Innate and acquired responses usually work together to eliminate pathogens. T cells help B cells to make antibody and can also eradicate intracellular pathogens by activating macrophages and by killing virally infected cells. Innate and acquired responses usually work together to eliminate pathogens.

All these cells develop from pluripotent stem cells in the fetal liver and in bone marrow. B cells mature within the bone marrow, but T cells must travel to the thymus to complete their development. Adaptive immune responses are generated in the lymph nodes, spleen, and mucosa-associated lymphoid tissue. These are referred to as the secondary lymphoid tissues. In the spleen and lymph nodes, the activation of lymphocytes by antigen occurs in distinctive B- and T-cell compartments of lymphoid tissue. A striking morphologic feature of the B-cell area is the secondary follicle containing the germinal center, where B-cell responses occur within a meshwork of follicular dendritic cells. The mucosa-associated lymphoid tissues, including the tonsils, adenoids, and Peyer’s patches, defend mucosal surfaces. Diffuse collections of lymphoid cells are present throughout the lung and the lamina propria of the intestinal wall.

THREE LEVELS OF DEFENSE

To establish an infection, the pathogen must first overcome numerous surface barriers, such as enzymes and mucus, that either are directly antimicrobial or inhibit attachment of the microbe. Because neither the keratinized surface of skin nor the mucus-lined body cavities are ideal habitats for most organisms, microbes must breach the ectoderm. Any organism that breaks through this first barrier encounters the two further levels of defense, the innate and acquired immune responses.

IMMUNE RECOGNITION

The body can potentially respond to almost anything that can be bound by the receptors of either the innate or the acquired immune system. Molecules recognized by receptors on lymphocytes are generically referred to as antigens and can range from small chemical structures to highly complex molecules. Both the T-cell receptor and the antibody that is embedded in the B-cell membrane, the B-cell receptor, have binding sites1,2 that are only 600 to 1700 Å. Therefore, these receptors recognize only a small part of a complex antigen, referred to as the antigenic epitope. For these reasons, complex antigens consist of a mosaic of individual epitopes.

Antigens that elicit immune responses are termed immunogens. Not all antigens are naturally immunogenic. Small, nonimmunogenic antigens are called haptens and must be coupled to larger immunogenic molecules, termed carriers, to stimulate a response. Large protein antigens usually contain epitopes equivalent to carriers and haptens and are therefore inherently immunogenic. Carbohydrates, by contrast, must often be coupled to proteins in order to be immunogenic, as is the case for the polysaccharide antigens used in the Haemophilus influenzae type b vaccine. Even large protein antigens with adequate numbers of carrier epitopes can be made more immunogenic by combining them with an adjuvant — a substance...
Allele: An alternative form of a gene.

Allogeneic: Genetically dissimilar individuals of the same species; usually used in the context of organ or cell transplantation (i.e., allografts).

Allotypes: Antigenic determinants that differ among individuals of the same species, such as the epitopes of the Rh blood group system or epitopes of the HLA system.

Anergy: A potentially reversible form of immunologic tolerance in which lymphocytes become functionally unresponsive.

Antibody-dependent cellular cytotoxicity (ADCC): The killing of antibody-coated target cells by Fc receptor-bearing leukocytes, including natural killer cells, macrophages, and neutrophils.

Apoptosis: A specific form of cell death mediated by enzymatic degradation of DNA and that, in contrast to necrosis, is not associated with signs of inflammation. Also called programmed cell death.

B1 cells: A minor population of B lymphocytes that secrete polyspecific low-affinity IgM antibodies. Most express CD5 on their cell surface and may be self-renewing.

B2 cells: The chief population of B lymphocytes, B2 cells arise from stem cells in the bone marrow, do not express CD5, and secrete highly specific antibody within the secondary lymphoid tissues.

CD antigen: Cell-surface antigens are classified according to the cluster of differentiation (CD), in which individual molecules are assigned a CD number on the basis of their reactivity to panels of monoclonal antibodies.

Chemokine: Chemotactic cytokines that regulate the transit of leukocytes from blood into tissues. Each type of leukocyte (e.g., neutrophil, lymphocyte, and eosinophil) bears chemokine receptors that guide it to particular chemokines in the tissue.

Clone: A group of genetically identical cells with a common ancestor.

