CHAPTER 4

Molecular and Cellular Basis of Immunity and Immunological Diseases

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- The immune system can be divided into innate and adaptive subsystems whose inappropriate activation leads to autoinflammatory and autoimmune diseases, respectively. Many rheumatic diseases are a combination of both processes.
- The innate immune system is activated by specific receptors that recognize patterns associated with pathogens, which activate a program of inflammation involving hundreds of genes.
- Cells of the innate immune system, including dendritic cells, natural killer (NK) cells, mast cells, eosinophils, and basophils, activate and modulate the adaptive immune response, directly combat pathogens, and respond to allergens.
- The adaptive immune response depends on antigen recognition by T and B cells, whose cell surface receptors are highly variable to respond to environmental insults. Normally, adaptive immune cells are tolerant to self.
- Different subsets of T lymphocytes, including T-helper, cytotoxic T cells, and T-regulatory cells, modulate the immune response to effectively combat pathogens yet limit autoimmunity. Dysregulation of T-cell function is seen in autoimmune disease.
- Antibody-producing B lymphocytes recognize and present soluble antigens. Autoantibodies contribute significantly to autoimmune diseases.

The vertebrate immune system protects the host from a wide variety of pathogens, including bacteria, viruses, fungi, and parasites. However, this remarkable versatility comes at the cost of autoimmune and autoinflammatory diseases that affect approximately 1 in 30 individuals. This chapter briefly reviews the cardinal molecular and cellular features of the immune system, including the molecular basis of recognition and response to pathogens, mechanisms of tolerance, and immunological memory. Knowledge of the immune system is critical to understanding rheumatologic disease. While the detailed pathophysiology of major autoimmune diseases remains elusive, genetic immune disorders and the effects of new biologic targeted treatments provide insights into many of the mechanisms of immunological disease.

OVERVIEW OF THE IMMUNE SYSTEM

The immune system can be divided into innate and adaptive subsystems (Figure 4-1). Innate immunity includes physical barriers such as skin and mucosa, phagocytic cells of the myelomonocytic lineage, natural killer (NK) lymphocytes, and serum constituents such as complement proteins. The innate immune system is "hard wired" to recognize pathogens through receptors that have evolved over hundreds of millions of years. In contrast, adaptive immune cells, namely T and B lymphocytes, display receptors derived from gene segments that are shuffled through the action of recombinase and somatic mutation enzymes. Both arms of the immune

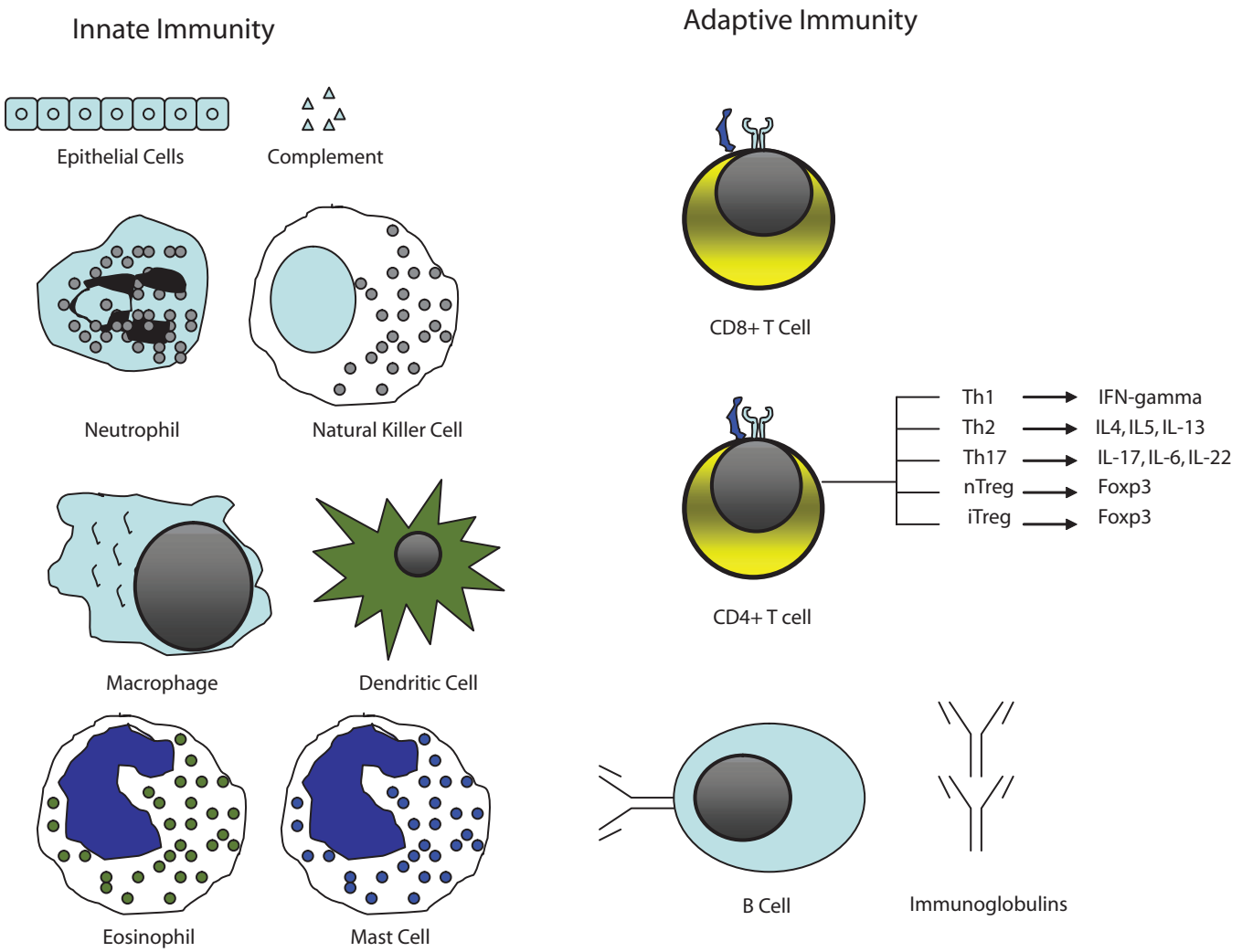


FIGURE 4-1

For discussion purposes, the cells of the immune system may be divided into the innate and the adaptive immune subsystems. Innate immunity includes epithelial cells, complement, phagocytic cells, and granulocytes. Innate immune cells have pattern recognition molecules that allow them to respond quickly to pathogens. Signals from the innate immune system activate the adaptive immune system, made up of T cells and B cells. T cells in turn may be divided into CD8+ T cells (cytotoxic T lymphocytes) and CD4+ T cells (T-helper cells). CD4+ T cells are subdivided into lineages of T-helper cells based on their unique cytokine and transcription factor profiles. B cells secrete immunoglobulin.

system coordinate host defense and can be responsible for immune-mediated disease. When the adaptive immune system causes pathology through T and B cell–mediated effects, this is termed *autoimmune disease.* The innate immune system can also inappropriately trigger inflammation without activation of the adaptive immune system; this is termed *autoinflammatory disease*. As will be described, many rheumatic diseases are a combination of both processes.

Stem cells of the immune system arise from the fetal yolk sac and populate the bone marrow, spleen, and liver. In the adult, bone marrow is the predominant source of lymphocytic and myelomonocytic progenitor cells. B cells mature in the bone marrow, T cells mature in the thymus, and monocytes develop at varying sites in the periphery. Lymphoid organs include the thymus, spleen, lymph nodes, gut-associated lymphoid tissue (GALT), and mucosa-associated lymphoid tissue (MALT) (Figure 4-2). The spleen, the major site where lymphocytes encounter blood-borne antigen, also clears the circulation of senescent red blood cells and foreign substances.

