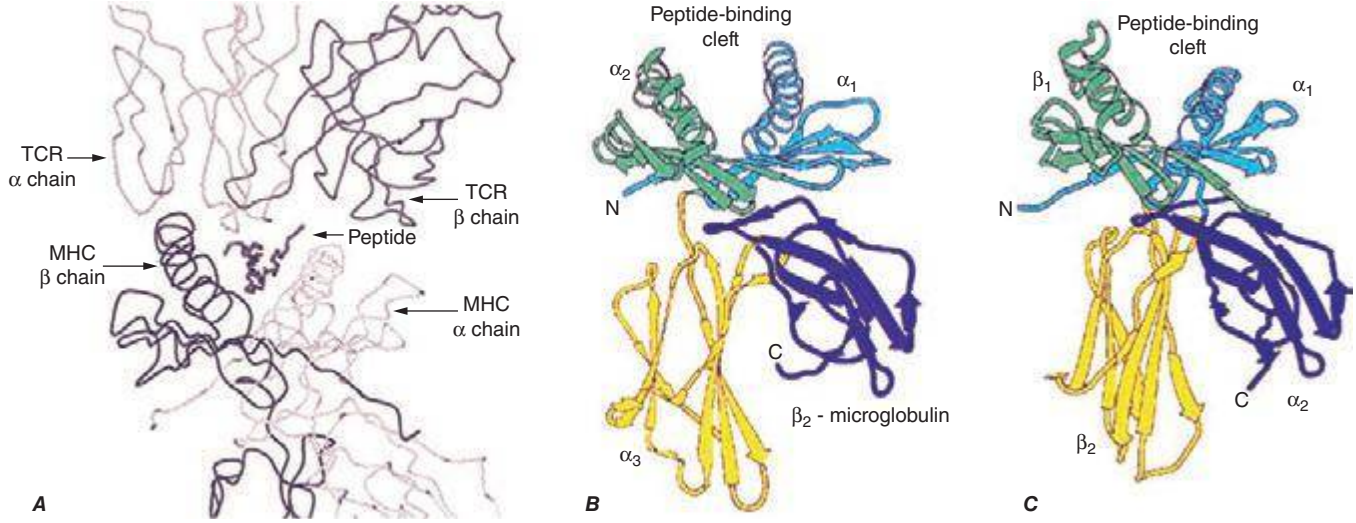

FIGURE 373e-2 ***A.*** The trimolecular complex of TCR (*top*), MHC molecule (*bottom*), and a bound peptide form the structural determinants of specific antigen recognition. Other panels (***B*** and ***C***) show the domain structure of MHC class I (***B***) and class II (***C***) molecules. The α_1 and α_2 domains of class I and the α_1 and β_1 domains of class II form a β-sheet platform that forms the floor of the peptide-binding groove, and α helices that form the sides of the groove. The α_3 (***B***) and β_2 domains (***C***) project from the cell surface and form the contact sites for CD8 and CD4, respectively. *(Adapted from EL Reinherz et al: Science 286:1913, 1999; and C Janeway et al: Immunobiology Bookshelf, 2nd ed. Garland Publishing, New York, 1997; with permission.)*

Those on chromosome 6p21 include MIC-A and MIC-B, which are encoded centromeric to HLA-B, and HLA-HFE, located 3 to 4 cM (centi-Morgan) telomeric of HLA-F. MIC-A and MIC-B do not bind peptide but are expressed on gut and other epithelium in a stress-inducible manner and serve as activation signals for certain γδ T cells, NK cells, CD8 T cells, and activated macrophages, acting through the activating NKG2D receptors. Ninety-one MIC-A and 40 MIC-B alleles are known, and additional diversification comes from variable alanine repeat sequences in the transmembrane domain. Due to this structural diversity, MIC-A can be recognized as a foreign tissue target during organ transplantation, contributing to graft failure. HLA-HFE encodes the gene defective in hereditary hemochromatosis **(Chap. 428)**. Among the non-HLA, class I–like genes, CD1 refers to a family of molecules that present glycolipids or other nonpeptide ligands to certain T cells, including T cells with NK activity; FcRn binds IgG within lysosomes and protects it from catabolism **(Chap. 372e)**; and Zn-α_2-glycoprotein 1 binds a nonpeptide ligand and promotes catabolism of triglycerides in adipose tissue. Like the HLA-A, -B, -C, -E, -F, and -G heavy chains, each of which forms a heterodimer with β2-microglobulin (Fig. 373e-2), the class I–like molecules, HLA-HFE, FcRn, and CD1 also bind to β_2-microglobulin, but MIC-A, MIC-B, and Zn-α_2-glycoprotein 1 do not.

