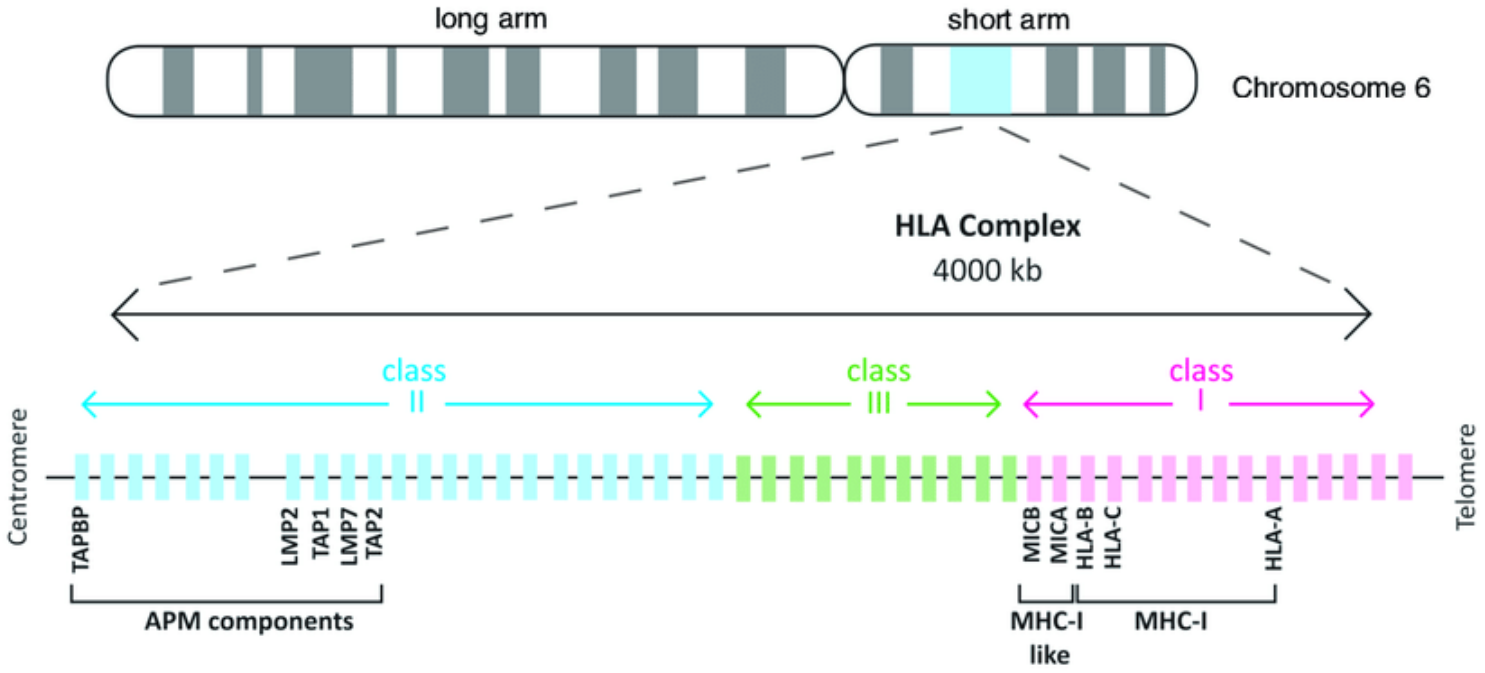
Major Histocompatibility Complex (MHC)

- The Major Histocompatibility Complex (MHC), in humans known as the Human Leukocyte Antigen (HLA) complex, is a gene cluster on chromosome 6 that encodes proteins crucial for the immune system's recognition of self and non-self.
- It's organized into three regions: I, II, and III, each encoding different MHC molecules.
- MHC genes are inherited as haplotypes, meaning individuals receive one haplotype from each parent, resulting in two sets of MHC molecules.