Ultimately, immune function depends on the ability of cells to localize within specific tissues and to interact with each other in a coordinated fashion. During normal homeostasis and inflammation, chemotactic cytokines

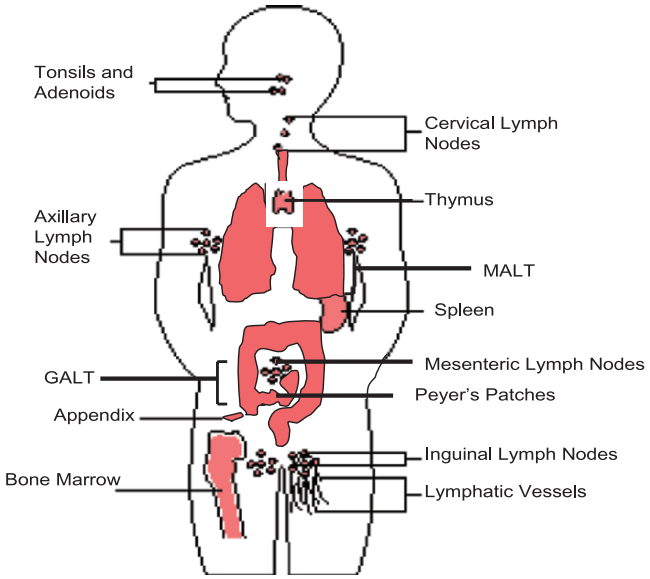


FIGURE 4-2

Immune system tissues are found throughout the body. They include large organs, such as the spleen and bone marrow, as well as aggregates of lymphatic tissue lining mucosal surfaces.

(*chemokines)* and their cognate receptors provide a flexible code for facilitating this cell trafficking. Limiting lymphocyte migration through pharmacological targeting of chemokines or their receptors is one strategy for immunosuppression. One drug that acts in this manner is *fingolimod*, a sphingosine 1-phosphate receptor agonist.

INNATE IMMUNITY

Innate immunity provides the body's initial encounter with pathogens. Phagocytic cells, that is, macrophages, dendritic cells (DCs), and neutrophils, recognize pathogens by using pathogen-associated molecular patterns (PAMPs). PAMPs, such as viral RNA and lipopolysaccharide (LPS), are essential molecules for microbial survival, which restricts major changes in their structure. Cells recognize PAMPs using pathogen-recognition receptors (PRRs), such as Toll-like receptors (TLRs), an evolutionarily ancient mechanism that is conserved in plants and animals (1,2). Other PRRs include NLRs (NOD-like receptors), and RLRs (RIG-I-like receptors) (Table 4-1).

The engagement of PRRs leads to the activation of signaling pathways that activate inflammation. The *NF-κB signaling pathway* can be activated by most TLRs and culminates in the transcriptional activation of hundreds of pro-inflammatory genes, including many pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, tumor necrosis factor (TNF), and chemokines, such as IL-8, that attract more innate immune cells. Activation of NLRs leads to the formation of a proteolytic signaling complex denoted the *inflammasome*, which processes a subset of these cytokines, leading to the secretion of IL-1 and IL-18 (3).

The importance of proinflammatory cytokines in rheumatic disease is exemplified by the effectiveness of TNF-alpha receptor antagonists like *etanercept*, *infliximab*, and *adalimumab* in the treatment of rheumatoid arthritis (RA). Conversely, dominant mutations in one of the TNF receptors (TNFR1) result in an autoinflammatory disorder termed *TRAPS* (TNFR-associated periodic syndrome). Mutations in constituents of the inflammasome give rise to diseases such as *familial Mediterranean fever* (FMF) and *neonatal onset multiorgan inflammatory disorder* (NOMID) (4). The latter disorder can be effectively treated with the IL-1 receptor antagonist *anakinra*. Mutation of proteins that recognize intracellular pathogens such as the NLR NOD2/CARD15 is associated with *Crohn's disease*.

TABLE 4-1. PATTERN RECOGNITION RECEPTORS (PRRs) IDENTIFIED IN EXPERIMENTAL ANIMALS AND HUMANS.[a]

PRR FAMILY	FAMILY MEMBERS	EXAMPLES OF PAMPs	EXAMPLES OF ASSOCIATED IMMUNE DISEASES
Toll-like receptors (TLRs)	TLR1-13	Zymosan, lipopolysaccharide, CpG oligonucleotides	Leprosy, atherosclerosis, asthma, inflammatory bowel disease
NOD-like receptors (NLRs)	NOD 1–5, NALP 1–14, CIITA, IPAF, NAIP	Low intracellular potassium, monosodium urate, peptidoglycan	Crohn's disease, Muckle–Wells syndrome, pseudogout, Familial Mediterranean fever
RIG-I-like receptors (RLRs)	RIG1, MDA5, LGP2	Double-stranded RNA	Increased susceptibility to RNA viruses

[a] Dozens of pattern recognition receptors (PRRs) have been identified in experimental animals and in humans. Although the pathogen-associated molecular pattern (PAMP) that each of these receptors recognizes has not been elucidated, mutations in PRRs have been linked to several human diseases. These include genetic mutations that lead to hyperactivation of the inflammasome (e.g, NALP3 and Muckle–Wells syndrome) and increased susceptibility to chronic inflammation (e.g., NOD2 and Crohn's disease). Chronic stimulation of the innate immune system through PRRs appears to be important in the chronic inflammation of rheumatic diseases. This is the rationale behind arthritis therapy with the drug etanercept, which blocks the action of TNF-alpha, a PRR signaling pathway target cytokine.

Innate Immune Cells

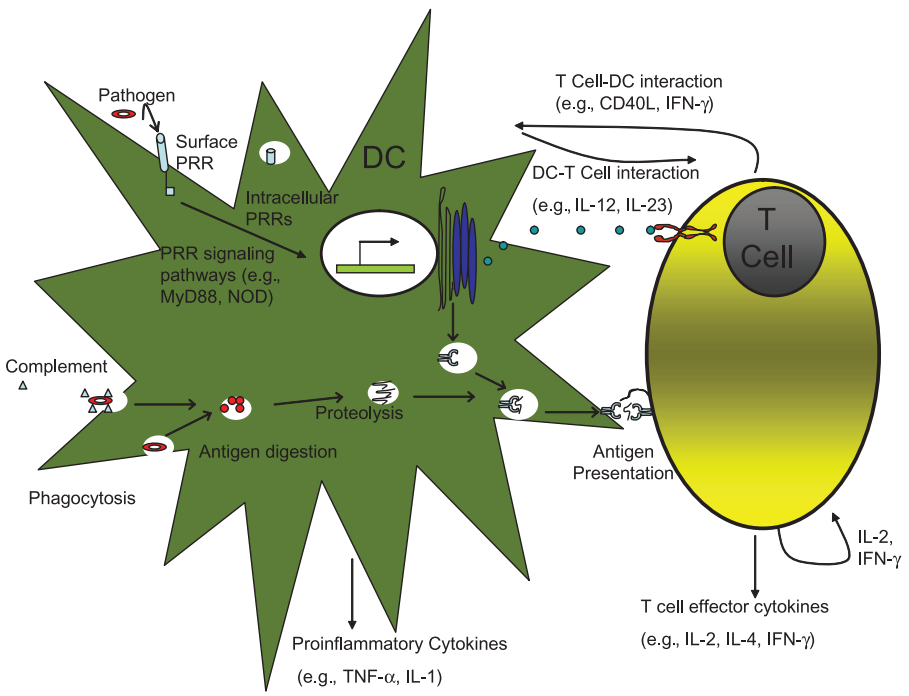
The release of pro-inflammatory cytokines activates other components of the innate and adaptive immune systems, and DCs are key to this connection (Figure 4-3) (5). Although derived from the bone marrow, DCs reside in the periphery. Most organs are thought to possess their own DC populations, where they act as sentinels for pathogens. Upon activation, they migrate to the lymph nodes and the spleen, where they present their antigens to T cells in the context of costimulatory molecules. *Adjuvants* increase the antigenicity of vaccines through their ability to activate DCs and other phagocytes. DCs produce an array of cytokines, including IL-12 and IL-23, that activate and regulate lymphocytes. Conversely, DCs and other phagocytic cells are activated by the products of lymphocytes, such as the cytokine interferon (IFN) gamma. A subset of DCs, plasmacytoid DCs, is the body's major producer of type I IFNs (6). IFNs are critical for host defense against viruses, but overproduction of IFN is a feature of rheumatic diseases, such as systemic lupus erythematosus (SLE).

