

5

MAJOR HISTOCOMPATIBILITY COMPLEX

- Immune system protects the body in a complex web of cellular interactions. These interactions are key in identifying different cell types, tissue types as well as in self vs non-self recognition.
- These interactions are mediated by many different classes of molecules. One such class of molecules are called MHC molecules.
- MHC = Major Histocompatibility complex. It is a group of tightly linked genes. The molecules encoded by these genes are called MHC molecules.
- MHC is known by many different names. In humans, it is called as human leukocyte antigen (HLA) complex; in mice, it is called as H-2 complex.
- MHC in humans is located on chromosome 6 and in mice on chromosome 17.
- MHC genes are divided into 3 classes viz. class I, II and III. It is due to this division of genes that MHC molecules are of 3 classes viz. class I, II and III.
- Organization of MHC genes in humans is shown below :

Complex	HLA Complex		
MHC Class	II	III	I

- ◆ **MHC Molecules :** MHC class I and class II molecules share many structural features, associate with products of antigen processing and present antigen to different T-cell types. Class III molecules are critical in function of immune system but do not share structural features with class I and class II molecules.
- ◆ **MHC Class-I Molecule :**

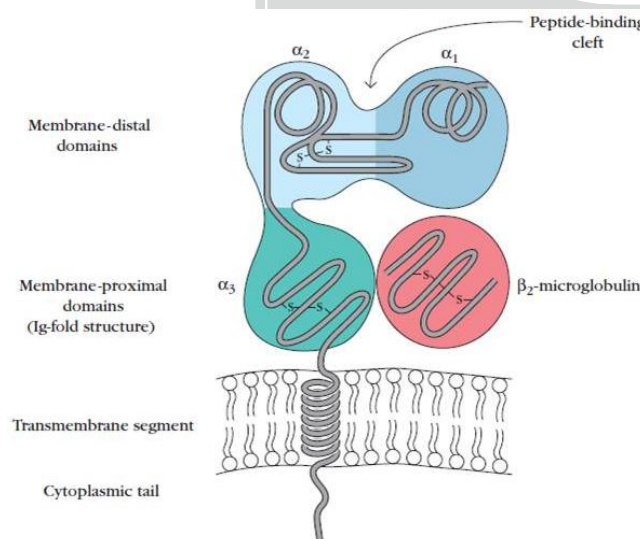


Figure : MHC Class-I Molecule

- It is a transmembrane glycoprotein.
- It has 2 types of polypeptides viz. 45 KDa α -chain and 12 KDa β_2 -microglobulin.
- α -chain is the transmembrane polypeptide and encoded by genes in MHC region.

- β_2 -microglobulin is *not* a transmembrane molecule and its gene is outside the MHC region.
- α -chain contains 3 domains viz. α_1 , α_2 and α_3 .
- α_3 is immunoglobulin fold domain.
- α_1 and α_2 together form antigen binding cleft.
- It is in this cleft that peptide antigen binds and is presented to CD8 T-cells.
- The size of peptide antigen is 8-10 amino acids.
- β_2 -microglobulin is also an immunoglobulin fold domain protein.
- Interaction of β_2 -microglobulin with class I α -chain is must for folding and expression of class I MHC molecules.
- If β_2 -microglobulin is absent then class I α -chain is synthesized but not expressed on the cell membrane. E.g. Daudi tumor.
- Association between α -chain and β_2 -microglobulin is non-covalent.
- Class I MHC molecules are expressed by *most not all* nucleated cells. Neurons lack class I MHC molecules. Highest expression is seen in lymphocytes.

