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360 Introduction to the Immune System

Immune-Mediated, Inflammatory, and Rheumatologic Disorders PART 11 Section 1 The Immune System in Health and Disease Barton F. Haynes, Kelly A. Cuttle,

Anthony S. Fauci

Introduction to the

Immune System ■ ■DEFINITIONS • Adaptive immune system—recently evolved system of immune responses mediated by T and B lymphocytes. Immune responses by these cells are based on specific antigen recognition by clonotypic receptors that are products of genes that rearrange during devel opment and throughout the life of the organism. Additional cells of the adaptive immune system include various types of antigenpresenting cells (APCs). • Antibody—B cell–produced molecules encoded by genes that rear range during B-cell development consisting of immunoglobulin heavy and light chains that together form the central component of the B-cell receptor (BCR) for antigen. Antibody can exist as B cell– surface antigen-recognition molecules or as secreted molecules in plasma and other body fluids. • Antigens—foreign or self-molecules that are recognized by the adap tive and innate immune systems resulting in immune cell triggering, T-cell activation, and/or B-cell antibody production. • Antigen-presenting cells (APCs)—a group of immune cells that process antigens to mediate both adaptive immune responses and the maintenance of peripheral tolerance. Classical APCs include dendritic cells, macrophages, and B cells. • Apoptosis—the process of programmed cell death whereby signal ing through “death receptors” on the surface of cells (e.g., tumor necrosis factor [TNF] receptors, CD95) leads to signaling cascades that involve activation of the caspase family of molecules and leads to DNA cleavage and cell death. Apoptosis, which does not lead to induction of inordinate inflammation, is to be contrasted with cell necrosis, which does lead to induction of inflammatory responses. • Autoimmune diseases—diseases such as systemic lupus erythemato sus and rheumatoid arthritis in which cells of the adaptive immune system such as autoreactive T and B cells become overreactive and produce pathogenic T-cell and antibody responses. • Autoinflammatory diseases—hereditary disorders such as heredi tary periodic fevers (HPFs) characterized by recurrent episodes of severe inflammation and fever due to mutations in controls of the innate inflammatory response, i.e., the inflammasome (see below and Table 360-5). Patients with HPFs also have rashes and serosal and joint inflammation, and some can have neurologic symptoms. Autoinflammatory diseases are different from autoimmune diseases in that evidence for activation

of adaptive immune cells such as autoreactive B cells is not present. • Autophagy—lysosomal degradation pathway mechanism of cells to dispose of intracellular debris and damaged organelles. Autophagy by cells of the innate immune system is used to control intracel lular infectious agents such as mycobacteria, in part by initiation of phagosome maturation and enhancing major histocompatibility complex (MHC) class II antigen presentation to CD4 T cells. • B-cell receptor (BCR) for antigen—complex of surface molecules that rearrange during postnatal B-cell development, made up of surface immunoglobulin (Ig) and associated Ig αβ chain molecules that recognize nominal antigen via Ig heavy- and light-chain variable

regions, and signal the B cell to terminally differentiate to make antigen-specific antibody. • B lymphocytes—bone marrow–derived lymphocytes that express surface immunoglobulin (the BCR for antigen) and secrete specific antibody after interaction with antigen. • B regulatory cells—a population of suppressive B cells that aid in the inhibition of inflammation through the release of cytokines such as interleukin-(IL) 10. • CD classification of human lymphocyte differentiation antigens—the development of monoclonal antibody technology led to the discov ery of a large number of new leukocyte surface molecules. From a series of International Workshop on Leukocyte Differentiation Antigens has come the cluster of differentiation (CD) classification of leukocyte antigens. • CD4 T cell—T lymphocyte subset that participates in adaptive immunity and helps B cells make antibody. • CD8 T cell—cytotoxic T lymphocyte subset that kills tumor cells and cells infected with pathogens. • Chemokines—soluble molecules that direct and determine immune cell movement and circulation pathways. • Complement—cascading series of plasma enzymes and effector proteins that function to lyse pathogens and/or target them to be phagocytized by neutrophils and monocyte/macrophage lineage cells of the reticuloendothelial system. • Co-stimulatory molecules—molecules of APCs (such as B7-1, B7-2, or CD40) that lead to T-cell activation when bound by ligands on activated T cells (such as CD28 or CD40 ligand). • Crystallopathies—nanoparticle- or microparticle-sized deposits of crystals, misfolded proteins, or airborne particulate matter that can stimulate the inflammasome and initiate inflammation and tissue damage. • Cytokines—soluble proteins that interact with specific cellular recep tors that are involved in the regulation of the growth and activation of immune cells and mediate normal or pathologic inflammatory and immune responses. • Dendritic cells—myeloid and/or lymphoid lineage APCs of the adaptive immune system. Immature dendritic cells (DCs), or DC precursors, are key components of the innate immune system by responding to infections with production of high levels of cytokines. DCs are key initiators of innate immune responses via cytokine pro duction and mediators of adaptive immune responses via presenta tion of antigen to T lymphocytes. • Ig fragment crystallizable (Fc) receptors (Rs)—receptors found on the surface of certain cells including B cells, natural killer (NK) cells, macrophages, neutrophils, and mast cells. Fc receptors bind to the Fc domains of antibodies that have attached to invading pathogen-infected cells. FcRs stimulate cytotoxic cells to destroy microbe-infected cells through antibody-dependent cell-mediated cytotoxicity (ADCC). Examples of important FcRs include CD16 (FcγRIIIa), CD23 (FcεR), CD32 (FcγRII), CD64 (FcγRI), and CD89 (FcαR). • Inflammasome—large cytoplasmic complexes of intracellular pro teins that link the sensing of microbial products and cellular stress to the proteolytic activation of IL-1β and IL-18 inflammatory cytokines. Activation of molecules in the inflammasome is a key step in the response of the innate immune system for intracellular recognition of microbial and other danger signals in both health and pathologic states. • Innate immune system—ancient immune recognition system of host cells bearing germline-encoded pattern recognition receptors (PRRs) that recognize pathogens and trigger a variety of mecha

nisms of pathogen elimination. Cells of the innate immune system include NK cell lymphocytes, monocytes/macrophages, DCs, neu trophils, basophils, eosinophils, tissue mast cells, and epithelial cells. • Innate lymphoid cells (ILCs)—lymphocytes that do not express the type of diversified antigen receptors on T cell and B cells. ILC1s,

ILC2s, and ILC3s are tissue resident cells and functionally may be analogous to CD4 TH1, TH2, and TH17 cells, respectively. • Natural killer (NK) cells—a type of ILC that kills target cells express

ing few or no human leukocyte antigen (HLA) class I molecules, such as malignantly transformed cells and virally infected cells. NK cells express receptors that inhibit killer cell function when self-MHC class I is present. Innate NK cells mirror the cytolytic functions of CD8 cytotoxic T cells of the adaptive immune system. • NK T cells—innate-like lymphocytes that use an invariant T-cell PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders receptor (TCR)-α chain combined with a limited set of TCR-β chains and coexpress receptors commonly found on NK cells. NK T cells recognize lipid antigens of bacterial, viral, fungal, and protozoal infectious agents. • Pathogen-associated molecular patterns (PAMPs)—invariant molec ular structures expressed by large groups of microorganisms that are recognized by host cellular PRRs in the mediation of innate immunity. • Pattern recognition receptors (PRR)—germline-encoded receptors expressed by cells of the innate immune system that recognize PAMPs. • T lymphocytes—thymus-derived lymphocytes that mediate adaptive cellular immune responses including T helper, T regulatory, and cytotoxic T lymphocyte effector cell functions. • T-cell exhaustion—state of T cells when the persistence of antigen disrupts memory T-cell function, resulting in defects in memory T-cell responses. Most frequently occurs in malignancies and in chronic viral infections such as HIV-1 and hepatitis C. • TCR for antigen—complex of surface molecules that rearrange during postnatal T-cell development made up of clonotypic TCR-α and -β chains that are associated with the CD3 complex composed of invariant γ, δ, ε, ζ, and η chains. TCR-α and -β chains recognize peptide fragments of protein antigen physically bound in APC MHC class I or II molecules, leading to signaling via the CD3 complex to mediate effector functions. • T follicular helper T cells (TFH)—CD4 T cells regulated by bcl-6 in B-cell follicle germinal centers that produce IL-4 and IL-21 and drive B-cell differentiation and affinity maturation in peripheral lymphoid tissues such as lymph node and spleen. • TH1 T cells—CD4 helper T-cell subset regulated by transcription factor T-bet that produces interferon (IFN)-γ, IL-2, and TNF-β and participates in cell-mediated immunity. • TH2 T cells—CD4 helper T-cell subset regulated by transcription fac tors STAT6 and GATA3 that produces IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13 and regulates antibody and eosinophil responses. • T regulatory cells (Treg)—CD4 or CD8 T cells regulated by the tran scription factor forkhead box P3 (FOXP3) that play roles in modulat ing immune responses to prevent harmful immune activation. Treg cells that prevent autoimmunity can arise in the thymus (thymic Tregs) after exposure to self-antigens on thymic epithelial cells or can arise outside the thymus and are called peripheral Tregs. Intestinal Tregs are essential to preventing pathogenic immune responses to the gut microbiome, thus preventing intestinal inflammation. • TH9 T cells—CD4 T cells regulated by the transcription factor PU.1 that secrete IL-9 and enhance inflammation in atopic disease and inflammatory bowel disease as well as mediate antitumor immunity. • TH13 T cells—T follicular helper cells (TFH) regulated by the GATA3 transcription factor that produce IL-4, IL-5, and IL-13. TH13 TFH induce high-affinity IgE antibody responses that cause anaphy lactic reactions to allergens. • TH17 T cells—CD4 T cells regulated by the transcription factor RORγt that secrete IL-17, IL-22, and IL-26 and play roles in autoim mune inflammatory disorders as well as defend against bacterial and fungal pathogens. •

Tolerance—B- and T-cell nonresponsiveness to antigens that results from encounter with foreign or self-antigens by B and T lympho cytes in the absence of expression of APC co-stimulatory molecules. Tolerance to antigens may be induced and maintained by multiple mechanisms either centrally (B-cell deletion in the thymus for T cells or bone marrow for B cells) or peripherally (by cell deletion or anergy at sites throughout the peripheral immune system).

