Major Histocompatibility Complex (MHC)

The **Major Histocompatibility Complex (MHC)** is a set of molecules displayed on cell surfaces that are responsible for lymphocyte recognition and antigen presentation. It is control the immune response through recognition of "self" and "non- self", consequently serve as targets in transplantation rejection.

There are three classes of MHC, **class I, class II and class III MHC**. The class I and class II molecules belong to a group known as the immunoglobulin supergene family, which includes immunoglobulins, T- cell receptors CD4, CD8 and others. In humans MHC resides on the short arm of chromosome 6, three genes HLA- A, HLA- B and HLA- C code for the class I MHC proteins while HLA- D determine the class II MHC proteins. MHC can bind numerous different peptides and some peptides can bind to several different MHC molecules and because this broad specificity, the binding between a peptide and an MHC is often referred to as "promiscuous".

The locus of MHC class III contains genes encoding tumor necrosis factor, lymphotoxin and complement components (C2 & C4). Class III MHC antigen not participate in MHC restriction or graft rejection.

MHC class I

Class I MHC antigens are classical (HLA- A, HLA- B and HLA- C) and non classical (HLA- E, HLA- F, HLA- G and HLA- X). These are glycoproteins found on surfaces of all nucleotide human cells, fibroblast, muscle cell, liver hepatocyte, neural cells, this contribute to the considerable success of liver transplantation. Class I antigens are involved of MHC restriction of cell mediated cytotoxicity (Tc).

MHC class I structure & function: Class I molecules are composed of two polypeptide chains, one encoded by the BCA region and another (β2 – microglobulin) that is encoded elsewhere. The MHC encoded polypeptide is about 350 amino acids long and glycosylated with molecular weight of about 45 kDa. This polypeptide folds into three separate domains called alpha -1, alpha -2 and alpha -3. β2 – microglobulin polypeptide is non – covalently associated with the alpha -3 domain. Between the alpha -1 and alpha -2 domains lies a region bounded by a beta-pleated sheet on the bottom and two alpha helices on the sides. This region is capable of binding via non covalent interactions a small peptide of about 10 amino acids and this small peptide is presented to a T- cell and defines the antigen epitope that the T- cell recognizes.

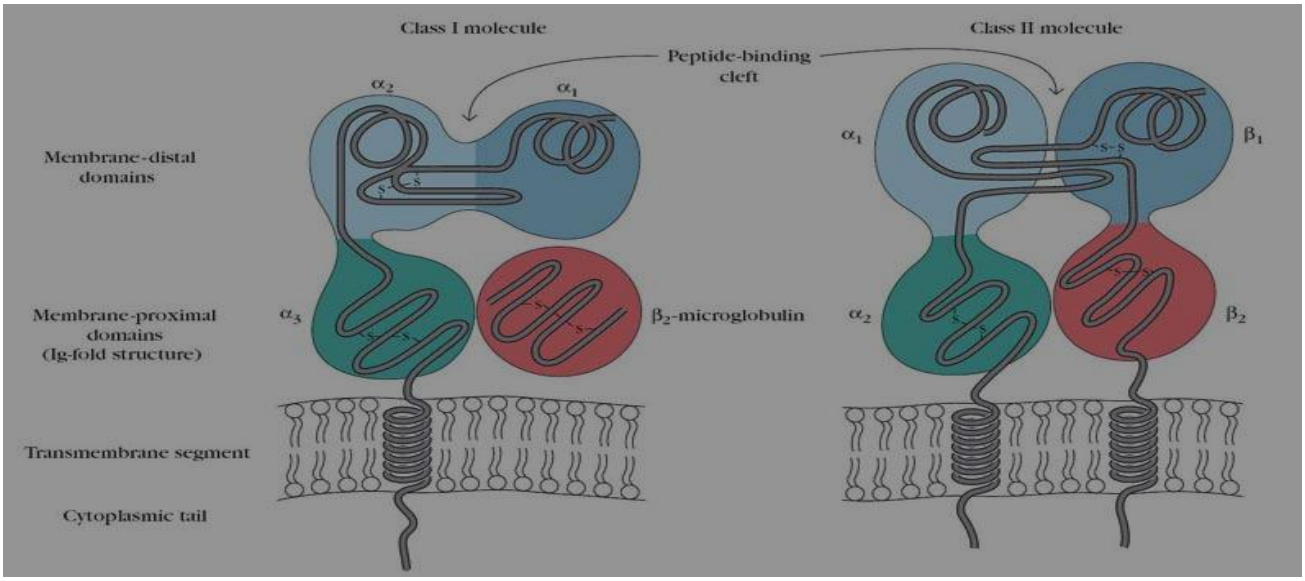
Class I MHC molecules bind peptides and present them to CD8 T cells. These peptides are derived from endogenous intracellular proteins that are digested in the cytosol. Then transported from cytosol into the cisternae of the cytoplasmic reticulum, where they interact with class I MHC molecules … this process known as the cytosolic or endogenous processing pathway.

