MAJOR HISTOCOMPATIBILITY COMPALEX

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Major histocompatibility complex (MHC)

- A tightly linked cluster of genes, the **major histocompatibility complex (MHC), is possessed by every mammalian species, whose** products play roles in intercellular recognition and in discrimination between self and nonself.

- The MHC participates in the development of both humoral and cellmediated immune responses.

- While antibodies or B cell receptors can recognize an antigen alone , T cell receptors recognize antigen that has been processed and presented with molecules encoded by major histocompatibility complex (MHC).

- The major histocompatibility complex is a collection of genes arrayed within a long continuous stretch of DNA on chromosome 6 in humans and on chromosome 17 in mice.

The MHC Encodes Three Major Classes of Molecules

The MHC is referred to as the **HLA complex in humans and** as the **H-2 complex in mice. Although the arrangement of** genes is somewhat different, in both cases the MHC genes are organized into regions encoding three classes of molecules:

- **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 peptide antigens to TC cells.

- **Class II MHC genes encode glycoproteins expressed** primarily on antigen-presenting cells (macrophages, dendritic cells, and B cells), where they present processed antigenic peptides to TH cells.

- **Class III MHC genes encode, in addition to other** products, various secreted proteins that have immune functions, including components of the complement system and molecules involved in inflammation.

Mouse H-2 complex

Complex	H–2						
MHC class	I	II		III		I	
Region	K	IA	IE	S		D	
Gene products	H–2K	IA αβ	IE αβ	C′ proteins	TNF-α TNF-β	H–2D	H–2L

Human HLA complex

Complex	HLA							
MHC class	II			III		I		
Region	DP	DQ	DR	C4, C2, BF		B	C	A
Gene products	DP αβ	DQ αβ	DR αβ	C′ proteins	TNF-α TNF-β	HLA-B	HLA-C	HLA-A

FIGURE Simplified organization of the major histocompatibility complex (MHC) in the mouse and human. The MHC is referred to as the H-2 complex in mice and as the HLA complex in humans. In both species the MHC is organized into a number of regions encoding class I (pink), class II (blue), and class III (green) gene products. The class I and class II gene products shown in this figure are considered to be the classical MHC molecules. The class III gene products include complement (C′) proteins and the tumor necrosis factors (TNF-α and TNF-β).

MHC Molecules

Class I and class II MHC molecules are membrane-bound glycoproteins that are closely related in both structure and function.

Both function as highly specialized antigen-presenting molecules that form unusually stable complexes with antigenic peptides, displaying them on the cell surface for recognition by T cells.

In contrast, class III MHC molecules are a group of unrelated proteins that do not share structural similarity and common function with class I and II molecules. These include complement proteins.

Class I MHC Molecule

- Class I MHC molecules contain a 45-kilodalton (kDa) α chain associated noncovalently with a 12-kDa β_2-**microglobulin** molecule.

- The α chain is a transmembrane glycoprotein encoded by polymorphic genes within the A, B, and C regions of the human HLA complex and within the K and D/L regions of the mouse H-2 complex.

- β_2-Microglobulin is a protein encoded by a highly conserved gene located on a different chromosome. Association of the α chain with β_2-microglobulin is required for expression of class I molecules on cell membranes.

- The α chain is anchored in the plasma membrane by its hydrophobic transmembrane segment and hydrophilic cytoplasmic tail.

Class I MHC Molecule

- The α chain of class I MHC molecules is organized into three external domains (α1, α2 and α3), each containing approximately 90 amino acids; a transmembrane domain of about 25 hydrophobic amino acids followed by a short stretch of charged (hydrophilic) amino acids; and a cytoplasmic anchor segment of 30 amino acids.

- β_2-Microglobulin is similar in size and organization to the α3 domain; it does not contain a transmembrane region and is noncovalently bound to the class I glycoprotein.

- Class I MHC molecule has two pairs of interacting domains: a membrane-distal pair made up of the α1 and α2 domains and a membrane-proximal pair composed of the α_3 domain and β_2-microglobulin.