Natural killer cells are a lymphocyte subset that can be included in the innate immune system because NK cells lack rearranging antigen receptors. Among the receptors NK cells do express, some can sense stressed or damaged cells. For example, NK cells can lyse virus-infected cells and tumors that lack major histocompatibility class (MHC) I molecules. NK cells also produce significant quantities of cytokines, such as IFN-gamma, that can influence the development of T cells. NKT cells are a unique subset of T cells with properties of NK cells that recognize lipid antigens presented by the molecule CD1d via a restricted set of T-cell receptors. NK T cells appear to be vital for combating certain fungal, protozoan, bacterial, and viral infections (7).

Eosinophils, basophils, and mast cells are cellular components of the innate immune system that are often

FIGURE 4-3

Dendritic cells (DC) reside inside peripheral tissues where they survey the environment for pathogens. After contact with a pathogen, a DC migrates to the regional lymph node to activate the adaptive immune response. DCs sense pathogens in one of several ways. One method is activation of intracellular and extracellular pattern recognition receptor (PRR) signaling pathways by pathogen-associated molecular patterns (PAMPs). Dendritic cells also ingest pathogens and break them down into peptides that are then presented to T cells in the context of major histocompatibility complex (MHC) molecules. In addition, complement can bind to the surface of pathogens, and phagocytes will recognize the complement–pathogen aggregates through complement receptors. After antigen recognition, the DC activates cells of the adaptive immune response either via direct cell contact at the immune synapse or through cytokine signaling. T cells and B cells in turn secrete cytokines that offer feedback to the dendritic cells, altering the DC cytokine secretion profile and regulating DC survival. Adaptive immune cells also signal to one another as well as engage in autocrine stimulation.



associated with allergic diseases, but these cells are also active participants in other aspects of immunity (8). Eosinophils, important for host defense against gastrointestinal parasites, secrete cytokines that regulate B cells and T cells, and exhibit strong effects on mucosal surfaces. Basophils and mast cells both express high affinity IgE receptor and release histamine. Basophils influence CD4+ T cells via the release of IL-4 and IL-13 and activate B cells via CD40 ligand. Mast cells are long-lived cells that undergo terminal differentiation and ultimately reside in well-vascularized tissues. They express TLRs, secrete pathogen-fighting toxins, respond to allergens, and secrete cytokines that influence CD4+ T-cell activity. Though mast cells are known to be involved in the pathogenesis of allergies and asthma, they also appear to be critical in the development of arthritis.

COMPLEMENT

The complement system consists of more than 30 serum and cell surface proteins that function as soluble innate immune receptors and amplifiers of antibody responses. Components of the complement system, such as C1q, C3, and mannan binding lectin (MBL), bind cellular and subcellular components of microbes as well as DNA, RNA, and membrane fragments released by endogenous cell death. The classic complement pathway begins with the activation of C1q by immunoglobulin-containing immune complexes, and the alternative complement pathway begins with the thioester activation of C3. Complement coats the surface of microorganisms. Receptors on phagocytic cells can then bind the complement, prompting ingestion of the microorganisms (*opsonization*). Complement also induces phagocytic cells to secrete cytokines through activation of the complement receptors and influences TLR signal transduction. Additionally, the inflammatory cascade initiated by complement binding recruits more phagocytes and mast cells to sites of tissue injury and promotes cytokine production that activates the adaptive immune response. Another complement function is the direct lysing of microorganisms through formation of the membrane attack complex (MAC), made up of C5-C9.

Interestingly, mutations in complement and complement regulatory protein gene deficiencies have been linked to several autoimmune and inflammatory diseases, including SLE (9). Complement H deficiency increases susceptibility to *hemolytic uremic syndrome* and *macular degeneration*. Deficiency of C1 inhibitor causes *hereditary angioedema*. C3 deficiency results in severe susceptibility to microbial pathogens, and deficiency of C5-C9 is associated with selective susceptibility to *Neisseria* species. Patients with mutations of MBL are also immunodeficient. Patients with C4 deficiency are the most susceptible to SLE and related autoimmune diseases, perhaps due to a failure to properly regulate the effects of immune complexes on adaptive immune cells.

ANTIGEN PRESENTATION AND MAJOR HISTOCOMPATIBILITY CLASS MOLECULES

An antigen can be defined as a substance that generates an immune response. What distinguishes adaptive immune cells from innate immune cells is the ability of B cells and T cells to express unique, highly antigen-specific receptors on their plasma membranes. Engagement of these receptors causes an individual B or T cell to expand into a clonal population of lymphocytes directed against the antigen-bearing pathogen. Expansion of lymphocytes that recognize host antigens rather than pathogenic antigens is one mechanism of autoimmune disease.

Although T and B cells use a similar strategy to produce their antigen-specific receptors, they recognize antigen very differently. B cells recognize soluble peptides, proteins, nucleic acids, polysaccharides, lipids, and small synthetic molecules. These antigens bind directly to the B-cell antigen receptor (BCR), a membrane-associated form of immunoglobulin. Consequently, B cells have no need for antigen-presenting cells. In contrast, T cells need antigen to be presented, that is, the T-cell antigen receptor (TCR) recognizes fragments only when they are bound to MHC molecules on the surface of other cells.

The two types of MHC molecules, class I and class II, are the most polymorphic human proteins, and expression of different MHC alleles correlates with susceptibility to autoimmune disease. In humans, the MHC [also termed *histocompatibility locus antigen* (HLA)] comprises a 3.6 Mbp DNA sequence on chromosome 6p. It is the single most gene-dense region of the human genome. HLA alleles associated with specific diseases include HLA-B27 with spondyloarthropathy and HLADRB1 with rheumatoid arthritis.

The three-dimensional structure of both classes of MHC creates a cleft, or groove, in which peptides are bound and can be recognized by T cells. Each MHC molecule binds a single peptide, but the total pool of MHC molecules can bind an array of peptides. The association of peptides with MHC molecules is determined by MHC molecule primary and secondary structures. The types of antigens that each MHC class binds are distinct: MHC class I molecules most often present endogenous peptides, while the MHC class II molecules present exogenous peptides. Class I molecules are con-

stitutively expressed on nearly all cells except neurons and red blood cells, whereas class II molecules are limited to B cells, macrophages, DCs, activated T cells, and activated endothelial cells. Cells that present antigen to T cells in the context of MHC class II are called *antigen presenting cells* (APCs).