The HLA class II region is also illustrated in Fig. 373e-1. Multiple class II genes are arrayed within the centromeric 1 Mb of the HLA region, forming distinct haplotypes. A *haplotype* refers to an array of alleles at polymorphic loci along a chromosomal segment. Multiple class II genes are present on a single haplotype, clustered into three major subregions: HLA-DR, -DQ, and -DP. Each of these subregions contains at least one functional alpha (A) locus and one functional beta (B) locus. Together these encode proteins that form the α and β polypeptide chains of a mature class II HLA molecule. Thus, the DRA and DRB genes encode an HLA-DR molecule; DQA and DQB genes encode HLA-DQ molecules; and DPA and DPB genes encode HLA-DP molecules. There are several DRB genes (*DRB1*, *DRB2*, *DRB3*, etc.), so that two expressed DR molecules are encoded on most haplotypes by combining the α-chain product of the DRA gene with separate β chains. More than 1000 alleles have been identified at the HLA-DRB1 locus, with most of the variation occurring within limited segments encoding residues that interact with antigens. Detailed analysis of sequences and population distribution of these alleles strongly suggest that this diversity is actively selected by environmental pressures associated with pathogen diversity. In the DQ region, both DQA1 and DQB1 are polymorphic, with 50 DQA1 alleles and over 300 DQB1 alleles. The current nomenclature is largely analogous to that discussed above for class I, using the convention "locus * allele."

In addition to allelic polymorphism, products of different DQA alleles can, with some limitations, pair with products of different DQB alleles through both *cis* and *trans* pairing to create combinatorial complexity and expand the number of expressed class II molecules. Because of the enormous allelic diversity in the general population, most individuals are heterozygous at all of the class I and class II loci. Thus, most individuals express six classic class I molecules (two each of HLA-A, -B, and -C) and many class II molecules—two DP, two to four DR, and multiple DQ (both *cis* and *trans* dimers).

OTHER GENES IN THE MHC

In addition to the class I and class II genes themselves, there are numerous genes interspersed among the HLA loci that have interesting and important immunologic functions. Our current concept of the function of MHC genes now encompasses many of these additional genes, some of which are also highly polymorphic. Indeed, direct comparison of the complete DNA sequences for eight of the entire 4-Mb MHC regions from different haplotypes show >44,000 nucleotide variations, encoding an extremely high potential for biologic diversity, and at least 97 genes located in this region are known to have coding region sequence variation. Specific examples include the TAP and LMP genes, as discussed in more detail below, which encode molecules that participate in intermediate steps in the HLA class I biosynthetic pathway. Another set of HLA genes, DMA and DMB, perform an analogous function for the class II pathway. These genes encode an intracellular molecule that facilitates the proper complexing of HLA class II molecules with antigen (see below). The *HLA class III region* is a name given to a cluster of genes between the class I and class II complexes, which includes genes for the two closely related cytokines tumor necrosis factor (TNF)-α and lymphotoxin (TNF-β); the complement components C2, C4, and Bf; heat shock protein (HSP) 70; and the enzyme 21-hydroxylase.

The class I genes HLA-A, -B, and -C are expressed in all nucleated cells, although generally to a higher degree on leukocytes than on nonleukocytes. In contrast, the class II genes show a more restricted distribution: HLA-DR and HLA-DP genes are constitutively expressed on most cells of the myeloid cell lineage, whereas all three class II gene families (HLA-DR, -DQ, and -DP) are inducible by certain stimuli provided by inflammatory cytokines such as interferon γ. Within the