• Trained immunity—the epigenetic, transcriptional, and functional reprogramming of innate immune cells to adapt to previous encoun ters with pathogens and respond to a second challenge in an altered manner. ■ ■INTRODUCTION The human immune system has evolved over millions of years from both invertebrate and vertebrate organisms to develop sophisticated defense mechanisms that protect the host from microbes and their virulence factors. The normal immune system has three key properties: a highly diverse repertoire of antigen receptors that enables recognition of a nearly infinite range of pathogens; immune memory, to mount rapid recall immune responses; and immunologic tolerance, to avoid immune damage to self-tissues. From invertebrates, humans have inherited the innate immune sys tem, an ancient defense system that uses germline-encoded proteins to recognize pathogens. Cells of the innate immune system, such as macrophages, DCs, and NK lymphocytes, recognize PAMPs that are highly conserved among many microbes and use a diverse set of PRR molecules. Important components of the recognition of microbes by the innate immune system include recognition by germline-encoded host molecules, recognition of key microbe virulence factors but not recognition of self-molecules, and nonrecognition of benign foreign molecules or microbes such as are found in mucosal or other bar rier microbiomes. Upon contact with pathogens, cells of the innate immune system may kill pathogens directly or, in concert with DCs, activate a series of events that both slow the infection and recruit the more recently evolved arm of the human immune system, the adaptive immune system. In addition, innate immune cells undergo epigenetic, transcriptional, and functional changes that allow adapted (either enhanced or reduced) innate cell responses to repeat encounters with pathogens, called trained immunity. Adaptive immunity is found only in vertebrates and is based on the generation of antigen receptors on T and B lymphocytes by gene rear rangements, such that individual T or B cells express unique antigen receptors on their surface capable of specifically recognizing diverse antigens of infectious agents in the environment. Coupled with specific recognition mechanisms that maintain tolerance (nonreactivity) to selfantigens or nonpathogenic microbes (Chap. 361), T and B lymphocytes bring both specificity and immune memory to vertebrate host defenses. This chapter describes the cellular components, key molecules (Table 360-1), and mechanisms that make up the innate and adaptive immune systems and describes how adaptive immunity is recruited to the defense of the host by innate immune responses. An appreciation of the cellular and molecular bases of innate and adaptive immune responses is critical to understanding the pathogenesis of inflam matory, autoimmune, infectious, and immunodeficiency diseases, as well as a wide range of diseases associated with inflammation such as atherosclerotic cardiovascular disease and neurodegenerative diseases. ■ ■THE INNATE IMMUNE SYSTEM All multicellular organisms, including humans, have developed the use of surface and intracellular germline-encoded molecules that recognize pathogens. Because of the myriad of human pathogens, host molecules of the human innate immune system sense “danger signals” and either recognize PAMPs, the common molecular structures shared by many pathogens, or recognize host cell molecules produced in response to infection such as heat shock proteins and fragments of the extracel lular matrix. PAMPs must be conserved structures vital to pathogen virulence and survival, such as bacterial endotoxin, so that pathogens cannot mutate

molecules of PAMPs to evade human innate immune responses. PRRs are host proteins of the innate immune system that recognize PAMPs as host danger signal molecules (Tables 360-2 and 360-3). Thus, recognition of pathogen molecules by hematopoietic and nonhematopoietic cell types leads to activation/production of the complement cascade, cytokines, or antimicrobial peptides as effector molecules. In addition, pathogen PAMPs as host danger signal mol ecules activate DCs to mature and to express molecules on the DC sur face that optimize antigen presentation to respond to foreign antigens.

TABLE 360-1 Human Leukocyte Surface Antigens—The CD Classification of Leukocyte Differentiation Antigens SURFACE ANTIGEN (OTHER NAMES) FAMILY MOLECULAR MASS, kDa DISTRIBUTION LIGAND(S) FUNCTION CD1a (T6, HTA-1) Ig

CD, cortical thymocytes, Langerhans type of DCs CD1b Ig

CD, cortical thymocytes, Langerhans type of DCs CD1c Ig

DC, cortical thymocytes, subset of B cells, Langerhans type of DCs CD1d Ig

Cortical thymocytes, intestinal epithelium, Langerhans type of DCs CD2 (T12, LFA-2) Ig

T, NK CD58, CD48, CD59, CD15 CD3 (T3, Leu-4) Ig γ:25–28, δ:21– 28, ε:20–25, η:21–22, ζ:16 T, NK T Associates with the TCR CD4 (T4, Leu-3) Ig

T, myeloid MHC-II, HIV gp120, IL-16, SABP CD7 (3A1, Leu-9) Ig

T, NK K-12 (CD7L) T- and NK-cell signal transduction and regulation of IFN-γ, TNF-α production CD8 (T8, Leu-2) Ig

T, subset of NK MHC-I T-cell selection, T-cell activation, signal transduction with p56lck CD14 (LPS-receptor) LRG 53–55 M, G (weak), not by myeloid progenitors CD16a (FcγRIIIa) Ig 50–80 NK, macrophages, neutrophils CD19 B4 Ig

B (except plasma cells), FDC CD20 (B1) Unassigned 33–37 B (except plasma cells) Not known Cell signaling, may be important for B-cell activation and proliferation CD21 (B2, CR2, EBV-R, C3dR) RCA

Mature B, FDC, subset of thymocytes CD22 (BL-CAM) Ig 130–140 Mature B CDw75 Cell adhesion, signaling through association with p72sky, p53/56lyn, PI3 kinase, SHP1, fLCγ C-type lectin 45 B, M, FDC IgE, CD21, CD11b, CD11c CD23 (FcεRII, B6, Leu-20, BLAST-2) CD28 Ig

T, plasma cells CD80, CD86 Co-stimulatory for T-cell activation; involved in the decision between T-cell activation and anergy CD32a (FcγRIIa) Ig

NK, macrophages, neutrophils CD40 TNFR 48–50 B, DC, EC, thymic epithelium, MP, cancers CD45 (LCA, T200, B220) PTP 180, 200, 210,

All leukocytes Galectin-1, CD2, CD3, CD4 CD45RA PTP 210, 220 Subset T, medullary thymocytes, “naive” T CD45RB PTP 200, 210, 220 All leukocytes Galectin-1, CD2, CD3, CD4 CD45RC PTP 210, 220 Subset T, medullary thymocytes, “naive” T CD45RO PTP

Subset T, cortical thymocytes, “memory” T CD64 (FcγRI) Ig 45–55 Macrophages and monocytes CD80 (B7-1, BB1) Ig

Activated B and T, MP, DC CD28, CD152 (CTLA-4) Co-regulator of T-cell activation; signaling through CD28 stimulates and through CD152 inhibits T-cell activation CD86 (B7-2, B70) Ig

Subset B, DC, EC, activated T, thymic epithelium CD89 (FCαR) Ig 55–100 Neutrophils, eosinophils, monocytes, and MP

CD1 molecules present lipid antigens of intracellular bacteria such as Mycobacterium leprae and

M. tuberculosis to TCRγδT cells or NK T cells TCRγδ T cells,

NK T cells CHAPTER 360 TCRγδ T cells,

NK T cells TCRγδ T cells,

NK T cells Introduction to the Immune System TCRγδ T cells,

NK T cells Alternative T-cell activation, T-cell anergy, T-cell cytokine production, T- or NK-mediated cytolysis, T-cell apoptosis, cell adhesion T-cell activation and function; ζ is the signal transduction component of the CD3 complex T-cell selection, T-cell activation, signal transduction with p56lck, primary receptor for HIV-1 Endotoxin (lipopolysaccharide), lipoteichoic acid, PI TLR4 mediates with LPS and other PAMP activation of innate immunity Fc portion of IgG Mediates phagocytosis and ADCC Not known Associates with CD21 and CD81 to form a complex involved in signal transduction in B-cell development, activation, and differentiation C3d, C3dg, iC3b, CD23, EBV Associates with CD19 and CD81 to form a complex involved in signal transduction in B-cell development, activation, and differentiation; Epstein-Barr virus receptor Regulates IgE synthesis, cytokine release by monocytes Fc portion of IgG Mediates phagocytosis and ADCC CD154 (CD40L) B-cell activation, proliferation, and differentiation; formation of GCs; isotype switching; rescue from apoptosis T and B activation, thymocyte development, signal transduction, apoptosis Galectin-1, CD2, CD3, CD4 Isoforms of CD45 containing exon 4 (A), restricted to a subset of T cells Isoforms of CD45 containing exon 5 (B) Galectin-1, CD2, CD3, CD4 Isoforms of CD45 containing exon 6 (C), restricted to a subset of T cells Galectin-1, CD2, CD3, CD4 Isoforms of CD45 containing no differentially spliced exons, restricted to a subset of T cells Fc portion of IgG Mediates phagocytosis and ADCC CD28, CD152 (CTLA-4) Co-regulator of T-cell activation; signaling through CD28 stimulates and through CD152 inhibits T-cell activation Fc portion of IgG Mediates phagocytosis and ADCC of IgA-coated pathogens (Continued)

TABLE 360-1 Human Leukocyte Surface Antigens—The CD Classification of Leukocyte Differentiation Antigens SURFACE ANTIGEN (OTHER NAMES) FAMILY MOLECULAR MASS, kDa DISTRIBUTION LIGAND(S) FUNCTION CD95 (APO-1, Fas) TNFR

Activated T and B Fas ligand Mediates apoptosis CD112 (nekton-2, PVRL2) Ig

Epithelial cells, endothelial cells, other tissues PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders CD134 (OX40) TNFR

Activated T OX40L (CD252) T-cell survival, cytokine stimulation CD137 (4-1BB) TNFR

Activated T, DCs, B, NK CD137L (41BBL) T-cell co-stimulation CD155 (PVR) Ig 50–65 DCs, NK, epithelial cells TIGIT, CD96, DNAM-1 T-cell inhibition (TIGIT, CD96), T-cell activation (DNAM-1) CD223 (LAG-3) Ig

NK, B, activated T MHC class II T-cell inhibition CD226 (DNAM-1) Ig

NK, monocytes, T CD112, CD155 T-cell activation (CD112), T-cell activation (CD155) CD252 (OX40L) TNFR 16–25 Antigen-presenting cells, endothelial cells CD272 (BTLA) Ig

Activated T HVEM T-cell inhibition CD274 (PD-L1) Ig

T, NK, myeloid, B, tumor cells CD278 (ICOS) Ig 55–60 Activated T ICOSL T-cell activation CD357 (GTTR) TNFR

Activated T, Tregs GITRL T-cell activation CD152 (CTLA-4) Ig 30–33 Activated T CD80, CD86 Inhibits T-cell proliferation CD154 (CD40L) TNF

