The HLA system (human leukocyte antigen) is a set of genes located on the short arm of chromosome 6, expressed as trans membrane glycoproteins on the surface of the body's cells. These molecules are responsible for allogeneic reactions and cellular and humoral immune responses.



Fig 12. Genes of the HLA System and Physical Map of the HLA Region

### III.1. Structure of the HLA System

From the centromere to the telomere, the locus is composed of three major regions:

- HLA Class I Region: This is the telomeric region of the chromosome where the genes B, C, and A are located. These genes encode the heavy chain of the MHC class I molecule.
- 2. HLA Class II Region: This is the centromeric region, also known as HLA DR. It is subdivided into HLA DP, HLA DQ, and HLA DR. These genes encode the  $\alpha$  and  $\beta$  chains of MHC class II molecules.
- 3. **HLA Class III Region**: This region encodes some complement proteins and certain cytokines.

# **III.2.** Key Characteristics of the MHC

- 1. **Polymorphism**: Multiple alleles exist for each locus.
- 2. **Haplotype Transmission (in blocks)**: Each individual inherits one paternal haplotype and one maternal haplotype as a complete block.

3. **Co-dominance**: All alleles are transmitted and expressed phenotypically, following Mendel's laws.

# **III.3. MHC Molecules**

### **III.3.1. MHC Class I Molecules**

These molecules are present on the surface of all body cells except neurons and red blood cells. They consist of a heavy peptide chain with three domains ( $\alpha 1$ ,  $\alpha 2$ ,  $\alpha 3$ ) non-covalently linked to an invariant chain called  $\beta 2$ -microglobulin.

The function of MHC class I molecules is to present endogenous peptides synthesized inside the cell.

MHC class I molecules are composed of four characteristic parts:

## A) The Antigenic Peptide-Binding Region (PBR):

Formed by the  $\alpha 1$  and  $\alpha 2$  domains. When folded, these domains create a single structure consisting of two elongated  $\alpha$ -helices resting on a sheet of eight antiparallel  $\beta$ -strands. This arrangement of the  $\alpha 1$  and  $\alpha 2$  domains forms a cavity where the antigenic peptide binds.

### B) The immunoglobulin-like region:

Formed by the  $\beta$ 2m and  $\alpha$ 3 domains, this region binds to CD8 expressed on the surface of cytotoxic T cells (CTLs). The binding site is located on the  $\alpha$ 3 domain.

## C) The transmembrane region:

This is a unique region, as the  $\beta 2m$  chain does not have a transmembrane segment.

## **D**) The intracytoplasmic region:

This region is also unique for the same reasons as the transmembrane region.



Fig 13. Structure of an MHC Class I Molecule

### **III.3.2. MHC Class II Molecules**

These molecules are expressed only on the surface of antigen-presenting cells (macrophages, dendritic cells, and B lymphocytes). They are composed of two chains,  $\alpha$  and  $\beta$ , each consisting of two domains.

The function of MHC class II molecules is to present peptides derived from exogenous (extracellular) antigens that have been phagocytized and fragmented within the endosomes of the antigen-presenting cell.

MHC class II molecules are composed of four characteristic parts:

### A) The Antigenic Peptide-Binding Region (PBR):

Formed by the polymorphic domains  $\alpha 1$  and  $\beta 1$ , each belonging to a different glycoprotein chain. The two domains forming the peptide-binding cavity are not joined by a covalent bond. The ends of the cavity are more open compared to those in MHC class I molecules.

### **B)** The immunoglobulin-Like region:

Formed by the  $\alpha 2$  and  $\beta 2$  domains. This region binds to CD4 on helper T cells (Th). Specifically, the external part of the  $\beta 2$  domain contains an interaction site for CD4.

#### C) The transmembrane region:

Composed of two segments, one from the  $\alpha$  chain and the other from the  $\beta$  chain.

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### D) The intracytoplasmic region:

Composed of two segments for the same reasons as the transmembrane region.



Fig 14. Structure of an MHC Class II Molecule.

### **III.4. Role of the MHC**

- Antigen presentation to Th (helper T) and T8 (cytotoxic T) lymphocytes: The MHC is responsible for activating lymphocytes and directing the immune response toward either a cellular or humoral response.
- Graft acceptance or rejection: The MHC plays a critical role in determining the acceptance or rejection of transplanted tissues.

## III.5. Other Antigen-Presenting Molecules: CD1

In addition to the classical antigen-presenting molecules (MHC class I and MHC class II), there is another family of membrane glycoproteins expressed by a limited number of cells. These include:

- Cortical thymocytes, which are often double-positive (CD4+, CD8+),
- Dendritic cells in the medullary zone,
- Langerhans cells present in the epidermis and certain other epithelia,
- A subset of B lymphocytes.

These molecules are involved in the presentation of microbial or endogenous lipid antigens to T lymphocytes. This family of molecules is known as **CD1**.