Organization of MHC genes and their types

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 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 (Figure 1):

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 (C4, C2, BF) and molecules involved in inflammation like tumor necrosis factor (TNF) and heat-shock proteins. Class III MHC region,which is flanked by the class I and II regions, encodes molecules that are critical to immune function but have little in common with class I or II molecules.

Inheritance of MHC genes

The loci constituting the MHC are highly **polymorphic;** that is, many alternative forms of the gene, or **alleles,** exist at each locus among the population. The genes of the MHC loci lie close together; for example, the recombination frequency within the H-2 complex is only 0.5%—crossover occurs only once in every 200 mitotic cycles. For this reason, most individuals inherit the alleles encoded by these closely linked loci as two sets, one from each parent. Each set of alleles is referred to as a **haplotype.** An individual inherits one haplotype from the mother and one haplotype from the father. In outbred populations, the offspring are generally heterozygous at many loci and will express both maternal and paternal MHC alleles. The alleles are *codominantly expressed;* that is, both maternal and paternal gene products are expressed in the same cells. If mice are inbred (that is, have identical alleles at all loci), each H-2 locus will be

homozygous because the maternal and paternal haplotypes are identical, and all offspring therefore express identical haplotypes.

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 1: 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 Structure and function:

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. Both types of membrane glycoproteins 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.

Class I Molecules Have a Glycoprotein Heavy Chain and a Small Protein Light Chain

Class I MHC molecules contain a 45-kilodalton (kDa) α chain associated noncovalently with a 12-kDa β_2 –**microglobulin** molecule (Figure 2). 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 (Figure 1). 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. Structural analyses have revealed that 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 α3 domain; it does not contain a transmembrane region and is noncovalently bound to the class I glycoprotein. Sequence data reveal homology between the α3 domain, β_2-microglobulin, and the constant-region domains in immunoglobulins. 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 α3 domain and β_2-microglobulin (Figure 2). This *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. Because of the structural similarity with the immunoglobulin constant regions, class I MHC molecules and β_2-microglobulin are classified as members of the immunoglobulin superfamily.

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 TC 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. In the absence of β_2-microglobulin, the class I MHC α chain is not expressed on the cell membrane.

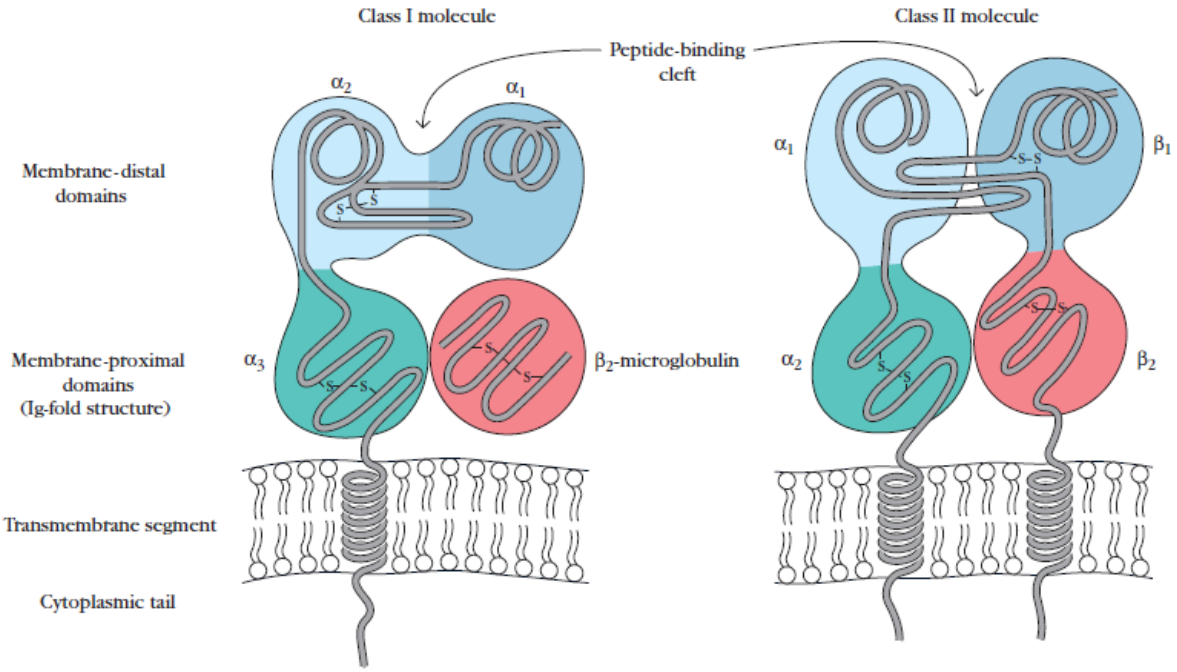

Figure 2: Schematic diagrams of a class I and a class II MHC molecule showing the external domains, transmembrane segment, and cytoplasmic tail. The peptide-binding cleft is formed by the membrane- distal domains in both class I and class II molecules. The membrane-proximal domains possess the basic immunoglobulinfold structure; thus, class I and class II MHC molecules are classified as members of the immunoglobulin superfamily

Class II Molecules Have Two Nonidentical Glycoprotein Chains

Class II MHC molecules contain two different polypeptidechains, a 33-kDa α- chain and a 28-kDa β chain, which associate by noncovalent interactions (see Figure 2b). 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-proximal α2 and β2 domains, like the membrane-proximal α3/β2-microglobulin domains of class I MHC molecules, 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 α1 and β1 domains and forms the antigen binding cleft for processed antigen. X-ray crystallographic analysis reveals the similarity of class II and class I molecules. The peptide binding cleft of HLA-DR1, like that in class I molecules, 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; class I presents more of a socket, class II an open-ended groove.

An unexpected difference between crystallized class I and class II molecules was observed for human DR1 in that the latter occurred as a dimer of αβ heterodimers, a "dimer of dimers". The dimer is oriented so that the two peptide-binding clefts face in opposite directions.

Exercise : What are the differences in structure of classI and classII MHC molecules?