T CELL RECEPTOR

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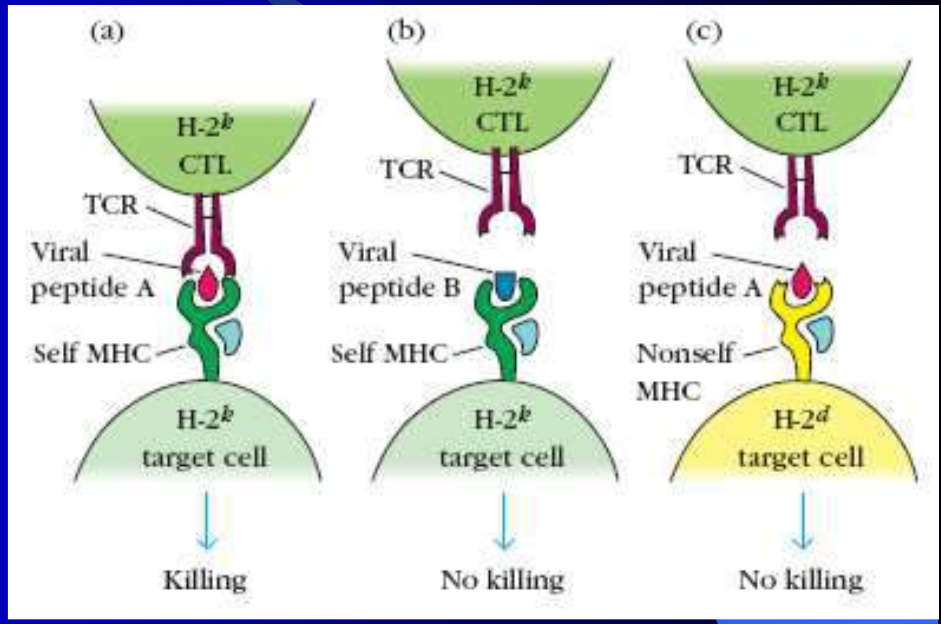
- **The antigen specific nature of T cell response clearly implies that T cells possess an antigenspecific**
- **and clonally restricted receptor**
- **However, the identity of this receptor remained unknown long after B-cell receptor (immunoglobulin molecule) had beenidentified.**
  - **First, the T-cell receptor is membrane bound and does not appear in a soluble form as the B-cell receptor does;**
  - **Second, most T-cell receptors are specific not for antigen alone but for antigen combined with a molecule encoded by the major histocompatibility complex (MHC).**
- **Therefore assessment of its structure by classic biochemical methods was complicated**

Self-MHC Restriction of the T-Cell Receptor

- By the early 1970s, immunologists had learned to generate cytotoxic T lymphocytes (CTLs) specific for virus-infected target cells.
- For example, when mice were infected with lymphocytic choriomeningitis (LCM) virus, they would produce CTLs that could lyse LCM-infected target cells in vitro.
- Yet these same CTLs failed to bind free LCM virus or viral antigens.
- Why didn't the CTLs bind the virus or viral antigens directly
- as immunoglobulins did?

- Zinkernagel and P. C.Doherty in 1974 demonstrated that antigen recognition by T cells is specific not for viral antigen alone but for antigen associated with an MHC Molecule
- T cells were shown to recognize antigen only when presented on the membrane of a cell by a self- MHC molecule.
- This attribute, called *self-MHC restriction*, distinguishes recognition of antigen by T cells and B cells.



