MHC MOLECULES- DEFINITION, PROPERTIES, CLASS, TYPES

- The major histocompatibility complex can be defined as a tightly linked cluster of genes whose products play an important role in intercellular recognition and discrimination between self and non-self.
- The term 'histo' stands for tissue, and 'compatibility' refers to 'getting along or agreeable'. On the other hand, the term 'complex' refers to the 'genes that are localized to a large genetic region containing multiple loci'.
- These genes code for antigens which involve the determination of the compatibility of the transplanted tissue. The compatible tissues will be accepted by the immune system, while the histoincompatible ones are rejected.
- The rejection of foreign tissue leads to an immune response to cell surface molecules. The concept was first identified by Peter Gorer and George Snell. The main function of MHC molecules is to bring the antigen to the cell surface for recognition by T cells. In humans, the genes coding for MHC molecules are found in the short arm of chromosome 6.

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Major Histocompatibility Complex (MHC) Molecules Characteristics

- The Major Histocompatibility complex is a genetic locus that encodes the glycoprotein molecules (transplantation antigens) which are responsible for tissue rejection of grafts between genetically unidentical individuals.
- It is also the molecule that binds the peptide antigens processed by Antigen-presenting Cells and presents them to T-cells, hence they are responsible for antigen recognition by the T-cell receptors.
- Unlike the B-cell receptors that directly interact with the antigens, the T-cell receptors have an intertwined relationship with the MHC molecule, in that T-cell receptors can only receive and bind processed antigens in the form of peptides that are bound to the MHC molecule, and therefore, T-cell receptors are specific for MHC molecules.

- In humans, the Major Histocompatibility complex is known as Human Leukocyte Antigen (HLA). There are three common MHC molecules, i.e, class I, class II, and class III MHC proteins.
- Generally, the MHC molecules have a broad specificity for peptide antigens, and many different peptides can be presented by any given MHC allele, binding a single peptide at a time.
- The α helices forming the binding clefts are the site of the amino acid residues that are polymorphic (varying allelic forms) in MHC proteins, meaning that different alleles can bind and present different peptide antigens. For all these reasons, MHC polymorphism has a major effect on antigen recognition.
- The MHC in humans is known as the **human leukocyte antigen (HLA) complex**.

HLA complex

In humans, the HLA complex of genes is located on the short arm of chromosome 6, containing several genes that are critical to immune function. The HLA complex of genes is classified into three classes as follows:

1. **Class I:** HLA-A, HLA-B, and HLA-C.
2. **Class II:** HLA-DR, HLA-DQ, and HLA-DP. All of these are present within the HLA-D region of the HLA complex.
3. **Class III:** Complement loci that encode for C2, C4, and factor B of the complement system and TNF alpha and beta.

Gene Products of the HLA Complex

1. **Class I MHC genes** encode glycoproteins expressed on the surface of nearly all nucleated cells; the major function of the class I gene products is presentation of endogenous peptide antigens to $CD8^+$ T cells.
2. **Class II MHC genes** encode glycoproteins expressed predominantly on APCs (macrophages, dendritic cells, and B cells), where they primarily present exogenous antigenic peptides to $CD4^+$ T cells.
3. **Class III MHC genes** encode several different proteins, some with immune functions, including components of the complement system and molecules involved in inflammation.

Major Histocompatibility Complex (MHC) Types

- In humans, the MHC molecules are divided into three types: Class I, Class II, and Class III.
- **Class I MHC** molecules are coded from three different locations called A, B, and C, and these molecules are expressed in all nucleated cells.

- **Class II MHC** genes are located in the D region, and there are several loci such as DR, DQ, and DP, and these molecules are expressed only in antigen-presenting cells. Class III MHC genes are coded in the region between Class I and Class II genes.
- **Class III MHC** genes code for cytokines and complement proteins, which play an important role during the immune response.