Activated CD4+ T, subset CD8+ T, NK, M, basophil CD279 (PD-1) Ig 50–55 B, T, TFH PD-L1 (CD274), PD-L2 (CD273) Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; BTLA, band T lymphocyte attenuators; CTLA, cytotoxic T lymphocyte–associated protein; DC, dendritic cells; DNAM-1, DNAX accessory molecule-1; EBV, Epstein-Barr virus; EC, endothelial cells; ECM, extracellular matrix; Fcγ RIII, low-affinity IgG receptor isoform A; FDC, follicular dendritic cells; G, granulocytes; GC, germinal center; GITR, glucocorticoid-induced TNFR-related protein; GPI, glycosyl phosphatidylinositol; HTA, human thymocyte antigen; HVEM, herpesvirus entry mediator; ICOS, inducible T-cell co-stimulator; Ig, immunoglobulin; IgG, immunoglobulin G; LAG-3, lymphocyte-activation gene 3; LCA, leukocyte common antigen; LPS, lipopolysaccharide; MHC-I, major histocompatibility complex class I; MP, macrophages; Mr, relative molecular mass; NK, natural killer cells; P, platelets; PBT, peripheral blood T cells; PD-1, programmed cell death-1; PI, phosphatidylinositol; PI3K, phosphatidylinositol 3-kinase; PLC, phospholipase C; PTP, protein tyrosine phosphatase; PVR, polio virus receptor; PVRL2, polio virus receptor-related 2; RCA, regulators of complement activation; SABP, seminal actin binding protein; TCR, T-cell receptor; TFH, T follicular helper cells; TIGIT, T-cell immunoreceptor with Ig and ITIM domains; TNF, tumor necrosis factor; TNFR, tumor necrosis factor receptor. Note: For an expanded list of cluster of differentiation (CD) human antigens, see Harrison’s Online at accessmedicine.com; and for a full list of CD human antigens from the most recent Human Workshop on Leukocyte Differentiation Antigens (VII), D Mason, P Andre, A Bensussan, et al (eds): Leucocyte Typing VII. Oxford: Oxford University Press, 2002. Source: Compiled from T Kishimoto et al (eds): Leukocyte Typing VI. New York: Garland Publishing, 1997; R Brines et al: Immunol Today 18S:1, 1997; and D Mason et al:

CD antigens 2002. Blood 99:3877, 2002. ■ ■PATTERN RECOGNITION Major PRR families of proteins include transmembrane proteins, such as the Toll-like receptors (TLRs) and C-type lectin receptors (CLRs), and cytoplasmic proteins, such as the retinoic acid–inducible gene (RIG)- 1-like receptors (RLRs) and NOD-like receptors (NLRs) (Table 360-4). A major group of PRR collagenous glycoproteins with C-type lectin domains are termed collectins and include the serum protein mannosebinding lectin (MBL). MBL and other collectins, as well as two other protein families—the pentraxins (such as C-reactive protein and serum amyloid P) and macrophage scavenger receptors—all have the property of opsonizing (coating) bacteria for phagocytosis by macrophages and TABLE 360-2 Major Components of the Innate Immune System Pattern recognition receptors (PRRs) Toll-like receptors (TLRs), C-type lectin receptors (CLRs), retinoic acid–inducible gene (RIG)-1-like receptors (RLRs), and NOD-like receptors (NLRs) Antimicrobial peptides α-Defensins, β-defensins, cathelin, protegrin, granulysin, histatin, secretory leukoprotease inhibitor, and probiotics Cells Macrophages, dendritic cells, innate lymphoid cells (ILC1, ILC2, ILC3, NK cells, lymphoid tissue inducer [LTi] cells), mucosal-associated invariant T (MAIT) cells, NK-T cells, neutrophils, eosinophils, mast cells, basophils, and epithelial cells Complement components Classic and alternative complement pathway, and proteins that bind complement components Cytokines Autocrine, paracrine, endocrine cytokines that mediate host defense and inflammation, as well as recruit, direct, and regulate adaptive immune responses Abbreviation: NK, natural killer.

(Continued) DNAM-1 (CD226), TIGIT T-cell activation (DNAM-1), T-cell inhibition (TIGIT) OX40 T-cell survival, cytokine stimulation PD-1 (CD279) Inhibit TCR activation CD40 Co-stimulatory for T-cell activation, B-cell proliferation and differentiation Inhibits T-cell proliferation can also activate the complement cascade to lyse bacteria. Integrins are cell-surface adhesion molecules that affect attachment between cells and the extracellular matrix and mediate signal transduction that reflects the chemical composition of the cell environment. For example, integrins signal after cells bind bacterial lipopolysaccharide (LPS) and activate phagocytic cells to ingest pathogens. There are multiple connections between the innate and adaptive immune systems; these include (1) a plasma protein, LPS-binding protein, that binds and transfers LPS to the macrophage LPS recep tor, CD14; (2) the human family of proteins called Toll-like receptor proteins (TLRs), some of which are associated with CD14, bind LPS, and signal epithelial cells, DCs, and macrophages to produce cytokines and upregulate cell-surface molecules that signal the initiation of adaptive immune responses (Fig. 360-1, Table 360-3); and (3) families of intracellular microbial sensors called NLRs and RLRs. Proteins in the Toll family can be expressed on macrophages, DCs, and B cells as well as on a variety of nonhematopoietic cell types, including respira tory epithelial cells. Eleven TLRs have been identified in humans (Table 360-3). Upon ligation, TLRs activate a series of intracellular events that lead to the killing of bacteria- and viral-infected cells as well as to the recruitment and ultimate activation of antigen-specific T and

B lymphocytes (Fig. 360-1). Importantly, signaling by massive amounts of LPS through TLR4 leads to the release of high levels of cytokines that mediate LPS-induced shock. Mutations in TLR4 proteins in mice pro tect from LPS shock, and TLR mutations in humans can protect from LPS-induced inflammatory diseases such as LPS-induced asthma. Table 360-4 lists diseases caused by gene variants in nucleic acid–sensing Toll family and related receptors. Two other families of cytoplasmic PRRs are the NLRs and the RLRs. These families, unlike the TLRs, are composed primarily of soluble

TABLE 360-3 Pattern Recognition Receptors (PRRs) and Their Ligands PRR LOCALIZATION LIGAND ORIGIN OF THE LIGAND TLR TLR1 Plasma membrane Triacyl lipoprotein Bacteria TLR2 Plasma membrane Lipoprotein Bacteria, viruses, parasite, self TLR3 Endolysosome dsRNA Virus TLR4 Plasma membrane LPS Bacteria, viruses, self TLR5 Plasma membrane Flagellin Bacteria TLR6 Plasma membrane Diacyl lipoprotein Bacteria, viruses TLR7 (human TLR8) Endolysosome ssRNA Virus, bacteria, self TLR9 Endolysosome CpG-DNA Virus, bacteria, protozoa, self TLR10 Endolysosome Unknown Unknown TLR11 Plasma membrane Profilin-like molecule Protozoa RLR RIG-I Cytoplasm Short dsRNA, triphosphate dsRNA RNA viruses, DNA virus MDA5 Cytoplasm Long dsRNA RNA viruses (Picornaviridae) LGP2 Cytoplasm Unknown RNA viruses NLR NOD1 Cytoplasm iE-DAP Bacteria NOD2 Cytoplasm MDP Bacteria CLR Dectin-1 Plasma membrane β2-Glucan Fungi Dectin-2 Plasma membrane β2-Glucan Fungi MINCLE Plasma membrane SAP130 Self, fungi Abbreviations: CLR, C-type lectin receptors; dsRNA, double-strand RNA; iE-DAP, D-glutamyl-meso-diaminopimelic acid moiety; LGP2, Laboratory of Genetics and Physiology 2 protein encoded by the gene DHX58; MDA5, melanoma differentiation-associated protein 5; MDP, MurNAc-L-Ala-D-isoGln, also known as muramyl dipeptide; MINCLE, macrophage-inducible C-type lectin; NLR, NOD-like receptor; NOD, NOTCH protein domain; RIG, retinoic acid–inducible gene; RLR, RIG-like receptors; SAP130, Sin-3 associated protein 130; TLR, Toll-like receptor. Source: Reproduced with permission from O Takeuchi: Pattern recognition receptors and inflammation. Cell 140:805, 2010. Triacylated lipopeptides Diacylated lipopeptides Flagellin Unknown LPS CD14 TLR4 TLR2 TLR1 TLR2 TLR6 TLR5 TLR10 MYD88 MYD88 TIRAP TRIF TRAM TRIF IRF3 TLR3 dsRNA Endosome IRF3 Inflammatory cytokines and/ or chemokines Nucleus IFN-β FIGURE 360-1 Overview of major TLR signaling pathways. All TLRs signal through MYD88, with the exception of TLR3. TLR4 and the TLR2 subfamily (TLR1, TLR2, TLR6) also engage TIRAP (Toll-interleukin 1 receptor domain-containing adapter protein). TLR3 signals through TRIF (Toll-interleukin 1 receptor domain-containing adapter-inducing interferon-β). TRIF is also used in conjunction with TRAM (TRIF-related adaptor molecule) in the TLR4-MYD88-independent pathway. Dashed arrows indicate translocation into the nucleus. dsRNA, double-strand RNA; IFN, interferon; IRF3, interferon regulatory factor 3; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinases; NF-κB, nuclear factor-κB; ssRNA, single-strand RNA; TLR, Toll-like receptor. (Reproduced with permission from D Van Duin et al: Triggering TLR signaling in vaccination. Trends Immunol 27:49, 2006.)

 Flagellin TLR11 Plasma membrane MYD88 TLR9 CpG IRAK ssRNA Endosome TLR7 or TLR8 TRAF-6 NF-κB MAPK NF-κB

TABLE 360-4 Diseases Caused by Gene Variants in Nucleic Acid-Sensing Receptors and Related Proteins CHANGE IN FUNCTION LOCATION LIGAND OR PARTNER GENE PROTEIN DNASE1 DNASE1 LOF Extracellular dsDNA (NETs) SLE

Yes DNASE1L3 DNASE1L3 LOF Extracellular Nucleosomes exposed on microparticles or apoptotic bodies TLR7 TLR7 GOF Endosomal ssRNA, 2’3’cGMP SLE 17

Yes TLR9 TLR9 – Endosomal CpG dsDNA N/A – No MyD88 MyD88 – Endosomal TLRs N/A (GOF) – No ADA2 ADA2 LOF Endolysosomal Adenosine, Sneddon syndrome

No 2’-deoxyadenosine Vasculitis, autoinflammation, immunodeficiency, and hematologic defects syndrome (DADA2) DNASE2 DNASE2 LOF Lysosomal Exogenous DNA Autoinflammatory-pancytopenia syndrome TREX1 TREX1 LOF Cytoplasmic DNA (retroviral/retrotransposon) AGS 1

Yes Chilblain lupus

Vasculopathy, retinal, with cerebral leukoencephalopathy and systemic manifestations Susceptibility to SLE

TMEM173 STING LOF Cytoplasmic cGAMP and excess DNA STING-associated vasculopathy, infantile-onset CGAS cGAS – Cytoplasmic Cytosolic DNA N/A (GOF) – No SAMHD1 SAMHD1 LOF Cytoplasmic dNTPs Chilblain lupus?