MODELS OF RECOGNITION

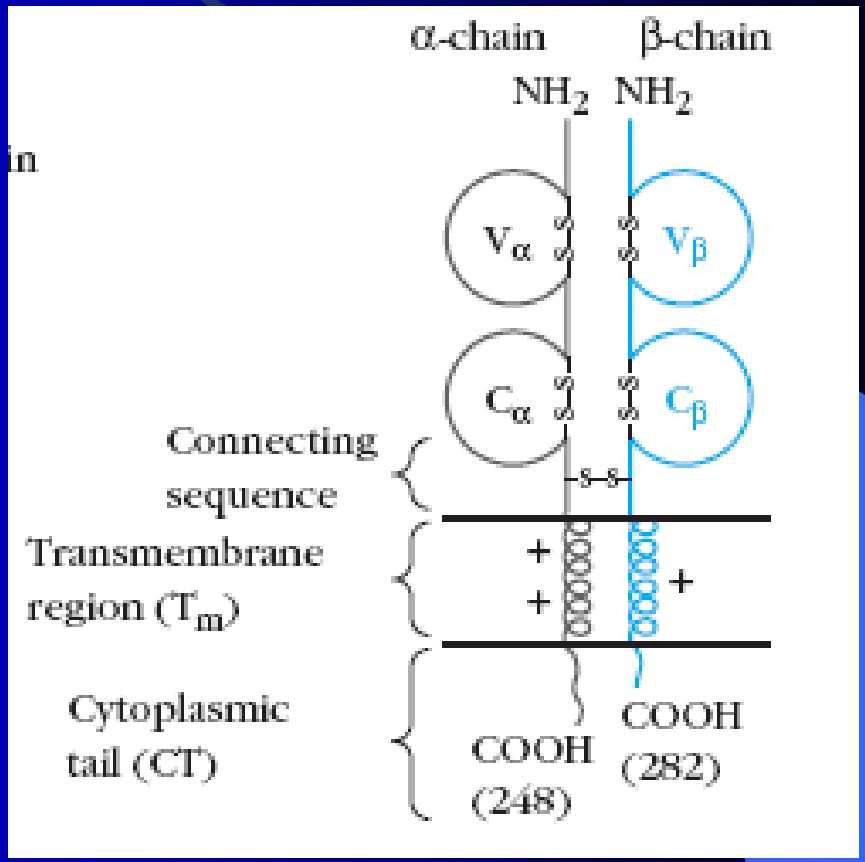
- Two models were proposed to explain the MHC restriction of the T-cell receptor.
  - The ***dual-receptor model*** envisioned a T cell with two separate receptors, one for antigen and one for class I or class II MHC molecules.
  - The ***altered-self model*** proposed that a single receptor recognizes an alteration in self-MHC molecules induced by their association with foreign antigens.

IDENTIFICATION OF T CELL RECEPTORS

- A combination of immunologic, biochemical, and molecular-biological manipulations revealed –
- The molecule responsible for T-cell specificity was found to be a heterodimer composed of
  - either α and β chains
  - or γ and δ chains.
- T Cells that express approximately 10^5 TCR molecules on their surface.
- Further, the T-cell receptor is associated on the membrane with a signal-transducing complex, CD3,

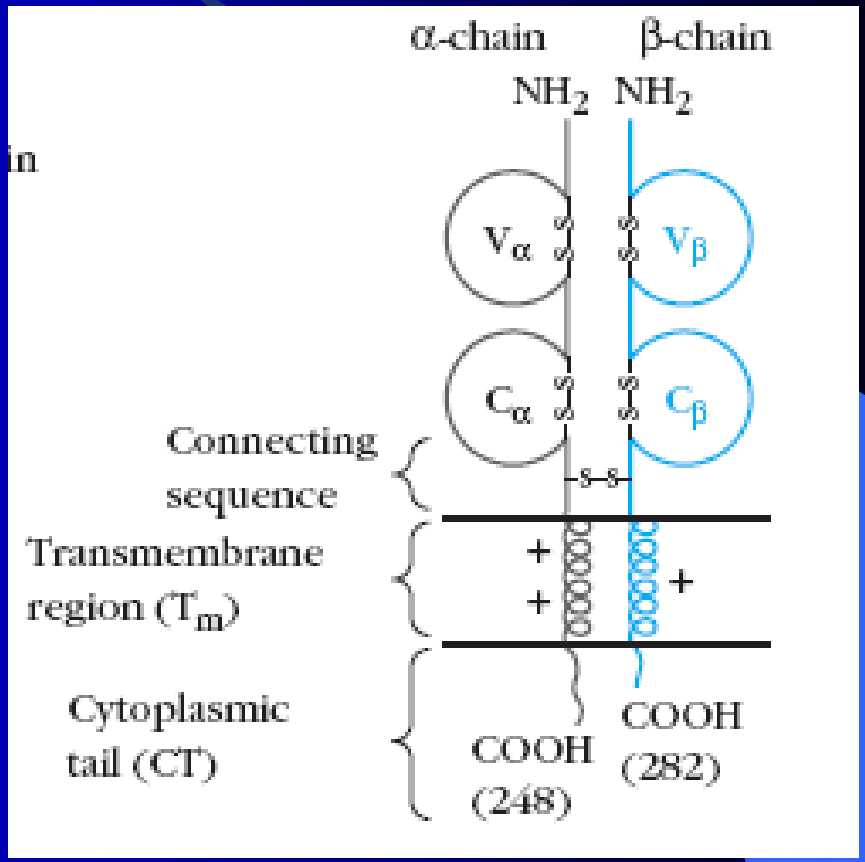
Structure and Role of αβ and γδ T-Cell Receptors:

- The domain structures of and TCR heterodimers are strikingly similar to that of the immunoglobulins
- They are are classified as members of the immunoglobulin superfamily
- Each chain in a TCR has two domains containing an intrachain disulfide bond that spans 60–75 amino acids.



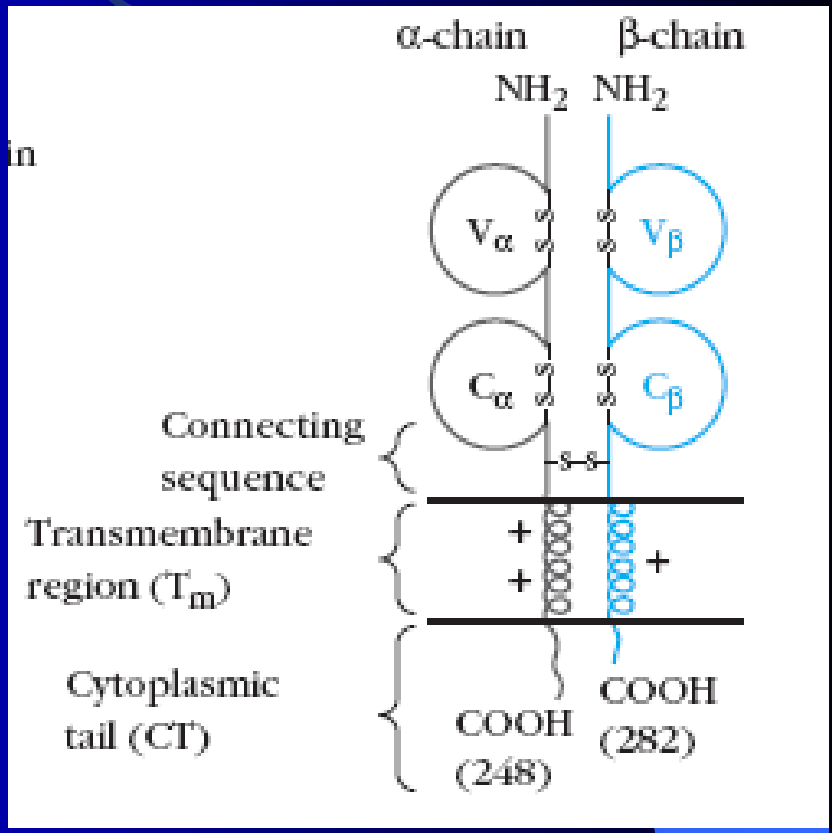
Structure and Role of αβ and γδ T-Cell Receptors:

- **The amino-terminal domain in both chains exhibits marked sequence variation, but the sequences**
- **The remainder of each chain are conserved.**
- **Thus the TCR are structurally homologous to the V and C domains of immunoglobulins,**
- **The TCR variable domains have three hypervariable regions, which appear to be equivalent to the complementarity determining regions (CDRs) in Ig molecule**



