

# The Biology of the Immune System

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Intact immunity is fundamental for survival. The human immune system has evolved with the sophisticated biologic capacity to distinguish self from nonself and for memory through the process of clonal expansion. The ability to distinguish even subtle differences from self, and among myriad antigens, is possible by the rearrangement of genes that encode immunoglobulins and T-cell receptors, as well as by the requirement for T cells to recognize antigens in the context of presentation by HLA molecules encoded within the major histocompatibility complex. Modulation of immune function initiated by antigenic stimulation and cell-cell interactions is facilitated by a plethora of soluble mediators such as cytokines. This overview of the biology of the immune system provides a framework for understanding physiologic immune responses and how lacunar defects within the immune system explain the pathogenesis of immunologic disorders. Through such understanding, potential targets can be identified for therapeutic modulation of the immune system.

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THE RAISON D'ÊTRE of the immune system is to distinguish self from nonself and thereby enable survival in a hostile environment. The ontogeny of this host defense system begins during the first month of gestation with hematopoietic stem cells located in the yolk sac.<sup>1</sup> By the third month of gestation, hematopoiesis occurs predominantly in the liver until the skeletal elements are formed. Thereafter, bone marrow is the major site of hematopoiesis. The hematopoietic stem cells differentiate into granulocytes, monocytes, and lymphocytes, as well as megakaryocytes and erythrocytes (Figure 1-1). Beginning 2 months into gestation, lymphocytes destined to become T cells emigrate from the bone marrow into the developing thymus for their further maturation. The maturation of B lymphocytes occurs in bone marrow under the influence of the stromal reticular cells. By birth, the immune system has developed into a sophisticated network, connecting central locations of immune cell production with peripheral tissues for immune surveillance. These peripheral components of the immune system include the blood, thymus, lymphatic system, spleen, skin, and mucosa. Host defense is the culmination of elegantly orchestrated cellular and molecular interactions within the immune system and between the immune system and the rest of the body. The following overview of this complex subject was synthesized from articles available through the MEDLINE database and textbooks. References selected for this article were

chosen for their scientific impact in immunology and their clarity, and are but a sample of the relevant literature.

## DISCRIMINATION OF SELF FROM NONSELF

Survival requires both the ability to mount a destructive immune response against nonself and the inability to mount a destructive immune response against self. The inability to react to self is known as *tolerance*. Tolerance implies that host lymphocytes are not activated by interaction with self tissues. The inability to pathologically respond to self that is acquired during B-cell or T-cell ontogeny is known as central tolerance. The inability of mature T cells and B cells to pathologically respond to self is known as peripheral tolerance. Accordingly, autoimmunity defines a state in which tolerance to self is lost.<sup>3</sup> If such activation by self occurs with sufficient magnitude and for sufficient duration, then host tissue damage occurs. However, not all autoimmune responses are harmful. For example, T cells recognize antigen in the context of also recognizing self major histocompatibility complex (MHC) molecules.<sup>4</sup> Likewise, antibody specificity for autologous immunoglobulins (Ig) is one component of immunoregulation known as the anti-idiotypic network.<sup>5</sup> Pathologic immune responses may also be the consequence of a bystander effect from a physiologic protective immune response. Balanced between tolerance and immunity is survival.

## INNATE AND ADAPTIVE IMMUNITY

Antigen-nonspecific defense mechanisms that are used by the host immediately or within several hours of encountering antigen are referred to as *innate immunity*.<sup>6</sup> These include physical barriers, such as epithelium, fatty acids, mucus, and cilia; soluble factors, such as proteins of the complement cascade, chemokines (that induce leukocyte migration), and cytokines (that modulate leukocyte function); and leukocytes other than T cells and B cells. These innate immune responses are activated in response to inherent or elaborated chemical properties of the insulting agent.

Antigen-specific defense mechanisms are dependent on adaptive immunity anchored by T cells and B cells.<sup>6,7</sup> Initiation of adaptive immune responses requires antigen processing, recognition of antigenic epitopes by T cells and B cells, and clonal expansion and differentiation of these antigen-specific lymphocytes into effectors.<sup>8</sup> The potential repertoire for antigen-specific receptors expressed on T cells and B cells is the result of random rearrangement of the genes encoding the T-cell receptor (TCR) and Ig, respectively.<sup>9,10</sup> The capacity for Ig genes to undergo somatic mutation further enhances the fine specificity and affinity of antibodies. However, TCR genes do not undergo somatic mutation since their specificity, selected for during thymic ontogeny, must be retained for maintenance of self-nonsel discrimination. Another hallmark of adaptive immunity is the capacity for memory, which enables the host to mount a more rapid immune response on reexposure to the same antigen. The central principle of adaptive immunity and the basis for immunologic memory is the antigen-driven clonal expansion of T cells and B cells.

Innate and adaptive immunity are not mutually exclusive mechanisms of host defense. Rather, they are complementary,<sup>6</sup> with lacunar defects in either system resulting in host vulnerability. The interplay of innate and adaptive immunity is exemplified by Ig activation of complement via the classic pathway and by the elaboration from phagocytic leukocytes of chemokines and cytokines that attract and modulate T-cell and B-cell activation and function.

## LEUKOCYTE POPULATIONS

The leukocyte constituents of the immune system include granulocytes, specialized antigen-presenting cells, and lymphocytes.<sup>11</sup> A number of phenotypic markers are used to characterize and distinguish leukocyte subsets and functions. The International Workshop on Human Leukocyte Differentiation Antigens provides oversight for assignment of leukocyte differentiation antigens with a cluster of differentiation (CD) number.<sup>12</sup> Designated CD molecules now total 166, and current updates are available on the World Wide Web at <http://www.ncbi.nlm.nih.gov/prov>.

Granulocytes include neutrophils, eosinophils, basophils, and mast cells. Neutrophils, monocytes, and macrophages are important effectors for phagocytic destruction of antigens targeted by antibody and complement and predominate in acute inflammatory responses, especially against extracellular bacteria and in immune complex-mediated diseases. Eosinophils are specialized for destruction of helminths and other parasites and participate in late-phase allergic inflammation. Basophils and mast cells are distinct lineages that both express cell surface high-affinity receptors for IgE (FcεR1) and serve a central role in immediate hypersensitivity immune responses.

Leukocytes specialized for processing and presenting antigen for adaptive immune responses include monocytes, macrophages, Langerhans cells, Kupffer cells, and dendritic cells.<sup>13</sup> All these cell populations express both class I and class II MHC molecules for use in displaying antigen processed through alternative intracellular mechanisms for recognition by TCR.<sup>8,14</sup> Macrophages and monocytes participate in inflammatory and often granulomatous immune responses throughout the body, while Langerhans cells and Kupffer cells process antigen encountered in the skin and liver, respectively. Dendritic cells reside predominantly within the lymphoid tissues and are the most potent antigen-presenting cells. B cells also have the potential to process and display antigen in the context of MHC molecules following internalization of antigen engaged by their membrane Ig.

Lymphocytes consist of 3 major populations: T cells, B cells, and natural killer cells.<sup>1</sup> T cells are phenotypically defined by their cell surface expression of a transmembrane heterodimeric receptor, known as the TCR, that binds antigen properly displayed by antigen-presenting cells.<sup>8,9,14</sup> B cells are phenotypically defined by their cell surface expression of transmembrane Ig that can bind unprocessed antigen independent of antigen-

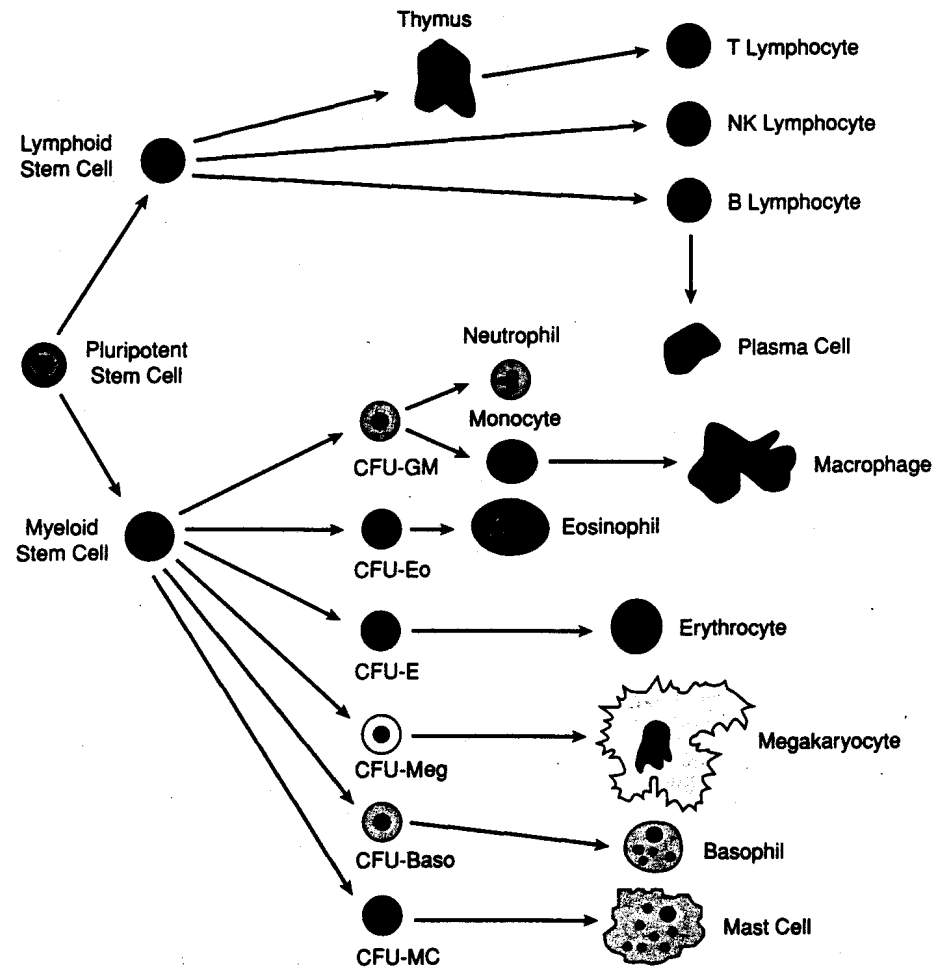


Figure 1-1.—Differentiation of hematopoietic stem cells. Pluripotent stem cells differentiate into lymphoid stem cells or myeloid stem cells. T, natural killer (NK), and B lymphocytes are derived from lymphoid stem cells. Myeloid stem cells differentiate into lineage-specific precursors that are colony-forming units (CFUs). Neutrophils, monocytes, and macrophages differentiate from a common granulocyte monocyte CFU (CFU-GM). Eosinophils (Eo), basophils (Baso), and mast cells (MC) differentiate from distinct CFUs, as do the nonleukocyte hematopoietic cells, megakaryocytes (Meg) and erythrocytes (E). Modified with permission from Nelson.<sup>2</sup>