Yes AGS 5

RNASEH2A RNASEH2A LOF Cytoplasmic RNA in RNA-DNA hybrids AGS 4

Yes RNASEH2B RNASEH2B LOF Cytoplasmic RNA in RNA-DNA hybrids AGS 2

Yes RNASEH2C RNASEH2C LOF Cytoplasmic RNA in RNA-DNA hybrids AGS 3

Yes IFIH1 MDA5 GOF Cytoplasmic Long dsRNA AGS 7

Yes RIGI DDX58 GOF Cytoplasmic Short dsRNA Singleton-Merten syndrome 2

No MAVS MAVS – Cytoplasmic – N/A (GOF) – No AIM2 AIM2 – Cytoplasmic Cytosolic dsDNA N/A – No IFI16 IFI16 – Nuclear Viral DNA or damaged self-DNA N/A (GOF) – No Note: See the online catalogue of human genes and genetic disorders (OMIM) at https://omim.org. Abbreviations: GOF, gain of function; LOF, loss of function; N/A, not applicable; SLE, systemic lupus erythematosus. Source: Reproduced with permission from CG Vinuesa CG et al: Innate virus-sensing pathways in B cell systemic autoimmunity. Science 380:478, 2023. intracellular proteins that scan host cell cytoplasm for intracellular pathogens (Tables 360-2 and 360-3). The intracellular microbial sensors, NLRs, after triggering, form large cytoplasmic complexes termed inflammasomes, which are aggre gates of molecules including NOD-like receptor pyrin (NLRP) proteins (Table 360-5). Inflammasomes activate inflammatory caspases and IL-1β in the presence of nonbacterial danger signals (cell stress) and bacterial PAMPs. Mutations in inflammasome proteins can lead to chronic inflammation in a group of periodic febrile diseases called autoinflammatory syndromes. Polymorphisms in inflammasome com ponents can either protect or enhance risk of infections or autoimmune/ autoinflammatory diseases (Table 60-4). Inflammasomes are activated upon sensing of PAMPs. Crystallopathies are diseases caused by tissue crystal deposition such as monosodium urate that can activate the inflammasome and, in the case of urate deposition, can lead to gout with arthritis or renal disease. ■ ■EFFECTOR CELLS OF INNATE IMMUNITY Cells of the innate immune system and their roles in the first line of host defense are listed in Table 360-6. Equally important as their roles in the mediation of innate immune responses are the roles that each cell type plays in recruiting T and B lymphocytes of the adaptive immune system to engage in specific pathogen responses. Monocytes-Macrophages Monocytes arise from precursor cells within bone marrow (Fig. 360-2) and circulate with a half-life ranging

AUTOIMMUNE OR AUTOINFLAMMATORY

DISEASE IN OMIM LUPUS

SUSCEPTIBILITY

ALLELES OMIM

NUMBER SLE16

Yes

No

Yes Singleton-Merten syndrome 1

from 1 to 3 days. Monocytes leave the peripheral circulation via capil laries and migration into a vast extravascular cellular pool. Tissue macrophages arise from monocytes that have migrated out of the circulation and by in situ proliferation of macrophage precursors in tis sue. Common locations where tissue macrophages (and certain of their specialized forms) are found are lymph node, spleen, bone marrow, perivascular connective tissue, serous cavities such as the peritoneum, pleura, skin connective tissue, lung (alveolar macrophages), liver (Kupffer cells), bone (osteoclasts), central nervous system (microglia cells), and synovium (type A lining cells). In general, monocytes-macrophages are on the first line of defense associated with innate immunity and ingest and destroy microorgan isms through the release of toxic products such as hydrogen peroxide (H2O2) and nitric oxide (NO). Inflammatory mediators produced by macrophages attract additional effector cells such as neutrophils to the site of infection. Macrophage mediators include prostaglandins; leukotrienes; platelet activating factor; cytokines such as IL-1, TNF-α, IL-6, and IL-12; and chemokines (Tables 360-7 and 360-8). Although monocytes-macrophages were originally thought to be the major APCs of the immune system, it is now clear that cell types called dendritic cells are the most potent and effective classical APCs in the body (see below). Monocytes-macrophages mediate innate immune effector functions such as destruction of antibody-coated bac teria, tumor cells, or even normal hematopoietic cells in certain types of autoimmune cytopenias. Monocytes-macrophages ingest bacteria

TABLE 360-5 Mutations in Innate Inflammasome Molecules Associated with Clinical Disease Inherited Inflammasomopathies INHERITED PATTERN

AND EFFECT PHENOTYPE MUTATED GENE DISEASE NLRP1 NLRP1-associated autoinflammation with arthritis and dyskeratosis Autosomal dominant GoF Hyperkeratotic ulcerative skin lesions, fever, arthritis, ANA NLRP3 Cryopyrin-associated periodic syndromes (CAPS) Autosomal dominant GoF Spectrum from cold-induced urticaria and fever to CNS inflammation and bone overgrowth NLRC4 Autoinflammatory infantile fever with enterocolitis (AIFEC) Autosomal dominant GoF Recurrent MAS, enterocolitis, cold-induced fever and urticaria, CNS inflammation MEFV Familial Mediterranean fever (FMF) Autosomal recessive LoF or gene-dosage-dependent autosomal dominant GoF Genetic Polymorphisms in Inflammasome Components and Human Infectious Diseases INFECTIOUS AGENT/DISEASE GENE VARIANT ID Candida albicans (recurrent vulvovaginal

candidiasis) NLRP3 rs74163773 Increased Risk Chlamydia trachomatis NLRP3 rs12065526 Unknown Risk HCV NLRP3 rs1539019; rs35829419 Unknown; increased Protection HIV-1 NLRP3 rs10754558 Increased Protection IFI16 rs1417806 Increased Protection HPV NLRP1 rs11651270 Increased Protection NLRP3 rs10754558 Increased Protection HSV-2 IFI16 rs2276404 Increased Protection HTLV NLRP3 rs10754558 Increased Protection Microbial infection in lungs NLRC4 rs212704 Decreased Risk Mycobacterium leprae NLRP1 rs2670660, rs12150220 Increased Protection rs2137722 (Haplotype) Mycobacterium tuberculosis NLRP3 rs10754558 Increased Protection rs10754558 Increased Risk CARD8 rs6509365 Unknown Risk NLRC4 rs385076 Decreased Protection Plasmodium vivax NLRP1 rs12150220 Increased Risk Renal parenchymal infections NLRP3 rs4612666 Increased Protection Streptococcus pneumoniae NLRP1 rs11651270 Increased Risk CARD8 rs2043211 Increased Trypanosoma cruzi NLRP1 rs11691270 Increased Risk CASP1 rs501192 Unknown Risk Genetic Polymorphisms in Inflammasome Components and Autoimmune in Polygenic Autoinflammatory Diseases Addison disease NLRP1 rs12150220 Increased Risk Ankylosing spondylitis NLRP3 rs4612666 Increased Risk MEFV rs224204 Unknown Risk CARD8 rs2043211 Increased Protection Autoimmune thyroiditis NLRP1 rs12150220, rs2670660 Increased Risk AIM2 rs855873 Unknown Risk Behçet disease AIM2 rs855873 Unknown Risk IFI16 rs6940 Decreased Celiac disease NLRP3 rs35829419 Increased Protection; risk IBD: Crohn’s disease (CD) and ulcerative colitis (UC) NLRP3 rs35829419 Increased Risk (men) Increased Protection rs10754558 Increased Risk rs10925019 Unknown Risk rs4925648 Unknown Risk rs4353135, rs55646866; rs4266924, rs6672995, rs10733113

PREDOMINANT

EFFECTOR CELLS CHAPTER 360 Keratinocytes Monocytes, granulocytes (neutrophils), chondrocytes Introduction to the Immune System Monocytes/macrophages Fever, serositis, rash, SAA amyloidosis Neutrophils, monocytes, serosal and synovial fibroblasts EFFECT ON INFLAMMASOME ACTIVATION ASSOCIATION Decreased; unknown Risk (Continued)

TABLE 360-5 Mutations in Innate Inflammasome Molecules Associated with Clinical Disease INFECTIOUS AGENT/DISEASE GENE VARIANT ID IBD: Crohn’s disease (CD) and ulcerative colitis (UC) (Cont.) MEFV rs182674, rs224217, rs224225, rs224224, rs224223, rs224222 PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders CARD8 rs2043211 Increased Risk Protection rs1972619 Unknown Risk HS purpura MEFV rs3743930 Unknown Risk Kawasaki disease NLRP1 rs11651270, rs8079034, rs3744717, rs11078571, rs16954813, rs8079727 Multiple sclerosis NLRP3 rs3806265, rs10754557 Unknown Risk rs35829419 Increased Risk NLRC4 rs479333 Decreased Protection PFAPA CARD8 rs140826611 Unknown Risk Psoriasis NLRP1 rs8079034 Unknown Risk NLRP3 rs3806265, rs10754557 Unknown Risk rs10733113 Unknown Risk CARD8 rs2043211 Increased Risk AIM2 rs2276405 Unknown Protection Psoriatic JIA NLRP3 rs4353135 Decreased Risk rs3806265 Unknown Risk MEFV rs224204 Unknown Risk Rheumatoid arthritis NLRP1 rs878329 Unknown Risk NLRP3 rs35829419 Increased Risk rs10754558 Increased Risk rs10159239, rs4925648, rs4925659 CASP5 rs9651713 Unknown Risk SLE NLRP1 rs12150220, rs2670660 Increased Risk Systemic sclerosis NLRP1 rs8182352 Unknown Risk Type 1 diabetes NLRP1 rs12150220 Increased Risk rs2670660, rs11651270 Increased Protection NLRP3 rs10754558 Increased Protection Vitiligo NLRP1 rs12150220 Increased Risk rs2670660 Increased Risk rs8182352 Unknown Risk rs6502867 Unknown Risk rs1008588 Unknown Risk Note: Mutated gene and respective syndrome name are reported

for inflammasomopathies, as well as inheritance pattern and effect of mutations, clinical phenotype, and predominant disease effector cells. Inflammasome variants previously associated with infectious agents and/or diseases are briefly resumed from literature (https://www

.ncbi.nlm.nih.gov/pubmed). Significantly associated polymorphisms were grouped according to the infectious agent/disease. Infectious agent or disease (in alphabetical order), gene name (gene), identification number of polymorphism (ID), resulting effect on inflammasome activation ("increased," "decreased," or "unknown"), cohort origin (cohort) and eventually specifications (severity, etc.), sample size (n), and type (case/control or cases only), association result ("risk" or "protection"), and respective reference are reported. Abbreviations: ANA, antinuclear antibodies; CNS, central nervous system; GoF, gain-of-function; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPV, human papillomavirus; HS, Henoch-Schönlein; HSV, herpes simplex virus; HTLV, human T-lymphotropic virus; IBD, inflammatory bowel disease; JIA, juvenile idiopathic arthritis;

LoF, loss-of-function; MAS, macrophage activation syndrome; PFAPA, periodic fever with aphthous stomatitis, pharyngitis, and cervical adenitis; SAA, serum amyloid A; SLE, systemic lupus erythematosus. Source: Reproduced with permission from FP Fernandes et al: Inflammasome genetics and complex diseases: A comprehensive review. Eur J Hum Genet 28:1307, 2020. or are infected by viruses, and in doing so, they frequently undergo programmed cell death or apoptosis. Macrophages that are infected by intracellular infectious agents are recognized by DCs as infected and apoptotic cells and are phagocytosed by DCs. In this manner, DCs "cross-present" infectious agent antigens of macrophages to T cells. Activated macrophages can also mediate antigen-nonspecific lytic activity and eliminate cell types such as tumor cells in the absence of antibody. This activity is largely mediated by cytokines (i.e., TNF-α and IL-1). Monocytes-macrophages express lineage-specific molecules (e.g., the cell-surface LPS receptor, CD14) as well as surface receptors for a number of molecules, including the Fc region of IgG, activated complement components, and various cytokines (Table 360-7).