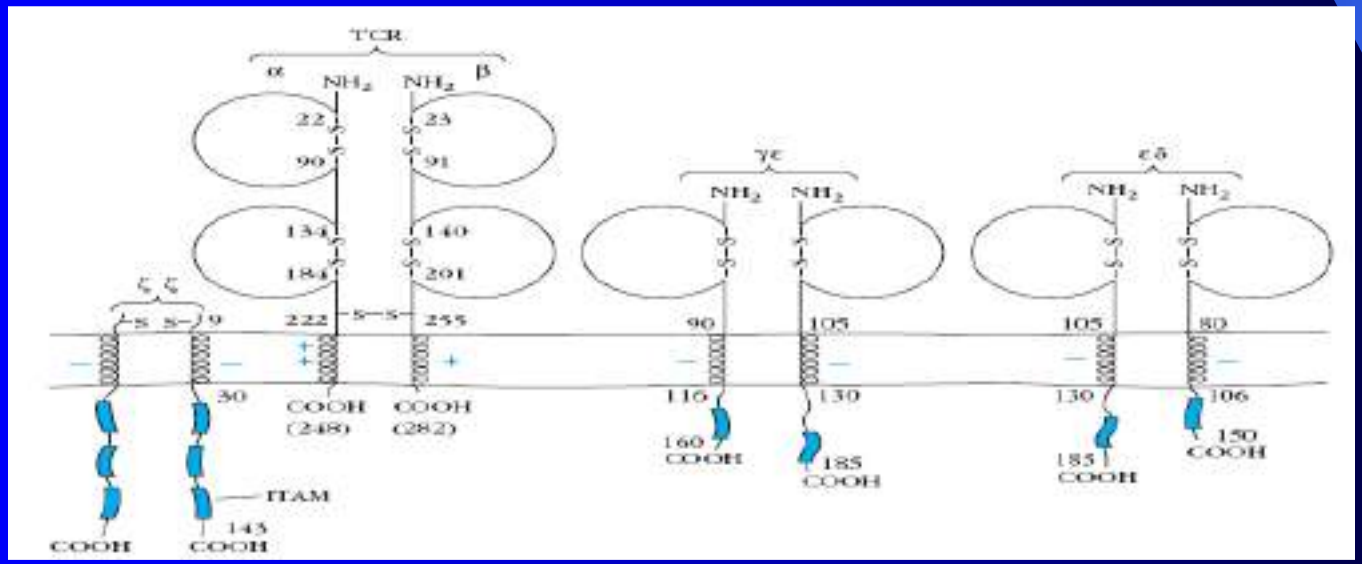
Structure and Role of αβ and γδ T-Cell Receptors:

- **In addition to the constant domain,**
  - **each TCR chain contains a short connecting sequence, in which a cysteine residueforms a disulfide link with the other chain of the heterodimer.**
  - **Has a short transmembrane region of 21 or 22 amino acids**
- **The transmembrane domains of both chains are unusual in that they contain positively charged amino acid residues.**
- **These residues enable the chains of the TCR heterodimer to interact with chains of the signal-transducing CD3 complex.**
- **Finally, each TCR chain contains a short cytoplasmic tail of 5–12 amino acids at the carboxyl-terminal end.**