Complementarity-determining region (CDR): The surface of the variable region of an antibody or T-cell receptor that binds to antigen. The CDR consists of three subregions: CDR1, CDR2, and CDR3. Also known as the hypervariable region.

Costimulatory molecule: A molecule that provides additional (“second”) signals for lymphocyte activation beyond those provided through the antigen receptor.

Cytokines: A large family of low-molecular-weight soluble proteins involved in regulating cellular activity, particularly (but by no means exclusively) within the immune system.

Cytotoxic T cell: A T lymphocyte (which usually expresses CD8) that kills its target cell on recognizing complexes of peptides and major-histocompatibility-complex molecules on the target-cell membrane.

Epitope: The structure on the antigen that is recognized by an antigen receptor (antibody or T-cell receptor).

Gene library: A collection of cloned genes from which individual genes of interest can be selected (for example, by antibody screening after the expression of the gene in bacteria).

Germ line: The genetic material carried by ova and sperm. The germ line contains the genes that parents transmit to their offspring.
that nonspecifically enhances antigen-specific immunity. Many microorganisms inherently possess adjuvant activity in the form of immunostimulatory molecules such as lipopolysaccharide and muramyl dipeptide.

INNATE IMMUNE RESPONSES

Cellular Components of Innate Responses

The innate immune system consists of all the immune defenses that lack immunologic memory. Thus, a characteristic of innate responses is that they remain unchanged however often the antigen is encountered. These types of responses developed earlier in evolution than acquired responses. Nonetheless, defects in these evolutionarily primitive innate immune mechanisms, such as those that occur in chronic granulomatous disease (in which there is defective killing of phagocytosed microorganisms) can be fatal. (This subject will be discussed in more detail later in the Advances in Immunology series.)

Macrophages (derived from blood-borne monocytes) possess receptors for carbohydrates that are not normally exposed on the cells of vertebrates, such as mannose, and therefore can discriminate between “foreign” and “self” molecules. In addition, both macrophages and neutrophils have receptors for antibodies and complement, so that the coating of microorganisms with antibodies, complement, or both enhances phagocytosis. The engulfed microorganisms are subjected to a wide range of toxic intracellular molecules, including superoxide anion, hydroxyl radicals, hypochlorous acid, nitric oxide, antimicrobial cationic proteins and peptides, and lysozyme. Phagocytes also remove the body’s own dead or dying cells. Dying cells in necrotic tissue release substances that trigger an inflammatory response, whereas cells that are dying as a result of apoptosis (programmed cell death resulting in the digestion of DNA by endonucleases) express molecules on their cell surface, such as phosphatidyl serine, that identify them as candidates for phagocytosis.

A key cellular component of innate immunity — and one of the most intensely studied components during the past decade — is the interdigitating dendritic cell (Fig. 1). Cells of this type, which include Langerhans’ cells in skin, constantly but quietly endocytose extracellular antigens. However, they become activated and behave as antigen-presenting cells when pattern-recognition receptors on their surface recognize distinctive pathogen-associated molecular patterns on the surface of microorganisms. Endogenous danger signals, such as the release of interferon-α from virally infected cells or an increase in heat-shock proteins as a result of necrotic cell death, also activate dendritic cells. Molecules that act as pattern-recognition receptors on dendritic cells include the lipopolysaccharide receptor, the mannose receptor, and members of a family of molecules called toll. Pathogen-associated molecular patterns include yeast-cell-wall mannans, lipopolysaccharides on the surface of gram-negative bacteria, and teichoic acids, which are present on gram-positive bacteria.

Activation causes dendritic cells to up-regulate the expression of B7 costimulatory molecules (also known as CD80 and CD86) on their surface. Costimulatory molecules are molecules that provide the signals necessary for lymphocyte activation in addition to those provided through the antigen receptor. These activated dendritic cells migrate to the local draining lymph node, where they present antigen to T cells. The antigen is processed intracellularly into short peptides by means of proteolytic cleavage before it is presented by major-histocompatibility-complex (MHC) molecules on the surface of dendritic cells.