Although most T cells recognize peptides, gamma delta T cells, representing about 5% of peripheral blood T cells, can recognize nonpeptide antigen, such as prenyl pyrophosphate derivatives of mycobacteria. A subset of these cells, known as Vdelta2^{+} T cells, do not need APCs to recognize antigen and may act as APCs themselves to direct other T-cell responses.

MAJOR HISTOCOMPATIBILITY CLASS CLASS I

Major histocompatibility class class I molecules are synthesized and assembled within the endoplasmic reticulum (ER). Two proteins comprise the MHC class I molecule. The alpha chain, encoded by genes within the HLA locus (HLA-A, -B, and -C), associates with a non–MHC-encoded protein, beta$_2$ microglobulin. Class I molecules bind peptides that are 9 to 11 amino acids in length. Peptides from pathogens in the cytosol, such as viruses, as well as normal cellular proteins are degraded in the proteasome and then transferred to the ER by the TAP transporter molecules, also encoded within the MHC locus. Within the ER, these endogenous peptides bind the nascent MHC class I molecules. In addition, mechanisms allow certain exogenous antigens to be cross-presented by class I, such as fusion of endosomes with the ER. This occurs most efficiently in activated DCs. The MHC I molecule–peptide complexes translocate to the plasma membrane, where they engage T cells. The T-cell accessory molecule, CD8, binds to class I molecules; thus, *CD8+ T cells are class I restricted*.

MHC CLASS II

Major histocompatibility class class II molecules bind extracellular peptides. Class II molecules are composed of two chains that are products of different MHC genes (HLA-DR, -DQ, and -DP) than MHC class I. Antigen processing by MHC class II–expressing APCs occurs in three steps: extracellular antigens are ingested, internalized, and proteolyzed (Figure 4-3). MHC class II molecules are synthesized and assembled in the ER, but they are prevented from binding endogenous antigens because the class II complex associates with a molecule called the invariant chain. After export from the Golgi complex, the invariant chain is removed by the action of proteases and HLA-DM. Endosomes containing the ingested extracellular peptides then fuse with MHC class II–containing vesicles exported from the Golgi. This action allows processed, extracellularly derived antigen to bind to class II molecules. The T-cell accessory molecule, CD4, binds to class II molecules; therefore, *CD4+ T cells are class II restricted*. The bare lymphocyte syndrome (BLS) is a primary immunodeficiency resulting from the absence of MHC class II expression.

T CELLS

The T-Cell Receptor and Antigen Recognition

Antigen-recognition and signal-transducing elements aggregate at the plasma membrane to form the T-cell receptor (TCR) complex. Four TCR genes encode the subunits responsible for antigen recognition: alpha, beta, gamma, and delta. These TCR genes are members of the immunoglobulin superfamily. Like other immunoglobulin genes, the TCR genes undergo DNA rearrangement of variable (V), diversity (D), joining (J), and constant (C) region segments. Recombination of gene segments is generated by the action of several enzymes, including the recombinase-activating genes RAG-1 and RAG-2. The rearranged genes are then transcribed and translated to produce protein subunits. Heterodimers of these subunits come together to create either the alpha beta or gamma delta receptors, which function as the T cell's antigen-recognition units. The majority of T cells in peripheral blood, lymph nodes, and spleen express alpha beta receptors.

Diversity-generating mechanisms allow humans to produce 10^{16} possible antigen-specific alpha beta T-cell receptors. V-region gene segments are highly polymorphic, and recombinant assembly of the different V, D, and J segments allows for a wide array of possible antigen receptors. The enzyme terminal deoxytransferase further expands the receptor repertoire by inserting random nucleotides at the junctions between the gene segments.

T-cell receptor genes show allelic exclusion, that is, if one chromosome undergoes rearrangement and produces a functional receptor chain, the genes on the other chromosome are prevented from rearranging. Hence, each T-cell clone expresses only one antigen receptor, and antigen-specific T cells develop in unimmunized or naive individuals independent of exposure to antigen. Subsequent antigen exposure leads to clonal selection or expansion of lymphocytes with the appropriate antigen receptors. Clonal selection improves the efficiency of the immune response and produces immunological memory.

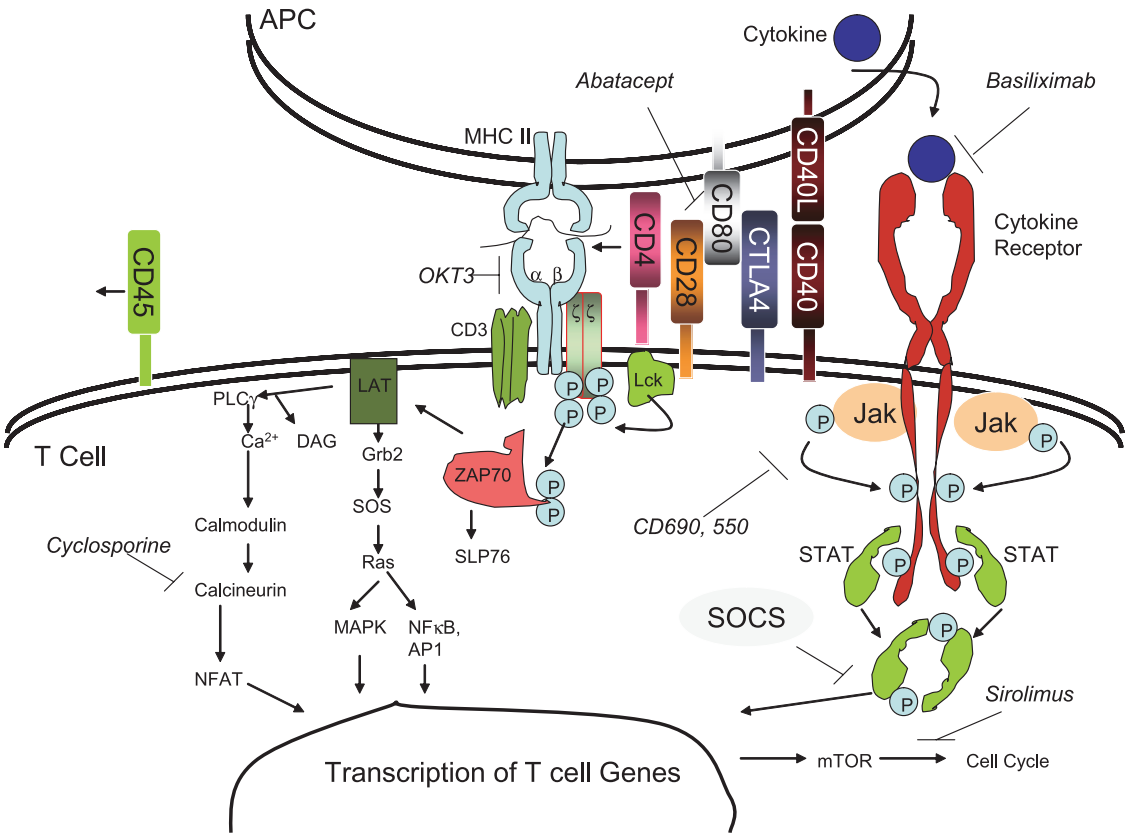
Mutations in the genetic machinery for V(D)J recombination have been linked to a variety of *severe combined immunodeficiency* (SCID) conditions in humans (10). Deficiency in RAG-1 or RAG-2 leads to a virtual lack of all mature T and B lymphocytes, whereas impairment of RAG-1 and RAG-2 without total loss of function leads to a distinct phenotype called *Omenn syndrome*. Mutations in another recombination gene, ARTEMIS, cause *RS-SCID,* a condition with absence of mature B cells and T cells, normal NK cells, and increased radiosensitivity. Rearrangement of the TCR genes requires double-stranded breaks in the genome, and the kinase ataxia telangiectasia mutated (ATM) regulates this potentially hazardous action. ATM deficiency leads to *ataxia–telangiectasia* (A-T), an autosomal recessive genomic instability syndrome.