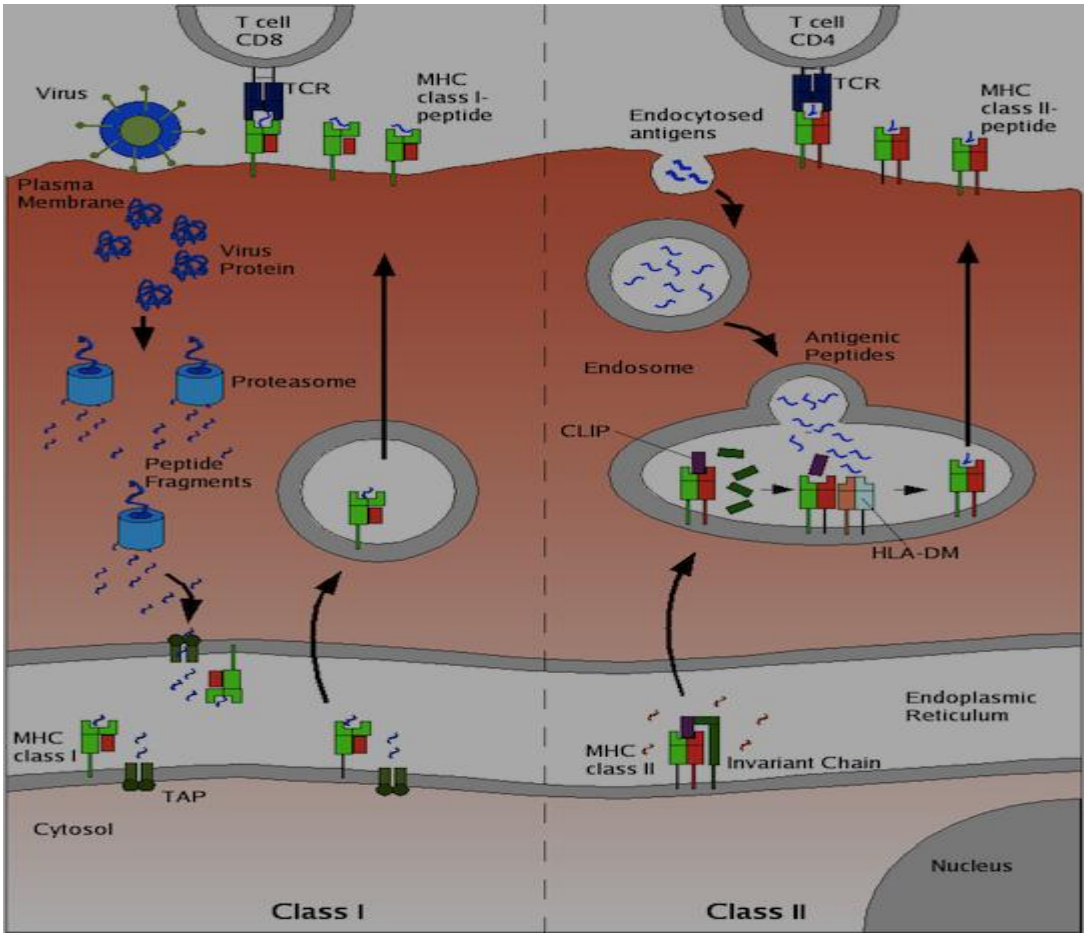
MHC class II

Class II MHC antigens are classical (HLA- DP, HLA- DQ and HLA- DR) and non classical (HLA- DM and HLA- DO). HLA- DM facilitates the loading of antigenic peptides into the class II MHC, DO serve as regulator of class II antigen processing. So, these antigens are glycoproteins found on the surface of macrophages, B- cells, Dendritic cells, Langerhans cells of skin and activated T cells. Class II antigens react with the CD4 molecule on the helper T- cells which secrete cytokines.

MHC class I structure & function: class II molecules are composed of two polypeptide chains, both encoded by D region. These polypeptides (alpha and beta) are about 230 and 240 amino acids long respectively and are glycosylated giving