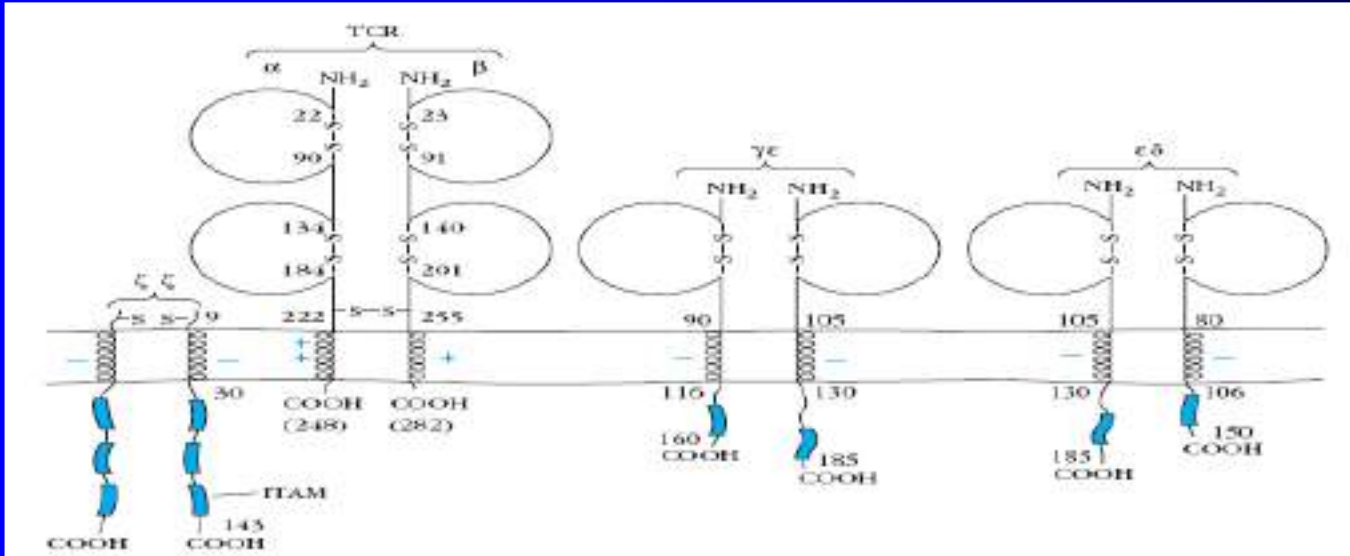
T-Cell Receptor Complex: TCR-CD3

- T-cell receptor associates with **CD3,** forming the TCR-CD3 membrane complex
- CD3 accessory molecule participates in signal transduction *after* of T cell with antigen
- It does not influence interaction with antigen.
- Loss of the genes encoding either CD3 or the TCR chains results in loss of the entire molecular complex from the membrane**.**



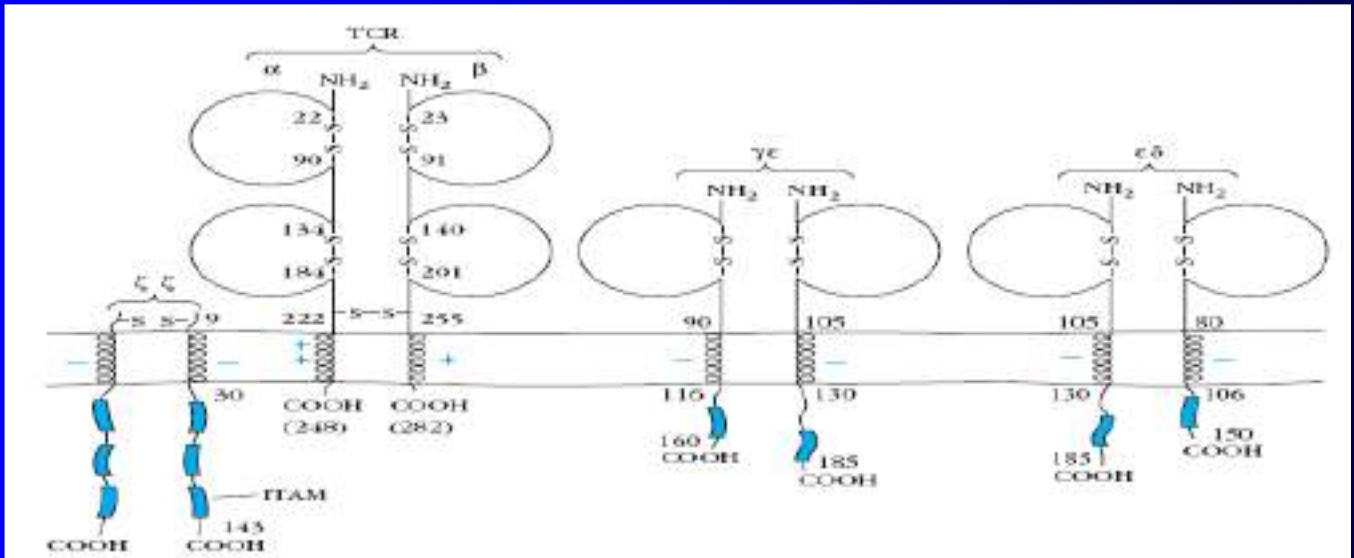
CD3 molecule

- CD3 is a complex of five invariant polypeptide chains that associate to form three dimers:
  - a heterodimer of gamma and epsilon chains,
  - a heterodimer of delta and epsilon chains
  - a homodimer of two zeta chains or a heterodimer of zeta and eta chains



