respond to antigens that enter through breaches in the epithelium. Pharyngeal tonsils and Peyer's patches of the intestine are two anatomically defined mucosal lymphoid tissues. At any time, more than half the body's lymphocytes are in the mucosal tissues (reflecting the large size of these tissues), and many of these are memory cells.

Within the peripheral lymphoid organs, T lymphocytes and B lymphocytes are segregated into different regions (Fig. 6-8). In lymph nodes the B cells are concentrated in discrete structures, called *follicles*, located around the periphery, or cortex, of each node. If the B cells in a follicle have recently responded to an antigen, this follicle may contain a central region called a *germinal center*. The T lymphocytes are concentrated in the paracortex, adjacent to the follicles. The follicles contain the follicular dendritic cells that are involved in the activation of B cells, and the paracortex contains the dendritic cells that present antigens to T lymphocytes. In the spleen, T lymphocytes are concentrated in periarteriolar lymphoid sheaths surrounding small arterioles, and B cells reside in the follicles.

Lymphocyte Recirculation

Lymphocytes constantly recirculate between tissues and home to particular sites; naive lymphocytes traverse the peripheral lymphoid organs where immune responses are initiated, and effector lymphocytes migrate to sites of infection and inflammation. This process of lymphocyte recirculation is most important for T cells, because naïve T cells have to circulate through the peripheral lymphoid organs where antigens are concentrated and effector T cells have to locate and eliminate microbes at any site of infection. In contrast, plasma cells remain in lymphoid organs and the bone marrow and do not need to migrate to sites of infection because they secrete antibodies that are carried to distant tissues.

Major Histocompatibility Complex (MHC) Molecules: The Peptide Display System of Adaptive Immunity

The function of MHC molecules is to display peptide fragments of protein antigens for recognition by antigen-specific T cells. Because MHC molecules are fundamental to the recognition of antigens by T cells and are linked to many autoimmune diseases, it is important to briefly review the structure and function of these molecules. MHC molecules were discovered as products of genes that evoke rejection of transplanted organs, and their name derives from their role in determining tissue compatibility between individuals. In humans the MHC molecules are called *human leukocyte antigens* (HLA) because they were initially detected on leukocytes by the binding of antibodies. The genes encoding HLA molecules are clustered on a small segment of chromosome 6 (Fig. 6-9). The HLA system is highly polymorphic, meaning that there are many alleles of MHC genes (in the thousands) in humans and each individual's HLA alleles differ from those inherited by most other individuals in the population. This, as we see subsequently, constitutes a formidable barrier in organ transplantation.

On the basis of their structure, cellular distribution and function, MHC gene products are classified into two major classes.

- *Class I MHC molecules* are expressed on all nucleated cells and platelets. They are heterodimers consisting of a polymorphic α, or heavy, chain (44-kD) linked noncovalently to a smaller (12-kD) nonpolymorphic protein called β_2-microglobulin. The α chains are encoded by three genes, designated *HLA-A*, *HLA-B*, and *HLA-C*, that lie close to one another in the MHC locus (Fig. 6-9). The extracellular region of the α chain is divided into three domains: α_1, α_2, and α_3. The α_1 and α_2 domains form a cleft, or groove, where peptides bind. The polymorphic amino acid residues line the sides and the base of the peptide-binding groove, explaining why different class I alleles bind different peptides.

  Class I MHC molecules display peptides that are derived from proteins, such as viral and tumor antigens, that are located in the cytoplasm and usually produced in the cell, and class I–associated peptides are recognized by CD8+ T lymphocytes. Cytoplasmic proteins are degraded in proteasomes and peptides are transported into the endoplasmic reticulum (ER) where the peptides bind to newly synthesized class I molecules. Peptide-loaded MHC molecules associate with β_2-microglobulin to form a stable trimer that is transported to the cell surface. The nonpolymorphic α_3 domain of class I MHC molecules has a binding site for CD8, and therefore the peptide-class I complexes are recognized by CD8+ T cells, which function as CTLs. In this interaction, the TCR recognizes the MHC-peptide complex, and the CD8 molecule, acting as a coreceptor, binds to the class I heavy chain. Since CD8+ T cells recognize peptides only if presented as a complex with class I MHC molecules, CD8+ T cells are said to be *class I MHC-restricted*. Because one of the important functions of CD8+ CTLs is to eliminate viruses, which may infect any nucleated cell, and tumors, which may arise from any nucleated cell, it makes good sense that all nucleated cells express class I HLA molecules and can be surveyed by CD8+ T cells.
- *Class II MHC molecule*s are encoded in a region called *HLA-D*, which has three subregions: *HLA-DP*, *HLA-DQ*, and *HLA-DR*. Each class II molecule is a heterodimer consisting of a noncovalently associated α chain and β chain, both of which are polymorphic. The extracellular portions of the α and β chains both have two domains designated α_1 and α_2, and β_1 and β_2. Crystal structure of class II molecules has revealed that, similar to class I molecules, they have peptide-binding clefts facing outward (Fig. 6-9). This cleft is formed by an interaction of the α_1 and β_1 domains, and it is in this portion that most class II alleles differ. Thus, as with class I molecules, polymorphism of class II molecules is associated with differential binding of antigenic peptides.

  Class II MHC molecules present antigens that are internalized into vesicles, and are typically derived from extracellular microbes and soluble proteins. The internalized proteins are proteolytically digested in endosomes or lysosomes. Peptides resulting from proteolytic cleavage then associate with class II heterodimers in the vesicles, and the stable peptide-MHC