There are two classes of MHC molecules, class I and class II. There are three main types of class I molecules, HLA-A, B, and C, and three main kinds of class II molecules, HLA-DR, DQ, and DP. The MHC class II molecules present the peptides to the T-cell receptor on the surface of helper T cells. Dendritic cells are particularly efficient at initiating (priming) immune responses for which immunologic memory has not been established — that is, they activate so-called naive T cells (Fig. 1). (This subject will be discussed in more detail later in the series.)

Unlike macrophages and neutrophils, eosinophils are only weakly phagocytic and, on activation, probably kill parasites mainly by releasing cationic proteins and reactive oxygen metabolites into the extracellular fluid. They also secrete leukotrienes, prostaglandins, and various cytokines.

Basophils and mast cells have similar functional characteristics, but there is little evidence that blood basophils develop into tissue mast cells. Both types of cells possess high-affinity receptors for IgE (FcεR) and thereby become coated with IgE antibodies. These cells are important in atopic allergies such as eczema, hay fever, and asthma, in which allergen binding to the IgE cross-links the FcεR. This event triggers the cell to secrete inflammatory mediators such as histamine, prostaglandins, and leukotrienes. (This subject will be discussed in more detail later in the series.)

Natural killer cells destroy infected and malignant cells. They recognize their targets in one of two ways. Like many other cells, they possess Fc receptors that bind IgG (FcγR). These receptors link natural killer cells to IgG-coated target cells, which they kill by a process called antibody-dependent cellular cytotoxicity. The second system of recognition that is characteristic of natural killer cells relies on the killer-activating receptors and killer-inhibitory receptors of these cells (Fig. 2). The killer-activating receptors recognize a number of different molecules present on the surface of all nucleated cells, whereas the killer-inhibitory receptors recognize MHC class I molecules, which are also usually present on all nucleated...
If the killer-activating receptors are engaged, a “kill” instruction is issued to the natural killer cell, but this signal is normally overridden by an inhibitory signal sent by the killer-inhibitory receptor on recognition of MHC class I molecules (Fig. 2). Although all nucleated cells normally express MHC class I molecules on their surface, they can sometimes lose this ability. This loss may occur as a result of either microbial interference with the expression mechanism — for example, after herpesvirus infection — or malignant transformation. Therefore, cells that lack MHC class I surface molecules are in some way abnormal. This lack of MHC class I molecules means that there is no inhibitory signal from the killer-inhibitory receptor, and the natural killer cell kills the abnormal target cell by inserting the pore-forming molecule perforin into the membrane of the target cell and then injecting it with cytotoxic granzymes.

Figure 1. Function of Interdigitating Dendritic Cells. Pathogen-associated molecular patterns (PAMPs) allow the pattern-recognition receptors on the dendritic cells and macrophages of the innate immune response to differentiate between potentially harmful foreign microorganisms and self constituents. These cells are also stimulated by endogenous activators such as interferon-α, heat-shock proteins, and tumor necrosis factor α that are released as a result of infection. The activated antigen-presenting cells then present a cell-surface complex of a major-histocompatibility-complex (MHC) molecule and peptide, derived by intracellular processing of the foreign antigen, to the T-cell receptors on the highly specific CD28-bearing naive T cells, which become activated in the acquired immune response. Activation also causes dendritic cells to enhance their expression of B7 costimulatory molecules.
The role of erythrocytes and platelets in immune responses is sometimes overlooked, but because they have complement receptors, they play an important part in the clearance of immune complexes consisting of antigen, antibody, and components of the complement system.

**Soluble Factors in Innate Defense**

Innate responses frequently involve complement, acute-phase proteins, and cytokines. The early events of complement activation, which are based on an enzymatic amplifying cascade comparable to that seen in blood clotting, can be triggered by one of three pathways. The classic pathway is activated by antigen–antibody complexes, the alternative pathway by microbial-cell walls, and the lectin pathway by the interaction of microbial carbohydrates with mannose-binding protein in the plasma.

Irrespective of the source of activation, the outcome is the generation of a number of immunologically active substances. For example, a proteolytic-cleavage fragment of complement component C3, the C3b molecule, becomes deposited on the surface of microorganisms. This event enhances phagocytosis of the microbe, because phagocytic cells have cell-surface receptors for C3b. The complement fragments C3a, C4a, and C5a cause the release of inflammatory mediators from mast cells. C5a also acts as a powerful neutrophil chemoattractant. The complement components C5b, C6, C7, C8, and C9 form the membrane-attack complex, which perforates cell membranes and thereby leads to the death of the target cell.