- The and chains are encoded by the same gene, but differ in their carboxyl-terminal ends because of differences in RNA splicing of the primarytranscript.
- About 90% of the CD3 complexes examined to date incorporate the (ζζ) homodimer; the remainder have the (ζη) heterodimer.
- TCR heterodimer determines the ligand-binding specificity, whereas the CD3 complex are required for membrane expression of the T-cell receptor and for signal transduction
- All the CD3 peptides are members of the immunoglobulin superfamily

- The cytoplasmic tails of the CD3 chains contain a motif called the **immunoreceptor tyrosine-based activation motif (ITAM).**
- ITAMs are found in a number of other receptors, including the Ig-/Ig- heterodimer of the B-cell receptor complex and the Fc receptors for IgE and IgG.
- The ITAM sites have been shown to interact with tyrosine kinases and to play an important role in signal transduction.
- In CD3, the γ, δ & ε chains each contain a single copy of ITAM, whereas the ζ and η chains contain three copies



T-Cell Accessory Membrane Molecules

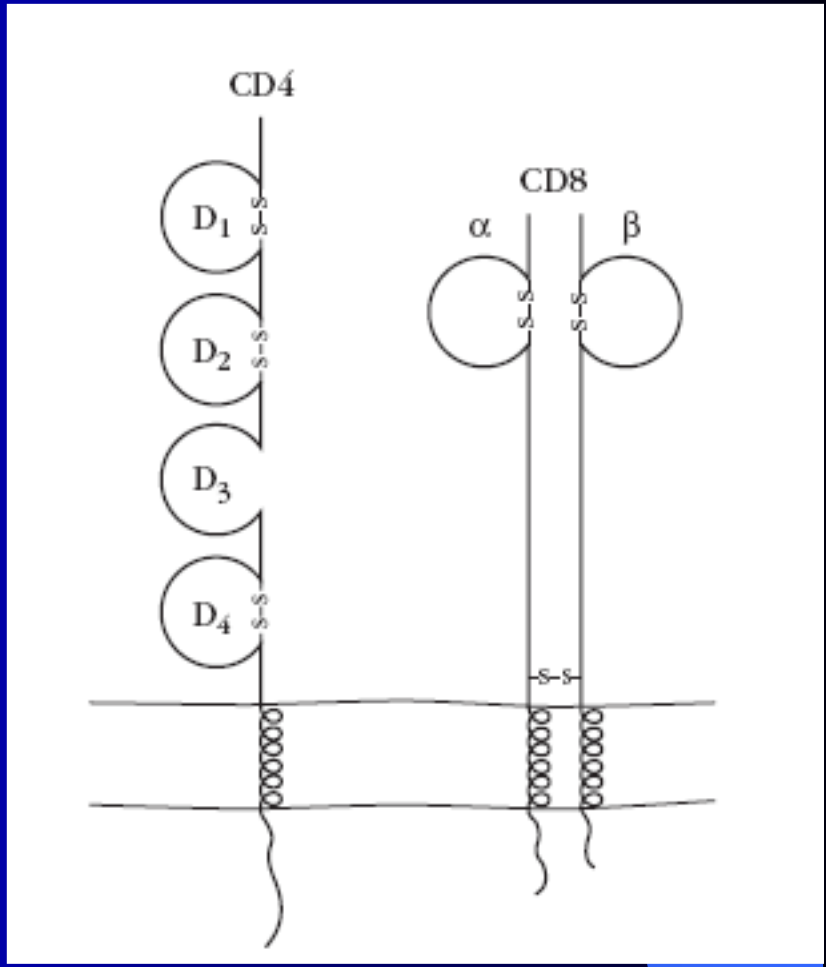
- Although recognition of antigen-MHC complexes is mediated solely by the TCR-CD3 complex, various other membrane molecules play important accessory roles in antigen recognition and T-cell activation
- Some of these molecules strengthen the interaction between T cells andantigen-presenting cells or target cells, some act in signaltransduction, and some do both.

CD4 and CD8 Coreceptors Bind to Conserved Regions of MHC Class II or I Molecules.