presenting cells.<sup>10</sup> T-cell receptors and Ig are the products of rearranging genes and are unique to T cells and B cells, respectively, and provide specificity for antigen recognition.<sup>9,10</sup> Natural killer cells are morphologically large granular lymphocytes and are phenotypically defined by the absence of either transmembrane cell surface TCR or Ig and the presence of the cell surface molecules CD16 (FcγRIII, the receptor for the Fc region of secreted IgG) and CD56 (the neural cell adhesion molecule-1).<sup>15</sup> T cells and B cells are responsible for clonally specific immune responses, while natural killer cells provide innate cytotoxic immune responses directed against virus-infected cells and tumor cells. Natural killer cells also cooperate with adaptive immune responses through Fc-bound IgG and the production of cytokines.<sup>6</sup>

### MHC AND ANTIGEN PRESENTATION

The MHC encodes the human leukocyte antigens (HLA), which are the molecular basis for T-cell discrimination of

self from nonself. Structurally, there are 2 classes of HLA molecules (Figure 1-2). Class I HLA molecules are cell surface heterodimeric structures. The α chain is a 44-kd, highly polymorphic glycoprotein encoded within the MHC on chromosome 6. This α chain noncovalently associates with β<sub>2</sub>-microglobulin, a 12-kd, nonpolymorphic glycoprotein encoded by a non-HLA gene on chromosome 15.<sup>17</sup> Class II HLA molecules are also cell surface heterodimeric structures, composed of 34-kd α chains and 29-kd β chains, both of which are encoded within the MHC.<sup>18</sup> The conformation of class I and class II HLA molecules provides each with a groove in which linear peptides, 8 to 25 amino acids in length, are displayed for recognition by the TCR.<sup>16</sup> The TCR recognizes a composite of the antigen and the HLA molecule, and is referred to as recognizing the antigen in the context of self.

### Class I HLA Molecules

There are 3 major class I genes, designated *HLA-A*, *-B*, or *-C*. More than 50 al-

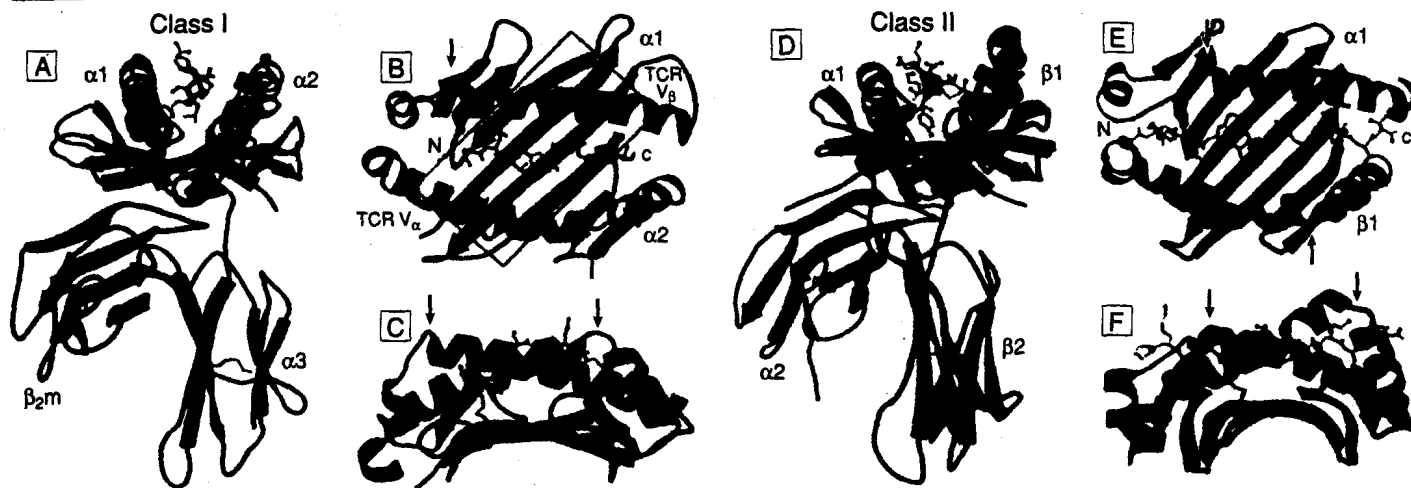


Figure 1-2.—Structure of HLA molecules. Class I HLA molecule (A: side view of  $\alpha 1$ ,  $\alpha 2$ , and  $\alpha 3$  domains in noncovalent association with  $\beta_2$ -microglobulin [ $\beta_2m$ ]; an endogenously derived linear peptide antigen [yellow] is displayed in the groove formed by the  $\alpha 1$  and  $\alpha 2$  domains for recognition by the T-cell receptor [TCR] of an antigen-specific  $CD8^+$  T cell; B: top view of  $\alpha 1$  and  $\alpha 2$  domains; the region of the class I HLA molecule recognized in conjunction with the linear antigenic peptide by the TCR  $V_\alpha$  and  $V_\beta$  chains is outlined by the rectangle; C: lateral view of  $\alpha 1$  and  $\alpha 2$  domains). Class II HLA molecule (D: side view of  $\alpha 1$ ,  $\alpha 2$ ,  $\beta 1$ , and  $\beta 2$  domains; the exogenously derived linear peptide antigen is displayed in the groove formed by the  $\alpha 1$  and  $\beta 1$  domains for recognition by an antigen-specific  $CD4^+$  T cell; E: top view of  $\alpha 1$  and  $\beta 1$  domains, which contain a linear peptide in the antigen-binding groove; F: lateral view of  $\alpha 1$  and  $\beta 1$  domains). Arrows in B, C, E, and F indicate high points on the topography of the HLA molecules that are likely to be important for engagement with the TCR. Modified with permission from Bjorkman.<sup>16</sup>

leles have been defined for the *HLA-A* gene, more than 75 alleles have been defined for the *HLA-B* gene, and more than 30 alleles have been defined for the *HLA-C* gene.<sup>19</sup> Assuming a different allele for each gene pair, an individual will express 2 *HLA-A*, 2 *HLA-B*, and 2 *HLA-C* molecules, for a total of 6 distinct class I HLA molecules (Figure 1-3). The antigen-binding groove in each of these class I HLA molecules can accommodate a large array of antigenic peptides, each of which fits into the antigen-binding groove in a unique configuration.<sup>16,17</sup>

Virtually all nucleated cells of the body display transmembrane class I HLA molecules in association with the nontransmembrane  $\beta_2$ -microglobulin molecule. The extracellular region of each *HLA-A*, *-B*, or *-C* molecule has 3 domains, designated  $\alpha 1$ ,  $\alpha 2$ , and  $\alpha 3$ .<sup>20,21</sup> The antigen-binding groove is formed by the  $\alpha 1$  and  $\alpha 2$  domains. Residues in the  $\alpha 3$  domain interact with  $CD8$  molecules, thereby restricting TCR recognition of antigen displayed in the context of autologous class I HLA molecules to  $CD8^+$  T cells.<sup>22</sup>

Antigenic peptides displayed in the groove of class I HLA molecules are hydrolyzed from proteins synthesized within antigen-presenting cells and are therefore referred to as endogenous antigens (Figure 1-4).<sup>8,13,14,23</sup> The hydrolyzed peptides complex in the cytoplasm with transport-associated proteins that direct the peptides to the endoplasmic reticulum. There they are loaded into the binding groove of class I HLA molecules and transported through the Golgi apparatus into exocytotic vesicles for cell surface expression. Endogenous synthesis of pro-

teins indicates the intracellular presence of the genes encoding them. This is consistent with the specificity of  $CD8^+$  T cells for viruses, intracellular bacteria, and tumor antigens. An exception to  $CD8^+$  T-cell recognition of antigens presented only in the context of autologous class I HLA molecules is the ability of host  $CD8^+$  T cells to directly recognize donor class I HLA molecules during allograft rejection. In these allogeneic responses, the TCR is thought to recognize the allogeneic non-self class I HLA molecules as altered self.

### Class II HLA Molecules

There are 3 major categories of class II HLA molecules, designated *HLA-DR*, *-DQ*, and *-DP*.<sup>16-20</sup> Both the  $\alpha$  and the  $\beta$  chain for each of these heterodimeric structures are encoded within the MHC and expressed as transmembrane proteins. The *HLA-DR* subregion of the MHC encodes 1 nonpolymorphic  $\alpha$  chain and 2 polymorphic  $\beta$  chains. The *HLA-DQ* subregion of the MHC encodes 1 polymorphic  $\alpha$  chain and 1 polymorphic  $\beta$  chain. The *HLA-DP* subregion of the MHC encodes 1 nonpolymorphic  $\alpha$  chain and 1 polymorphic  $\beta$  chain. Assuming a different allele at each polymorphic gene pair, an individual can express 10 forms of class II HLA molecules (4 *DR*, 4 *DQ*, and 2 *DP*), each of which is capable of displaying a large array of linear antigenic peptides (Figure 1-3).

