Major Histocompatibility Complex(MHC)

Types & Functions

Major Histocompatibility Complex

The major histocompatibility complex (MHC) is a group of genes involved in the immunological recognition of self (the cells of an organism) and nonself (exogenous cells belonging to invading organisms, infectious diseases) in animal species

In humans these genes are called ***H*uman *L*eukocyte *A*ntigen** or **HLA** genes, as they were first discovered through antigenic differences between white blood cells from different individuals; in the mouse they are known as the **H-2 genes**.

The major histocompatibility complex is located on **chromosome 6** in humans and **chromosome 17** in the mouse and extends over 4×10^6 base pairs.

major histocompatibility complex (MHC), whose products play roles in intercellular recognition and in discrimination between self and nonself.

The MHC participates in the development of both humoral and cell mediated immune responses. While antibodies may react with antigens alone, most T cells recognize antigen only when it is combined with an MHC molecule.

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 I MHC molecules encoded by the K and D regions in mice and by the A, B, and C loci in humans

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.
The two chains of the class II MHC molecules are encoded by the IA and IE regions in mice and by the DP, DQ, and DR regions in humans.

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.

class III MHC regions, encodes molecules that are critical to immune function but have little in common with class I or II molecules.
Class III products include the complement components and inflammatory Cytokines, including tumor necrosis factor (TNF) and heat-shock proteins .

The protein products of MHC class I and class II genes are highly polymorphic

Because of the polygeny of the MHC, every person will express at least three different antigen-presenting MHC class I molecules and three (or sometimes four) MHC class II molecules on his or her cells

The term polymorphism comes from the Greek *poly*, meaning many, and *morphe*, meaning shape or structure.

There are more than 200 alleles of some human MHC class I and class II genes , each allele being present at a relatively high frequency in the population.

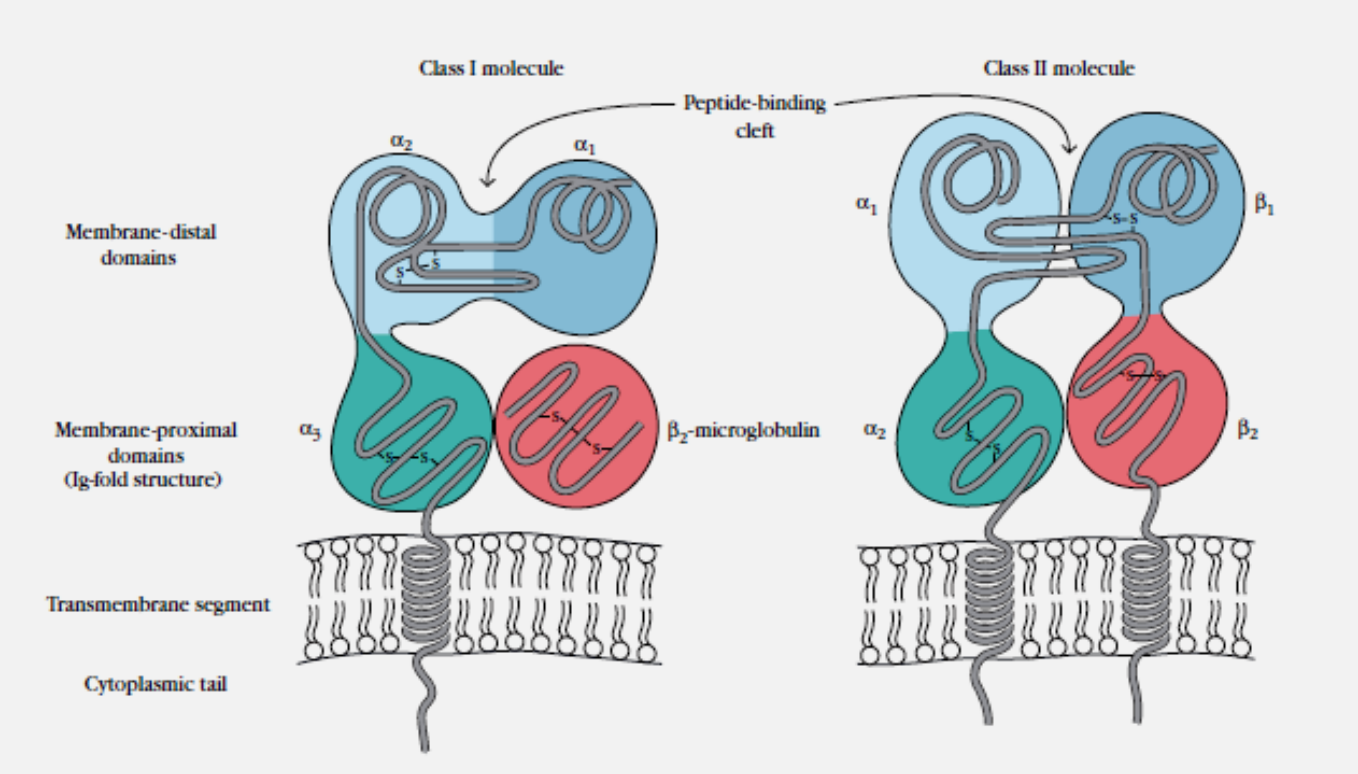
MHC genes are always codominatly expressed