The molecules collectively referred to as acute-phase proteins enhance resistance to infection and promote the repair of damaged tissue. Plasma levels of these proteins change rapidly in response to infection, inflammation, and tissue injury. In addition to some complement components, the acute-phase proteins include C-reactive protein (a useful marker of inflammation, particularly in diseases such as rheumatoid arthritis), serum amyloid A protein, proteinase inhibitors, and coagulation proteins.

Cytokines constitute another group of soluble mediators. They act as messengers both within the immune system and between the immune system and other systems of the body, forming an integrated network that is highly involved in the regulation of immune responses. The presence of a cytokine is sensed by a cell by means of specific cytokine receptors. However, the distinction between cytokines and cytokine receptors is sometimes blurred, because there is no clear boundary between these two categories.

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**Figure 2. A System Used by Natural Killer Cells to Recognize Normal Cells and Cells That Lack Major-Histocompatibility-Complex Class I Surface Molecules.**

Killer-activating receptors recognize a number of molecules present on the surface of normal, nucleated cells, and in the absence of an inhibitory signal from killer-inhibitory receptors, which recognize major-histocompatibility-complex (MHC) class I molecules, the receptors issue an order to the natural killer cells to attack and kill the other cell. The cytotoxic granules of the natural killer cells, which contain perforin and granzymes, become polarized at the interface with the target cell and are then released into the cell.
are soluble forms of cytokine receptors and membrane-anchored forms of some cytokines.

In addition to acting as messengers, some cytokines have a direct role in defense; for example, the interferons that are released by virally infected cells establish a state of viral resistance in the surrounding cells. Cytokines and their antagonists are increasingly being used as therapeutic agents. For example, a combination of interleukin-2 and interferon-α has proved valuable in the treatment of melanoma. Infliximab, a chimeric monoclonal antibody against tumor necrosis factor α, has had strikingly beneficial effects in patients with rheumatoid arthritis.

The Acute Inflammatory Response

Infection with a pathogen triggers an acute inflammatory response in which cells and molecules of the immune system move into the affected site. The activation of complement generates C3b, which coats the surface of the pathogen. The neutrophil chemoattractant and activator C5a is also produced, and together with C3a and C4a triggers the release of histamine by degranulating mast cells. This in turn causes the contraction of smooth muscles and a rapid increase in local vascular permeability. Substances released from the pathogen and from damaged tissues up-regulate the expression of adhesion molecules on vascular endothelium, alerting passing cells to the presence of infection. The cell-surface molecule L-selectin on neutrophils recognizes carbohydrate structures such as sialyl-Lewis x on the vascular adhesion molecules. The neutrophil rolling along the vessel wall is arrested in its course by these interactions. As the neutrophil becomes activated, it rapidly sheds L-selectin from its surface and replaces it with other cell-surface adhesion molecules, such as the integrins. These integrins bind the molecule E-selectin, which appears on the blood-vessel wall under the influence of inflammatory mediators such as bacterial lipopolysaccharide and the cytokines interleukin-1 and tumor necrosis factor α. Complement components, prostaglandins, leukotrienes, and other inflammatory mediators all contribute to the recruitment of inflammatory cells, as does an important group of chemoattractant cytokines called chemokines. (This subject will be discussed in more detail later in the series.) The activated neutrophils pass through the vessel walls, moving up the chemotactic gradient to accumulate at the site of infection, where they are well placed to phagocytose any C3b-coated microbes (Fig. 3). Mutations in the genes for a number of different adhesion molecules have been described in patients with leukocyte-adhesion deficiencies, some of which are associated with life-threatening infections.

ACQUIRED IMMUNE RESPONSES

The development of lymphocytes and the myeloid lineage from primordial stem cells in the fetal liver and in bone marrow is guided by interactions with stromal cells (such as fibroblasts) and by cytokines (including stem-cell factor and various colony-stimulating factors). The initial stages of lymphocyte development do not require the presence of an antigen, but once these cells express a mature antigen receptor, their survival and further differentiation become antigen-dependent.