T-Cell Receptor Signal Transduction

T-cell receptor alpha beta or gamma delta subunits provide an elegant solution to the problem of antigen recognition, but these subunits do not transmit activation signals. The antigen-recognizing subunits associate with nonpolymorphic signaling subunits called the *invariant chains*, which include the CD3 family of molecules (gamma, delta, and epsilon) and the zeta chain (Figure 4-4). These subunits contain domains called *immune tyrosine-based activation motifs* (ITAMs), domains that are also present on B-cell and Fc receptors. The ITAMs are phosphorylated by *protein tyrosine kinases* (PTKs) and serve to recruit other signaling molecules. Some lymphocyte receptors have motifs called

FIGURE 4-4

A CD4+ T cell and an APC interact at the immune synapse. The T-cell receptor, comprised of the alpha beta subunits, CD3 invariant chains, and CD4 coreceptor, contacts the MHC–peptide complex. Costimulatory signals are transmitted through a series of molecules, including CD28 and CD40L. Engagement of peptide in the context of MHC brings the CD4-linked tyrosine kinase Lck into proximity with the beta alpha subunits and CD3, while excluding the phosphatase CD45. Lck phosphorylates immune tyrosine-based activation motifs (ITAMs) on CD3. This triggers a phosphorylation cascade that ultimately activates the transcription factors, including NFAT and NF-κB, which bind the DNA and modulate gene expression. APCs also activate T cells through cytokines, particularly via the JAK/STAT signaling pathway. Drugs that block the activation of T cells are shown in italics.



immunoreceptor tyrosine-based inhibitory motifs (ITIMs), which recruit phosphatases and attenuate signaling. In the resting T cell, a kinetic balance between PTKs and tyrosine phosphatases keeps TCR signaling through the ITAMs at a low basal level.

When the TCR engages the MHC–antigen complex of an APC, rearrangement of the plasma membrane surrounding the TCR changes the relative distribution of PTKs and tyrosine phosphatases near the cell surface; this redistribution of signaling molecules is referred to as the *immune synapse* (Figure 4-4) (11). The first step in TCR signaling is tyrosine phosphorylation of receptor subunits and adapter molecules such as LAT (linker of activated T cells) and SLP-76. This is mediated by a series of PTKs including Lck (a PTK bound to the CD4+ and CD8+ molecules), Zap-70 (zeta-associated protein of 70 kDa), and members of the Tec family. This in turn leads to the elevation of intracellular calcium, which activates the phosphatase calcineurin. Calcineurin dephosphorylates NFAT (nuclear factor of activated T cells), allowing the translocation of this transcription factor to the nucleus. The immunosuppressive drugs *cyclosporine* and *tacrolimus* work by inhibiting calcineurin and NFAT activation; conversely, mutations that inhibit calcium channel function are a cause of primary immunodeficiency. TCR signaling also activates other transcription factors such as NF-κB, Fos, and Jun, which modulate the expression of genes encoding cytokines, receptors, and other proteins that carry out T-cell functions.

T cells are also activated by cytokines, some of which are made by other cells, and some of which are made by T cells themselves. Many, but not all, cytokines bind to receptors that are members of a cytokine receptor superfamily that signals via Janus kinases (JAKs). An important class of substrates for JAKs are the STATs (signal transducers and activators of transcription), a family of seven transcription factors with distinct but critical functions in host defense. Cytokine signaling is negatively regulated by inhibitors of cytokine signal transduction, including SH2-containing phosphatases (SHP), protein inhibitors of activated STATs (PIAS), and suppressors of cytokine signaling (SOCS). Absence of SHP1, SOCS1, or SOCS3 is associated with systemic autoimmune disease in mouse models. Conversely, patients with mutations of *JAK3*, or its associated receptor subunit the common gamma chain, have SCID due to failure in signaling by IL-2, IL-4, IL-7, IL-15, and IL-21. Pharmacological targeting of JAK3 is being studied as a new class of immunosuppressant drugs (12).

Costimulation

Occupancy of the T-cell receptor alone does not lead to T-cell activation; occupancy of other costimulatory molecules is necessary to provide a full activation signal (13). T cells that only receive a TCR signal can become *anergic* or unable to achieve full activation. Receptors that provide costimulation include: CD28, ICOS (inducible costimulator), PD-1, and adhesion molecules (CD11a/CD18, CD2, and others). Mutation of ICOS is one cause of common variable immunodeficiency (CVID). A number of receptors in the TNF-receptor family also function as lymphocyte costimulators. The counter-receptors for CD28 are CD80 and CD86, which are expressed on APCs. Interruption of CD28-dependent costimulation with the drug *abatacept* is efficacious in treating rheumatoid arthritis. A CD28-related molecule, CTLA-4, which also binds CD80 and CD86, downregulates immune responses; its deficiency is associated with lethal autoimmune disease in mice.

T-Cell Development

Precursor T cells originate in the bone marrow from hematopoietic stem cells and migrate to the thymus. As they mature, T cells move from the thymic cortex to the medulla. The most immature T cells, known as double-negative (DN) T cells, lack the surface markers CD4 and CD8; these cells do not express a mature TCR but do express the pre–T-cell receptor, which comprises the beta chain, an invariant protein called pre-T alpha, CD3, and zeta proteins. These cells mature into double-positive (DP) T cells, which express CD4 and CD8 and undergo alpha chain rearrangement to form TCR alpha beta heterodimers. DP thymocytes mature to become single-positive (SP) thymocytes, which express either CD4 or CD8, as well as a complete TCR. Mature SP T cells migrate out from the thymic medulla to populate the peripheral lymphoid tissues.

The development of T cells depends on signals from the thymic stroma, which direct multipotent cells towards the T-cell fate. Forkhead box N1 (FOXN1) is a transcription factor that is essential for thymic organogenesis and the attraction of hematopoietic stem cells to the thymus. Mutations of FOXN1 result in the "nude" phenotype in mice and humans, characterized by athymia and hairlessness. Another important stromal signal is Notch1 signaling; mutation of Notch1 results in developmental arrest of T cells.

The vast majority of T cell precursors generated in the thymus die there. Much of the T-cell death that occurs in the thymus is due to programmed cell death (*apoptosis*). To survive, potential T cells must first produce TCRs at the DP stage that can recognize self-MHC molecules, a process called *positive selection*. Cells lacking an appropriate receptor undergo "death by neglect," that is, they do not receive further maturation signals from the thymic stroma. Of the SP thymocytes that do develop, some recognize self-MHC molecules and self-peptides with high avidity. These potentially autoreactive T cells are also eliminated, a

process called *negative selection or clonal deletion.* The removal of potentially harmful T cells in the thymus is termed *central tolerance*. Of course, not all potential self-peptides are expressed in the thymus. This problem is addressed by a transcription factor, autoimmune regulator (AIRE), which induces the ectopic transcription of organ-specific non-thymic peptides in thymic epithelium (14). Patients with mutations in *AIRE* have an autoimmune disorder called APECED (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy) syndrome, which results from failure of negative selection of T cells responsive to tissue-specific antigens.