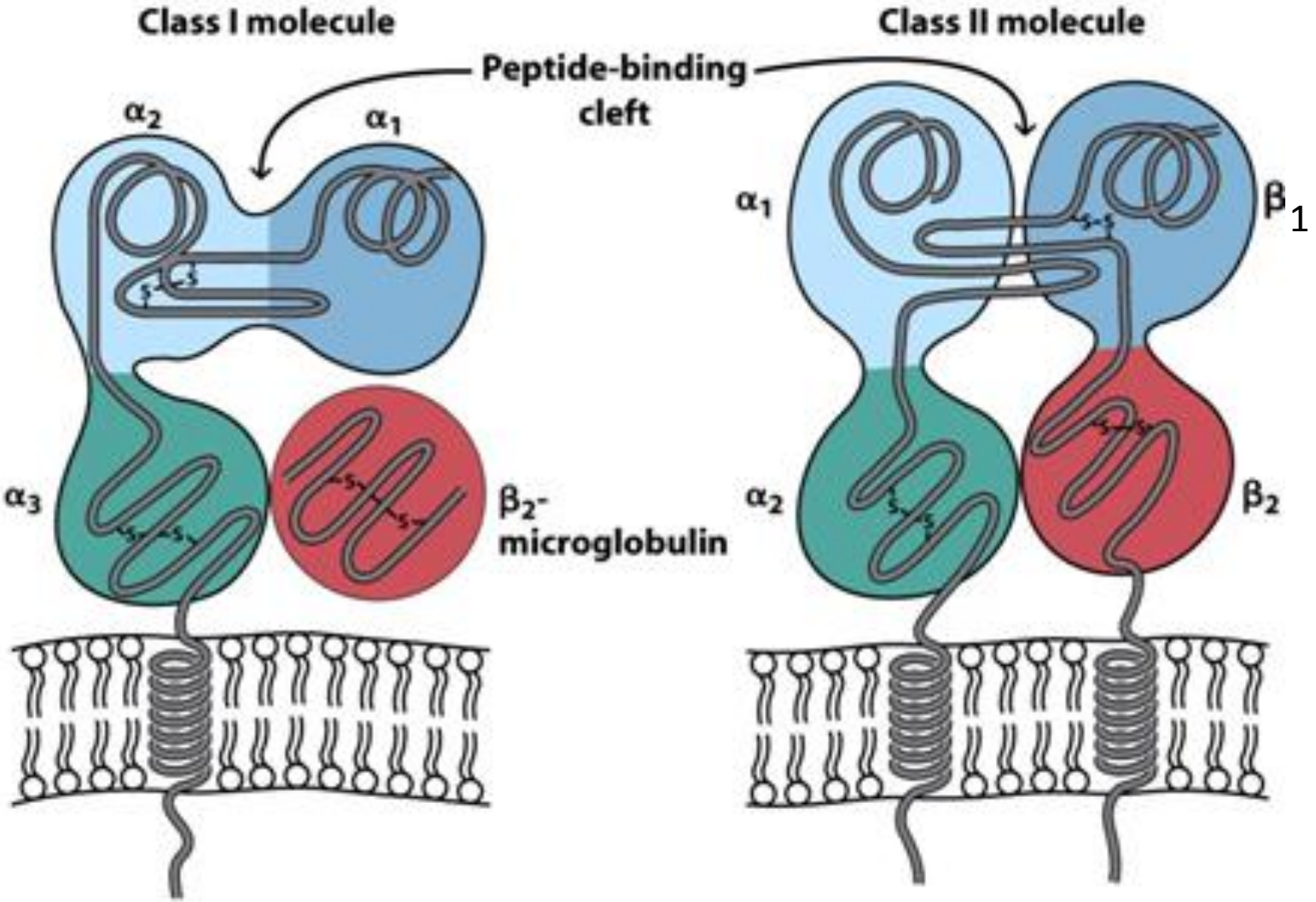
The number of different MHC molecules expressed on the cells of most people is greater because of the extreme polymorphism of the MHC and the co dominant expression of MHC gene products.