General Organization

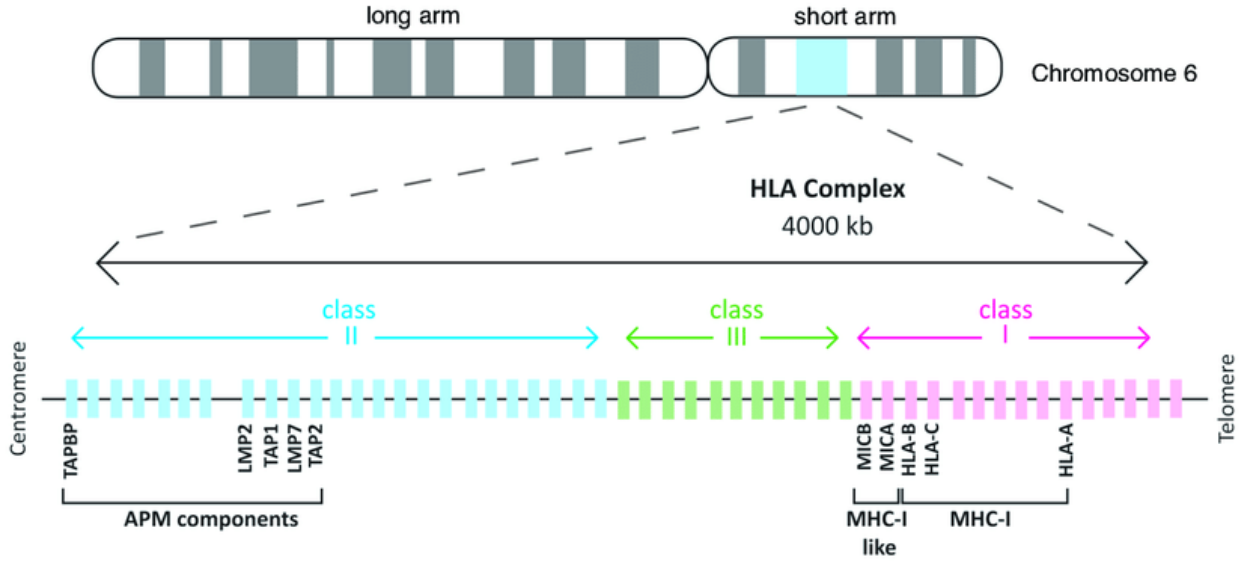
- **Chromosomal Location:**

The MHC genes are located on chromosome 6 in humans.

- **Regions:**

The MHC is divided into three regions:

- **Class I:** Encodes molecules (HLA-A, B, C) expressed on most nucleated cells, presenting antigens to cytotoxic T cells (CD8+).
- **Class II:** Encodes molecules (HLA-DR, DQ, DP) expressed primarily on antigen-presenting cells, presenting antigens to helper T cells (CD4+).
- **Class III:** Encodes proteins involved in complement system and other immune functions.



- **Polymorphism:**

MHC genes are highly polymorphic, meaning there are many different versions (alleles) of the genes, contributing to individual diversity.

- **Structure:**

MHC class I and II molecules have a specific structure that allows them to bind and present peptide antigens to T cells.

Inheritance:

- **Haplotypes:**

Individuals inherit one haplotype from each parent, meaning they inherit two sets of MHC molecules.

- **Co-dominant Expression:**

Both maternal and paternal MHC alleles are expressed in the same cells, resulting in a diverse repertoire of MHC molecules.

- **No Recombination:**

MHC genes are closely linked on chromosome 6, making recombination (crossing over) infrequent.

- **Diversity:**

The combination of maternal and paternal haplotypes and the polymorphism within MHC genes lead to a high degree of diversity in the MHC molecule repertoire across individuals.

- ✓ In summary, the MHC is a complex gene cluster on chromosome 6 that encodes molecules essential for immune function.
- ✓ Its organization into three regions and the high degree of polymorphism, combined with the inheritance of haplotypes, contribute to a diverse and crucial immune response.

Inheritance of MHC genes

MHC genes are inherited as a set, or haplotype, from each parent, resulting in individuals expressing two sets of MHC molecules.
This inheritance pattern contributes to high diversity within populations. MHC genes, located on chromosome 6, are divided into three classes: class I, class II, and class III.
Elaboration:

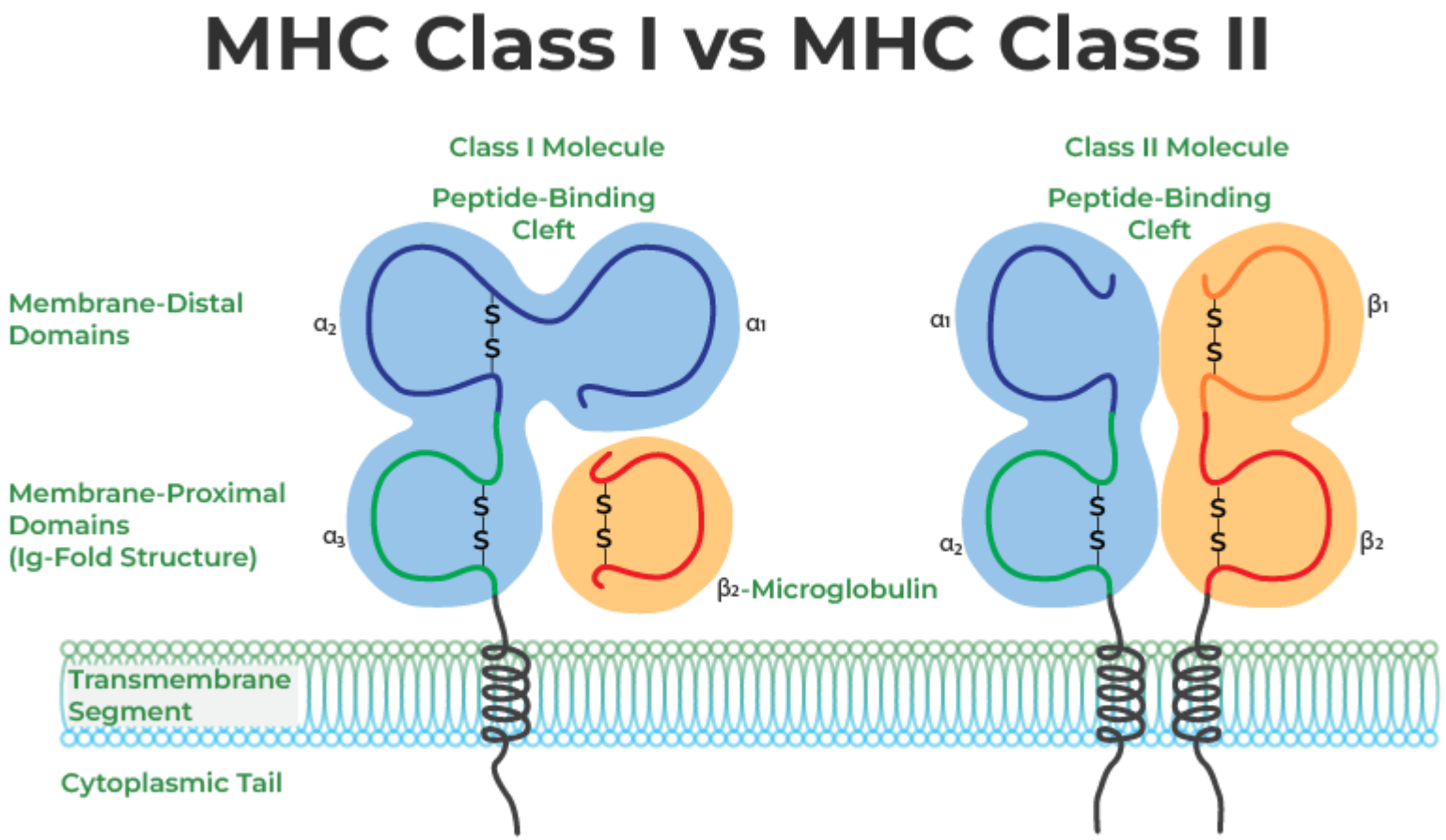
- **Haplotype Inheritance:**

Individuals inherit one haplotype from their mother and one from their father, each containing a set of closely linked MHC genes.

- **Mendelian Inheritance:**

MHC genes are inherited according to Mendelian principles, with each parent contributing one set of MHC alleles.

Structure of MHC I and II



MHC Class I:

MHC Class I:

- **Composition:**

A heavy chain (α-chain) and a beta-2 microglobulin (β2m).

- **Structure:**

The α-chain has three external domains (α1, α2, and α3), a transmembrane segment, and a cytoplasmic tail. The β2m is a non-covalently associated small protein.

- **Peptide Binding:**

The α1 and α2 domains form a groove that can accommodate peptides, typically 8-10 amino acids in length.

- **Function:**

Expressed on all nucleated cells, MHC I presents antigens derived from within the cell (e.g., viral peptides) to CD8+ T cells, initiating a cytotoxic immune response, according to microbenotes.

- **Peptide Loading:**

MHC I molecules are loaded with peptides in the endoplasmic reticulum (ER) with the help of the TAP (transporter associated with antigen processing) complex.

MHC Class II:

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- **Composition:**

An alpha chain and a beta chain.