(Continued) EFFECT ON INFLAMMASOME ACTIVATION ASSOCIATION Unknown Risk Increased (haplotype) Risk Unknown Risk Dendritic Cells Human DCs contain several subsets, including myeloid DCs and plasmacytoid DCs. Myeloid DCs can differentiate into either macrophages-monocytes or tissue-specific DCs. In contrast to myeloid DCs, plasmacytoid DCs are potent producers of TLR-7 dependent type I IFN (e.g., IFN-α) in response to free virus and virusinfected cells. The maturation of DCs is regulated through cell-to-cell contact and soluble factors, and DCs attract immune effectors through secretion of chemokines. When DCs come in contact with bacterial products, viral proteins, or host proteins released as danger signals from distressed host cells (Fig. 360-2), infectious agent molecules bind to various TLRs and activate DCs to release cytokines and chemokines that drive cells of the innate immune system to become activated to

TABLE 360-6 Cells of the Innate Immune System and Their Major Roles in Triggering Adaptive Immunity CELL TYPE MAJOR ROLE IN INNATE IMMUNITY MAJOR ROLE IN ADAPTIVE IMMUNITY Macrophages Phagocytose and kill bacteria; produce antimicrobial peptides; bind LPS; produce inflammatory cytokines Plasmacytoid dendritic cells (DCs) of lymphoid lineage Produce large amounts of interferon-α (IFN-α), which has antitumor and antiviral activity, and are found in T-cell zones of lymphoid organs; they circulate in blood Myeloid DCs are of two types: interstitial and

Langerhans-derived Interstitial DCs are strong producers of IL-12 and IL-10 and are located in T-cell zones of lymphoid organs, circulate in blood, and are present in the interstices of the lung, heart, and kidney; Langerhans DCs are strong producers of IL-12; are located in T-cell zones of lymph nodes, skin epithelia, and the thymic medulla; and circulate in blood ILC1 cells Weakly cytotoxic, dependent on T-bet transcription factor, first line of defense against viruses and bacteria ILC2 cells Mediate innate responses to parasites/helminths, repair damaged tissues by producing amphiregulin ILC3 cells Innate immune response to extracellular bacteria and gut microbiome Lymphoid tissue inducer (LTi) cells Critical for formation of secondary lymphoid tissue during embryogenesis Natural killer (NK) cells Kill foreign and host cells that have low levels of MHC+ selfpeptides. Express NK receptors that inhibit NK function in the presence of high expression of self-MHC. NK-T cells Lymphocytes with both T-cell and NK surface markers that recognize lipid antigens of intracellular bacteria such as Mycobacterium tuberculosis by CD1 molecules and kill host cells infected with intracellular bacteria Neutrophils Phagocytose and kill bacteria, produce antimicrobial peptides Produce nitric oxide synthase and nitric oxide, which inhibit apoptosis in lymphocytes and can prolong adaptive immune responses Eosinophils Kill invading parasites Produce IL-5, which recruits Ig-specific antibody responses Mast cells and basophils Release TNF-α, IL-6, and IFN-γ in response to a variety of bacterial PAMPs Epithelial cells Produce antimicrobial peptides; tissue-specific epithelia produce mediator of local innate immunity; e.g., lung epithelial cells produce surfactant proteins (proteins within the collectin family) that bind and promote clearance of lung-invading microbes Abbreviations: GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-4, IL-5, IL-6, IL-10, and IL-12, interleukin 4, 5, 6, 10, and 12, respectively; ILC, innate lymphoid cell; MHC, major histocompatibility complex: LPS, lipopolysaccharide; PAMP, pathogen-associated molecular patterns; TGF, transforming growth factor; TH, helper T cell; TNF-α, tumor necrosis factor-alpha. Source: Reproduced with permission from R Medzhitov, CA Janeway: Curr Opinion Immunol 9:4-9; 1997. respond to invading organisms, and recruit T and B cells of the adap tive immune system to respond. Plasmacytoid DCs produce antiviral IFN-α that activates NK cell killing of pathogen-infected cells; IFN-α also activates CD8 T cells to mature into antipathogen cytotoxic (killer) T cells. Following contact with pathogens, both plasmacytoid and myeloid DCs produce chemokines that attract helper and cytotoxic T cells, B cells, polymorphonuclear cells, and naïve and memory T cells as well as regulatory T cells to ultimately dampen the immune response once the pathogen is controlled. TLR engagement on DCs upregulates MHC class II, B7-1 (CD80), and B7-2 (CD86), which enhance DCspecific antigen presentation and induce cytokine production. Thus, DCs are important bridges between early (innate) and later (adaptive) immunity. DCs also modulate and determine the types of immune responses induced by pathogens via the TLRs expressed on DCs (TLR7–9 in plasmacytoid DCs, TLR4 on monocytoid DCs) and via

the TLR adapter proteins that are induced to associate with TLRs

(Fig. 360-1, Table 360-1). In addition, other PRRs, such as C-type lectins, NLRs, and mannose receptors, upon ligation by pathogen products, activate cells of the adaptive immune system and, like TLR stimulation, by a variety of factors, determine the type and quality of the adaptive immune response that is triggered.

Produce IL-1 and TNF-α to upregulate lymphocyte adhesion molecules and chemokines to attract antigen-specific lymphocyte. Produce IL-12 to recruit TH1 T helper cell responses; upregulate co-stimulatory and MHC molecules to facilitate T and B lymphocyte recognition and activation.

Macrophages and dendritic cells, after LPS signaling, upregulate co-stimulatory molecules B7-1 (CD80) and B7-2 (CD86) that are required for activation of pathogen-specific T cells. There are also Toll-like proteins on B cells and dendritic cells that, after LPS ligation, induce CD80 and CD86 on these cells for T-cell antigen presentation. CHAPTER 360 Introduction to the Immune System IFN-α is a potent activator of macrophage and mature DCs to phagocytose invading pathogens and present pathogen antigens to

T and B cells. Interstitial DCs are potent activators of macrophage and mature DCs to phagocytose invading pathogens and present pathogen antigens to T and B cells. Produce IFN-γ to recruit CD4 TH1 T cells Produce IL-4, IL-5, IL-13; recruit CD4 TH2 T cells Produce IL-22, IL-17, GM-CSF, lymphotoxin; recruit CD4 TH17 T cells Produce lymphotoxin for lymph node and Peyer's patch development in which adaptive immune responses occur Produce TNF-α and IFN-γ, which recruit TH1 helper T-cell responses Produce IL-4 to recruit TH2 helper T-cell responses, IgG1 and IgE production Produce IL-4, which recruits TH2 helper T cell responses, and recruit IgG1- and IgE-specific antibody responses Produces TGF-β, which triggers IgA-specific antibody responses Innate Lymphoid Cells ILCs are comprised of ILC1, ILC2, ILC3, lymphoid tissue inducer (LTi), and NK cells. ILC1, ILC2, ILC3, and LTi are primarily tissue resident cells. ILCs develop from a common lymphoid precursor in the bone marrow and then differentiate into one of five ILC types—ILC1, ILC2, ILC3, LTi, or NK cells—based on their development (Fig. 360-3A) and function (Fig. 360-3B). NK cells and ILC1s depend on T-bet transcription factor for their development and function and produce IFN-γ. NK cells are innate analogues to CD8 cytotoxic T cells in that they both mediate granzyme and perforinbased cytotoxic cell activity. ILC1s mirror CD4 TH1 lymphocytes and react to intracellular pathogens such as viruses and to tumors. ILC2s are the analogues of TH2 CD4 T cells and are dependent on GATA3 and RORα factors and produce type 2 cytokines, such as IL-5 and IL-13. ILC2s respond to extracellular parasites and allergens. ILC3s and LTi cells are dependent on transcription factor retinoic acid receptor-related orphan receptor γt (RORγt) and produce IL-17. ILC3s are analogues of CD4 TH17 lymphocytes and attack extracellular pathogens such as bacte ria and fungi. LTi cells are critical for the formation of lymph nodes and Peyer's patches in gut during fetal development (Fig. 360-3B). In the intestine, a critical function of the immune system is not only to quickly respond to pathogens but also to ignore benign

Stem cell PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders B cell Plasmacytoid dendritic cell Natural killer cell Monocyte/ macrophage Dendritic cell Neutrophilic, eosinophilic, or basophilic granulocyte Antibodies antigen presentation IL-12 antigen presentation IL-1, IL-6 phagocytosis of microbes IFN-α antigen presentation GATA3 GATA3 RORγt PU 1 Fox3p Tbet Bcl6 TFH13 cell TH1 cell TH2 cell TH17 cell TH9 cell T regulatory cell T follicular helper cell (TFH) IL-13 IFN-γ IL-4 IL-5 IL-13 IL-17 IL-22 IL-9 IL-10 TGF-β IL-21 Cytotoxic T-cell responses B-cell affinity maturation in germinal centers IgE allergic reaction FIGURE 360-2 Model of immune effector cell development. Hematopoietic stem cells differentiate into T cells, antigen-presenting dendritic cells, natural killer cells, macrophages, granulocytes, or B cells. Foreign antigen is processed by dendritic cells, macrophages, and B cells, and peptide fragments of foreign antigen are presented to CD4+ and/or CD8+ T cells. CD8+ T-cell activation leads to induction of cytotoxic T lymphocyte (CTL) or killer T-cell generation, as well as induction of cytokine-producing CD8+ cytotoxic T cells. Granulocytes (neutrophils, eosinophils, or basophils) are effector cells of the innate immune system and mediate anti-infectious agent activity by cytokine production, infectious agent killing, or both. TH1 CD4+ T cells play an important role in defense against intracellular microbes and help in the

generation of CD8+ cytotoxic T cells. TH2 CD4+ T cells producing interferon (IFN) γ or interleukin (IL) 4, IL-5, or IL-13 regulate Ig class switching and determine the type of antibody produced. TH17 cells secrete IL-17 and IL-22, TH9 cells secrete IL-9, and TFH13 cells secrete IL-4, IL-5, and IL-13. TH17 and TH9 CD4 T cells are linked to mediation of autoimmune disease, and TFH13 cells are linked to IgE-mediated anaphylaxis. CD4+ T regulatory cells produce IL-10 and transforming growth factor (TGF)-β and downregulate T- and B-cell responses once the microbe has been eliminated. Each of the types of CD4+ T cells are regulated by different transcription factors, and the key transcription factors are shown in the circles above each CD4+ T-cell type.