- T cells can be subdivided into two populations according to their expression of CD4 or CD8 membrane molecules
- CD4 T cells recognize antigen that is combined with class II MHC molecules and function largely as helper cells,
- CD8 T cells recognize antigen that is combined with class I MHC molecules and function largely as cytotoxic cells

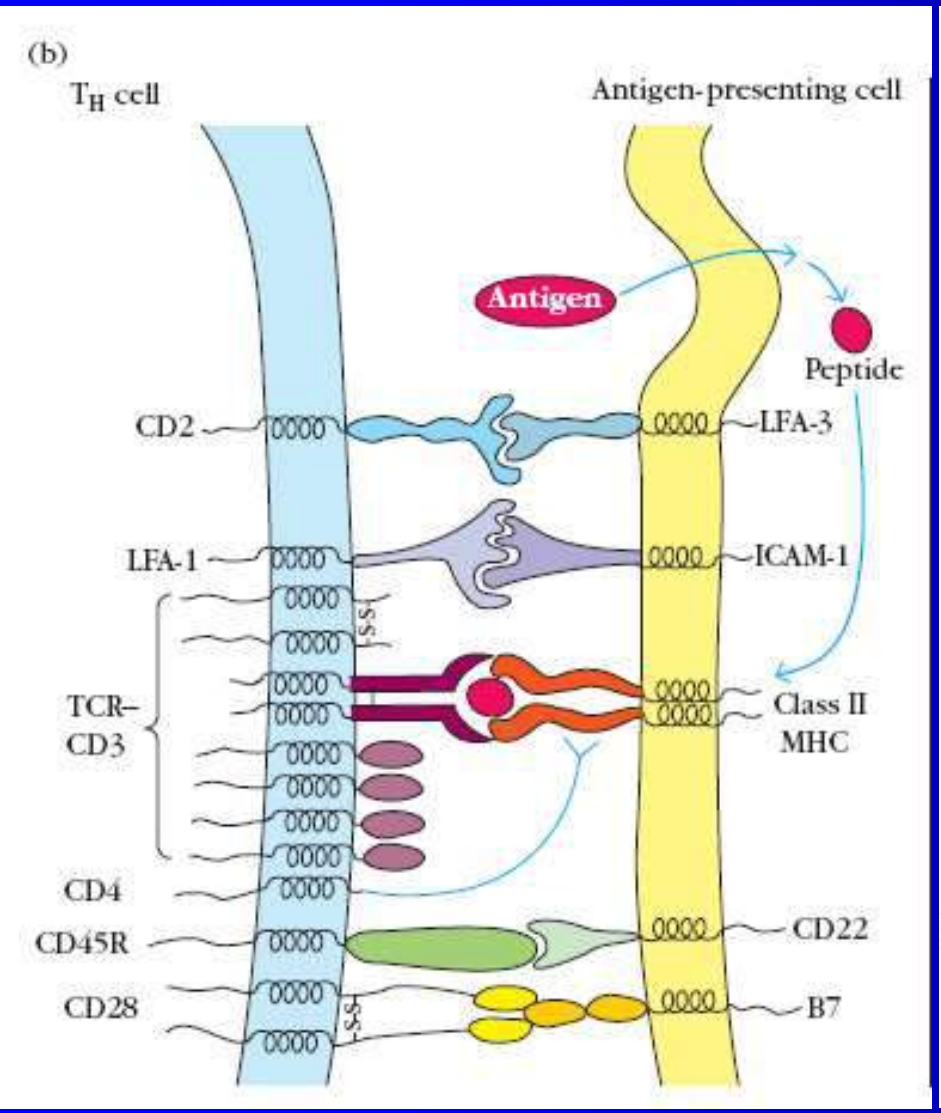
- **CD4 is a 55-kDa monomeric membrane glycoprotein that contains four extracellular immunoglobulin-like domains (D1–D4), a hydrophobic transmembrane region, and a long cytoplasmic tail containing three serine residues that can be phosphorylated.**

