

MAJOR HISTOCOMPATIBILITY COMPLEX (MHC)

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MAJOR HISTOCOMPATIBILITY COMPLEX (MHC)

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1. Core Definition and Immunological Role

The Major Histocompatibility Complex (MHC) refers to a highly polymorphic locus of genes found in most vertebrates that encodes for cell-surface proteins crucial for the adaptive immune system. The primary function of the MHC is to regulate the immune response by presenting small peptide fragments, derived from proteins, to T lymphocytes. This mechanism allows the immune system to distinguish between host cells (presenting "self" peptides) and cells invaded by pathogens or otherwise abnormal (presenting "non-self" or altered self peptides). The MHC complex is, therefore, intrinsically involved in the immune response, acting as the foundation for T-cell mediated immunity.

In humans, the MHC is referred to as the **Human Leukocyte Antigen (HLA) system**. These molecules are essential for initiating the adaptive immune response. When T cells encounter antigens presented by MHC molecules, they are either activated to destroy the presenting cell (if the antigen is foreign) or signaled to initiate a broader immune cascade, such as antibody production by B cells. The profound importance of the MHC lies in its role as the gatekeeper of immune recognition, determining which antigens stimulate a response and which are ignored, thereby preventing autoimmune reactions while ensuring rapid defense against pathogens.

2. Genetic Organization and Polymorphism

The MHC genes are clustered together on a single chromosome (Chromosome 6 in humans) and are characterized by extreme polymorphism--meaning that numerous different alleles exist for each gene within the population. This genetic diversity is the highest known in the mammalian genome and is vital for species survival, ensuring that a population, even if exposed to a novel pathogen, will have individuals capable of mounting an effective immune response. The MHC locus is generally divided into three major regions: Class I, Class II, and Class III.

Unlike most genes, MHC genes are expressed codominantly; an individual expresses alleles inherited from both parents, maximizing the variety of antigens that can be presented to T cells. This extensive polymorphism, while beneficial for pathogen defense, is the primary obstacle in tissue and organ transplantation, as the immune system of the recipient recognizes the donor's MHC molecules (allogeneic MHC) as foreign, leading to powerful transplant rejection responses. The specific combinations of MHC alleles, known as **haplotypes**, are inherited as a unit and are the defining feature of an individual's immunological identity.

3. Molecular Structure and Function of MHC Class I

MHC Class I molecules are expressed on the surface of virtually all nucleated cells in the body, which includes almost every cell except red blood cells. Their primary function is to present peptides derived from proteins synthesized within the cell's cytoplasm (endogenous antigens), which typically signal the presence of viral infection or malignant transformation. The structure of a functional MHC Class I molecule is a heterodimer consisting of two non-covalently linked polypeptide chains: a heavy alpha chain (encoded by HLA-A, HLA-B, or HLA-C genes) and a lighter chain called **beta-2 microglobulin**.

The alpha chain forms three external domains ($\alpha 1$, $\alpha 2$, and $\alpha 3$). The peptide-binding groove, which holds the antigenic fragment for T cell recognition, is formed by the $\alpha 1$ and $\alpha 2$ domains. This groove typically accommodates short peptides, usually 8 to 10 amino acids in length. The complex presents these internal peptides to **CD8+ cytotoxic T lymphocytes (CTLs)**. If the CTL recognizes a foreign peptide (e.g., a viral protein), it triggers the cytotoxic T cell to destroy the infected host cell, thereby halting the spread of intracellular pathogens.

4. Molecular Structure and Function of MHC Class II

MHC Class II molecules exhibit a more restricted expression pattern, primarily found only on specialized **Antigen-Presenting Cells (APCs)**, such as dendritic cells, macrophages, and B lymphocytes. Their function is to present peptides derived from proteins internalized by the APC from the extracellular environment (exogenous antigens). This process involves phagocytosis or endocytosis, followed by proteolytic degradation within endosomal or lysosomal compartments.