Lymphoid precursor T cell IFN-α antigen presenting Antibodydependent cellular cytotoxicity tumor cell killing CD4+ T cell CD8+ cytotoxic T cell Kill pathogeninfected cells Differentiation/ activation Kill tumor cells Linked to autoimmune disease mediation T-cell function downregulation; prevent autoimmune disease Antibody responses; stimulate eosinophils

TABLE 360-7 Cytokines and Cytokine Receptors CYTOKINE RECEPTOR CELL SOURCE CELL TARGET BIOLOGIC ACTIVITY IL-1α, β Type I IL-1r, type II IL-1r Monocytes/macrophages,

B cells, fibroblasts, most epithelial cells including thymic epithelium, endothelial cells IL-2 IL-2r α, β, common γ T cells T cells, B cells, NK cells, monocytes-macrophages IL-3 IL-3r, common β T cells, NK cells, mast cells Monocytes-macrophages, mast cells, eosinophils, bone marrow progenitors IL-4 IL-4r α, common γ T cells, mast cells, basophils T cells, B cells, NK cells, monocytes-macrophages, neutrophils, eosinophils, endothelial cells, fibroblasts IL-5 IL-5r α, common γ T cells, mast cells, eosinophils Eosinophils, basophils, murine B cells IL-6 IL-6r, gp130 Monocytes-macrophages,

B cells, fibroblasts, most epithelium including thymic epithelium, endothelial cells IL-7 IL-7r α, common γ Bone marrow, thymic epithelial cells IL-8 CXCR1, CXCR2 Monocytes-macrophages, T cells, neutrophils, fibroblasts, endothelial cells, epithelial cells IL-9 IL-9r α, common γ T cells Bone marrow progenitors,

B cells, T cells, mast cells IL-10 IL-10r Monocytes-macrophages, T cells, B cells, keratinocytes, mast cells IL-11 IL-11r α, gp130 Bone marrow stromal cells Megakaryocytes, B cells, hepatocytes IL-12 (35-kDa and 40-kDa subunits) IL-12r Activated macrophages, dendritic cells, neutrophils IL-13 IL-13r/IL-4r α T cells (TH2) Monocytes-macrophages, B cells, endothelial cells, keratinocytes IL-14 Unknown T cells Normal and malignant B cells Induces B-cell proliferation, inhibits antibody secretion, and expands selected B-cell subgroups IL-15 IL-15r α, common γ, IL2r β Monocytes-macrophages, epithelial cells, fibroblasts IL-16 CD4 Mast cells, eosinophils, CD8+

T cells, respiratory epithelium IL-17 IL-17r CD4+ T cells Fibroblasts, endothelium, epithelium, macrophages IL-18 IL-18r (IL-1Rrelated protein) Keratinocytes, macrophages T cells, B cells, NK cells Upregulates IFN-γ production, enhances NK cell cytotoxicity IL-21 IL-δγ chain/IL-21R CD4 T cells NK cells Downregulates NK cell–activating molecules, NKG2D/ DAP10; produced by T follicular helper cells in B-cell germinal centers that stimulate B-cell maturation IL-22 IL-22 R1/IL-10R2 DC, T cells Epithelial cells Innate responses against bacterial pathogens; promotes hepatocyte survival IL-23 IL-12Rb1/IL23R Macrophages, other cell types T cells Opposite effects of IL-12 (↑IL-17, ↑IFN-γ) IL-24 IL-20R1/IL-20R2 IL-22R1/IL-20R2 Macrophages, TH2 cells

All cells Upregulates adhesion molecule expression, neutrophil and macrophage emigration, mimics shock, fever, upregulates hepatic acute-phase protein production, facilitates hematopoiesis CHAPTER 360 Promotes T-cell activation and proliferation, B-cell growth, NK-cell proliferation and activation, enhanced monocyte/macrophage cytolytic activity Stimulates hematopoietic progenitors Introduction to the Immune System Stimulates TH2 helper T-cell differentiation and proliferation; stimulates B-cell Ig class switch to IgG1 and IgE anti-inflammatory action on T cells, monocytes; produced by T follicular helper cells in B-cell germinal centers that stimulate B-cell maturation Regulates eosinophil migration and activation T cells, B cells, epithelial cells, hepatocytes, monocytes-macrophages Induces acute-phase protein production, T- and B-cell differentiation and growth, myeloma cell growth, and osteoclast growth and activation T cells, B cells, bone marrow cells Differentiates B-, T-, and NK-cell precursors, activates

T and NK cells Neutrophils, T cells, monocytes-macrophages, endothelial cells, basophils Induces neutrophil, monocyte, and T-cell migration, induces neutrophil adherence to endothelial cells and histamine release from basophils, and stimulates angiogenesis; suppresses proliferation of hepatic precursors Induces mast cell proliferation and function, synergizes with IL-4 in IgG and IgE production and T-cell growth, activation, and differentiation Monocytes-macrophages,

T cells, B cells, NK cells, mast cells Inhibits macrophage proinflammatory cytokine production, downregulates cytokine class II antigen and B7-1 and B7-2 expression, inhibits differentiation of TH1 helper T cells, inhibits NK cell function, stimulates mast cell proliferation and function, B-cell activation, and differentiation Induces megakaryocyte colony formation and maturation, enhances antibody responses, stimulates acute-phase protein production T cells, NK cells Induces TH1 T helper cell formation and lymphokineactivated killer cell formation; increases CD8+ CTL cytolytic activity; ↓IL-17, ↑IFN-γ Upregulates VCAM-1 and C-C chemokine expression on endothelial cells and B-cell activation and differentiation, and inhibits macrophage proinflammatory cytokine production T cells, NK cells Promotes T-cell activation and proliferation, angiogenesis, and NK cells CD4+ T cells, monocytes- macrophages, eosinophils Promotes chemoattraction of CD4+ T cells, monocytes, and eosinophils; inhibits HIV-1 replication; inhibits T-cell activation through CD3/T-cell receptor Enhances cytokine/chemokine secretion; promotes delayed-type reactions Nonhematopoietic cells such as fibroblasts Promotes wound healing (Continued)

TABLE 360-7 Cytokines and Cytokine Receptors (Continued) CYTOKINE RECEPTOR CELL SOURCE CELL TARGET BIOLOGIC ACTIVITY IL-25 (also called IL-17E) IL-17RB CD4 T cells, mast cells Fibroblasts, endothelium, epithelium, macrophages IL-26 IL-20R1/IL-10R2 TH1, TH17 T cells, synovial cells Epithelial cells Proinflammatory; induces cytokine production PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders IL-27 gp130t wsx-1 Myeloid cells such as macrophages and DCs Myeloid lineage cells; epithelial cells IL-28A (IFN-λ2) IFN-λ receptor 1, IL-28Rα, IL-10Rβ Myeloid lineage cells; epithelial cells IL-28B (IFN-λ3) IFN-λ receptor 1, IL-28Rα, IL-10Rβ Myeloid lineage cells; epithelial cells IL-29 (IFN-λ1) IFN-λ receptor 1, IL-28Rα, IL-10Rβ IL-30 (p28 of IL-27) Activated macrophages and

DCs; epithelial malignancies IL-27Rα; gp130+wsx-1 IL-31 IL-31RA/ oncostatin MRβ Eosinophils, CD4 T cells Epithelial cells, monocytes Pruritis, proinflammatory IL-32 (NK4) ? Monocytes, T cells, NK cells, epithelial cells IL-33 (NF-HEV; IL-1 F11) ST-2 Endothelial cells, epithelial cells, fibroblasts, mucosal epithelium IL-34 (C16of77) CSF-1R, PTP-E, CD138 Neurons, Treg, myeloid cells Anti-

inflammatory myeloid cell proliferation IL-35 IL-12Rβ2/ IL-12Rβ2, gp130/ gp130, IL-12Rb2/ gp130 Tregs, Bregs Macrophages, T cells Prevents TH1 and TH17 proliferation; induced Treg/Breg proliferation/anti-inflammatory IL-36R Keratocytes Mucosal epithelial cells Monocytes-macrophages Langerhans cells CD4 T cells IL-36α IL36β IL36γ IL36RA (IL-1 F5) IL-38 IL-10 F10 IL-1R, IL-36R, IL-1RA PL1 Epithelial cells, B cells Epithelial cells, macrophages, DCs, T cells, B cells, plasma cells IL-39 ? Macrophages, DCs, B cells Neutrophils Proinflammatory IL-40 ? B cells, bone marrow/stroma B cells Involved in IgA production, B-cell homeostasis and development IFN-α Type I interferon receptor All cells All cells Promotes antiviral activity; stimulates T-cell, macrophage, and NK-cell activity; direct antitumor effects; upregulates MHC class I antigen expression; used therapeutically in viral and autoimmune conditions IFN-β Type I interferon receptor All cells All cells Antiviral activity; stimulates T-cell, macrophage, and NK-cell activity; direct antitumor effects; upregulates MHC class I antigen expression; used therapeutically in viral and autoimmune conditions IFN-γ Type II interferon receptor T cells, NK cells All cells Regulates macrophage and NK-cell activations; stimulates immunoglobulin secretion by B cells; induction of class II histocompatibility antigens; TH1 T-cell differentiation TNF-α TNFrI, TNFrII Monocytes-macrophages, mast cells, basophils, eosinophils, NK cells, B cells, T cells, keratinocytes, fibroblasts, thymic epithelial cells TNF-β TNFrI, TNFrII T cells, B cells All cells except erythrocytes Cell cytotoxicity, lymph node and spleen development LT-β LTβR T cells All cells except erythrocytes Cell cytotoxicity, normal lymph node development G-CSF G-CSFr; gp130 Monocytes-macrophages, fibroblasts, endothelial cells, thymic epithelial cells, stromal cells GM-CSF GM-CSFr, common β T cells, monocytes-macrophages, fibroblasts, endothelial cells, thymic epithelial cells

Proinflammatory; induces cytokine production T cells Collaborates with other cytokines to activate T-cell differentiation Epithelial cells Enhanced clearance of viral infections Epithelial cells Enhanced clearance of viral infections Epithelial cells Enhanced clearance of viral infections Monocytes Anti-inflammatory cytokines; upregulation of breast and prostate cancer metastasis Monocytes, macrophages, bone marrow stroma Angiogenesis, IL-2 production in bone marrow, proinflammatory T cells, mast cells eosinophils, basophils, ILC2s Alarmin cytokine, proinflammatory Epithelial cells, macrophages, DCs, T cells, B cells, plasma cells TH responses, proinflammatory Blocks IL-36; anti-inflammatory All cells except erythrocytes Fever, anorexia, shock, capillary leak syndrome, enhanced leukocyte cytotoxicity, enhanced NK-cell function, acute phase protein synthesis, proinflammatory cytokine induction Myeloid cells, endothelial cells Regulates myelopoiesis; enhances survival and function of neutrophils; clinical use in reversing neutropenia after cytotoxic chemotherapy Monocytes-macrophages, neutrophils, eosinophils, fibroblasts, endothelial cells Regulates myelopoiesis; enhances macrophage bactericidal and tumoricidal activity; mediator of dendritic cell maturation and function; upregulates NK-cell function; clinical use in reversing neutropenia after cytotoxic chemotherapy (Continued)