The extracellular region of each class II HLA chain has 2 domains, designated  $\alpha 1$ ,  $\alpha 2$  and  $\beta 1$ ,  $\beta 2$ .<sup>18</sup> The antigen-binding groove is formed by intermolecular association of an  $\alpha 1$  and a  $\beta 1$  domain (Figure 1-2). Therefore, both chains contribute to

the antigen recognition complex for TCR. Residues in the  $\beta 2$  domain interact with  $CD4$  molecules,<sup>24,25</sup> thereby restricting TCR recognition of antigen displayed in the groove of class II HLA molecules to  $CD4^+$  T cells. Class II HLA molecules are constitutively expressed only on monocytes, macrophages, dendritic cells, and B lymphocytes. However, class II HLA molecules can be expressed by virtually all nucleated cells stimulated with interferon  $\gamma$  ( $IFN-\gamma$ ).<sup>26</sup>

Antigenic peptides displayed in the groove of class II HLA molecules are derived from proteins phagocytosed or endocytosed by antigen-presenting cells (Figure 1-4).<sup>8,18,14</sup> These exogenous antigens are hydrolyzed within endosomes where the linear peptide fragments are loaded into class II HLA molecules in the endosome membrane by concomitant degradation of an invariant chain that occupies the antigen-binding groove prior to peptide loading. Fusion of the endosome with the plasma membrane results in cell surface display of the linear peptide in the context of the class II HLA molecule. Exogenous antigens include most bacteria, parasites, and virus particles released from other cells.

### HLA and Disease

The capacity of an individual to mount an immune response to antigens that are recognized in the context of HLA molecules is inherently dependent on the potential of their HLA antigen-binding grooves to accommodate the linear peptides derived from a complex antigen. Differences as subtle as a single amino acid substitution at a critical residue of an HLA

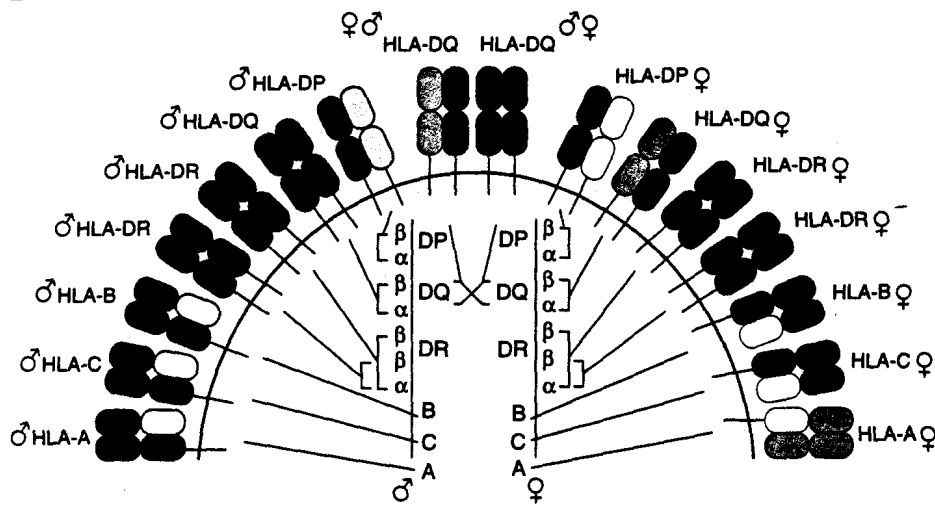


Figure 1-3.—Repertoire of HLA molecules. An individual's cells can express 6 class I HLA molecules (HLA-A, -B, -C) and 10 class II HLA molecules (HLA-DR, -DQ, -DP). Each shaded oval represents a domain within an HLA molecule. The class I HLA molecules all contain 3 domains and are expressed in association with  $\beta_2$ -microglobulin. Each parental HLA complex contributes 1 HLA-A (dark and light gray), 1 HLA-B (dark and light brown), and 1 HLA-C molecule (dark and light green).  $\beta_2$ -Microglobulin is nonpolymorphic and is shown as a white oval. The class II HLA molecules are heterodimers formed by a 2-domain  $\alpha$  chain and a 2-domain  $\beta$  chain. Because the DR $\alpha$  and DP $\alpha$  chains are nonpolymorphic (illustrated by the same dark-blue shading for paternal and maternal DR $\alpha$  chains and the same orange shading for paternal and maternal DP $\alpha$  chains), the highly polymorphic DR $\beta$  (illustrated by 4 shades from red to pink) and DP $\beta$  (dark and light yellow) chains determine the total number of DR molecules (4) and DP molecules (2); thus, each parental HLA complex contributes 2 DR molecules formed by 1 nonpolymorphic DR $\alpha$  chain in association with either of 2 polymorphic DR $\beta$  chains from each parental HLA complex; and, each parental HLA complex contributes 1 DP molecule formed by the association of the nonpolymorphic DP $\alpha$  chain with the polymorphic DP $\beta$  chain encoded on either parental HLA complex. The DQ $\alpha$  and DQ $\beta$  chains are both polymorphic (illustrated by different shading for paternal and maternal DQ $\alpha$  and DQ $\beta$  chains), thereby providing the options for *cis* and *trans* association of the DQ $\alpha$  and DQ $\beta$  chains for a total of 4 HLA-DQ molecules; thus, each parental HLA complex contributes 1 DQ molecule formed by association of the DQ $\alpha$  chain and DQ $\beta$  chain encoded on the same chromosome. Two additional DQ molecules are formed by association of the DQ $\alpha$  chain from each parental chromosome with the DQ $\beta$  chain from the other parental chromosome. Molecules derived from the paternal HLA complex are illustrated with thicker borders than the molecules derived from the maternal HLA complex.

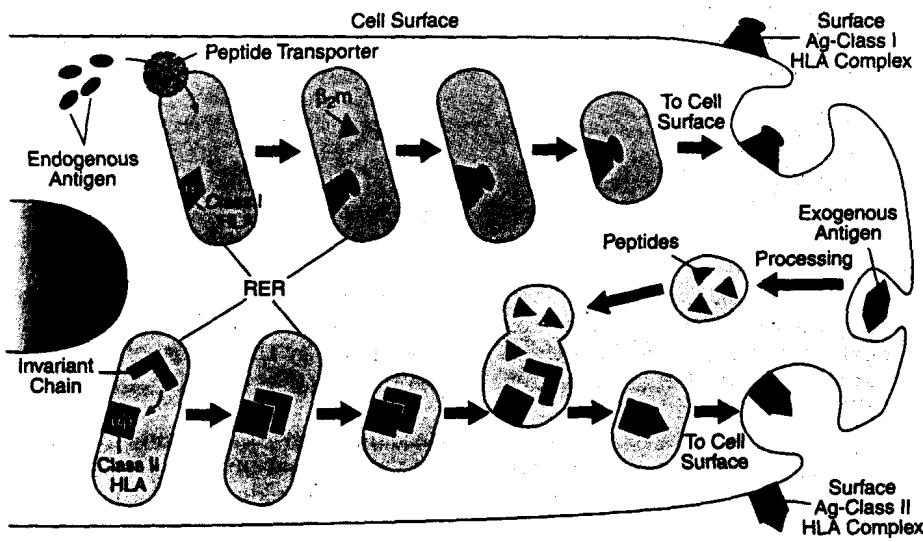


Figure 1-4.—Antigen processing. Endogenously derived linear peptides are transported from the cytoplasm to the rough endoplasmic reticulum (RER) where the peptides are loaded into the antigen (Ag)-binding groove of a class I HLA molecule, which is subsequently expressed on the cell surface in association with  $\beta_2$ -microglobulin ( $\beta_2m$ ). Exogenously derived antigen is hydrolyzed within lysosomes into linear peptides that replace an invariant chain in the antigen-binding groove of a class II HLA molecule, which is subsequently expressed on the cell surface. Modified with permission from Goodman.<sup>23</sup>

molecule can alter the ability to bind antigenic peptide fragments and change an individual from an immune responder to an immune nonresponder or low re-

sponder. For example, in a subset of patients with juvenile-onset diabetes, disease susceptibility is linked to the absence of aspartate at position 57 in polymorphic