CD4+ T-Cell Differentiation

CD4+ T cells are also known as T-helper cells because of their role in promoting the function of other immune cells. Classically, CD4+ cells have been thought to differentiate into one of two primary effector cell types: T-helper 1 (Th1) and T-helper 2 (Th2) cells (Figure 4-1). Precisely how T-helper cell lineage differentiation occurs is the subject of intense study, but cytokines produced by DCs and macrophages are clearly important in the outcome. Macrophages and dendritic cells promote differentiation of naive CD4+ cells into Th1 cells by secreting IL-12. In addition, T-cell transcription factors, such as Stat6, GATA-3, Stat4, and T-Bet are also critical (15).

T-helper 1 cells secrete cytokines that promote cell-mediated immunity. The key Th1 cytokine is IFN-gamma, which enhances the ability of macrophages to kill ingested microorganisms, upregulates MHC class I expression on many cell types, and suppresses Th2 responses. Mutations that affect the IL-12/IFN-gamma axis cause susceptibility to intracellular microorganisms, especially atypical *Mycobacteria*. Mutation of Tyk2, the Jak kinase responsible for signaling by IL-12 and type I IFNs, is one cause of primary immunodeficiency known as *HyperIgE syndrome* (HIES).

T-helper 2 cells are essential for defense against helminth infections and the host response to allergens. IL-4 promotes the differentiation of naive CD4+ T cells into Th2 cells, which produce IL-4, IL-5, IL-10, and IL-13. These cytokines promote humoral and allergic-type responses. IL-4 inhibits macrophage activation, blocks the effects of IFN-gamma, promotes mast cell growth, and induces B cells to produce IgE. IL-5 induces eosinophilia, and IL-10 inhibits macrophage antigen presentation and decreases expression of MHC I molecules. The importance of IL-10 is underscored by the finding that IL-10 knockout mice develop severe autoimmune disease.

The simple dichotomy between Th1 and Th2 cells has recently been called into question with the discovery of other types of CD4+ cells that produce neither IFN-gamma nor IL-4, but rather produce other inflammatory cytokines. So-called Th17 cells produce IL-17, IL-6, IL-22, G-CSF (granulocyte-colony stimulating factor), and TNF-alpha (16). Th17 cell differentiation and maintenance is promoted by transforming growth factor (TGF)-beta 1, IL-6, and IL-23, and it is inhibited by both IFN-gamma and IL-4. Th17 cells are abundant in the lamina propria of the small intestine in mice and seem to be important in host defense against extracellular bacteria. IL-17 is overproduced in many autoimmune and autoinflammatory disorders, in which it appears to play a major pathogenic role. In addition, although individual mouse T cells tend to produce cytokines related to one of the above subsets, human T cells can produce a wider variety of cytokines and are not as easily classified by the above criteria.

Regulatory T Cells and Maintenance of Peripheral Tolerance

Another set of CD4+ cells, dubbed T regulatory (Treg) cells, is essential for limiting immune responses; as such, it is critical for *peripheral tolerance* (17). Tregs have the remarkable ability to suppress proliferation and cytokine production by effector T cells through mechanisms that are at present not well understood. The transcription factor FoxP3 (forkhead box P3) is both necessary and sufficient for Treg function. *Natural Treg*s (nTregs), arising in the thymus, express molecules such as CD25 and GITR that are usually restricted to activated T cells. In addition, naive T cells can be driven to differentiate into *induced* or iTregs under the influence of the cytokine TGF-beta1. Mutation of FoxP3 produces the *scurfy* phenotype in mice and *IPEX* (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) syndrome in humans, both of which are manifested by T-cell attack on multiple organs and autoantibody production.

Though important, Treg cells are not the only mediators of peripheral tolerance. Another mechanism is elimination of activated T cells through repetitive stimulation. Repeatedly stimulated $CD4^+$ T cells can undergo autocrine cell death through interactions between the TNF-ligand FasL and its receptor Fas/CD95. *Autoimmune lymphoproliferative syndrome* (ALPS), characterized by lymphadenopathy, accumulation of an unusual subset of $CD4^-CD8^-$ double-negative peripheral T cells, and frequent autoimmune disease, is caused in most cases by dominant negative germline mutations in the gene coding for Fas. Naive T cells activated through the TCR without appropriate costimulation can also become anergic, a more temporary form of peripheral immune tolerance. Because of positive selection towards self-MHC, it is thought that most peripheral T cells are constantly receiving low levels of activation signals from self-peptide MHC complexes in the periphery, and this may modulate T-cell responses as well.

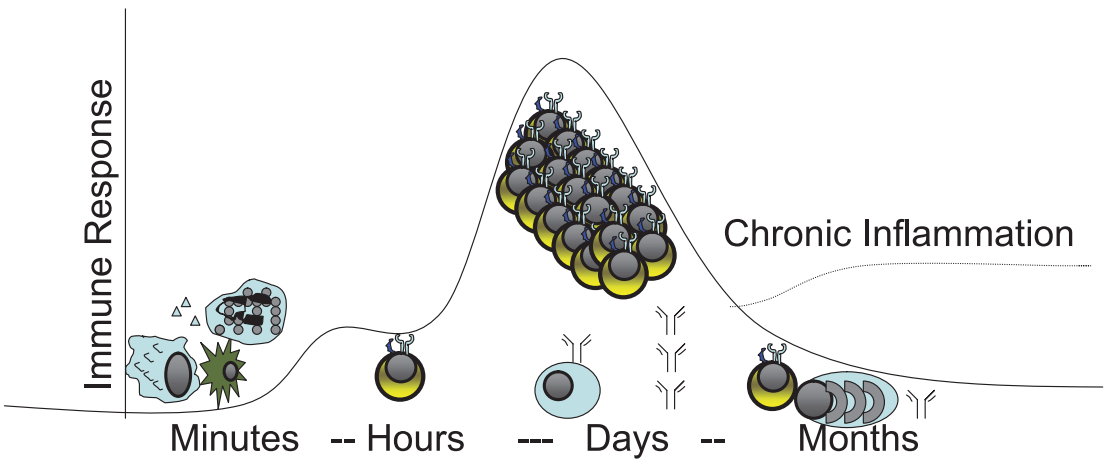
CD8+ T Cells

CD8+ T cells, also known as cytotoxic T lymphocytes (CTLs), recognize antigen in the context of MHC I molecules. Because MHC I molecules present antigens synthesized by the target cell, CTLs play a prominent role in defense against intracellular pathogens, particularly viruses, protozoa, and bacteria, as well as cancer. During primary infection, antigen-specific CTL clones expand rapidly, and at the peak of response can represent a substantial fraction of all T cells. After the infection is cleared, this initial burst is followed by a rapid depletion of these cells, probably due to the cells outgrowing their cytokine supply (Figure 4-5). A small number of CD8+ T cells then become memory T cells, allowing the host rapid, heightened responses to future infections with a specific pathogen. Although the exact events producing the memory phenotype are unknown, cytokines including IL-2, IL-7, and IL-15 are important for CD8+ memory cell generation and maintenance (15). Lack of CD4+ help or IL-2 during primary stimulation of CD8+ T cells can promote the expression of molecules like PD1, which negatively regulates proliferation, or TRAIL, which induces apoptosis and blocks effective memory cell formation. This can occur in chronic infections such as human immunodeficiency virus (HIV).

