tissue at sites of infection and for binding of activated and memory T cells to endothelium at sites of inflammation.

EFFECTOR MOLECULES OF T CELLS

CD40L: Activated CD4+ T cells express a surface protein called CD40L which binds to CD40 on B cells, macrophages, dendritic cells and endothelial cells and activate all of these. CD40L is an important mediator of many of the effector functions of T cells.

Fas ligand: Activated T cells also express a ligand for apoptosis inducing receptor (Fas). Engagement of Fas to Fas ligand on T cells results in apoptosis and is important in eliminating T cells that are repeatedly stimulated by antigens. Fas ligand also provides one of the mechanisms by which cytotoxic T cells kill their targets.

Cytokine receptors: Activated T cells also express receptors for various cytokines, which bind to cytokines secreted by same or other T cells.