(Continued) TABLE 360-7 Cytokines and Cytokine Receptors CYTOKINE RECEPTOR CELL SOURCE CELL TARGET BIOLOGIC ACTIVITY M-CSF M-CSFr (c-fms protooncogene) Fibroblasts, endothelial cells, monocytes-macrophages, T cells, B cells, epithelial cells including thymic epithelium LIF LIFr-α; gp130 Activated T cells, bone marrow stromal cells, thymic epithelium OSM OSMr; LIFr; gp130 Activated monocytesmacrophages and T cells, bone marrow stromal cells, some breast carcinoma cell lines, myeloma cells SCF SCFr (c-kit protooncogene) Bone marrow stromal cells and fibroblasts Type I, II, III TGF-β receptor Most cell types Most cell types Downregulates T-cell, macrophage, and granulocyte responses; stimulates synthesis of matrix proteins; stimulates angiogenesis TGF-β

(3 isoforms) Lymphotactin/ SCM-1 XCR1 NK cells, mast cells, doublenegative thymocytes, activated CD8+ T cells MCP-1 CCR2 Fibroblasts, smooth-muscle cells, activated PBMCs MCP-2 CCR1, CCR2 Fibroblasts, activated PBMCs Monocytes-macrophages,

T cells, eosinophils, basophils, NK cells MCP-3 CCR1, CCR2 Fibroblasts, activated PBMCs Monocytes-macrophages,

T cells, eosinophils, basophils, NK cells, dendritic cells MCP-4 CCR2, CCR3 Lung, colon, small intestinal epithelial cells, activated endothelial cells Eotaxin CCR3 Pulmonary epithelial cells, heart Eosinophils, basophils Potent chemoattractant for eosinophils and basophils; induces allergic airways disease; acts in concert with IL-5 to activate eosinophils; antibodies to eotaxin inhibit airway inflammation TARC CCR4 Thymus, dendritic cells, activated T cells MDC CCR4 Monocytes-macrophages, dendritic cells, thymus MIP-1α CCR1, CCR5 Monocytes-macrophages, T cells Monocytes-macrophages,

T cells, dendritic cells, NK cells, eosinophils, basophils MIP-1β CCR5 Monocytes-macrophages, T cells Monocytes-macrophages,

T cells, NK cells, dendritic cells RANTES CCR1, CCR2, CCR5 Monocytes-macrophages, T cells, fibroblasts, eosinophils CCR6 Dendritic cells, fetal liver cells, activated T cells LARC/MIP-3α/ Exodus-1 ELC/MIP-3β CCR7 Thymus, lymph node, appendix Activated T cells and B cells Chemoattractant for B and T cells; receptor upregulated on EBV-infected B cells and HSV-infected T cells I-309/TCA-3 CCR8 Activated T cells Monocytes-macrophages,

T cells SLC/TCA-4/ Exodus-2 CCR7 Thymic epithelial cells, lymph node, appendix, and spleen DC-CK1/PARC Unknown Dendritic cells in secondary lymphoid tissues

Monocytes-macrophages Regulates monocyte-macrophage production

and function CHAPTER 360 Megakaryocytes, monocytes, hepatocytes, possibly lymphocyte subpopulations Induces hepatic acute-phase protein production; stimulates macrophage differentiation; promotes growth of myeloma cells and hematopoietic progenitors; stimulates thrombopoiesis Introduction to the Immune System Neurons, hepatocytes, monocytes-macrophages, adipocytes, alveolar epithelial cells, embryonic stem cells, melanocytes, endothelial cells, fibroblasts, myeloma cells Induces hepatic acute-phase protein production; stimulates macrophage differentiation; promotes growth of myeloma cells and hematopoietic progenitors; stimulates thrombopoiesis; stimulates growth of Kaposi’s sarcoma cells Embryonic stem cells, myeloid and lymphoid precursors, mast cells Stimulates hematopoietic progenitor cell growth, mast cell growth; promotes embryonic stem cell migration T cells, NK cells Chemoattractant for lymphocytes; only known chemokine of C class Monocytes-macrophages, NK cells, memory T cells, basophils Chemoattractant for monocytes, activated memory

T cells, and NK cells; induces granule release from CD8+ T cells and NK cells; potent histamine-releasing factor for basophils; suppresses proliferation of hematopoietic precursors; regulates monocyte protease production Chemoattractant for monocytes, memory and naïve

T cells, eosinophils,? NK cells; activates basophils and eosinophils; regulates monocyte protease production Chemoattractant for monocytes, memory and naïve

T cells, dendritic cells, eosinophils,? NK cells; activates basophils and eosinophils; regulates monocyte protease production Monocytes-macrophages,

T cells, eosinophils, basophils Chemoattractant for monocytes, T cells, eosinophils, and basophils T cells, NK cells Chemoattractant for T and NK cells Activated T cells Chemoattractant for activated T cells; inhibits infection with T-cell tropic HIV-1 Chemoattractant for monocytes, T cells, dendritic cells, and NK cells, and weak chemoattractant for eosinophils and basophils; activates NK-cell function; suppresses proliferation of hematopoietic precursors; necessary for myocarditis associated with coxsackievirus infection; inhibits infection with monocytotropic HIV-1 Chemoattractant for monocytes, T cells, and NK cells; activates NK-cell function; inhibits infection with monocytotropic HIV-1 Monocytes-macrophages,

T cells, NK cells, dendritic cells, eosinophils, basophils Chemoattractant for monocytes-macrophages, CD4+, CD45Ro+ T cells, CD8+ T cells, NK cells, eosinophils, and basophils; induces histamine release from basophils; inhibits infections with monocytotropic HIV-1 T cells, B cells Chemoattractant for lymphocytes Chemoattractant for monocytes; prevents glucocorticoid-induced apoptosis in some T-cell lines T cells Chemoattractant for T lymphocytes; inhibits hematopoiesis Naïve T cells May have a role in induction of immune responses (Continued)

TABLE 360-7 Cytokines and Cytokine Receptors (Continued) CYTOKINE RECEPTOR CELL SOURCE CELL TARGET BIOLOGIC ACTIVITY TECK CCR9 Dendritic cells, thymus, liver, small intestine GRO-α/MGSA CXCR2 Activated granulocytes, monocytemacrophages, and epithelial cells PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders GRO-β/MIP-2α CXCR2 Activated granulocytes and monocyte-macrophages NAP-2 CXCR2 Platelets Neutrophils, basophils Derived from platelet basic protein; neutrophil chemoattractant and activator IP-10 CXCR3 Monocytes-macrophages, T cells, fibroblasts, endothelial cells, epithelial cells MIG CXCR3 Monocytes-macrophages, T cells, fibroblasts SDF-1 CXCR4 Fibroblasts T cells, dendritic cells,? basophils,? endothelial cells Fractalkine CX3CR1 Activated endothelial cells NK cells, T cells, monocytes-macrophages PF-4 Unknown Platelets, megakaryocytes Fibroblasts, endothelial cells Chemoattractant for fibroblasts; suppresses proliferation of hematopoietic precursors; inhibits endothelial cell proliferation and angiogenesis Abbreviations: B7-1, CD80; B7-2, CD86; Breg, regulatory B cells; CCR, CC-type chemokine receptor; CXCR, CXC-type chemokine receptor; DC, dendritic cell; DC-CK, dendritic cell chemokine; EBV, Epstein-Barr virus; ELC, EB11 ligand chemokine (MIP-1b); G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; GRP, growth-related peptide; HSV, herpes simplex virus; IFN, interferon; Ig, immunoglobulin; IL, interleukin; IP-10, IFN-γ-inducible protein-10; LARC, liver- and activation-regulated chemokine; LIF, leukemia inhibitory factor; MCP, monocyte chemotactic protein; M-CSF, macrophage colony-stimulating factor; MDC, macrophage-derived chemokine; MGSA, melanoma growth-stimulating activity; MHC, major histocompatibility complex; MIG, monokine induced by IFN-γ; MIP, macrophage inflammatory protein; NAP, neutrophil-activating protein; NK, natural killer; OSM, oncostatin M; PARC, pulmonary- and activation-regulated chemokine; PBMC, peripheral blood mononuclear cells; PF, platelet factor; RANTES, regulated on activation, normally T cell–expressed and –secreted; SCF, stem cell factor; SDF, stromal

cell–derived factor; SLC, secondary lymphoid tissue chemokine; TARC, thymus- and activation-regulated chemokine; TCA, T-cell activation protein; TECK, thymus-expressed chemokine; TGF, transforming growth factor; TH1 and TH2, helper T cell subsets; TNF, tumor necrosis factor; Treg, regulatory T cells; VCAM, vascular cell adhesion molecule. Sources: Data from JS Sundy et al: Appendix B, in Inflammation, Basic Principles and Clinical Correlates, 3rd ed. J Gallin, R Snyderman (eds). Philadelphia, Lippincott Williams and Wilkins, 1999; J Ye et al: Frontiers in Pharmacology 11; HM Lazear et al: Immunity 43:15, 2015; J Catalan-Dibene et al: J Interferon and Cytokine Research 38:423, 2018. microorganisms or environmental antigens. Inability to prevent immune responses to the gut microbiome can be a factor in the cause of inflammatory bowel diseases (Chap. 337). In healthy individuals, a subset of RORγt+ ILCs, possibly ILC3s, stimulate naïve CD4 T cells to differentiate into peripheral Tregs that suppress immune responses to microbiome organisms. NK cells express surface receptors for the Fc portion of IgG (FcR) (CD16) and for NCAM-I (CD56), and many NK cells express T lineage markers, particularly CD2, CD7, and CD8, and proliferate in response to IL-2. NK cells arise in both bone marrow and thymic microenviron ments. In addition to mediating cytotoxicity to foreign or malignant cells, NK cells also mediate ADCC. ADCC is the binding of an opso nized (antibody-coated) target cell to an Fc receptor-bearing effector cell via the Fc region of antibody, resulting in target cell lysis. NK cell cytotoxicity is the MHC-unrestricted, non-antibody-mediated killing of target cells, which are usually malignant cell types, transplanted for eign cells, or virus-infected cells. Thus, NK cell cytotoxicity may play an important role in immune surveillance and destruction of malig nant and virus-infected host cells. NK cell hyporesponsiveness is also observed in patients with Chédiak-Higashi syndrome, an autosomal recessive disease associated with fusion of cytoplasmic granules and defective degranulation of neutrophil lysosomes. NK cells have a variety of surface receptors that have inhibitory or activating functions (Table 360-9). NK immunoglobulin superfamily receptors include the killer cell immunoglobulin-like activating or inhibitory receptors (KIRs), many of which have been shown to have HLA class I ligands. The KIRs are made up proteins with either two (KIR2D) or three (KIR3D) extracellular immunoglobulin domains (D). Moreover, their nomenclature designates their function as either inhibitory KIRs with a long (L) cytoplasmic tail and immunoreceptor tyrosine-based inhibitory motif (ITIM) (KIRDL) or activating KIRs