molecular weights of about 33 kDa and 28 kDa. These polypeptides fold into two separate domains; alpha- 1 and alpha -2 for the alpha poly peptide and beta -1 and beta -2 for the beta polypeptide. The open groove of class II molecules accommodates slightly longer peptides of 13-18 amino acids.

Class II MHC molecules bind peptides and present these peptides to the CD4 T cells leading to secretion cytokines, like class I molecules it can bind a variety of peptides these peptides are derived from exogenous proteins (either self or non self) which are degraded with in the endocytic processing pathway.





"Diagram show function of MHC class I and class II "

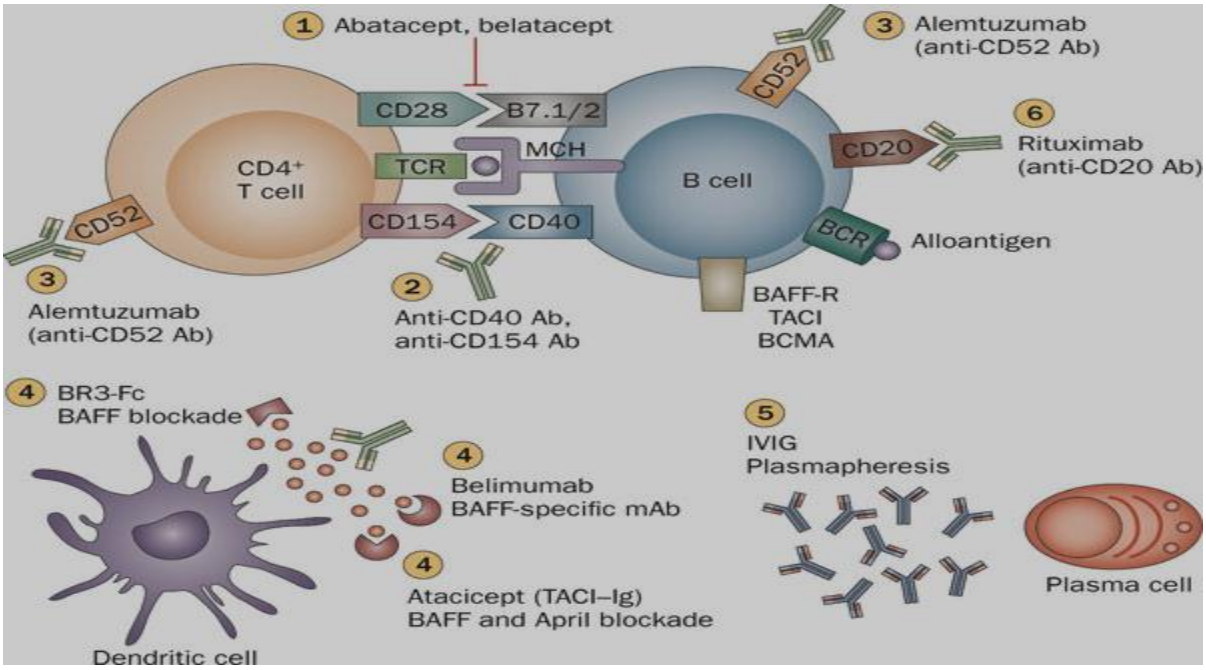
T and B- Lymphocytes

B- cell maturation, activation and differentiation:

An immature B cell bearing IgM in its membrane leaves the bone marrow and matures to express both membrane bound IgM and IgD with a single antigenic specificity. These called naïve B cells which have not encountered antigen, circulate in the blood and lymph and are carried to the secondary lymphoid organs, most notably the spleen and lymph nodes. The generation of mature B- cells first occurs during embryonic stages and continues throughout life. Before birth, yolk sac, fetal liver and fetal bone marrow is the major sites of B- cell maturation; after birth maturation take place in the bone marrow. B-cell development begins as lymphoid precursor cells differentiate into **progenitor B cell** which proliferate and differentiate into **precursor B cells**, this maturation and differentiation requires the microenvironment provided by the bone marrow stromal cells. The IL-7 secreted by the stromal cells binds the IL-7 receptor on the pre-B cell and drive the maturation process.

After export of B – cells from the bone marrow, activation, proliferation and differentiation occur in the periphery in response to antigen. Activation of B- cell occur in the presence of antigen, and in their absence the naïve B- cell in the periphery have a short life span and dying within a few weeks by apoptosis. Activation of B- cell by a thymus dependent antigen involve sequences events :

1. Antigen cross-link Igs receptors generating signal no.(1) which leads to increased expression of class II MHC and costimulatory B7. Antigen – antibody complexes are internalized by receptor – mediated endocytosis and degraded to peptides, some of which are bound by class II MHC and presented on the membrane as peptide – MHC complexes.
2. T_H cell recognizes antigen – class II MHC on B cell membrane. This plus costimulatory signal activates T_H cell.
3. (1) T_H cell begins to express CD40L.
   (2) Interaction of CD40 and CD40L provides signal no.(2)
   (3) B7-CD28 interactions provide costimulation to the T_H cell.
4. (1) B- cell begins to express receptors for various cytokines.
   (2) Binding of cytokines released from T_H cell in a directed fashion sends signals that support the progression of B- cell to DNA synthesis and to differentiation.

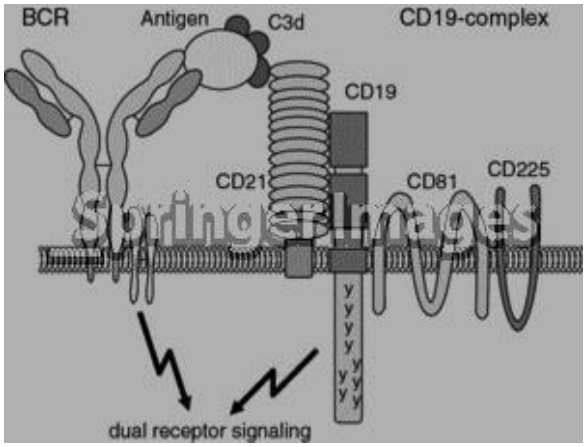


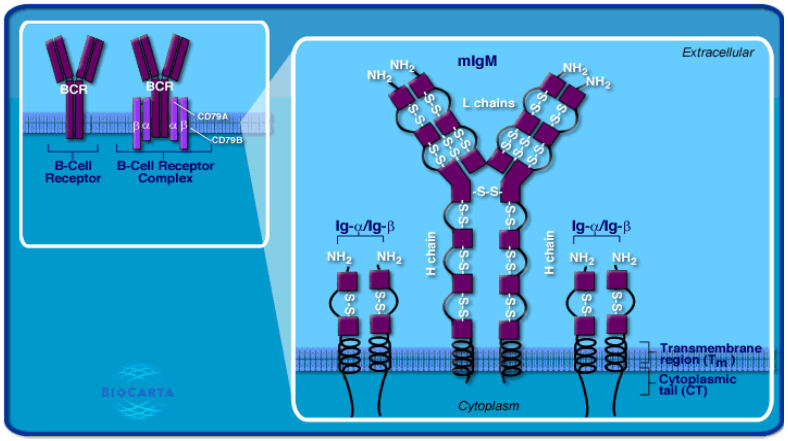
B- cell receptors:

The B- cell receptor (BCR) is a transmembrane protein complex composed of membrane- bound immunoglobulin (mIg) and disulfide- linked heterodimers called Ig- α/ Ig- β . Molecules of this heterodimer associate with an mIg molecule to form a BCR. The Ig- α chain has a long cytoplasmic tail containing 61 amino acids; the tail of Ig- β chain contains 48 amino acids, the tails in both Ig- α and Ig- β long enough to interact with intracellular signaling molecules.

In B- cell there are coreceptor provides simulatory modifying signals and another membrane protein, CD22 provides inhibitory signals. The B- cell coreceptor is a complex of three proteins: CD19, CD21 and CD81. CD19 is the key member of this complex and has a long cytoplasmic tail that provides docking sites for molecules that augment signals delivered by the BCR complex.

In addition to the stimulatory coreceptor, another molecule CD22 which is constitutively associated with the B- cell receptor in resting B- cells, delivers a negative signal that makes activation of B- cells more difficult.





Comparison of primary and secondary antibody responses:

Property	*primary response*	*secondary response*
Responding B cell	Naïve B cell	Memory cell
Time of peak response	7-10 days	3-5 days
Magnitude of peak antibody respons	varies depend on Ag	100 – 1000 times higher
Isotype produced	IgM predominates	IgG predominates
Ag	thymus dependent & thymus independent	thymus dependent
Antibody affinity	lower	higher

T- *cell maturation, activation and differentiation:*

In most cases, both the maturation of progenitor T cells in thymus and the activation of mature T- cells in the periphery are influenced by involvement of MHC molecules. Progenitor T- cells begin to migrate to the thymus from the early sites of hematopoiesis in the eighth or ninth week of gestation in humans. In the thymus, developing T- cells known as thymocytes, proliferate and differentiate along developmental pathways that generate functionally distinct subpopulations of mature T- cell.

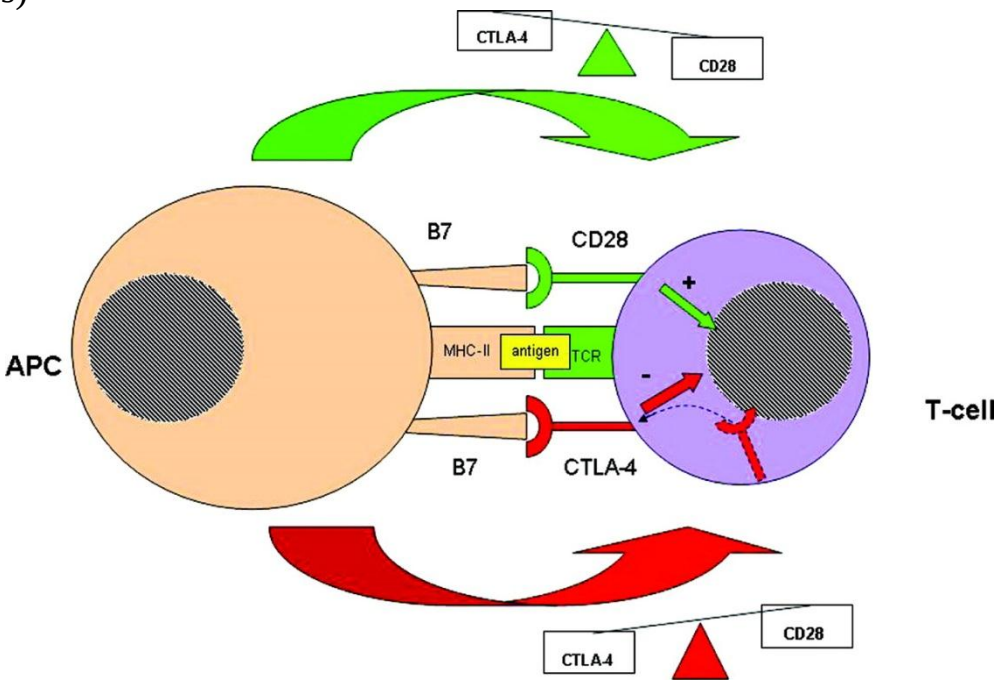
The thymus occupies a central role in T- cell biology. Aside from being the main source of all T- cells, it is where T- cells diversity and then shaped into an effective primary T- cell repertoire by extraordinary pair of selection processes, so thymocytes undergo two selection processes in the thymus:

- Positive selection for thymocytes bearing receptors capable of binding self- MHC molecules, which results in MHC restriction. Cells that fail positive selection are eliminated within the thymus by apoptosis.
- Negative selection that eliminates thymocytes bearing high- affinity receptors for self- MHC molecules alone or self- antigen presented by self- MHC, which results in self- tolerance.

The central event in the generation of humoral and cell- mediated immune response is the activation and clonal expansion of T- cells. T- cell activation is initiated by interaction of the TCR – CD3 complex with a processed antigenic peptide bound either a class I ($CD8^+$ cells) or class II ($CD4^+$ cells) MHC molecule on the surface of an antigen presenting cell. Interaction of a T- cell with antigen initiates a cascade of biochemical events that induces the resulting T- cell to enter the cell cycle, proliferating and differentiating into memory and effector cells. Also, Naïve T- cells require more than one signal for activation and subsequent proliferation into effector cells:

- Signal 1, the initial signal, is generated by interaction of an antigenic peptide with the TCR – CD3 complex.
- Signal 2, costimulatory signal, it is provided primarily by interactions between CD28 on the T- cell and members of the B7 family on the antigen – presenting cell.

These two activation signals trigger entry of the T- cell into the G1 phase of the cell cycle at the same time induce transcription of the gene for IL-2 and IL-2 receptor (CD25) this increased 100- fold in the activation, proliferation and differentiation naive of T- cell. T- cell activation generating a clone of progeny cells, which differentiate into memory and effector cell populations. The various effector cells carry out specialized functions such as cytokine secretion and B- cell help (activated $CD4^+$ T_H cells) and cytotoxic killing activity ($CD8^+$ CTLs)



((Interaction of B7 family members on APCs with CD28 delivers the costimulatory signal, while engagement of the closely related CTLA-4 (CD152) molecule with B7 produces an inhibitory signal and down regulates the activation of the T- cell))

T- cell receptor:

T- cell receptor is differs from B- cell antigen binding receptor in important ways, it is membrane bound and does not appear in soluble form as B- cell receptor. the antigen – binding interaction of T- cell receptors is weaker than that of antibodies and requiring more sensitive assays, finally most T- cell receptors are specific not for antigen alone but for antigen combined with (MHC) this attribute, called self- MHC restriction.

T- cell receptor is associated on the membrane with a multicomponent signal transducing complex CD3 whose function is similar to that of the Ig- α/ Ig- β complex of the B- cell receptor.

The molecule responsible for T- cell specificity is a heterodimer composed of either α and β or γ and δ chains. The α and β TCR like the antibody is characterized by high degree of specificity and consider a signature molecule of the adaptive immune system, By contrast to γ and δ TCR function in a manner more consistent with innate immunity. The domain structure of αβ and γδ TCR heterodimers are strikingly similar to those of immunoglobulins. They are classified as members of immunoglobulin superfamily. Each chain in a TCR has two domains containing an interaction disulfide bound that spans 60 – 75 amino acids, the amino terminal domain in both chains exhibits marked sequence variation but the sequences is conserved in each chain. Finally, each TCR chain contains a short cytoplasmic tail of five to 12 amino acids at the carboxyl-terminal end.