The Structure of Antigen-Specific Molecules

The B-Cell Receptor and Soluble Antibodies

Antibodies consist of two identical heavy chains and two identical light chains that are held together by disulfide bonds. The N terminal of each chain possesses a variable domain that binds antigen through three hypervariable complementarity-determining regions (Fig. 4). The C terminal domains of the heavy and light chains form the constant regions, which define the class and subclass of the antibody and govern whether the light chain is of the κ or λ type. The amino acid sequence of the constant region of the heavy chains specifies five classes of immunoglobulins (IgG, IgA, IgM, IgD, and IgE), four subclasses of IgG, and two subclasses of IgA. These classes and subclasses have different functions. Each type of antibody can be produced as a circulating molecule or as a stationary molecule. The latter type has a hydrophobic transmembrane sequence that anchors the molecule in the B-cell membrane, where it functions as the B-cell receptor.

All immunoglobulins are glycoproteins and contain 3 to 13 percent carbohydrate, depending on the class of the antibody. The carbohydrate is essential in maintaining the structure of the antibody. The basic antibody “monomeric unit” (which is biochemically a tetramer) is bivalent, with two antigen-binding arms of identical specificity. Each of these arms can be cleaved proteolytically in the laboratory to yield individual monovalent antigen-binding fragments (Fab) (Fig. 4). Another part of the immunoglobulin molecule, the Fc region, contains most of the constant region of the heavy chains. The secretary IgA at mucosal surfaces is a tetravalent “dimer,” whereas circulating IgM is a decavalent “pentamer.” These IgA and IgM polymers are stabilized by a polypeptide, the J (joining) chain. Secretary IgA also contains a molecule called secretary component, which may protect the IgA against proteolytic cleavage within the gastrointestinal tract.

The T-Cell Receptor

Unlike antibodies, T-cell receptors are produced only as transmembrane molecules. They consist of α/β or γ/δ heterodimers; each α, β, γ, and δ chain contains a variable domain and a constant domain. As in the antibody molecule, the variable domains contain three complementarity-determining regions (Fig. 4), which in the case of the α/β T-cell receptor...
recognize a complex formed by a peptide seated within the groove of an MHC molecule. Most γ/δ T cells do not recognize antigen in the form of peptide–MHC complexes, although MHC-like ("non-classic MHC") molecules such as CD1 may present certain antigens (particularly lipids and glycolipids) to some γ/δ T cells. Other γ/δ T cells do recognize antigen directly, just as antibody molecules do.

The Diversity of Antigen Receptors

It has been estimated that lymphocytes are capable of producing about $10^{15}$ different antibody variable regions (B cells) and a similar number of T-cell–receptor variable regions. Remarkably, the vast diversity of the immune repertoire originates from fewer than 400 genes. This extraordinary feat is achieved by unique recombination processes that cut, splice, and modify variable-region genes.

The genetic components that encode the immunoglobulins lie on three chromosomes: the IGH cluster (named for the heavy chain and located on chromosome 14), the IGK cluster (named for the κ light chain and located on chromosome 2), and the IGL cluster (named for the λ light chain and located on chromosome 22). Within the IGH cluster are four types of gene segments: V (variable), D (diversity), J (joining), and C (constant). The IGK and IGL clusters lack D segments. All these segments contain multiple genes; in the IGH cluster, for example, there are about 50 functional V segments.

The T-cell receptor genes have a similar organization and also contain V, D, J, and C segments. The
The laying down of genetic instructions for the variable region involves the recombination of genes from the \( V, D, \) and \( J \) segments. The recombination process joins one gene segment of each type (e.g., \( VDJC \) in the case of the immunoglobulin heavy chain) to form a linear coding unit for each chain of the receptor. Each lymphocyte uses a different combination of these gene segments to form the genetic code of its antigen receptor. The recombination process is subject to splicing inaccuracies that cause slight variations in the nucleotides at the \( VDJ \) junctions. Furthermore, the enzyme terminal deoxynucleotidyltransferase can insert additional nucleotides around the \( VDJ \) junctions before they are ligated. Both the splicing errors and the added nucleotides further increase diversity and impart to each B-cell or T-cell clone a molecularly unique receptor (Fig. 5).

A series of nuclease and ligase enzymes do the cutting and pasting of the gene segments. Defects in the recombination-activating genes \( RAG-1 \) and \( RAG-2 \), which encode two of the enzymes that mediate the recombination of variable-region genes in both B cells and T cells, are responsible for one form of severe combined immunodeficiency; affected patients are unable to produce functional lymphocytes bearing antigen receptors. (This subject will be discussed in more detail later in the series.)