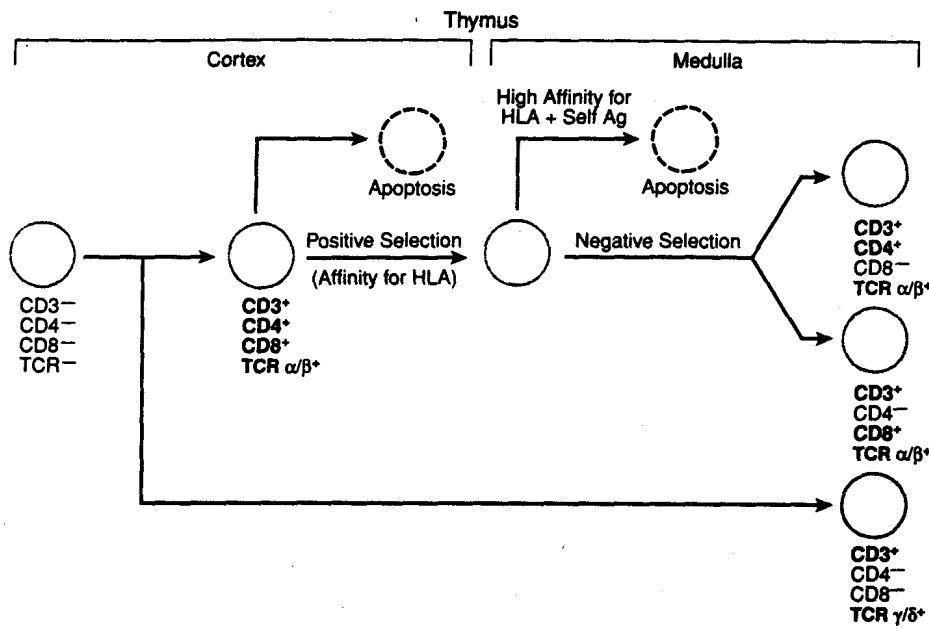
forms of DQ $\beta$  chains.<sup>27,28</sup> Conversely, normal or decreased susceptibility to this disease is conferred by having aspartate a position 57 in these DQ $\beta$  chains. More than 100 diseases have been associated with particular HLA haplotypes, and the strength of this association can be calculated to yield a relative risk.<sup>29</sup> One of the highest relative risks is for ankylosing spondylitis in HLA-B27<sup>+</sup> Caucasian Americans, who are approximately 90 times more likely to develop the disease than those who are HLA-B27<sup>-</sup>.<sup>30,31</sup> The relative risk for developing rheumatoid arthritis is significantly increased in individuals whose HLA-DR  $\beta$  chains share an 8-amino acid sequence from residues 67 to 74 in the HLA-DR4  $\beta$  chain.<sup>32,34</sup> The potential to mount a protective immune response to infectious agents or vaccines has also been linked to an individual's HLA haplotype and has important epidemiologic implications for immunization strategies.

### Non-HLA Presentation of Antigen

Unlike conventional peptide antigens that are presented by class I and class II HLA molecules to CD8<sup>+</sup> and CD4<sup>+</sup> T lymphocytes, respectively, neither class I nor class II HLA molecules are known to present carbohydrate or lipid antigens. Nonetheless, our immune system can discriminate self and nonself polysaccharides (eg, ABO blood group system antibodies). In addition, CD4-CD8<sup>-</sup> T cells constitute a discrete subpopulation (approximately 5%-10%) of circulating T cells. It is now established that the TCR on CD4-CD8<sup>-</sup> T cells are capable of recognizing lipid or lipoglycan antigens presented by CD1 molecules.<sup>35,36</sup> These CD1 molecules are a family of nonpolymorphic,  $\beta_2$ -microglobulin-associated glycoproteins expressed on most antigen-presenting cells. There are 5 different isotypes of CD1, and they are conserved in mammalian species with structures similar to class I MHC  $\alpha 1$  and  $\alpha 2$  domains. CD1 presentation of nonpeptide antigens has been proposed as a mechanism to enhance the ability of the immune system to recognize microbial lipids.

### T LYMPHOCYTES

The specificity and sensitivity of T cells for recognition of the antigenic trimolecular complex posed by a peptide in the antigen-binding groove of an HLA molecule are the property of the TCR.<sup>3,14,37</sup> Key to an individual developing a competent and protective repertoire of T cells is the process of positive and negative selection that occurs in the thymus during T-cell ontogeny (Figure 1-5).<sup>38-41</sup> In the cortical region of the thymus, T cells whose antigen receptor fails to bind to self-HLA molecules are programmed to die by apoptosis, whereas T cells whose antigen recep-



**Figure 1-5.**—Intrathymic maturation of T lymphocytes. Approximately 95% of lymphocytes undergoing the maturation process in the thymus never complete maturation and die by apoptosis within the thymus. Initial survival within the thymic cortex depends on the ability of the T-cell receptor (TCR) to recognize self-HLA molecules (positive selection). However, if cells with such TCR engage, with high affinity, autoantigens displayed by self-HLA while in the thymic medulla, then such autoreactive T cells are also eliminated by apoptosis (negative selection). The vast majority of mature T cells emerging from the thymus for population of peripheral blood and lymphoid organs are TCR  $\alpha/\beta^+$  with a CD4<sup>+</sup>/CD8<sup>+</sup> ratio of approximately 2:1. Molecules expressed on the T-cell surface are shown in boldface and molecules not expressed on the T-cell surface are shown in lightface. Some thymocytes rearrange the  $\gamma$  and  $\delta$  TCR genes to form TCR  $\gamma/\delta^+$  T cells that are usually CD4<sup>-</sup>CD8<sup>-</sup>. Ag indicates antigen.

tor binds to self-HLA molecules survive (positive selection) and migrate to the medulla of the thymus. In the medulla, T cells whose antigen receptor binds with high affinity to self-HLA molecules displaying autoantigens undergo apoptosis (negative selection). Approximately 5% of thymocytes survive both positive and negative selection and emigrate as mature T cells. Approximately 75% of peripheral blood mononuclear leukocytes are T cells.

### T-Cell Antigen Receptor Complex

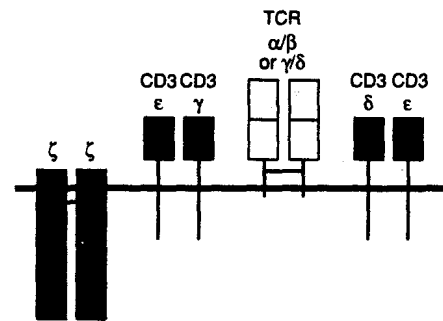
The TCR is a disulfide-linked heterodimer expressed on T cells early during intrathymic ontogeny in association with several signal-transducing transmembrane molecules known as the CD3 complex.<sup>41</sup> Approximately 90% of mature T cells use 1  $\alpha$  chain and 1  $\beta$  chain to form the TCR.<sup>42,43</sup> The remaining mature T cells use 1  $\gamma$  chain and 1  $\delta$  chain to form the TCR.<sup>42</sup> Both pairs of TCR heterodimers are the transmembrane products of rearranging genes that provide clonal diversity by random juxtapositioning of discontinuous gene segments encoding variable, diversity (for the  $\beta$  and  $\delta$  chains), joining, and constant region loci.<sup>42,43</sup> The extracellular region of each chain has 2 domains. The amino-terminal (or variable) domain is encoded by the gene sequence established by the juxtaposed exons from the variable, diversity (for the  $\beta$  and  $\delta$  chains), and joining loci. A variable

domain is highly polymorphic and provides clonal specificity for antigen. The carboxy terminal (constant) domain is encoded by an exon from the constant region locus. A constant domain is monomeric and provides a structural scaffold for the antigen-binding variable domain. The estimated number<sup>44</sup> of possible TCR  $\alpha/\beta$  specificities is  $10^{15}$  and of possible TCR  $\gamma/\delta$  specificities is  $10^{18}$ . The TCR is noncovalently associated with the CD3 complex, which is composed of 3 pairs of dimers, to form the TCR complex (Figure 1-6).<sup>45,46</sup> The CD3 subunits are designated  $\gamma$ ,  $\delta$ , and  $\epsilon$ . These subunits are organized as  $\gamma/\epsilon$  and  $\delta/\epsilon$  heterodimers that associate with a  $\zeta/\zeta$  homodimer from the Fc $\gamma$ R family of proteins and transduce signal after the TCR binds antigen.

T-cell activation requires more than signaling through the TCR complex.<sup>47</sup> In fact, TCR complex signaling alone can result in T-cell anergy (Figure 1-7). An important costimulatory second signal for T-cell activation is ligation of the CD28 T-cell surface molecule by the CD80 or CD86 cell surface molecules expressed by the antigen-presenting cell (Figure 1-7).<sup>48,49</sup>

### T-Cell Subpopulations

Mature TCR  $\alpha/\beta^+$  cells are phenotypically composed of 2 major subpopulations defined by cell surface reciprocal expression of CD4 or CD8.<sup>38-41</sup> During intrathymic ontogeny, most developing



**Figure 1-6.**—T-cell receptor (TCR) complex. The antigen-binding TCR is either an  $\alpha/\beta$  or a  $\gamma/\delta$  heterodimer. Signal transduction requires the associated CD3  $\epsilon/\gamma$  and CD3  $\delta/\epsilon$  heterodimers and the  $\zeta/\zeta$  homodimer.

T cells progress through stages in which the cells are sequentially CD4<sup>-</sup>CD8<sup>-</sup>, then CD4<sup>+</sup>CD8<sup>+</sup>, and then either CD4<sup>+</sup>CD8<sup>-</sup> or CD4<sup>-</sup>CD8<sup>+</sup> (Figure 1-5). CD4<sup>+</sup>CD8<sup>-</sup> T cells recognize antigen presented in the context of class II HLA molecules and CD4<sup>-</sup>CD8<sup>+</sup> T cells recognize antigen presented in the context of class I HLA molecules.<sup>50,51</sup> Approximately two thirds of peripheral blood T cells are CD4<sup>+</sup> and approximately one third are CD8<sup>+</sup>.