- **Structure:**

Each chain has two external domains (α1 and α2 for the alpha chain, and β1 and β2 for the beta chain).

- **Peptide Binding:**

The peptide binding groove is formed by the α1 and β1 domains. These molecules can bind peptides that are typically 13-18 amino acids in length.

- **Function:**

Expressed on antigen-presenting cells (APCs) like dendritic cells, macrophages, and B cells, MHC II presents antigens derived from outside the cell (e.g., microbial peptides)
to CD4+ T cells, which are crucial for initiating an adaptive immune response, according to microbenotes.

- **Peptide Loading:**

MHC II molecules load peptides in endosomes and lysosomes after phagocytosis of antigens.

Comparison of **MHC Class I** and **MHC Class II** structures

Feature	**MHC Class I**	**MHC Class II**
Expressed on	All nucleated cells	Antigen-presenting cells (APCs): dendritic cells, macrophages, B cells
Peptides presented	Endogenous (intracellular, e.g., viral) peptides	Exogenous (extracellular, phagocytosed) peptides
Peptide-binding groove	Formed by α1 and α2 domains	Formed by α1 and β1 domains
Chains	One α chain (with 3 domains: α1, α2, α3) and β2-microglobulin (β2m)	Two chains: α (α1, α2) and β (β1, β2)
Peptide length	Binds peptides of 8–10 amino acids	Binds peptides of 13–25 amino acids
Anchor domains	α3 domain interacts with CD8 co-receptor	β2 domain interacts with CD4 co-receptor
Polymorphism location	Mainly in α1 and α2 domains	Mainly in α1 and β1 domains
Stabilized by	β2-microglobulin (non-covalently associated)	Non-covalently associated α and β chains
Antigen source	Cytosolic proteins (processed by proteasome)	Extracellular proteins (processed in endosomes)
Associated T cell type	$CD8^+$ cytotoxic T cells	$CD4^+$ helper T cells

Distribution of **MHC Class I** and **MHC Class II** molecules:

Feature	**MHC Class I**	**MHC Class II**
Cell types expressing	All **nucleated cells** - Epithelial cells - Endothelial cells - Fibroblasts - Hepatocytes, neurons, etc. - Also on **APCs** (e.g., macrophages, dendritic cells)	**Professional Antigen-Presenting Cells (APCs)** only: - **Dendritic cells** - **Macrophages** - **B cells**
Absent on	- **Red blood cells** (anucleate)	- Most non-immune cells (e.g., epithelial, muscle, neurons)
Constitutive expression	Yes, in almost all nucleated cells	Yes, but only in APCs
Inducible by cytokines	Upregulated by **interferon-α, -β, and -γ**	Upregulated by **interferon-γ**
Expression level	High in lymphocytes; moderate in other tissues	High in dendritic cells; moderate in macrophages and B cells

HLA expression

HLA expression refers to the presence of Human Leukocyte Antigens (HLA) on the surface of cells. HLA class I molecules are found on most nucleated cells, while HLA class II molecules are primarily expressed by antigen-presenting cells and activated T cells. This expression allows the immune system to distinguish between self and non-self cells.

HLA Class I Expression:

- **Ubiquitous:**

HLA class I molecules are expressed on almost all nucleated cells in the body, with exceptions like some cells in the central nervous system.

- **Function:**

They present peptides (fragments of proteins) from inside the cell to CD8+ T cells (killer T cells), initiating a cytotoxic response to eliminate infected or cancerous cells.

- **Examples:**

Platelets, reticulocytes, and some cancer cells can also express HLA class I.

HLA Class II Expression:

- **Antigen Presenting Cells:** HLA class II molecules are primarily found on antigen-presenting cells (APCs) such as B cells, dendritic cells, macrophages, and monocytes.
- **Function:** They present peptides from outside the cell to CD4+ T cells (helper T cells), initiating an immune response.
- **Other Cells:** Some T cells and endothelial cells can also express HLA class II.

Factors Affecting HLA Expression:

- **Genetic Polymorphism:**

Individuals have different HLA alleles, which can lead to variations in HLA expression levels and types.

- **Tissue and Cell Specificity:**

HLA expression can vary between different tissues and cell types.

- **Disease:**

In some diseases, like cancer, HLA expression can be altered, with some cancer cells losing or down-regulating HLA expression to evade immune recognition.

- **Cytokines:**

Cytokines like IFN-γ can induce or suppress HLA expression on certain cells