The particular combination of MHC alleles found on a single chromosome is known as an MHC haplotype. Expression of MHC alleles is codominant, with the protein products of both the alleles at a locus being expressed in the cell, and both gene products being able to present antigens to T cells

Structure of MHC

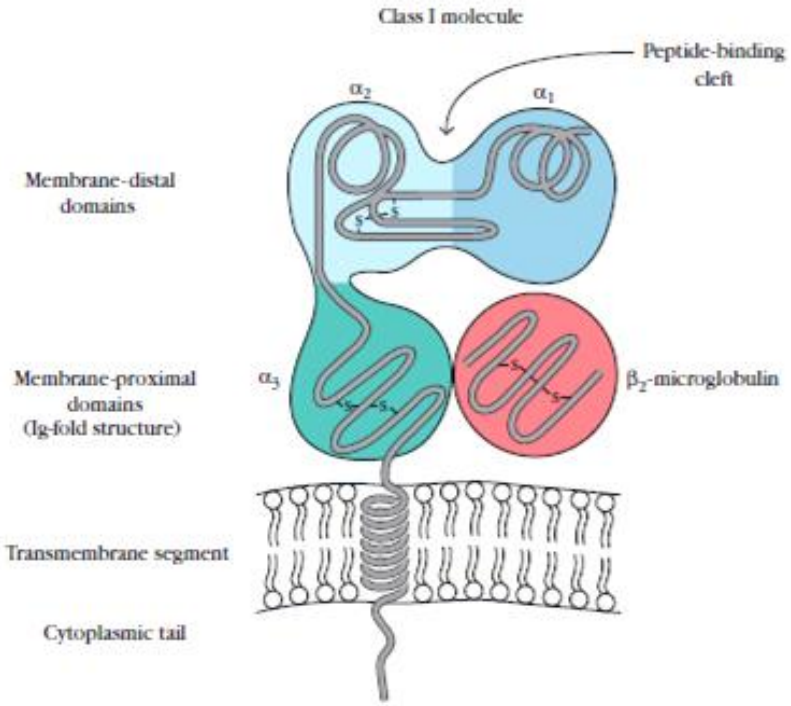
Class I and class II MHC molecules are membrane-bound glycoproteins that are closely related in both structure and function.
Both class I and class II MHC molecules have been isolated and purified and the three-dimensional structures of their extracellular domains have been determined by x-ray crystallography.




Class I molecule
Class II molecule
Peptide-binding cleft
α2
α1
α3
β2-microglobulin
α1
β1
α2
β2

MHC-I Structure

Class I MHC molecules contain a α chain (45KD) associated noncovalently with a β**2-microglobulin (12KD)** 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

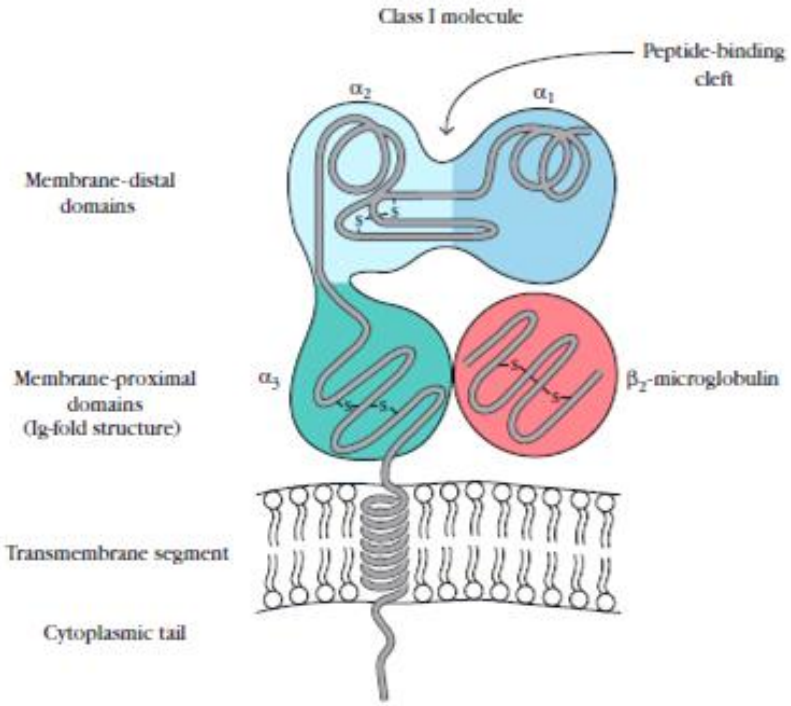
β 2-Microglobulin is a protein encoded by a highly conserved gene located on a different chromosome. Association of the α chain with β 2-microglobulin is required for expression of class I molecules on cell membranes.