Approximately 5% to 10% of peripheral blood T cells are CD4<sup>-</sup>CD8<sup>-</sup>. The ligand for these cells is poorly defined, but includes nonclassical MHC molecules, whose genes are being defined, as well as non-MHC-encoded but structurally MHC-like molecules, such as CD1, which is coexpressed with  $\beta_2$ -microglobulin and serves as an antigen-presenting molecule for glycolipids produced by mycobacteria and nocardia species.<sup>5,26,26</sup>

Functionally, T cells can be defined by their capacity to modulate immune responses by help or suppression or to effect cytotoxic immune responses. Although helper function is often associated with CD4<sup>+</sup> T cells and suppressor and cytotoxic function is often associated with CD8<sup>+</sup> T cells, these correlations are not absolute. T cells can also be categorized by the profile of cytokines they produce (Figure 1-8).<sup>52</sup> Naive T cells produce interleukin (IL) 2 upon activation, and then differentiate into subpopulations that produce distinct combinations of cytokines. Of the plethora of cytokines identified, 2 major reciprocal patterns of cytokine production have emerged to help elucidate the mechanistic basis for clinically distinct inflammatory responses.<sup>53</sup> T cells that produce predominantly IL-2, IFN- $\gamma$ , and tumor necrosis factor  $\beta$  (TNF- $\beta$ ) are referred to as T<sub>H</sub>1 cells. T cells that produce predominantly IL-4, IL-5, IL-9, IL-10, and IL-13 are referred to as T<sub>H</sub>2 cells. Production of IL-12 by macrophages during antigen presentation drives T-cell differen-

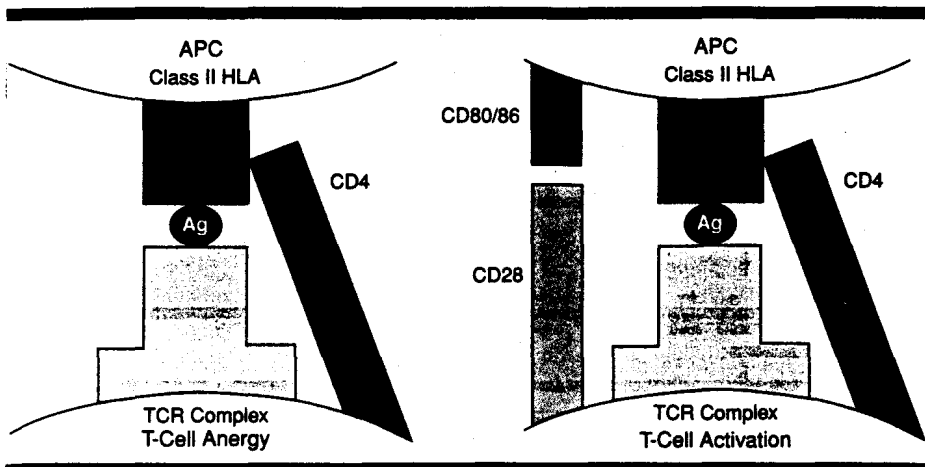


Figure 1-7.—T-lymphocyte activation. The T-cell receptor (TCR) recognizes antigen (Ag) presented in the context of HLA molecules. T-lymphocyte activation requires complex signaling through both the TCR complex and ligation of CD28 by CD80/86 on the antigen-presenting cell (APC). Lack of the CD28 costimulatory signal results in anergy rather than activation.

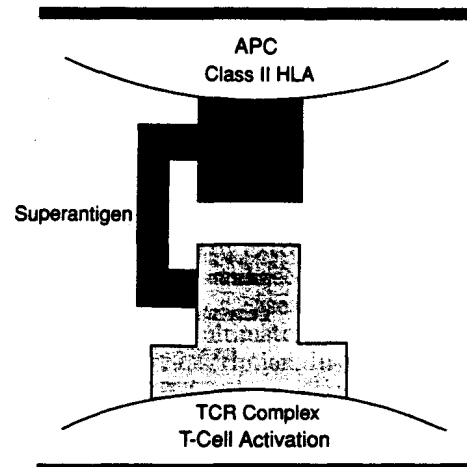


Figure 1-9.—Superantigen activation of T lymphocytes. Superantigens activate T lymphocytes by engaging the T-cell receptor (TCR) and the class II HLA molecule at sites distinct from the conventional antigen (Ag)-binding groove. APC indicates antigen-presenting cell.

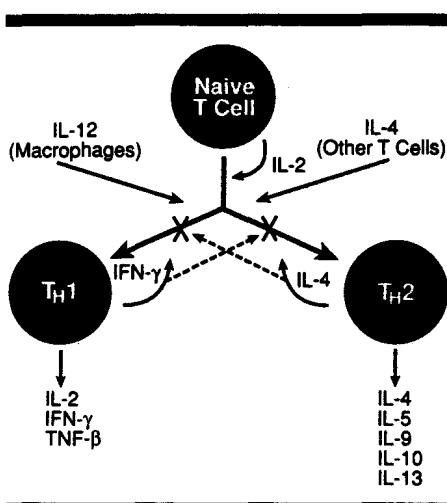


Figure 1-8.—Differentiation of  $T_H1$  and  $T_H2$  lymphocytes. Interleukin (IL) 12 and interferon (IFN)  $\gamma$  induce the differentiation of  $T_H1$  cells, and IFN- $\gamma$  antagonizes the differentiation of  $T_H2$  cells. Interleukin 4 induces the differentiation of  $T_H2$  cells and antagonizes the differentiation of  $T_H1$  cells.  $T_H1$  cells induce cell-mediated inflammation, and  $T_H2$  cells induce humoral-mediated allergic inflammation. TNF indicates tumor necrosis factor.

tiation toward  $T_H1$  cells, for which IFN- $\gamma$  is an autocrine agonist for  $T_H1$  cells and an antagonist for  $T_H2$  cells. Conversely, IL-4 enhances the differentiation of  $T_H2$  cells and antagonizes the differentiation of  $T_H1$  cells. The consequence of these reciprocal cytokine patterns is the generation of cell-mediated immune responses by  $T_H1$  cells and of humoral allergic immune responses by  $T_H2$  cells. Both  $CD4^+$  T cells and  $CD8^+$  T cells can exhibit  $T_H1$  or  $T_H2$  cytokine profiles.

### Superantigens

Conventional antigens are presented to T cells as linear peptides displayed within the antigen-binding groove of HLA molecules.<sup>8,13,14</sup> Superantigens are bacterial or retroviral products that bind directly to class II HLA molecules out-

side the antigen-binding groove and without intracellular processing.<sup>54</sup> Superantigens stimulate both naive and memory T cells by also binding to TCR outside their conventional antigen-binding site (Figure 1-9), with specificity for TCR  $\beta$  chain variable region residues conserved within a family or families of TCR  $\beta$  chain genes. Hence, the number of T cells stimulated by a superantigen is determined by the number of T cells using that family of TCR variable region genes rather than by the size of a clonally restricted population of T cells responding to conventional antigen. Prototype superantigens include many of the *Staphylococcus aureus* exotoxins and products of *Streptococcus pyogenes*, *Yersenia enterocolitica*, and *Mycoplasma arthritidis*. The plethora of cytokines released by the polyclonal stimulation of 10% to 20% of T cells by some superantigens is responsible for clinical conditions such as toxic shock syndrome and has been hypothesized as a mechanism for activation of some autoimmune diseases.

### B LYMPHOCYTES

The hallmark of B cells is their production of Ig. During B-cell ontogeny, the stages of B-cell maturation can be identified by progressive rearrangement of the Ig heavy and light chain genes and by distinct changes in cell surface phenotype (Figure 1-10).<sup>55-58</sup> B-cell maturation depends on bone marrow stromal cells and stromal cell-produced IL-7.<sup>59</sup> Immature and mature B cells express CD19 and CD20. Immature B cells also express CD10 and subsequently transmembrane IgM. Mature B cells cease expression of CD10 and coexpress transmembrane IgM and IgD. Approximately 15% of peripheral blood mononuclear leukocytes are B cells.

### Immunoglobulin and the B-Cell Antigen Receptor Complex

The basic structure of Ig is 2 identical disulfide-linked heavy chains to each of which is disulfide-linked an identical  $\kappa$  or  $\lambda$  light chain (Figure 1-11).<sup>60,61</sup> The antigen specificity of an antibody resides in the highly polymorphic amino-terminal variable region of each heavy ( $V_H$ ) and light ( $V_L$ ) chain that, as a pair, form an antigen-binding site. The carboxy terminal (Fc) region of the heavy chains of Ig provide functional attributes for effecting antibody-dependent immune responses, such as complement fixation and binding to cell surface Fc receptors.

Ig heavy chains are encoded on chromosome 14. The Ig  $\kappa$  light chain is encoded on chromosome 2 and the Ig  $\lambda$  light chain is encoded on chromosome 22. Rearrangement of exons within an Ig gene is required for successful production of Ig heavy and light chains.<sup>10</sup> The variable region of an Ig heavy chain is the product of 3 exons randomly juxtaposed from the variable, diversity, and joining gene loci located at the 5' end of the Ig heavy chain gene (Figure 1-12).<sup>65</sup> The variable region of an Ig light chain is the product of 2 exons randomly juxtaposed from the variable and joining gene loci located at the 5' end of the  $\kappa$  chain gene or the  $\lambda$  chain gene. These gene rearrangements, which encode sequences for the variable region of Ig heavy chains and Ig light chains, are the basis for generating a repertoire of antibodies with approximately  $10^{11}$  antigen specificities.