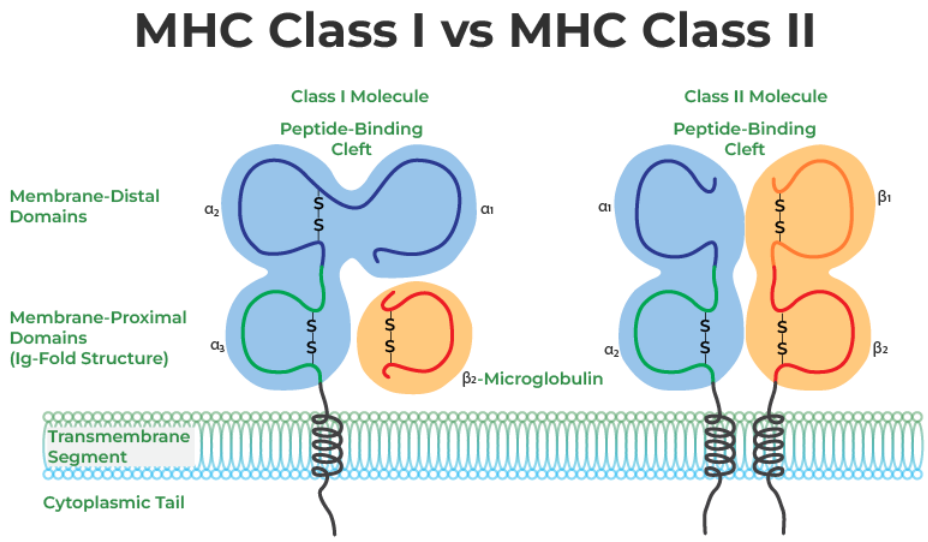
Class I MHC Molecule

- The structure of the Class I MHC molecule consists of two polypeptide chains, α and β. These two chains are connected by non-covalent bonds. The α chain is characterized as an internal membrane glycoprotein with a molecular weight of 45000 Da (in humans). B chain, on the other hand, is an extracellular microglobulin with a molecular mass of 12kDa.
- The α chain is made up of approximately 350 amino acids and is also divided into three globular domains, α_1, α_2, and α_3. Each of these domains contains roughly 90 amino acids. The N-terminal of the α chain is the place of the α_1 domain, while α_2 and α_3 are present after α_1. The α_2 domain is characterized by the formation of a loop of 63 amino acids; the loop is formed due to an intrachain disulfide bond. α_3 also contains a disulfide bond enclosing 86 amino acids. The α_1 and α_2 domains interact to form peptide-binding units of the class I MHC molecule.
- Moreover, the α chain also consists of a stretch of 26 hydrophobic amino acids that hold the α chain on the plasma membrane. This transmembrane segment is present in the form of an α helix at the hydrophobic region of the plasma membrane. An intracellular domain or the carboxyl-terminal of the α chain is located inside the cell, and it contains around 30-40 amino acids.
- T-Cell (cytotoxic T cell) has specificity towards cells containing peptides associated with Class I MHC due to the presence of CD8 antigen on the surface of T-Cell.

Class II MHC Molecule

- Class II MHC molecules are heterodimers and characterized by two non-covalently connected polypeptide chains. The chains are termed a heavy chain (α, 30kDa) and a light chain (β, 26kDa).
- Similar to class I MHC molecules, class II MHC molecules are also characterized by an extracellular amino-terminal domain, a transmembrane domain, and an intracellular carboxy-terminal tail.
- The class II MHC molecules are expressed on the surface of the antigen-presenting cells, such as B cells, dendritic cells, and macrophages.
- The α chain is divided into two domains, α_1 and α_2, while the β chain is also divided into two groups, β_1 and β_2. The β_2 domain is responsible for the binding of the T cell co-receptor CD4. The α_1 and β_1 domains, on the other hand, are involved in the formation of the antigen-binding sites. Peptides containing 13-20 amino acids can bind at the antigen-binding site of class II MHC.

- The presence of disulfide bonds in α_2, β_1, and β_2 domains is also an important structural feature of the class II MHC molecules.



Class III MHC Molecule

- There are several serum proteases which involved in the complement system that come under the group of class III MHC molecules.
- Class III MHC molecules do not have any involvement in antigen presentation.
- The complement components, such as C2, C4A, C4B, and factor B, are the most important compounds involved as class III MHC molecules. Apart from these, tumor necrosis factors α and β, and some heat shock proteins also come under this category.

Importance of MHC

1. Antibody molecules interact with antigen directly, but the T-Cell Receptor (TCR) only recognizes antigen presented by MHC molecules on another cell, the Antigen Presenting Cell. The TCR is specific for the antigen, but the antigen must be presented on a self-MHC molecule.
2. The TCR is also specific to the MHC molecule. If the antigen is presented by another allelic form of the MHC molecule in vitro (usually in an experimental situation), there is no recognition by the TCR. This phenomenon is known as **MHC restriction**.

Peptide antigens associated with class I MHC molecules are recognized by $CD8^+$ cytotoxic T lymphocytes, whereas class II-associated peptide antigens are recognized by $CD4^+$ helper T cells.