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

MHC-I Structure

The α chain of class I MHC molecules is organized into **three external domains** (α1, α2, and α3), each containing approximately 90 amino acids;

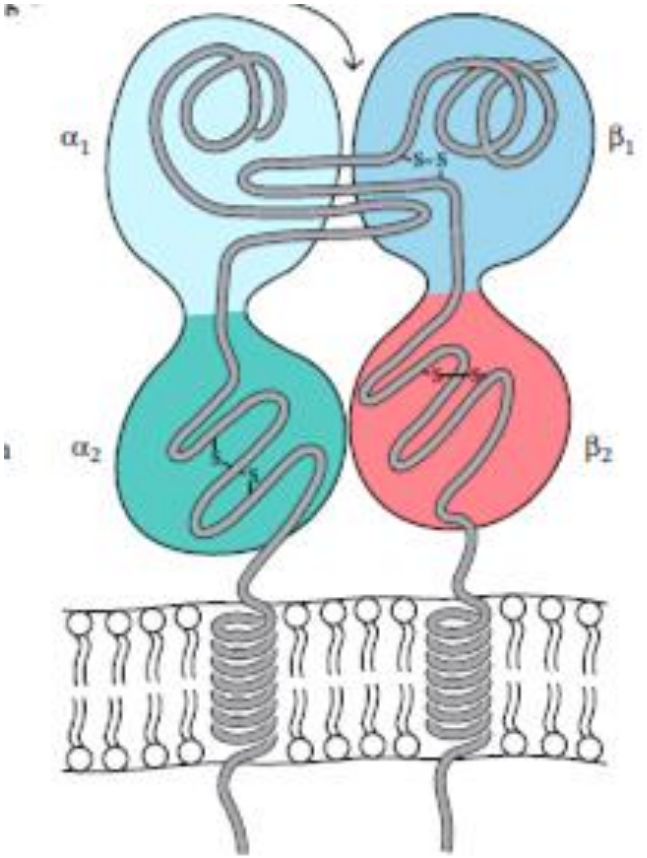
a **transmembrane domain** of about 25 hydrophobic amino acids followed by a short stretch of **charged (hydrophilic) amino acids**; and a **cytoplasmic anchor segment** of 30 amino acids.



The β 2-microglobulin is similar in size and organization to the α 3 domain; it does not contain a transmembrane region and is noncovalently bound to the class I glycoprotein.

MHC-II Structure

Class II MHC molecules contain two different polypeptide chains, a 33-kDa α chain and a 28-kDa β chain, which associate by noncovalent interactions



The 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:
α 1 and α 2 domains in one chain and β 1 and β 2 domains in the other.

The membrane-proximal α 2 and β 2 domains bear sequence similarity to the immunoglobulin-fold structure; for this reason, class II MHC molecules also are classified in the immunoglobulin superfamily.

The membrane-distal portion of a class II molecule is composed of the α 1 and β 1 domains and forms the antigenbinding cleft for processed antigen

Functions of MHC

Associated with Antigen presenting mechanism

Ability to differntiate self and non-self

Bring about defense against disease and infections

Mediate certain autoimmune diseases

. Induce the differentiation and maturation of T cell to form functional T cell repertoire

. Present antigen to initiate immune response with a phenomena known as MHC restriction

Endogenous Ag is presented to $CD8^+$ T cell by MHC class I molecule

Exogenous Ag is presented to $CD4^+$ T cell by MHC class II molecule