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

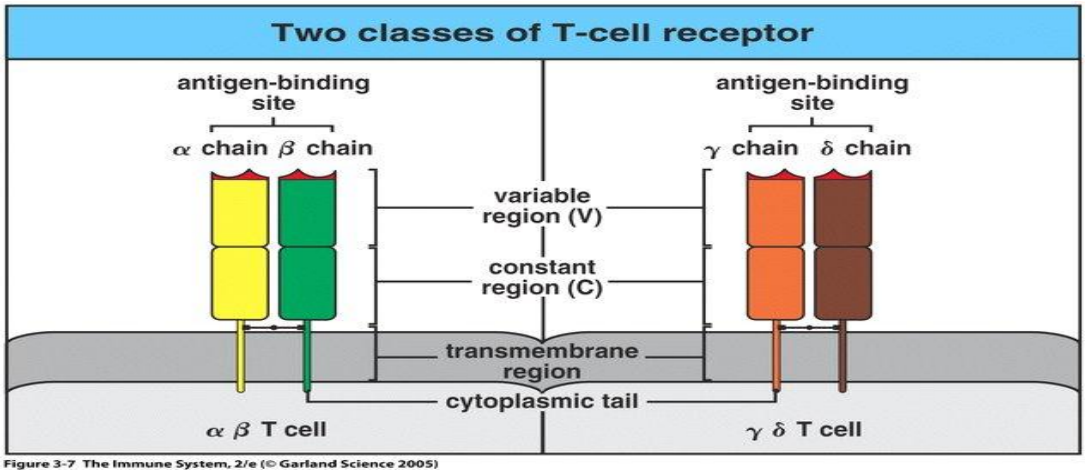
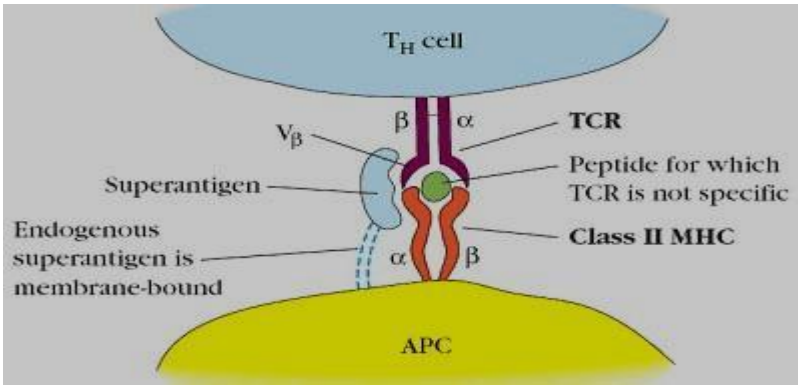


Figure 3-7 The Immune System, 2/e (© Garland Science 2005)

Superantigens

Superantigens are viral or bacterial proteins that bind simultaneously to the V_β domain of a T- cell receptor and to the α chain of a class II MHC molecule. Cross – linkage of a T-cell receptor and class II MHC molecule by either type of superantigen produces an activating signal that induces T- cell activation and proliferation. There are exogenous and endogenous antigen, exogenous antigens are soluble secreted bacterial proteins, including various exotoxins. Endogenous superantigens are membrane – embedded proteins produced by certain viruses, these viral proteins called minor lymphocyte-simulating (Mls) determinants.



Comparison of antigen recognition by T cells and B cells:

Characteristic	B- cells	T- cells
Interaction with antigen	involve binary complex of membrane Ig and Ag	Involves ternary complex of T- cell receptor, Ag and MHC.
Binding of soluble antigen	yes	No
Involvement of MHC molecules	None required	required to processed Ag
Chemical nature of antigens	protein, polysaccharide & lipid	Mostly protein
Epitope properties	Accessible, hydrophilic and containing sequential or non -sequential a.a.	Internal linear peptides and Ag bound to MHC molecules