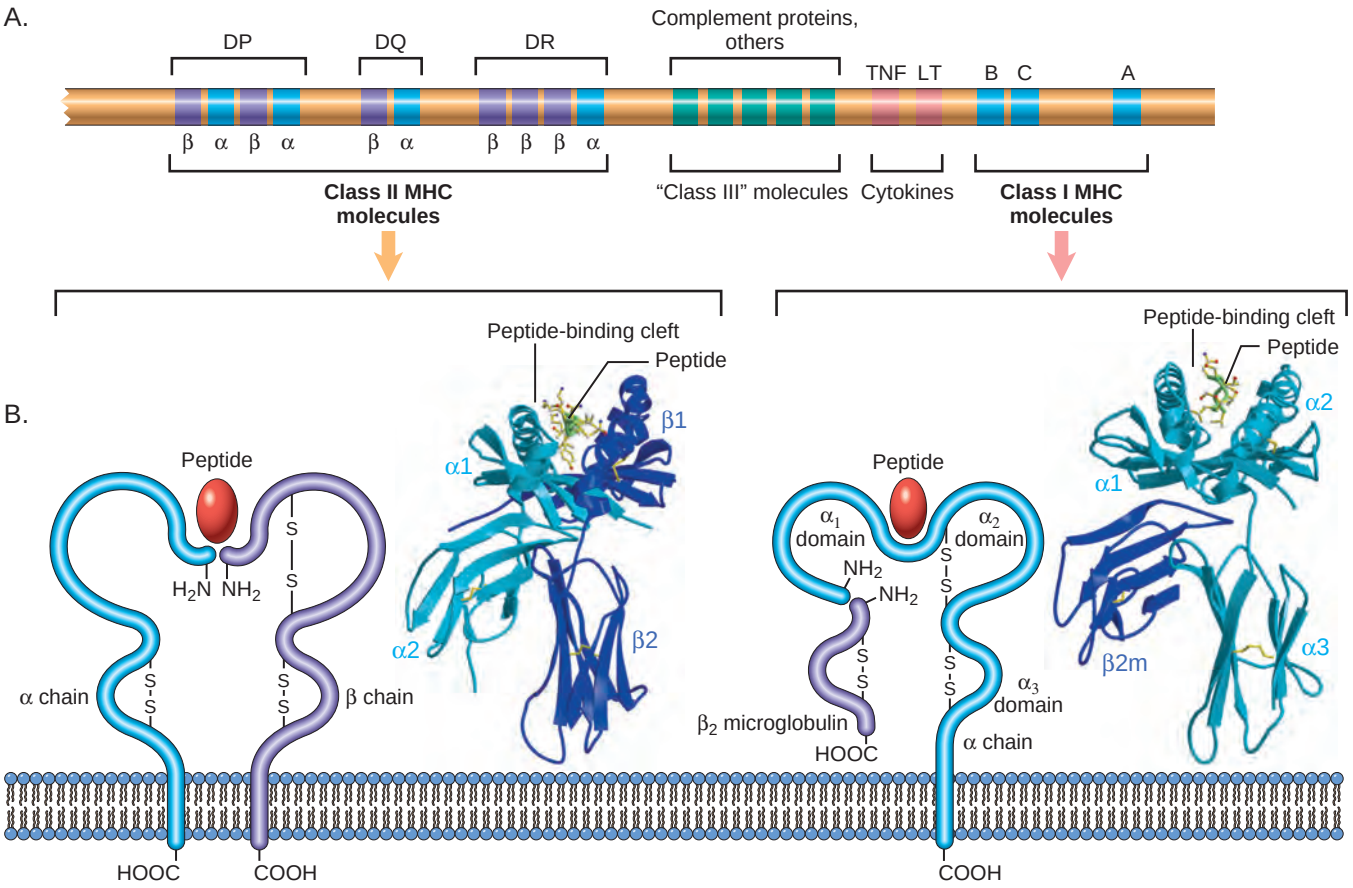

Figure 6-9 The human leukocyte antigen (HLA) complex and the structure of HLA molecules. **A,** The location of genes in the HLA complex. The relative locations, sizes, and distances between genes are not to scale. Genes that encode several proteins involved in antigen processing (the TAP transporter, components of the proteasome, and HLA-DM) are located in the class II region (not shown). **B,** Schematic diagrams and crystal structures of class I and class II HLA molecules. (Crystal structures are courtesy Dr. P. Bjorkman, California Institute of Technology, Pasadena, Calif.)

complexes are transported to the cell surface. The class II β_2 domain has a binding site for CD4, and therefore, the class II-peptide complex is recognized by CD4+ T cells, which function as helper cells. In this interaction, the CD4 molecule acts as the coreceptor. Because CD4+ T cells can recognize antigens only in the context of self class II molecules, they are referred to as *class II MHC-restricted*. In contrast to class I molecules, class II MHC molecules are mainly expressed on cells that present ingested antigens and respond to T-cell help (macrophages, B lymphocytes, and dendritic cells).

- The MHC locus also contains genes that encode some complement components and the cytokines tumor necrosis factor (TNF) and lymphotoxin, as well as some proteins that have no apparent role in the immune system.

The combination of HLA alleles in each individual is called the *HLA haplotype*. Any given individual inherits one set of HLA genes from each parent and thus typically expresses two different molecules for every locus. Because of the polymorphism of the HLA genes, virtually innumerable combinations of molecules exist in the population, and each individual expresses an MHC profile on his or her cell surface that is different from the haplotypes of most other individuals. It is believed that this polymorphism evolved to ensure that at least some individuals in a species would be able to display any microbial peptide and thus provide protection against any infection. This polymorphism also means that no two individuals (other than identical twins) are likely to express the same MHC molecules, and therefore grafts exchanged between these individuals are recognized as foreign and attacked by the immune system.

MHC molecules play several key roles in regulating T cell–mediated immune responses. First, because different antigenic peptides bind to different MHC molecules, it follows that an individual mounts an immune response against a protein antigen only if he or she inherits the genes for those MHC molecules that can bind peptides derived from the antigen and present it to T cells. The consequences of inheriting a given MHC (e.g., class II) gene depend on the nature of the antigen bound by the class II molecule. For example, if the antigen is a peptide from ragweed pollen, the individual who expresses class II molecules capable of binding the antigen would be genetically prone to allergic reactions against pollen. In contrast, an inherited capacity to bind a bacterial peptide may provide resistance to the infection by evoking a protective antibody response. Second, by segregating cytoplasmic and internalized antigens, MHC molecules ensure that the correct immune response is mounted against different microbes—CTL-mediated killing of cells harboring cytoplasmic microbes, and helper T cell–mediated antibody and macrophage activation to combat extracellular microbes.