The constant region of a light chain is derived from a single  $\kappa$  or  $\lambda$  constant exon located at the 3' end of their respective gene. By contrast, the 3' end of the Ig heavy chain gene contains exons that encode for 9 different constant regions that

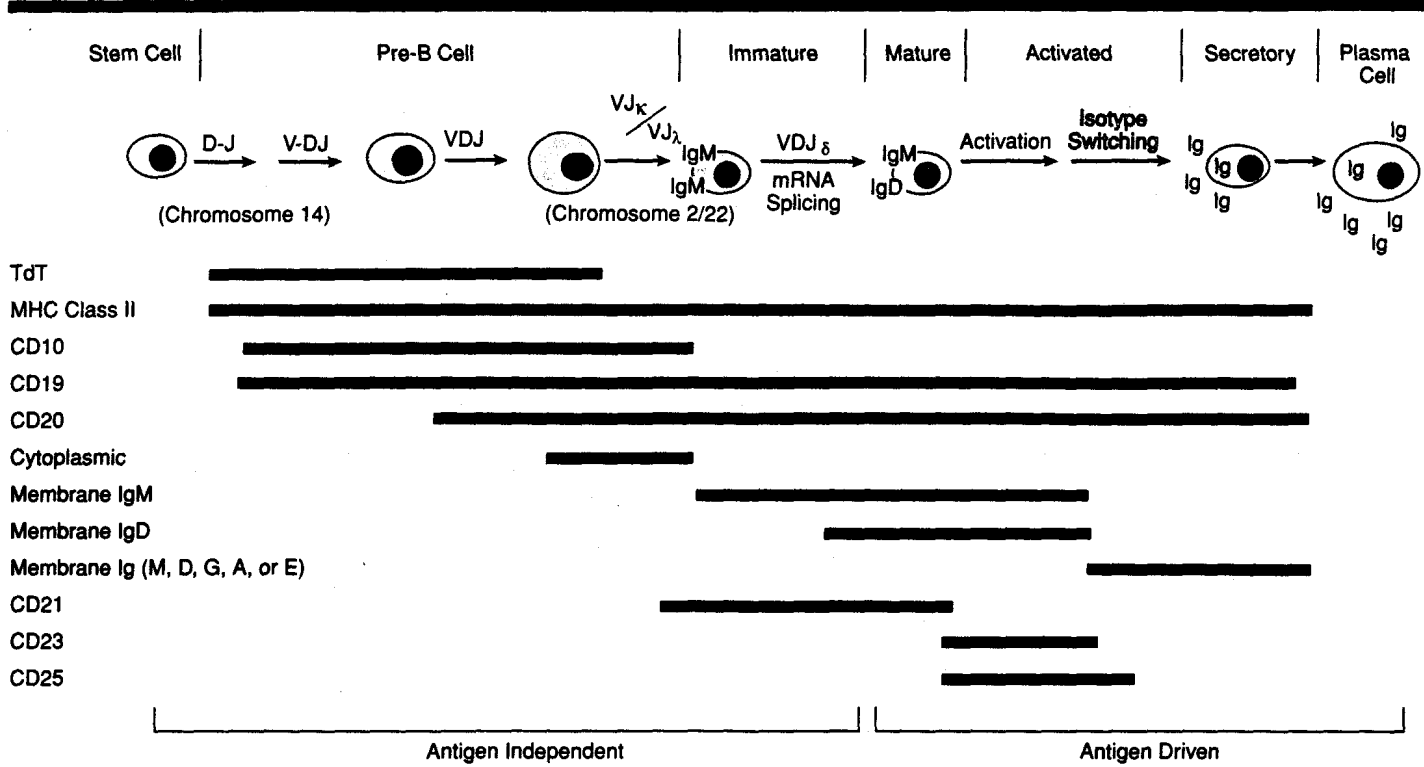


Figure 1-10.—B-cell differentiation from bone marrow stem cell to immunoglobulin (Ig)-secreting plasma cell. Correlation is made between the stages of B-cell development, Ig gene rearrangements, and the surface expression of Ig and B-cell markers. D-J, V-DJ, VDJ<sub>κ</sub>, and VDJ<sub>λ</sub> indicate initiation of Ig heavy chain gene rearrangement on the 14th chromosomes; TdT, terminal deoxynucleotidyl transferase, an intracellular enzyme; MHC, major histocompatibility complex; mRNA, messenger RNA; and VJ<sub>κ</sub> and VJ<sub>λ</sub>, initiation of Ig light chain gene rearrangements on chromosomes 2 and 22, respectively. Modified from Huston et al<sup>55</sup> with permission from the American Academy of Allergy, Asthma, and Immunology, Milwaukee, Wis.

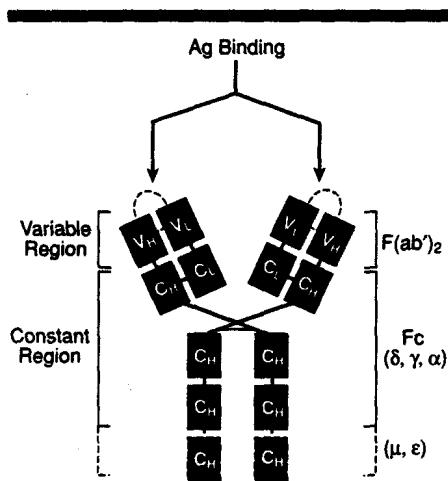


Figure 1-11.—Basic structure of immunoglobulin. The light (L) chains each contain 1 variable (V) and 1 constant (C) domain. The heavy (H) chains each contain 1 V region and either 3 C domains for δ, γ, and α or 4 C domains for μ and ε. The antigen (Ag)-binding specificity is created by the conformation and sequence of the V<sub>H</sub> and V<sub>L</sub> domains. Biologic activity is determined by the Fc region and varies for each isotype. Each of the antigen binding sites are referred to as a Fab region, and together as F(ab')<sub>2</sub>.

define an antibody as IgM, IgD, IgG3, IgG1, IgA1, IgG2, IgG4, IgE, or IgA2 (Figure 1-12).<sup>10,55-58,62</sup> Following rearrangement of the variable, diversity, and joining gene segments, the constant gene segments for the μ and the δ exons are used to produce IgM and IgD.<sup>63</sup> Isotype

switching from the IgM and IgD isotypes that characterize a naive mature B cell is T cell dependent and occurs at the DNA level by deletion of sequences between the expressed and the to-be-expressed exon. The rearranged 5' Ig heavy chain gene sequence encoding the Ig heavy chain variable region does not further rearrange with isotype switching. Thus, antigen specificity is maintained regardless of the Ig heavy chain isotype. The biologic properties of each of the Ig isotypes are summarized in the Table.

B-cell membrane Ig and secreted Ig are the alternative products of the differentially spliced Ig heavy chain gene (Figure 1-12).<sup>55,62,63</sup> Upon ligation by antigen, membrane Ig transduces an intracellular signal through the membrane Ig-associated heterodimer Ig-α/Ig-β transmembrane proteins (Figure 1-13) that are functionally analogous to the signal transducing CD3 molecules on T cells. The transmembrane Ig and Ig α/β molecules together form the B-cell antigen receptor complex.<sup>64-66</sup> Each naive B cell expresses membrane Ig with a unique (clonal) antigen-binding specificity. When the membrane Ig binds an antigen with sufficient affinity, clonal expansion occurs for increased production of Ig with that specificity. Repetitive antigen stimulation is associated with somatic hypermutation within the Ig gene segments encoding the

heavy and light chain variable regions. Where these somatic mutations result in Ig with greater antigen specificity, those daughter clones are preferentially expanded and produce antibody with higher affinity. This process of clonal expansion and somatic hypermutation occurs within the germinal centers of lymphoid organs.

### T-Cell-Dependent Stimulation of B Cells

T cells direct Ig isotype switching through a series of cell surface molecular interactions with B cells (Figure 1-14), resulting in reciprocal intracellular signaling and T-cell elaboration of cytokines.<sup>67-69</sup> First, peptides hydrolyzed from antigens, internalized by B cells after being bound by membrane Ig, are presented in the context of class II HLA molecules to CD4<sup>+</sup> T cells with the appropriate TCR. In addition to this antigen-specific interaction, the T-cell CD40 ligand (CD40L) engages the B-cell CD40 molecule. The absence or dysfunction of the CD40L-CD40 interaction prevents isotype switching and is clinically manifest as hyper-IgM immune deficiency.<sup>70</sup> Following T-cell activation, the T cell elaborates cytokines for which the B cell has receptors. T-cell elaboration of IL-4 induces B-cell switch to IgE and IgG4,<sup>52,71,72</sup> whereas transforming growth factor β in combination with IL-10 induces switch to IgA1 and IgA2.<sup>52,73,74</sup> By con-

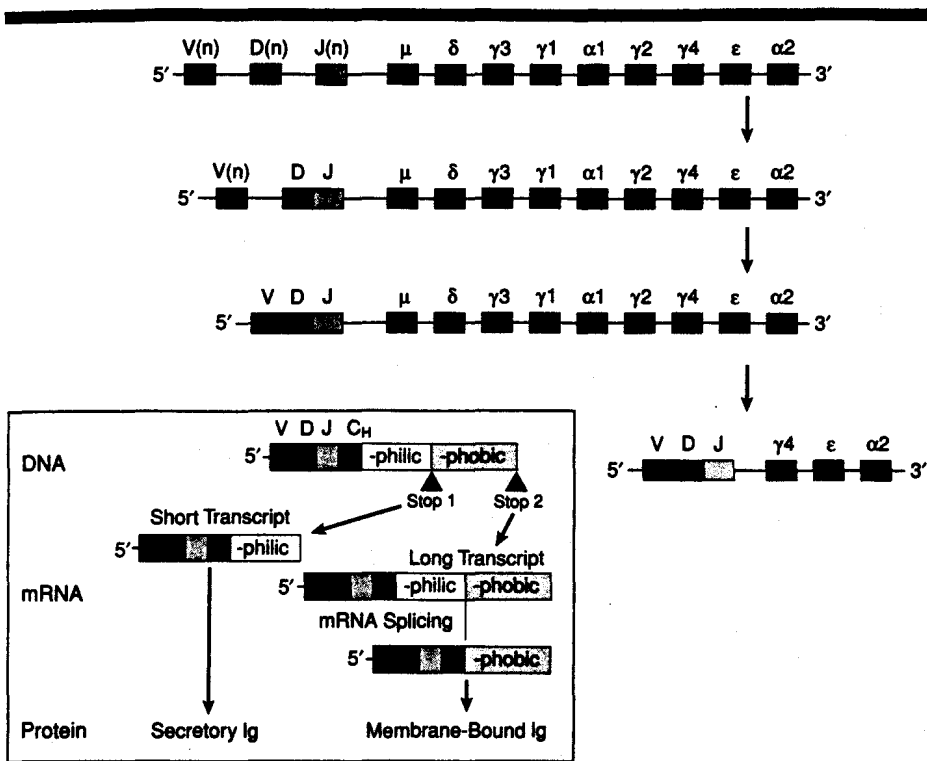


Figure 1-12.—Sequential rearrangement of the heavy chain gene exons. The orderly rearrangement of selected exons encoding variable (V), diversity (D), and joining (J) regions allows the transcription of messenger RNA (mRNA) complementary to a specific VDJ segment along with the  $\mu$  constant (C) region exons. Isotype switching requires further rearrangement to juxtapose the same VDJ segment with a more 3' C region gene, as is demonstrated for switching from  $\mu$  to  $\gamma 4$ . Inset illustrates that membrane-bound or secretory immunoglobulin can be produced from the same genes by use of different stop codons (shown in red) at the 3' end of each C region gene. If the first stop codon is used, a short transcript is obtained that is translated into a secretory protein containing a hydrophilic (-philic) carboxy terminus. Read through of the first stop codon results in a long transcript in which the hydrophilic coding region is removed by splicing. The ultimate protein product is anchored to the cell membrane via a hydrophobic (-phobic) carboxy terminus. Modified from Huston et al<sup>55</sup> with permission from the American Academy of Allergy, Asthma, and Immunology, Milwaukee, Wis.