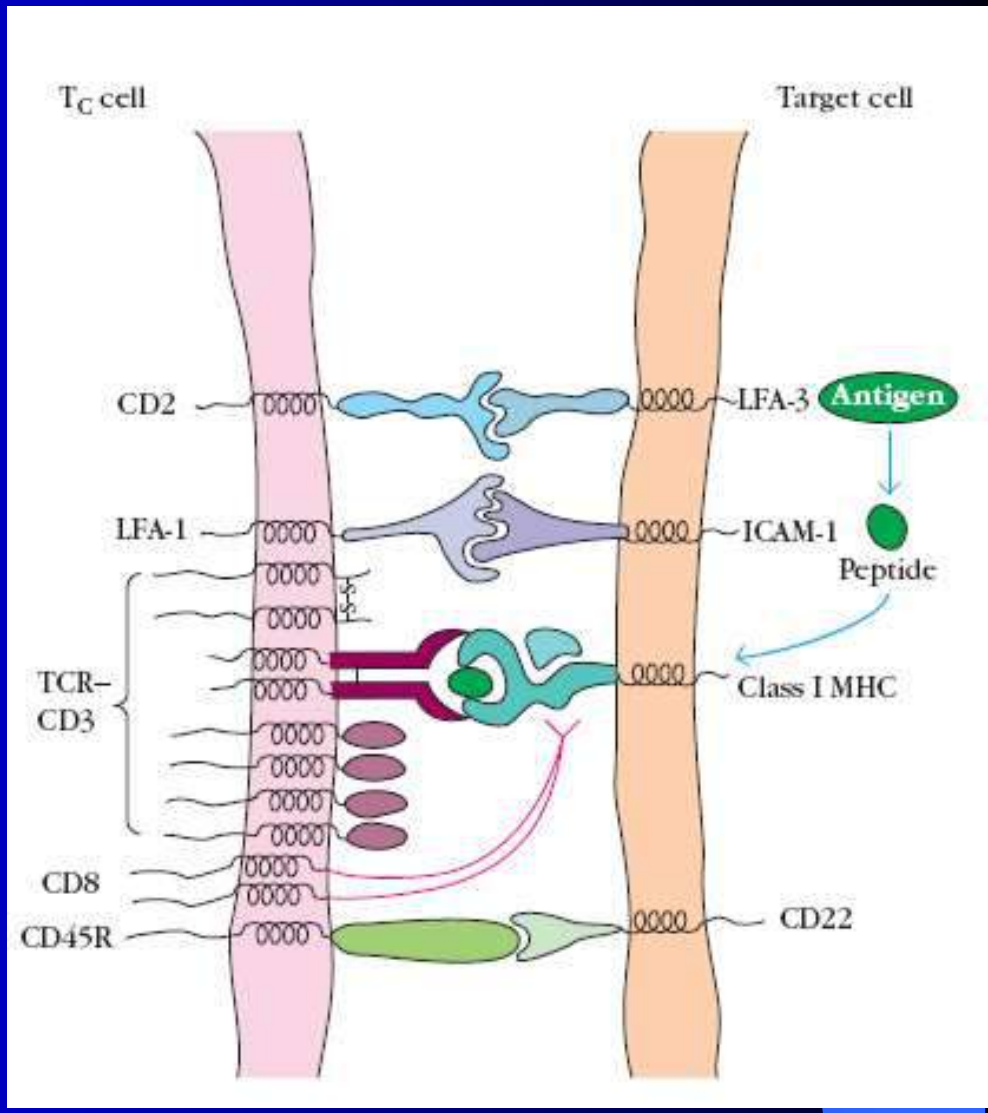
- **CD8 generally takes the form of a disulfide linked heterodimer αβ or αα homodimer. Both the chains of CD8 are small glycoproteins of approximately30–38 kDa. Each chain consists of a single extracellular immunoglobulin-like domain, a hydrophobic transmembrane region, and a cytoplasmic tail containing 25–27 residues, several of which can be phosphorylated**



Where to Get More Information

- CD4 and CD8 are classified as *coreceptors* based on their abilities to recognize the peptide-MHC complex and their roles in signal transduction.
- The extracellular domains of CD4 and CD8 bind to the conserved regions of MHC molecules on antigen-presenting cells (APCs) or target cells
- Binding of the CD4 and CD8 molecules serves to transmit stimulatory signals to the T cells


(b)
T_H cell
Antigen-presenting cell
Antigen
Peptide
CD2
LFA-3
LFA-1
ICAM-1
TCR–
CD3
Class II
MHC
CD4
CD45R
CD22
CD28
B7


T_C cell
Target cell
CD2
LFA-3
Antigen
LFA-1
ICAM-1
Peptide
TCR–
CD3
Class I MHC
CD8
CD45R
CD22