The sequences of T-cell receptors generally remain unaltered during cell division, but this is not the case with the B cell, which, in the germinal centers of secondary lymphoid organs, can undergo further rearrangements of \( V \) genes by a process referred to as receptor editing. This mechanism enables self-reactive B cells to see the error of their ways and redeem themselves by replacing one variable-region gene with a new variable-region gene. In this process, the existing \( V \) gene in the rearranged \( VDJ \) sequence is replaced by another \( V \) gene segment. The constant region specifies the class of the antibody (e.g., IgM or IgG), and during the immune response, the \( VDJ \) unit in B cells can join with different constant-region genes to alter the class of antibody in a process called class switching.

### Clonal Selection

There are no more than a few thousand lymphocytes specific for each antigen. Since each B cell is programmed to express only one of the vast number of potential antibodies, all the antigen-receptor molecules on a given lymphocyte have the same specificity. Such clones of lymphocytes are selected to participate in an immune response if they bear a receptor that can bind the relevant antigen, a process called clonal selection. The antigen-selected cells proliferate, leading to a rapid increase in the number of B or T cells that can recognize the antigen.
Antigens bear several different epitopes (Fig. 6), each with the capacity to bind to a unique clone.

Unlike the genes for T-cell receptors, the genes encoding B-cell receptors undergo a process of somatic hypermutation. This process occurs during B-cell proliferation within the germinal centers of secondary lymphoid tissues. The changes in amino acids in the antibody that result from this process fine-tune the recognition of antigen by B-cell receptors and determine the strength of binding (affinity) of the antibody. The stronger the binding to antigen, the greater the chance the B cell has of surviving and...
multiplying — a classic Darwinian mechanism of selecting cells that produce high-affinity antibodies. The result of clonal selection is a population of B cells with high affinity and exquisite antigen specificity for the immunizing antigen, as well as a memory of the encounter.

The proliferation of naive lymphocytes during the first encounter with an antigen, the primary immune response, generates both effector T and B cells (cytotoxic and helper T cells and antibody-secreting plasma cells) and memory T and B cells. The memory cells enable a quantitatively and qualitatively superior secondary immune response to be mounted after a subsequent encounter with the same antigen. Naive and memory T cells can, to some extent, be distinguished, because they often express different versions of the CD45 molecule (a tyrosine phosphatase that regulates cellular activation) on their surface; CD45RA is expressed on naive cells, and CD45RO is expressed on memory cells. Because memory cells are increased in number relative to naive cells and because memory cells are also more readily triggered, the secondary response is more rapid than the primary immune response. It produces a larger number of lymphocytes and, in the case of B cells, induces greater levels of antibody that has a greater affinity for the antigen than the antibody of the primary response.

The concept of vaccination is based on the fact that deliberate exposure to a harmless version of a pathogen generates memory cells but not the pathologic sequelae of the infectious agent itself. In this way, the immune system is primed to mount a secondary immune response with strong and immediate protection should the pathogenic version of the microorganism be encountered in the future.

**Major Populations of B Cells**

The B cells that develop earliest during ontogeny are referred to as B1 cells. Most B1 cells express CD5, an adhesion and signaling cell-surface molecule. They are the source of the so-called natural antibodies, which are IgM antibodies and are frequently polyreactive (i.e., they recognize several different antigens, often including common pathogens and autoantigens). In most cases, natural antibodies have a relatively low affinity.

Most B cells lack the CD5 molecule, and because they develop slightly later in ontogeny, they are referred to as B2 cells. Before they encounter antigen, mature B2 cells coexpress IgM and IgD antibodies on their cell surface, but by the time they become memory cells, they have usually switched to the use of IgG, IgA, or IgE as their antigen receptors. Complexes of antibodies with a newly encountered antigen and complement are localized in the follicular dendritic cells (a different type of cell from the interdigitating dendritic cell) within secondary lymphoid tissues. This event initiates the formation of the germinal centers, which are discrete areas within the spleen and lymph nodes where B-cell responses occur. Within these germinal centers, B2 cells that encounter the antigen undergo immunoglobulin class switching and begin to produce IgG, IgA, or IgE, and somatic hypermutation of their antigen-receptor genes occurs. Memory cells and plasma-cell precursors are also generated in the germinal centers. The final stages of differentiation of B2 cells into antibody-secreting plasma cells occur within the secondary lymphoid tissues but outside the germinal centers. Although generally short-lived, with a half-life of only a few days, some plasma cells survive for weeks, especially within the bone marrow.