Cytotoxic T lymphocytes have several strategies for mediating cell killing. Like NK cells, CTLs kill target cells directly using perforin and granzymes. Perforin, a homologue to the complement component C9, disrupts the plasma membrane through pore formation. This allows the CTL to insert granules containing granzymes, which are proteases that rapidly activate apoptosis in

FIGURE 4-5

The immune response begins when the cells of the innate immune system and complement engage pathogens. As the pathogens are neutralized, innate immune cells secrete cytokines that increase the number of phagocytes at the site of infection. APCs also migrate to the lymphatic tissue, where they stimulate the clonal expansion of B cells and T cells. As the immune response progresses, the specificity of the reaction increases. B cells refine their immunoglobulins through isotype/class switching and somatic hypermutation. CD8+ T cells lyse infected cells, and CD4+ T cells direct the B-cell response as well as increase the ability of phagocytes to neutralize pathogens. As the infection clears, there is attenuation of the immune response accomplished by the apoptosis of clonal T cells and decreased activation of innate immune cells. Memory cells develop, allowing a rapid response to any future encounters with pathogens. Failure to resolve the initial immune response produces chronic inflammation, a state of continued innate cell activation and adaptive cell reaction.



Immune Processes	Complement activation, phagocytosis, engagement of PRRs, activation of inflammasome	Migration of APCs to lymph nodes, expansion of CD8 clones, secretion of IgM then isotype switching	Apoptosis of CD8 cells, establishment of memory T cells and plasma B cells, decrease in inflammatory response
Primary Cells Involved	Macrophages, DCs, neutrophils, NK cells	B cells, T cells	B cells, T cells
Examples of Disorders	Chronic Granulomatous Disease, C3 deficiency, TRAPS, FMF	X-linked SCID, JAK3 deficiency, Hyper IgM syndrome, XLA	RA, SLE, ALPS

the target cells. CTLs also direct secretion of FasL, which binds the apoptosis-inducing receptor Fas on target cells. CTLs secrete cytokines such as TNF-alpha and IFN-gamma, which can attract phagocytes to sites of infection. Viruses can evade CD8+ T cells by down-regulating MHC class I molecules; fortunately, the loss of MHC molecules is a signal that activates NK cells. CTLs may also regulate themselves through cytotoxic activity. This is evident in patients with *familial hemophagocytic lymphohistiocytosis*, a fatal autosomal recessive disorder caused by mutations in perforin or other molecules involved in cytotoxic granule formation. These patients have uncontrolled activation of CTLs and overproduction of inflammatory cytokines.

B CELLS AND IMMUNOGLOBULINS

Another major component of the adaptive immune response is a class of lymphocytes termed *B cells*. Generated in the bone marrow, B cells produce immunoglobulins or antibodies. B cells can also function as antigen-presenting cells and share some features with innate immune cells. Immunoglobulins function as antigen receptors on B cells, but are also secreted and have major functions in host defense. Additionally, immunoglobulins are major contributors to immune-mediated disease.

Immunoglobulin molecules consist of four polypeptide chains: two identical light (L) chains and two identical heavy (H) chains, both of which have variable and constant regions. Structurally, the four chains assemble to form a Y-shaped molecule. The variable regions bind antigens, which, unlike in T cells, encompass many types of molecules, including proteins, lipids, carbohydrates, nucleic acids, or even drugs. The constant regions of the H chain form what is called the Fc region of the immunoglobulin molecule. Many of the effector functions of immunoglobulins, such as binding complement and receptors on phagocytic cells (Fc receptors), depend on the constant region of H chain.

There are two types of immunoglobulin L chains—kappa and lambda—and five types of H chains—mu, gamma, delta, epsilon, alpha. The five different classes or isotypes are designated IgM, IgG, IgD, IgE, and IgA, respectively. There are also subclasses of IgG (gamma l, gamma 2, gamma 3, and gamma 4) and IgA (alpha 1 and alpha 2). The antigen receptor on B cells is a membrane-bound form of IgM or IgD. After encounter with antigen and with the help of T cells, B cells proliferate and secrete immunoglobulins of different classes, a process known as heavy chain class or isotype switching. The secreted form of IgM molecules is a multimer of five Y-shaped immunoglobulin monomers joined by a J chain. IgA molecules form a dimer, which functions at epithelial surfaces and, when secreted, is associated with a secretory fragment.

B-Cell Development and Immunoglobulin Gene Rearrangement

Like other hematopoietic cells, B cells first develop in the fetal liver but later are produced in the bone marrow; like T cells, the cytokine milieu is important for the proliferation of stem cells and B-cell progenitors. As with T-cell development, successful B-cell development is dependent upon immunoglobulin gene rearrangement and the formation of a functional antigen receptor. As in T cells, B-cell development requires the recombination of V, D, and J genes that are separate from one another in the germline; a proper B-cell receptor repertoire is dependent upon the recombinase machinery. B-cell precursors first assemble heavy chain (chromosome 14) D and J genes, with subsequent joining of a V region to the DJ complex, forming a mu chain. H-chain rearrangements then cease. B-cell precursors that have not yet initiated immunoglobulin rearrangement are called pro-B cells, whereas precursors that express an H chain are called pre-B cells. In pre-B cells, the mu chains are mostly intracellular, but some are expressed on the cell surface in association with surrogate L chain to form the pre–B-cell receptor complex. This receptor signals the pre-B cell to proliferate and to rearrange the V and J regions of one of its L chain genes (kappa and lambda loci on chromosomes 2 and 22, respectively). Once a B-cell precursor successfully rearranges an H and L gene, the process stops, and the cell expresses surface immunoglobulin; it then is termed an immature B cell. Mature B cells express both membrane IgM and IgD.

Combinatorial rearrangement of H and L chain genes allows for 10^{11} possible antigen receptors and immunoglobulin molecules. Many precursor cells fail to make successful rearrangements or fail to express a functional pre–B-cell receptor, which results in apoptosis. In general, any mutation that impairs H-chain rearrangement or expression will block B-cell development.

B-Cell Activation and Differentiation

The B-cell receptor (BCR) signals similarly to the TCR, but unlike the TCR it has two functions. It initiates signals that activate B cells to proliferate but also binds and internalizes antigens. The antigens are processed, loaded onto class II molecules, and presented to CD4+ T cells. Structurally, the BCR consists of membrane-bound IgM associated with two transmembrane pro-

teins: Ig-alpha and Ig-beta Similar to the TCR-associated molecules, Ig-alpha and Ig-beta have ITAMs, which are phosphorylated by PTKs such as Lyn, Blk, and Fyn. This leads to the activation of additional PTKs, including Syk and Bruton's tyrosine kinase (Btk), which activate downstream pathways. Mutations of Btk underlie the disorder *X-linked agammaglobulinemia*. The B-cell transmembrane protein CD19 enhances BCR signaling, and deficiency of this molecule is a cause of *common variable immunodeficiency* (CVID). These patients, who make inadequate amounts of immunoglobulin, can be treated with replacement intravenous immunoglobulin.

Once a B-cell precursor expresses surface immunoglobulin, it can respond to exogenous and self-antigens. However, binding of antigens to the BCR on immature B cells does not trigger cellular activation; rather, binding induces a cellular response that leads to self-tolerance. Multivalent self-antigens tend to induce programmed cell death, whereas oligovalent self-antigens render immature B cells refractory to further stimulation. Such a cell may escape anergy by rearranging another L-chain immunoglobulin gene, changing its BCR specificity, and losing its self-reactivity; this process is known as *receptor editing*.

A subset of B cells, B1 cells, is produced early in ontogeny and is present predominantly in the peritoneal cavity. They have limited diversity of their antigen receptors. Most of the circulating IgM comes from B1 cells and is specific for carbohydrate products of bacteria.