#### Physical and Biologic Properties of Immunoglobulin Isotypes

Isotype	Molecular Weight,* kd	Molecular Form	Serum Concentration,* mg/mL	Serum Half-life,* d	Classic/Alternate C Activation†	Placental Transport	FcR Binding
IgM	900	Pentamer	2	5	+/-	No	Yes
IgD	180	Monomer	0.3	3	-/+	No	No
IgG1	150	Monomer	10	21	+++	Yes	Yes
IgG2	150	Monomer	5	21	++	Yes	Yes
IgG3	170	Monomer	1	7	+++	Yes	Yes
IgG4	150	Monomer	0.5	21	-/+	Yes	No
IgA1	160	Monomer or dimer	3	7	-/+	No	Yes
IgA2	160	Monomer or dimer	0.5	7	-/+	No	Yes
IgE	190	Monomer	0.0001	3	-/-	No	Yes

\*Approximate values.

†Plus sign indicates activation; minus sign, no activation; and double plus sign, strong activation.

trast, IFN- $\gamma$  antagonizes IL-4-induced switch to IgE.<sup>52</sup>

#### T-Cell-Independent Stimulation of B Cells

In contrast to the T-cell dependency of B-cell responses to most protein antigens, B cells can be activated and produce antibodies to some molecules independent of T cells.<sup>75,76</sup> T-independent B-cell activators include some polysaccharides, lipopolysaccharides, and polymeric proteins. By directly responding to these

molecules, B cells mount a rapid immune response to pathogens. However, T-independent B-cell activators are poor inducers of memory B cells and of affinity maturation of antibodies and do not induce isotype switch, all of which are T-cell-dependent qualities. Although T-independent B-cell activators induce antigen-specific antibodies, these molecules can also induce antibody production by B cells whose immunoglobulin has specificity for other antigens. Such polyclonal B-cell responses may be associated

with the production of both protective antibodies and autoantibodies. The latter may lead to transient clinical symptoms characteristic of autoimmune diseases.

#### INTRACELLULAR SIGNAL TRANSDUCTION

Transmission of cell surface activation signals initiated by extracellular engagement of ligands and receptors is accomplished through a cascade of metabolic pathways that ultimately initiate or inhibit gene transcription. In general, initial events in signal transduction involve the phosphorylation of tyrosines, serines, and threonines within the cytoplasmic domains of transmembrane proteins and in soluble cytoplasmic proteins. Phosphorylating enzymes are referred to as kinases and dephosphorylating enzymes are known as phosphatases. The serial activation and inactivation of the signal-transducing cytoplasmic proteins can lead to activation of the phospholipase metabolic pathways, changes in intracellular calcium, and activation of DNA-binding proteins. Signal transduction in B cells and T cells, initiated by ligation of their Ig receptor complex or TCR complex, respectively, uses what are referred to as the Src-family tyrosine kinases.<sup>47,77</sup> Signaling through cytokine receptors uses the Janus kinases (Jaks) and signal transducers and activators of transcription (STATs).<sup>78,80</sup> The importance of these components within the signal transduction pathways are evident by the consequence of their deficiency on immune function. In animal models,<sup>78</sup> a deficiency of STAT 1 impairs IFN-induced signal transduction, thereby increasing susceptibility to viral infection; STAT 4 deficiency impairs IL-12 signaling and development of T<sub>H</sub>1 cells; and STAT 6 deficiency impairs IL-4 signaling and the development of T<sub>H</sub>2 cells. In humans,<sup>78,80</sup> Jak 3 deficiency impairs signal transduction by the  $\gamma c$  cytokine receptor subunit, which is utilized by the receptors for IL-2, IL-4, IL-7, IL-9, and IL-15. As with a deficiency of  $\gamma c$ , a deficiency of Jak 3 results in severe combined immune deficiency. Since  $\gamma c$  is encoded on the X chromosome, the phenotypic expression of  $\gamma c$  deficiency is X linked, whereas the phenotype of Jak 3 deficiency is an autosomal recessive form of severe combined immune deficiency.

#### COMPLEMENT

Antibody-mediated immunity is facilitated by the complement system that consists of plasma proteins activated along an enzymatic cascade, resulting in a spectrum of bioactive molecules that facilitate opsonization, osmotic lysis of targeted cells, and recruitment of phagocytic cells.<sup>81</sup> Antigen-antibody complexes are efficient activators of the classic comple-

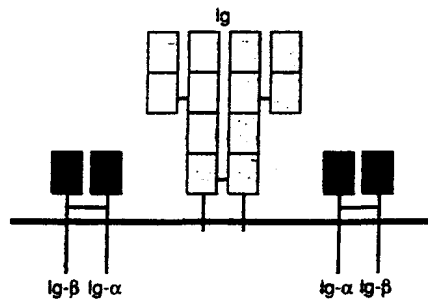


Figure 1-13.—B-cell antigen receptor complex. Transmembrane immunoglobulin binds antigen. Signal transduction is mediated by the associated Ig- $\alpha$ /Ig- $\beta$  heterodimers.

ment pathway that uses C1, C4, and C2 to activate C3 for catalyzation of C5-C9 activation and formation of the membrane attack complex. Independent of antibody, spontaneously activated C3 can bind to pathogenic organisms and thereby catalyze the alternative complement pathway for activation of C5-C9. Cleavage of C3 is a central event in the complement cascade and results in the generation of 2 important bioactive molecules, C3a and C3b. C3a and the subsequently generated C5a are potent inducers of mast cell degranulation, which promotes inflammation, while C3b binds covalently to the target cell surface and is the major mediator of opsonization through binding to its receptor, CD21, which is expressed by leukocytes. Deficiencies in C3 or in any of the C5-C8 components are associated with an increased risk for infection with encapsulated bacteria such as *Neisseria* species.<sup>82</sup> Deficiencies of C4 or C2 are associated with lupuslike autoimmune syndromes.<sup>83,84</sup> Deficiency of C1 esterase inhibitor, a serine protease that inhibits the spontaneous activation of C1 as well as several proteins in the fibrinolytic pathway, results in non-mast cell-mediated angioedema.<sup>85</sup> Because erythrocytes express CR1 (a receptor for both C4b and C3b), deficiency of the red cell membrane-bound complement regulatory proteins (CD59 or decay-accelerating factor) results in the disease paroxysmal nocturnal hemoglobinuria.<sup>86</sup> Thus, disorders of the complement system, which is a major part of the innate immune system, can be manifest as a wide spectrum of clinical disorders.

### CELL ADHESION MOLECULES

The ability of leukocytes to attach to extracellular matrices and to adhere to each other are necessary events for normal immune function.<sup>87</sup> Three families of adhesion molecules subserve these functions: selectins, integrins, and Ig superfamily adhesion molecules (Figure 1-15).