Structurally, MHC Class II molecules are heterodimers composed of two transmembrane chains of roughly equal size: an alpha chain and a beta chain, both of which are encoded within the MHC locus (specifically the HLA-DP, HLA-DQ, and HLA-DR regions). The peptide-binding groove, formed by the paired $\alpha 1$ and $\beta 1$ domains, is more open at the ends compared to Class I, allowing it to bind longer peptides, typically 12 to 25 amino acids. MHC Class II molecules present antigens exclusively to **CD4+ helper T lymphocytes (TH cells)**. Upon recognition of a foreign peptide, TH cells become activated and coordinate the broader immune response, stimulating B cell antibody production, macrophage activation, and enhancing CTL responses.

5. MHC Class III and Associated Genes

The Class III region of the MHC locus is genetically situated between the Class I and Class II regions. Unlike Classes I and II, which encode antigen-presenting molecules, the Class III region encodes a diverse array of proteins that are important for immune regulation but do not directly participate in peptide presentation. These genes are crucial for the inflammatory response and

complement cascade.

Key components encoded by the Class III region include several components of the **complement system** (C2, C4, and Factor B), which are critical for pathogen clearance and inflammation. Additionally, this region encodes genes for various heat shock proteins (HSP70), tumor necrosis factor (TNF), and lymphotoxin. While structurally and functionally distinct from the classical antigen-presenting molecules, the close genetic linkage of Class III genes to Class I and II means that they are often inherited together in the same haplotype, leading to observed statistical associations between certain HLA types and specific inflammatory or autoimmune conditions.

6. Role in Antigen Presentation Pathways

The distinction between MHC Class I and Class II function is rooted in two separate and highly specialized antigen processing pathways:

The Endogenous (Cytosolic) Pathway: This pathway processes proteins synthesized within the cell, primarily viral or aberrant host proteins. These proteins are tagged with ubiquitin and degraded into small peptides by the **proteasome**. These peptides are then transported into the endoplasmic reticulum (ER) via the **Transporter associated with Antigen Processing (TAP)**. Inside the ER, the peptides are loaded onto newly synthesized MHC Class I molecules, stabilized by chaperones, and the complete complex is then exported to the cell surface for presentation to CD8+ T cells.

The Exogenous (Endocytic) Pathway: This pathway handles antigens acquired from outside the cell by APCs. Once internalized into endosomes or lysosomes, the foreign proteins are degraded into peptides. Meanwhile, newly synthesized MHC Class II molecules in the ER are temporarily blocked by an invariant chain (Ii), preventing them from binding endogenous peptides. The Class II molecules are trafficked to a specialized endosomal compartment where the Ii is cleaved, leaving only a fragment called CLIP. The exogenous peptides displace CLIP, load onto the Class II molecule, and the stable complex is then transported to the cell surface for presentation to CD4+ T cells.

7. Clinical Significance: Transplantation and Disease Association

The MHC, particularly the HLA system, is the single most important genetic factor governing the success or failure of organ and tissue transplantation. Since the MHC genes are highly polymorphic, an individual's immune system will nearly always recognize the MHC molecules of a non-identical donor as foreign, a phenomenon known as **allorecognition**. This powerful immune response leads to transplant rejection unless the patient is maintained on severe immunosuppressive therapy. Achieving a close HLA match between donor and recipient is paramount for minimizing the risk of graft rejection, particularly in hematopoietic stem cell (bone

marrow) transplantation.

Furthermore, specific MHC haplotypes are associated with susceptibility or resistance to certain diseases, particularly autoimmune disorders. While the exact mechanistic link is complex, it is hypothesized that certain HLA alleles may be highly effective at binding and presenting self-peptides, thereby mistakenly activating autoreactive T cells. Classic examples include the strong association between the HLA-B27 allele and **ankylosing spondylitis**, and between HLA-DR4 and rheumatoid arthritis. The study of MHC-disease association provides critical insight into the genetic basis of immune-mediated pathologies.

8. Further Reading

[Major Histocompatibility Complex \(MHC\) - Wikipedia](#)

[Immunobiology: The Immune System in Health and Disease. Chapter 5: Antigen Recognition by T Cells](#)

[Human Leukocyte Antigen \(HLA\) System - Wikipedia](#)