Mature B cells with non–self-reactive BCRs enter secondary lymphoid tissues, such as the spleen and lymph nodes, where they may encounter foreign antigens. B-cell antigens are divided broadly into thymus-dependent (TD) and thymus-independent (TI) antigens. TD antigens are typically soluble protein antigens that require MHC class II–mediated T-cell help for antibody production, whereas TI antigens do not require such help. TI antigens often are multivalent, for example, bacterial polysaccharides. In general, TI responses generate poor immunological memory, induce minimal germinal-center formation (see below), and trigger IgG2 secretion. B cells responding to TI antigens have a distinct phenotype and localize in the marginal zone of the spleen. Dependence on these splenic B cells for responses to TI antigens may account for the poor responses to polysaccharide antigens seen in splenectomized individuals and in infants, because marginal zone B cells do not mature until about 2 years of age. For vaccines, this deficit can be overcome by coupling polysaccharides to a carrier protein, which triggers a TD response.

In the spleen, antigen-activated B cells migrate to T cell–rich zones in the periarteriolar lymphoid sheath searching for T-cell help. Failure to find this help likely results in anergy, but successful B-cell/T-cell collaboration produces short-lived oligoclonal proliferative foci (each derived from several B cells). Many of the B cells in these foci secrete IgM and undergo isotype switching, and IgM antibodies of a given antigen specificity can be converted to IgG, IgA, or IgE. These events depend on direct costimulatory signals from T cells, such as CD40 ligand/CD40 interactions and T-cell–derived cytokines such as IL-2, IL-4, IL-6, L-10, and IL-21. Mutations of CD40 or CD40L (TNF/TNFR members on T cells and B cells, respectively) underlie *hyper-IgM syndromes*. These patients lack germinal centers and have impaired class switch recombination in B cells owing to a lack of T cell stimulation. Interference with the CD40/CD40L interaction is being studied as a means of treating autoimmune disorders.

Some B cells migrate from these proliferative foci to primary follicles and enter the germinal-center pathway. Within a primary follicle, an oligoclonal expansion of B cells forms the dark zone. Eventually, these cells migrate into a region called the light zone, where they interact with helper T cells and follicular dendritic cells that have trapped and localized antigen on their surfaces. Under these conditions, antibody affinity is further altered by the introduction of mutations in B-cell variable gene segments, a process known as *somatic hypermutation*, which does not occur in T-cell receptor variable genes. As a consequence of random hypermutation, B cells possessing high affinity BCRs are selected for survival, whereas those that do not possess this affinity die. B cells in which somatic mutations generated an autoreactive BCR also are eliminated.

Passage through the germinal center leads to the formation of plasma-cell precursors and memory B cells; few antibody-secreting cells remain within the germinal center. Plasma cells lose their membrane immunoglobulin and many of the markers that identify B cells, including CD20, the target for the drug *rituximab* (18). Instead, plasma cells uniquely express high levels of CD38. Plasma cells secrete large amounts of immunoglobulin. They are generally short-lived cells and need constant replenishment to sustain high antibody levels, although a population of long-lived plasma cells can be maintained in the bone marrow. These may account for memory immunoglobulin persistence (19). Memory B cells are long-lived cells, carry somatically mutated V genes, and are morphologically distinct from naive B cells. They can be restimulated to rapidly generate a secondary antibody response.

Together, the extrafollicular and germinal-center pathways of B-cell differentiation lead to a coordinated humoral response that provides the very rapid production of low affinity antibodies, the subsequent production of high affinity antibodies, and the potential for a rapid recall response. Cytokines such as IL-2, IL-10, IL-6, and IL-21 promote differentiation into plasma cells, whereas CD40/CD40L interactions promote memory-

cell formation and inhibit plasma-cell generation. Cytokines also contribute to isotype switching. IL-4 enhances switching to IgE and IgG4; IL-10 to IgG1, IgG3, and IgA; and TGF-beta 1 to IgA. The enzyme activation-induced cytidine deaminase (AID), which participates in receptor editing, class switching, and somatic hypermutation, is key to the diverse B-cell response. AID deficiency is another cause of hyper-IgM syndromes.

AUTOIMMUNITY AND THE PATHOGENESIS OF IMMUNE-MEDIATED DISEASE

A fundamental aspect of the immune response is that pathogen-derived and MHC-disparate foreign antigens are recognized and eliminated, but the host generally does not attack its own tissues. This unresponsive state is referred to as self-tolerance, but as discussed, self/non-self recognition occurs on many levels. Innate immune cells recognize non-self through PRRs; similarly, the alternative complement pathway also recognizes microbial products. Cross-reactivity to self-antigens by PRRs could be an evolutionary hard-wired aspect of autoimmunity. For example, recognition of certain mammalian DNA or RNA sequences may be important in targeting autoantibodies to these ubiquitous molecules. Similarly, the repertoire of antigens recognized by adaptive immune cells, T and B cells, is immense and highly specific but the inherent self-reactivity of T cells and somatic mutation of B cells requires additional mechanisms, such as Tregs, to maintain peripheral immune tolerance. Fas-mediated deletion of activated T cells is another homeostatic mechanism that contributes to self-tolerance. In addition, cytokines like IL-10 and TGF-beta 1 help damp immune responses. Negative regulatory molecules also inhibit most immune activation events, for example, *pyrin* in inflammasome activation, *CTLA4* in T-cell activation, and *SOCS proteins* in cytokine signaling. Genetic ablation of many of these negative regulatory proteins in mice or mutations in humans results in autoimmune or autoinflammatory disease.

Classically, immune-mediated diseases have been characterized based on their predominant immunopathologic lesion. These categories are: immediate hypersensitivity due to production of IgE (e.g., allergies and anaphylaxis); antibodies against circulating or fixed cells (e.g., autoimmune thrombocytopenia, Goodpasture's syndrome); immune-complex disease (e.g., SLE, vasculitis); and delayed type hypersensitivity. While this classification has some utility, it is equally important to bear in mind that the components of the immune system are highly interdependent.

Some autoimmune diseases can be classified as mediated by adaptive immunity, such as diseases in which autoantibodies attack particular tissues, while others are clearly limited to the innate immune system, such as gout and the inherited periodic fevers. Most fall between these two extremes and can be thought of as resulting from pathological positive feedback between innate and adaptive immune mechanisms. For example, in rheumatoid arthritis, macrophages secrete cytokines, such as TNF and metalloproteinases, that help destroy the joint structure, but these cells depend on cytokines and cellular signals provided by T cells that are co-infiltrating the synovium. To complete the feedback loop, activated macrophages produce cytokines such as IL-12 that reinforce the production of T-cell–derived cytokines such as IFN-gamma. Rheumatoid factor–containing immune complexes present in the rheumatoid joint produced by autoreactive B cells can then amplify innate inflammatory responses through complement and Fc receptors on innate immune cells. Such an integrated model could explain why therapies directed against both the innate (e.g., anticytokine) and adaptive (e.g., anticostimulatory, anti–B cell) immune systems are effective in this disease. The extraordinary therapeutic advances that have been made recently in the treatment of rheumatologic disorders through the targeting of specific molecules with biologic agents have the added potential benefit of providing mechanistic insights that should permit even better therapies in the future.

SUMMARY

The human immune response is composed of highly antigen-specific cells that work in concert with cells involved in innate immunity. Ordinarily, this orchestrated process efficiently rids the host of pathogenic organisms, but not always. Immunological disease can occur as a consequence of dysregulation of many different parts of the immune system. Immunopathology also can occur as a byproduct of immune responses to foreign pathogens or tissue damage. Unlike rare single-gene disorders that are illustrative of the role of particular molecules in the immune system, a variety of mutations or polymorphisms in an array of separate immune system genes likely contribute to the genetic susceptibility to common rheumatologic diseases, and these loci are now being identified. The challenge for the future will be to use these insights into the immune system to design better therapies for rheumatic diseases.

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Suggested Reading

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