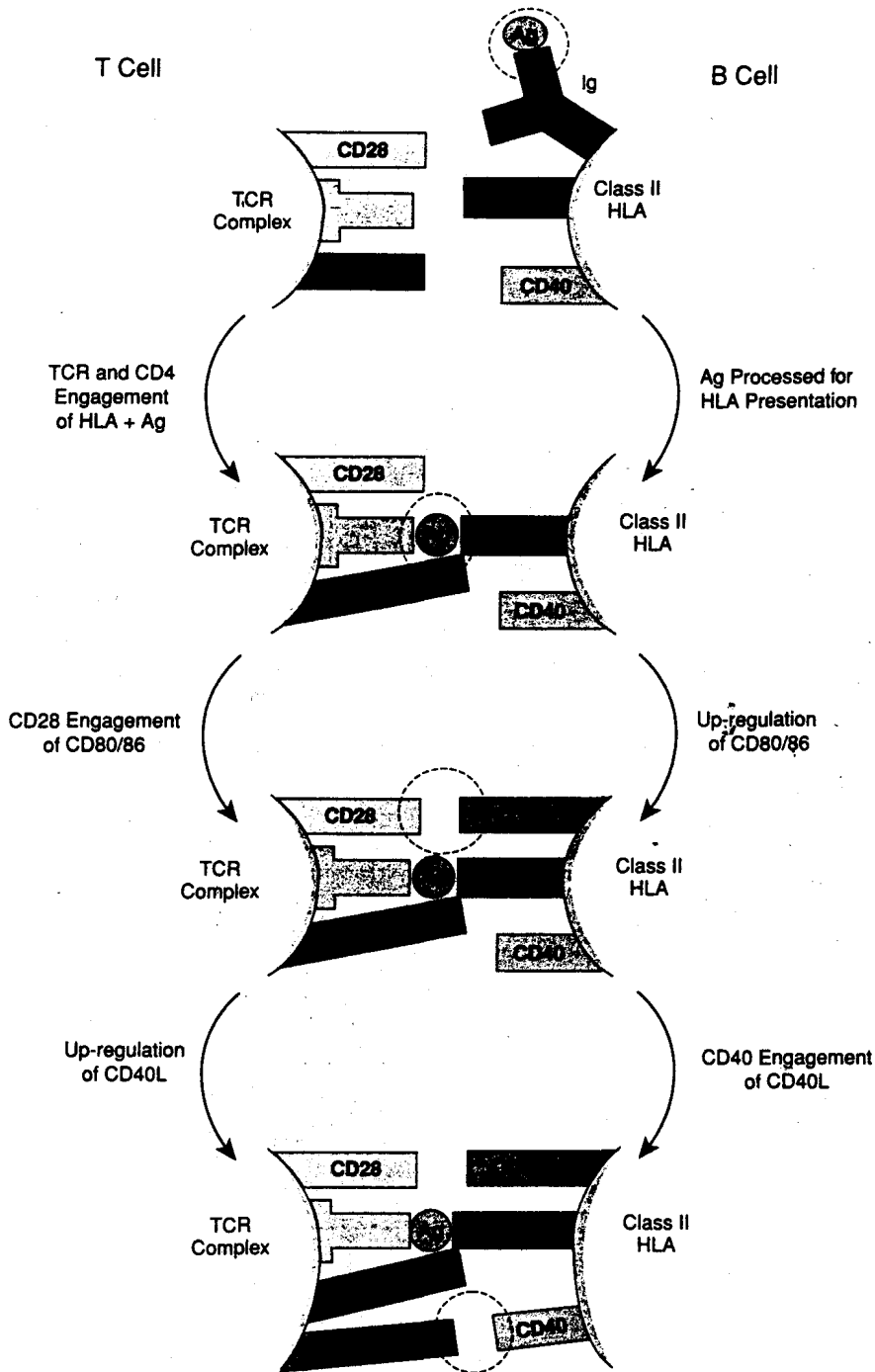


Figure 1-14.—Cascade of signaling events used by B and CD4<sup>+</sup> T lymphocytes. Exogenous antigen (Ag) bound by B-cell surface immunoglobulin (Ig) is endocytosed, processed, and displayed by class II HLA molecules. T-cell receptor (TCR)-CD4 engagement of Ag presented by class II HLA molecules up-regulates B-cell expression of CD80/86 for ligation of CD28 on the T cell. The cumulative effect is up-regulation of the CD40 ligand (CD40L) on T cells for engagement with CD40 on B cells. Each sequential activation event in the illustrated cascade is highlighted by a dashed circle. This cascade of signals results in T-cell production of cytokines and B-cell responsiveness to signals directing Ig isotype switch.

In addition to mediating adhesion, some of these molecules are also costimulatory during intercellular signaling.

Selectins are found on all leukocytes and function as lectins, which bind to carbohydrate moieties expressed by endothelial cells or other leukocytes. The 3 members of the selectin family are L-selectin, E-

selectin, and P-selectin. Each of the selectins participates in the process of leukocyte rolling along vascular endothelium.

The integrins and Ig superfamily adhesion molecules bind through protein-protein interactions and are important for stopping leukocyte rolling and mediating leukocyte aggregation and transendothe-

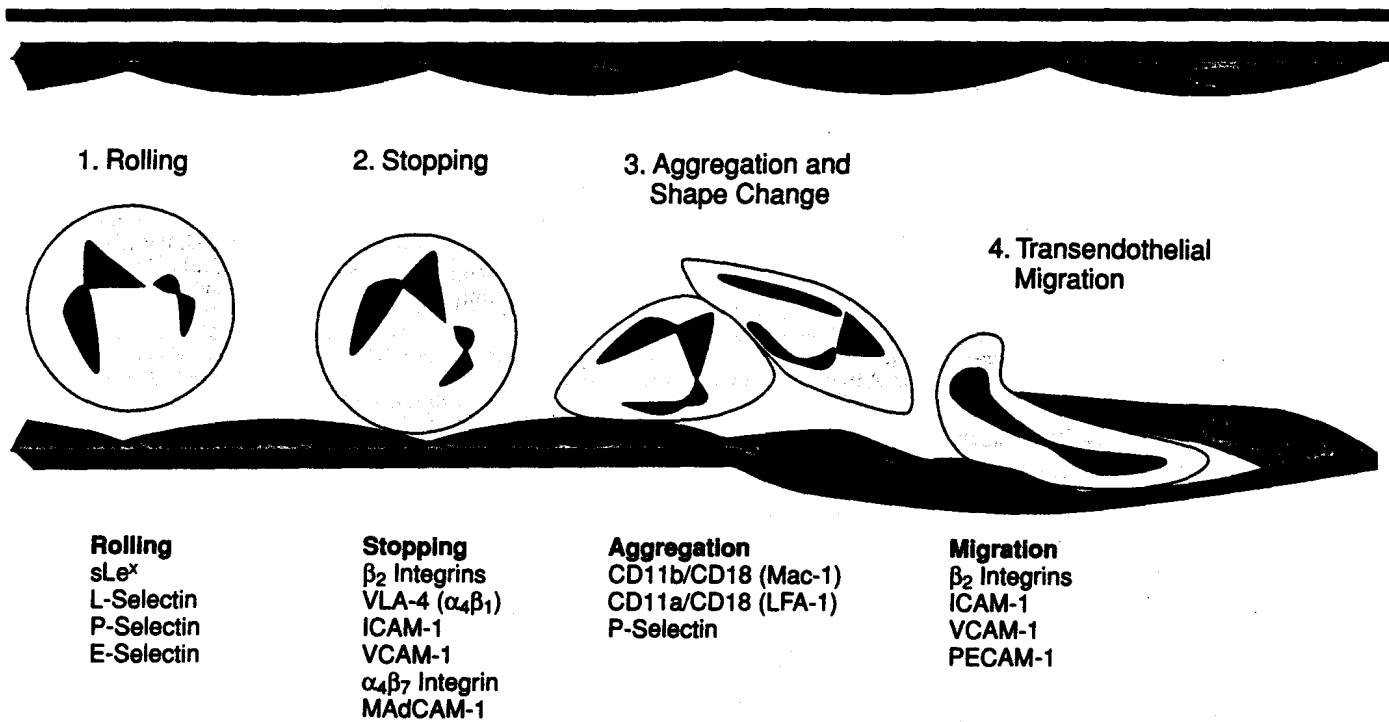


Figure 1-15.—Leukocyte emigration during inflammation. The sequence of intravascular events for leukocyte emigration are depicted with the relevant adhesion molecules for each step. sLe<sup>x</sup> indicates sialyl Lewis X; VLA, very late antigen; ICAM, intracellular adhesion molecule; VCAM, vascular cell adhesion molecule; MAdCAM, mucosal addressin cell adhesion molecule; LFA, leukocyte function-associated antigen; and PECAM, platelet endothelial cell adhesion molecule. Modified with permission from Smith.<sup>87</sup>

lial migration. The integrins are heterodimers and include the very late antigen (VLA) molecules (CD49a through CD49f), leukocyte function-associated antigen (LFA) 1 (CD11a), and Mac-1 (CD11b). The Ig superfamily adhesion molecules include the intercellular adhesion molecules (ICAMs), vascular cell adhesion molecules (VCAMs), LFA-2 (CD2), and LFA-3 (CD58). The biologic importance of these molecules for host defense is exemplified by the impairment of T-cell cytotoxic function with inhibition of either LFA-1-ICAM-1 (CD54) interactions or LFA-2-LFA-3 interactions. Clinically, mutations in CD18 (the  $\beta$  chain in the integrins LFA-1 and Mac-1) are manifest as recurrent bacterial infections due to an inability to mobilize leukocytes in sites of inflammation.<sup>88</sup> Interactions of VLA-4 (CD49d)/VCAM-1 (CD106) are especially important for eosinophil adhesion to endothelial cells during allergic late-phase immune responses.

#### APOPTOSIS VS IMMUNE PRIVILEGE

Cytotoxic T lymphocytes and natural killer cells have the capacity to kill target cells using either a perforin/granzyme system or through programmed cell death that can be triggered by either TNF or Fas ligand (FasL). The perforin/granzyme pathway is analogous to complement-mediated cytotoxicity in that perforin forms a pore in the cell membrane. By contrast, TNF and FasL, upon engaging their respective receptors (TNF receptor and

Fas), induce an intracellular transduction of signals that induce chromosomal degradation known as apoptosis.<sup>89,90</sup> The Fas/FasL system is thought to play a role in the control of autoimmunity and in immune privilege by certain tissues. For example, mice that are genetically deficient for Fas (lpr strain) or FasL (gld strain) display an autoimmune disorder characterized by a generalized and progressive lymphoproliferation. In the eye, constitutive expression of FasL by corneal tissue markedly reduces lymphocyte-mediated corneal destruction during inflammatory responses, whereas inflammatory destruction of the cornea will occur in the absence of FasL expression. The potential for constitutive FasL expression by other tissues relatively refractory to cell-mediated destruction may help explain a phenomenon previously known as immune privilege. The potential also may exist for therapeutic modulation of cell-mediated immune destruction of tissue through manipulation of Fas or FasL.

#### BASIC SCIENCE TO CLINICAL MEDICINE

The immune system should be viewed as a finely tuned machine whose purpose is to defend the host from the universe in which it lives. This challenge has been accomplished through an evolutionary process that provides a delicate balance between protection and self-destruction. Isolated defects in the immune system have resulted in clinical disorders

that have facilitated dissection of the cellular and molecular mechanisms governing the immune system. By elucidating these mechanisms, novel approaches to diagnosing immunologic disorders and modulating the immune system have begun to emerge. Through these advances, the clinical discipline of immunology has enormous potential to affect health care.

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