**T Cells and the Thymus**

Stem cells continuously migrate from the bone marrow to the thymus, where they develop into T cells. Recent evidence suggests that, despite the partial de-
generation of the thymus that occurs at puberty, T cells continue to develop in the thymus throughout life. T cells with \(\alpha/\beta\) T-cell receptors initially remain in the thymus, where they are subjected to a series of selection procedures (Fig. 7). Unlike the antibody molecule, which acts as the antigen receptor on B cells and recognizes antigen in its native (natural) state, the \(\alpha/\beta\) T-cell receptor recognizes short peptides that result from the intracellular processing of protein antigens, which are presented to the T-cell receptor by MHC molecules on the cell surface. The amino acids recognized by the T-cell receptor derive from both the MHC molecule and the antigenic peptide. Thus, the T-cell receptor recognizes an individual’s own MHC molecules (self) together with peptides derived from foreign antigens.

Since MHC molecules are highly polymorphic, the desirable immature T cells in each person in an outbred population are those that can recognize self MHC molecules but that are not autoreactive. This objective is achieved by thymic education, a process that involves both positive and negative selection. Cells are positively selected if they express a T-cell receptor capable of interacting with the MHC complex. Positive selection occurs on cortical epithelial cells. However, many of these cells are potentially harmful because their T-cell receptors have a high affinity for a complex of self peptide and a self MHC molecule (or even an MHC molecule alone). These autoimmune T cells are eliminated by the induction of apoptosis when they interact with dendritic cells and macrophages in the thymic medulla (negative selection). This leaves T cells with only a weak affinity for self MHC molecules. These cells form the pool of T cells that are exported from the thymus as single-positive (CD4 or CD8) cells. In the periphery they have the potential to recognize a complex of foreign peptide plus self MHC molecules and to become activated if the affinity of the interaction exceeds a certain threshold.

Figure 7. Positive and Negative Selection in the Thymus.
T cells need to detect foreign antigens presented by self major-histocompatibility-complex (MHC) molecules. Part of the T-cell receptor recognizes the foreign peptide, and part of it recognizes the self MHC molecule. The random nature of T-cell–receptor gene rearrangements means that only a minority of T cells are capable of performing this task. Many of the immature CD4 and CD8 double-positive T cells are useless because their T-cell receptors do not recognize self MHC molecules at all. These T cells eventually undergo apoptosis. Cells whose T-cell receptors have various affinities for binding self MHC molecules (usually containing a self peptide) are positively selected on cortical epithelial cells. However, many of these cells are potentially harmful because their T-cell receptors have a high affinity for a complex of self peptide and a self MHC molecule (or even an MHC molecule alone). These autoimmune T cells are eliminated by the induction of apoptosis when they interact with dendritic cells and macrophages in the thymic medulla (negative selection). This leaves T cells with only a weak affinity for self MHC molecules. These cells form the pool of T cells that are exported from the thymus as single-positive (CD4 or CD8) cells. In the periphery they have the potential to recognize a complex of foreign peptide plus self MHC molecules and to become activated if the affinity of the interaction exceeds a certain threshold.
plexes on the person’s own epithelial cells in the thymic cortex. Positive selection switches off the signal for spontaneous apoptosis that is otherwise triggered naturally in developing T cells. More than 95 percent of T cells are not selected at this stage and therefore die in the thymus. In contrast, negative selection involves the induction of apoptosis in any lymphocyte that expresses a T-cell receptor with a high affinity for the complex of a self peptide plus a self MHC molecule on dendritic cells and macrophages in the thymic medulla. (This subject will be discussed in more detail later in the series.)