◆ **MHC Class-II Molecule :**

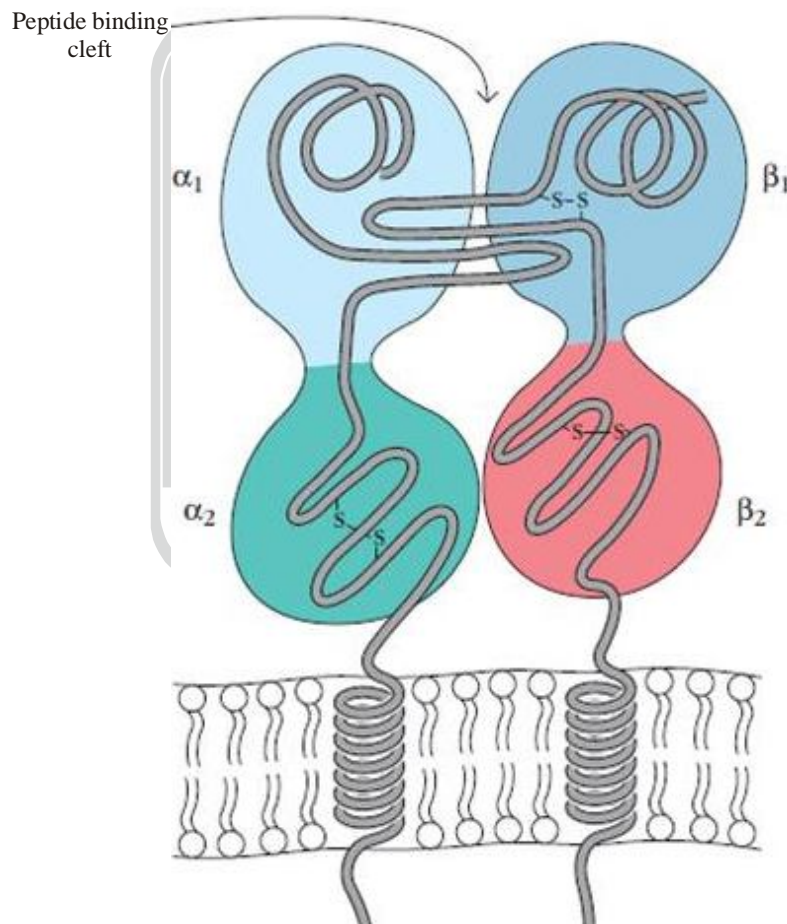


Figure : MHC Class-II Molecule

- It is a transmembrane glycoprotein.
- It contains 2 different polypeptide chains viz. 33 KDa α -chain and 28 KDa β -chain.
- Both these chains are transmembrane glycoproteins and interact with each other by non-covalent interactions.
- α and β -chains both have 2 domains each viz. α_1 , α_2 and β_1 , β_2 .
- α_2 and β_2 domains are immunoglobulin fold domains.

- α_1 and β_1 domains together make up antigen binding cleft.
- It is in this antigen binding cleft that peptide antigen is bound and presented to CD4 T-cells.
- The size of peptide antigen is 13-18 amino acids.
- MHC class II molecules are constitutively expressed only on the cell surface of antigen presenting cells (APCs). APCs include macrophages, dendritic cells and B-cells.
- Patients with bare lymphocyte syndrome lack MHC class-II molecules on their cells.

◆ **Inheritance of MHC alleles :**

- As explained earlier, MHC is a group of tightly linked genes.
- Location of each gene in this complex is called locus/loci.
- The form of gene found at a given locus in MHC complex can be from among many alleles.
- In other words, for every gene loci in MHC complex, many alleles exist. Thus, MHC is said to be polymorphic.
- MHC is also polygenic. It is different from being polymorphic.
- In polygenic, the gene itself has undergone duplication. The duplicated gene will have similar but not identical structure and function.
- As mentioned earlier, genes in MHC loci are tightly linked. It means they show very less recombination frequency.
- Due to this tight linkage, gene in MHC cluster are inherited together as a set of alleles.
- Each set of these alleles is referred to as a haplotype.
- Thus, an individual will inherit one haplotype from the mother and one haplotype from the father.
- The MHC haplotypes show codominant expression pattern i.e. both maternal and paternal genes are expressed in same cells.
- Because of strong linkage, MHC alleles also show a process of linkage disequilibrium. However, its discussion is beyond the scope.

◆ **Antigen Processing and Presentation :**

- Recognition of an antigen by T cell requires following steps :-
 1. Protein antigen is cleaved into small peptides.
 2. The peptide is bound to a MHC molecule to form peptide- MHC complex.
 3. Peptide - MHC complex displayed on the cell surface.
 4. Antigen recognized by T cells.
- It is the degradation of a protein antigen into many smaller peptides by a sequence of events that is called antigen processing.
- This degraded peptide then associates with MHC molecules in the cell interior and the peptide - MHC complexes are transported to the cell surface for antigen display. It is called antigen presentation.
- This process of antigen being presented as peptide - MHC complex is required because CD4 and CD8 T cells can recognize an antigen only when antigen is presented by self-MHC molecule. This is called self-MHC restriction.
- CD4 T-cells recognize antigen bound to MHC class II molecules, so they are MHC class II restricted.
- CD8 T-cells recognize antigen bound to MHC class I molecules, so they are MHC class I restricted.
- ◆ **Cytosolic Pathway :** In this, endogenous antigens of cells are processed using proteasome machinery in the cytosol. The peptides derived are bound with MHC class I molecule for antigen presentation to CD8 T cells. **E.g.:** Normal cellular proteins, tumor proteins, viral or bacterial proteins produced in infected cells.