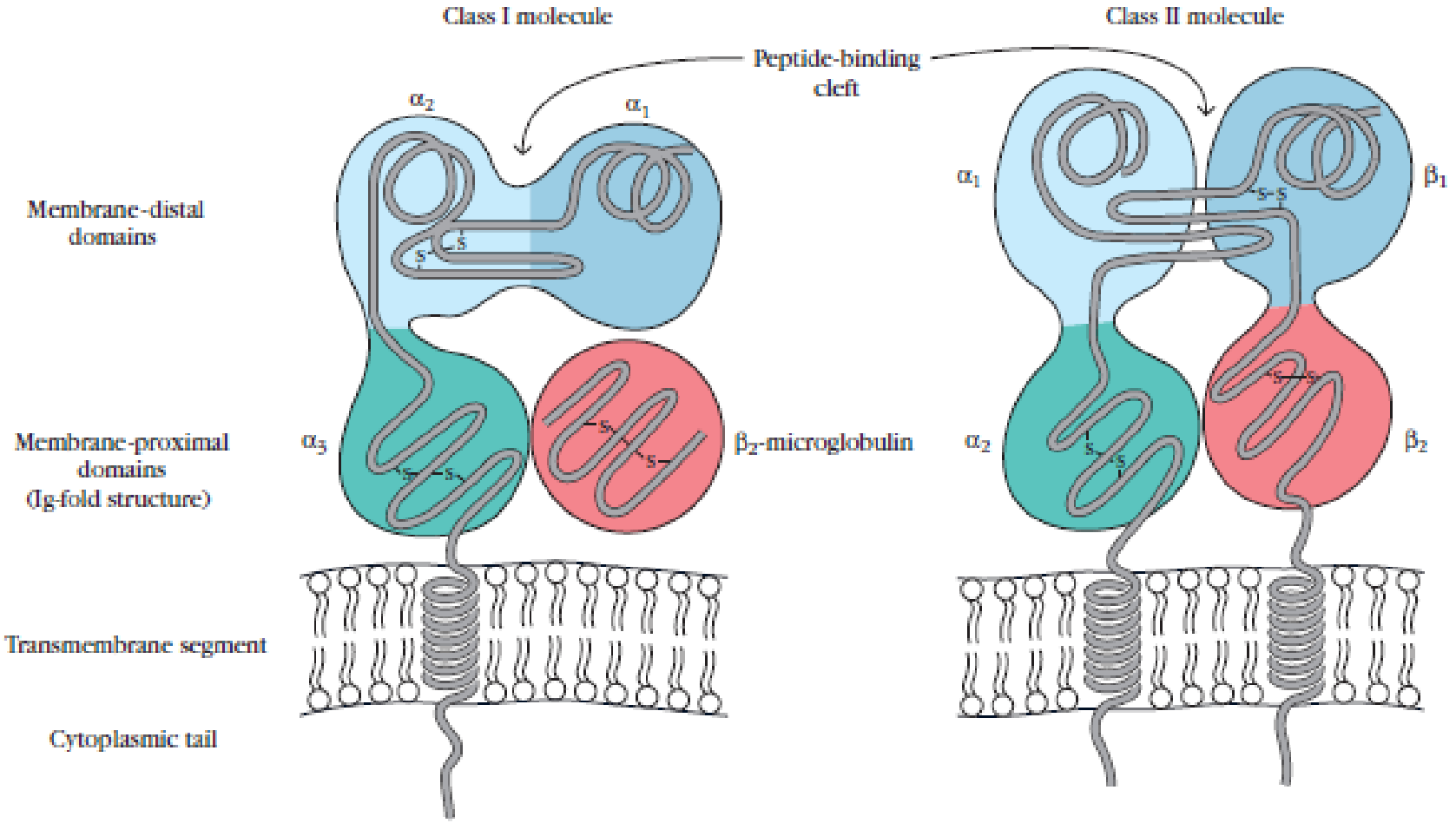

FIGURE Schematic diagrams of a class I and a class II MHC molecule showing the external domains, transmembrane segment, and cytoplasmic tail. The peptide-binding cleft is formed by the membrane-distal domains in both class I and class II molecules. The membrane-proximal domains possess the basic immunoglobulin-fold structure; thus, class I and class II MHC molecules are classified as members of the immunoglobulin superfamily.

Class I MHC Molecule

- The α1 and α2 domains interact to form a platform of eight antiparallel strands spanned by two long -helical regions. The peptide-binding cleft is located on the top surface of the class I MHC molecule, and it is large enough to bind a peptide of 8–10 amino acids.

- The α3 domain and β_2-microglobulin are organized into two pleated sheets each formed by antiparallel strands of amino acids.

Class I MHC Molecule

- The α3 domain appears to be highly conserved among class I MHC molecules and contains a sequence that interacts with the CD8 membrane molecule present on T_C cells.

- β_2-Microglobulin interacts extensively with the α3 domain and also interacts with amino acids of the α1 and α2 domains. The interaction of β_2-microglobulin and a peptide with a class I α chain is essential for the class I molecule to reach its fully folded conformation.

Class II MHC Molecule

- Class II MHC molecule contains two different polypeptide chains, a 33-kDa α chain and a 28-kDa β chain, which associate by noncovalent interactions. Like class I α chains, class II MHC molecules are membrane-bound glycoproteins that contain external domains, a transmembrane segment, and a cytoplasmic anchor segment.

- Each chain in a class II molecule contains two external domains: α1 and α2 domains in one chain and β1 and β2 domains in the other.

- The membrane-distal portion of a class II molecule is composed of the α1 and β1 domains and forms the peptide-binding cleft for processed antigen.

- The peptide-binding cleft of Class II MHC molecule is composed of a floor of eight antiparallel β strands and sides of antiparallel α helices. However, the class II molecule lacks the conserved residues that bind to the terminal residues of short peptides and forms instead an open pocket and represent open-ended groove while as class I presents more of a socket.

- The peptide-binding cleft in class I molecules is blocked at both ends, whereas the cleft is open in class II molecules. As a result of this difference, class I molecules bind peptides that typically contain 8–10 amino acid residues, while the open groove of class II molecules accommodates slightly longer peptides of 13–18 amino acids.

- Another difference is that class I binding requires that the peptide contain specific amino acid residues near the N and C termini; there is no such requirement for class II peptide binding.