During thymic education, the expression of a large number of T-cell–surface molecules is switched on and off in a highly regulated manner. Some of these, and many other cell-surface molecules with a role in immune responses, were originally characterized on the basis of their reactivity to panels of monoclonal antibodies. The antibodies produced by various laboratories were said to form a cluster when they could be grouped together because they recognized the same cell-surface molecule. This led to a nomenclature in which a given molecule was assigned a “cluster of differentiation,” or CD, number—for example CD1, CD2, and CD3. This CD nomenclature has become the standard way of referring to these cell-surface molecules.

The CD4 and CD8 molecules are of particular note with regard to T-cell development; together with the CD3 group of molecules, they form an essential part of the T-cell–receptor complex. CD4 binds to an invariant part of the MHC class II molecule, whereas CD8 binds to an invariant part of the MHC class I molecule. CD4 T cells usually act as helper T cells and recognize antigens presented by MHC class II molecules, whereas CD8 T cells are usually cytotoxic and recognize antigen presented by MHC class I molecules. Early in T-cell development in the thymus, immature T cells express both CD4 and CD8. If they have an appropriate T-cell receptor, these double-positive immature T cells have the potential to recognize an antigen-derived peptide presented by either MHC class I or MHC class II molecules. As T cells mature in the thymus, however, the expression of one of these molecules is lost, resulting in single-positive CD4 or CD8 T cells that recognize a peptide presented only by MHC class II or MHC class I molecules, respectively.

MHC class I molecules are expressed on all nucleated cells. This allows infected cells to signal their plight to cytotoxic CD8 T cells and establish intimate intercellular contacts by presenting the complex of foreign peptide and MHC molecule to the T-cell receptor of the effector cell. Since MHC class II molecules signal CD4 helper T cells to secrete cytokines, the effector function of the helper T cell does not always depend on the establishment of intimate contact with the cell that will respond to the cytokine. This explains why the immune system needs only a few kinds of specialized “professional antigen-presenting cells” (dendritic cells, B cells, and activated macrophages) to express MHC class II molecules.

A minority of T cells in the thymus use γ and δ chain genes to produce a T-cell receptor. These γ/δ T cells rapidly leave the thymus, and some may also develop outside the thymus, possibly in the gut. Thymus-derived γ/δ T cells migrate to various locations throughout the body, including the epithelium of the gastrointestinal tract, where they are thought to contribute to mucosal defenses. The range of their specificities remains to be fully characterized, but they include both proteinaceous and nonproteinaceous antigens from mycobacteria and other infectious organisms. In addition, they have an important immunoregulatory role because they influence antibody production and immunoglobulin class switching by B cells and modify T-cell responses. Precisely how they mediate these immunoregulatory functions also remains to be established.

**Tolerance Mechanisms**

Negative selection constitutes one form of immunologic tolerance in that it removes from the immune system T cells that recognize any of the body’s own antigens within the thymus. Tolerance of T cells induced in the thymus and of B cells in the bone marrow is called central tolerance, but another mechanism to prevent autoimmunity is necessary, because most tissue-specific antigens are not present in the thymus or bone marrow or are present in amounts too small for the induction of tolerance.

Mechanisms occurring elsewhere in the body, which are collectively referred to as peripheral tolerance, supplement central tolerance. They are thought to be based largely on incomplete activation signals given to the lymphocyte when it encounters self antigen in the periphery, a phenomenon that leads to a state of specific unresponsiveness termed anergy (associated with impaired intracellular signaling) or to apoptosis. (This subject will be discussed in more detail later in the series.)

Many autoreactive B cells undergo clonal deletion or become anergic as they mature within the bone marrow. Negative selection occurs in the bone marrow if B cells encounter high levels of self antigen, either in the soluble phase or as cell-membrane constituents. However, the deletion of self-reactive B cells may be more rigorously enforced in the germinal centers of secondary lymphoid tissues such as the spleen. Because B cells recognize native antigen, there is no role for MHC molecules in any of these processes. For self antigens that are present at relatively low levels, immunologic tolerance is often maintained only within the T-cell population. This is sufficient to maintain tolerance because it denies the help essential for antibody production by self-reactive B cells.
REFERENCES


CORRECTION

The Immune System (First of Two Parts)

The ligand for integrin-mediated arrest and adhesion of neutrophils to the vascular endothelium is intercellular adhesion molecule 1 (ICAM-1), not E-selectin as shown in Figure 3 and stated in the text on page 42, line 36 of the left-hand column.