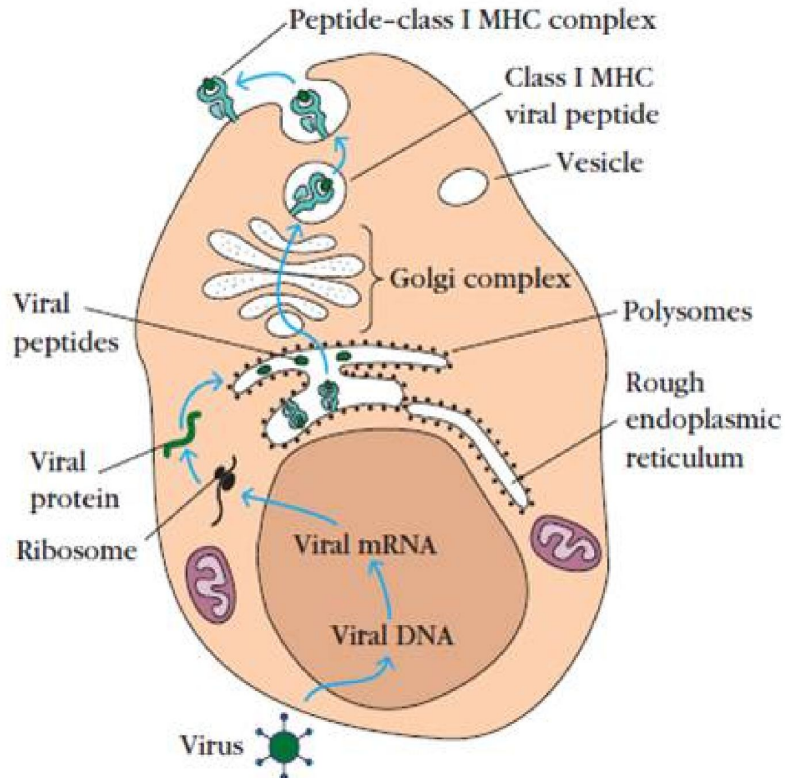


Figure : Cytosolic Pathway

- ◆ **Endocytic Pathway :** In this, exogenous antigens that are internalized by phagocytosis or endocytosis are processed in the endosome vesicle. The peptides derived are bound with MHC class II molecules and displayed on cell surface for antigen presentation to CD4 T cells.

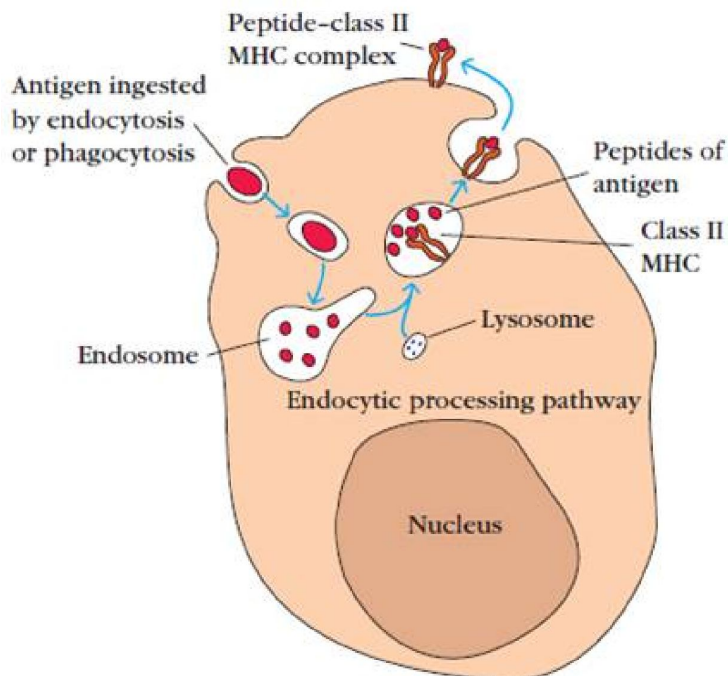


Figure : Endocytic Pathway