T cells, monocytesmacrophages, dendritic cells Thymic dendritic cell–derived cytokine, possibly involved in T-cell development Neutrophils, epithelial cells,? endothelial cells Neutrophil chemoattractant and activator; mitogenic for some melanoma cell lines; suppresses proliferation of hematopoietic precursors; angiogenic activity Neutrophils and? endothelial cells Neutrophil chemoattractant and activator; angiogenic activity Activated T cells, tumorinfiltrating lymphocytes,? endothelial cells,? NK cells IFN-γ-inducible protein that is a chemoattractant for T cells; suppresses proliferation of hematopoietic precursors Activated T cells, tumorinfiltrating lymphocytes IFN-γ-inducible protein that is a chemoattractant for T cells; suppresses proliferation of hematopoietic precursors Low-potency, high-efficacy T-cell chemoattractant; required for B lymphocyte development; prevents infection of CD4+, CXCR4+ cells by T-cell tropic HIV-1 Cell-surface chemokine/mucin hybrid molecule that functions as a chemoattractant, leukocyte activator, and cell adhesion molecule with a short (S) cytoplasmic tail (KIRDS). NK cell inactivation by KIRs is a central mechanism to prevent damage to normal host cells. Genetic studies have demonstrated the association of KIRs with viral infection outcome, or to outcomes in autoimmune or malignant diseases (Table 360-10). In addition to the KIRs, a second set of immunoglobulin superfam ily receptors includes the natural cytotoxicity receptors (NCRs), which include NKp46,

NKp30, and NKp44. These receptors help to mediate NK cell activation against target cells. The ligands to which NCRs bind on target cells have been recently recognized to be comprised of mol ecules of pathogens such as influenza, cytomegalovirus, and malaria, as well as host molecules expressed on tumor cells. Signaling lym phocytic activating molecule (SLAM) family receptors are expressed on hematopoietic cells, with SLAMF2 (CD48), SLAMF4 (2B4), and SLAMF7/CD2-like receptor activating cytotoxic cells (CRACCs) the most prominent on NK cells (Table 360-9). NK cell signaling is, therefore, a highly coordinated series of inhibit ing and activating signals that prevent NK cells from responding to uninfected, nonmalignant self-cells; however, they are activated to attack malignant and virally infected cells (Fig. 360-4). Recent evidence suggests that NK cells, although not possessing rearranging immune recognition genes, may be able to mediate recall for NK cell responses to viruses and for immune responses such as contact hypersensitivity. Some NK cells express CD3 and invariant TCR-α chains and are termed NK T cells. TCRs of NK T cells recognize lipid molecules of intracellular bacteria when presented in the context of CD1 molecules on APCs. Upon activation, NK T cells secrete effector cytokines such as IL-4 and IFN-γ. This mode of recognition of intracellular bacteria such as Listeria monocytogenes and Mycobacterium tuberculosis by NK T cells leads to induction of activation of DCs and is thought to be an important innate defense mechanism against these organisms.

TABLE 360-8 CC, CXC1, CX3, C1, and XC Families of Chemokines and Chemokine Receptors CHEMOKINE RECEPTOR CHEMOKINE LIGANDS CELL TYPES DISEASE CONNECTION CCR1 CCL3 (MIP-1α), CCL5 (RANTES), CCL7 (MCP-3), CCL14 (HCC1) T cells, monocytes, eosinophils, basophils CCR2 CCL2 (MCP-1), CCL8 (MCP-2), CCL7 (MCP-3), CCL13 (MCP-4), CCL16 (HCC4) Monocytes, dendritic cells (immature), memory T cells CCR3 CCL11 (eotaxin), CCL13 (eotaxin-2), CCL7 (MCP-3), CCL5 (RANTES), CCL8 (MCP-2), CCL13 (MCP-4) Eosinophils, basophils, mast cells, TH2, platelets CCR4 CCL17 (TARC), CCL22 (MDC) T cells (TH2), dendritic cells (mature), basophils, macrophages, platelets CCR5 CCL3 (MIP-1α), CCL4 (MIP-1α), CCL5 (RANTES), CCL11 (eotaxin), CCL14 (HCC1), CCL16 (HCC4) T cells, monocytes HIV-1 co-receptor (T cell–tropic strains), transplant rejection CCR6 CCL20 (MIP-3α, LARC) T cells (T regulatory and memory),

B cells, dendritic cells CCR7 CCL19 (ELC), CCL21 (SLC) T cells, dendritic cells (mature) Transport of T cells and dendritic cells to lymph nodes, antigen presentation, and cellular immunity CCR8 CCL1 (1309) T cells (TH2), monocytes, dendritic cells Dendritic cell migration to lymph node, type 2 cellular immunity, granuloma formation CCR9 CCL25 (TECK) T cells, IgA+ plasma cells Homing of T cells and IgA+ plasma cells to the intestine, inflammatory bowel disease CCR10 CCL27 (CTACK), CCL28 (MEC) T cells T-cell homing to intestine and skin CXCR1 CXCL8 (interleukin-8), CXCL6 (GCP2) Neutrophils, monocytes Inflammatory lung disease, COPD CXCR2 CXCL8, CXCL1 (GROα), CXCL2 (GROα), CXCL3 (GROα), CXCL5 (ENA-78), CXCL6 Neutrophils, monocytes, microvascular endothelial cells CXCR3-A CXCL9 (MIG), CXCL10 (IP-10), CXCL11 (I-TAC) Type 1 helper cells, mast cells, mesangial cells CXCR3-B CXCL4 (PF4), CXCL9 (MIG), CXCL10

(IP-10), CXCL11 (I-TAC) Microvascular endothelial cells, neoplastic cells CXCR4 CXCL12 (SDF-1) Widely expressed HIV-1 co-receptor (T cell–tropic), tumor metastases, hematopoiesis CXCR5 CXCL13 (BCA-1) B cells, follicular helper T cells Formation of B-cell follicles CXCR6 CXCL16 (SR-PSOX) CD8+ T cells, natural killer cells, and memory CD4+ T cells CX3CR1 CX3CL1 (fractalkine) Macrophages, endothelial cells, smooth-muscle cells XCR1 XCL1 (lymphotactin), XCL2 T cells, natural killer cells Rheumatoid arthritis, IgA nephropathy, tumor response Abbreviations: BCA-1, B-

cell chemoattractant 1; COPD, chronic obstructive pulmonary disease; CTACK, cutaneous T cell–attracting chemokine; ELC, Epstein-Barr I1-ligand chemokine; ENA, epithelial cell–derived neutrophil-activating peptide; GCP, granulocyte chemotactic protein; GRO, growth-regulated oncogene; HCC, hemofiltrate chemokine; IP-10, interferon inducible 10; I-TAC, interferon-inducible T-cell alpha chemoattractant; LARC, liver- and activation-regulated chemokine; MCP, monocyte chemoattractant protein; MDC, macrophage-derived chemokine; MEC, mammary-enriched chemokine; MIG, monokine induced by interferon-γ; MIP, macrophage inflammatory protein; PF, platelet factor; SDF, stromal cell–derived factor; SLC, secondary lymphoid-tissue chemokine; SR-PSOX, scavenger receptor for phosphatidylserinecontaining oxidized lipids; TARC, thymus- and activation-regulated chemokine; TECK, thymus-expressed chemokine; TH2, type 2 helper T cells. Source: From IF Charo, RM Ranshohoff: The many roles of chemokines and chemokine receptors in inflammation. N Engl J Med 354:610, 2006. Copyright © (2006) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. The receptors for the Fc portion of IgG (FcγRs) are present on NK cells, B cells, macrophages, neutrophils, and mast cells and mediate interactions of IgG with antibody-coated target cells, such as virally infected cells. Antibody-NK interaction via antibody Fc and NK cell FcR links the adaptive and innate immune systems and regulates the mediation of IgG antibody effector functions such as ADCC. There are both activation and inhibitory FcγRs. Activation FcRs, such as FcγRI (CD64), FcγRIIa (CD32a), and FcγRIIIa (CD16a), are characterized by the presence of an immunoreceptor tyrosine-based activating motif (ITAM) sequence, whereas inhibitory FcRs, such as FcγRIIb (CD32b), contain an ITIM sequence. There is evidence that dysregulation in IgG-FcγR interactions plays roles in arthritis, multiple sclerosis, and systemic lupus erythematosus. Neutrophils, Eosinophils, and Basophils Granulocytes are present in nearly all forms of inflammation and are amplifiers and effectors of innate immune responses (Fig. 360-2). Unchecked accu mulation and activation of granulocytes can lead to host tissue damage, as seen in neutrophil- and eosinophil-mediated systemic necrotizing vasculitis. Granulocytes are derived from stem cells in bone marrow.

Rheumatoid arthritis, multiple sclerosis CHAPTER 360 Atherosclerosis, rheumatoid arthritis, multiple sclerosis, resistance to intracellular pathogens, type 2 diabetes mellitus Allergic asthma and rhinitis Introduction to the Immune System Parasitic infection, graft rejection, T-cell homing to skin Mucosal humoral immunity, allergic asthma, intestinal T-cell homing Inflammatory lung disease, COPD, angiogenic for tumor growth Inflammatory skin disease, multiple sclerosis, transplant rejection Angiostatic for tumor growth Inflammatory liver disease, atherosclerosis (CXCL16) Atherosclerosis Each type of granulocyte (neutrophil, eosinophil, or basophil) is derived from a different subclass of progenitor cell that is stimulated to proliferate by colony-stimulating factors (Table 360-6). During termi nal maturation of granulocytes, class-specific nuclear morphology and cytoplasmic granules appear that allow for histologic identification of granulocyte type. Neutrophils express Fc receptor IIIa for IgG (CD16a) as well as receptors for activated complement components (C3b or CD35). Upon interaction of neutrophils with antibody-coated (opsonized) bacteria or immune complexes, azurophilic granules (containing myeloper oxidase, lysozyme, elastase, and other enzymes) and specific granules (containing lactoferrin, lysozyme, collagenase, and other enzymes) are released, and microbicidal superoxide radicals (O_2^-) are generated at the neutrophil surface. The generation of superoxide leads to inflam mation by direct injury to tissue and by alteration of macromolecules such as collagen and DNA. Eosinophils are potent cytotoxic effector cells for various para sitic organisms. In Nippostrongylus brasiliensis helminth infection, eosinophils are important cytotoxic effector cells for removal of these parasites.

Key to regulation of eosinophil cytotoxicity to N. brasiliensis

worms are antigen-specific T helper cells that produce IL-4, thus pro viding an example of regulation of innate immune responses by adap tive immunity antigen-specific T cells. Intracytoplasmic contents of eosinophils, such as major basic protein, eosinophil cationic protein, and eosinophil-derived neurotoxin, are capable of directly damaging tissues and may be responsible in part for the organ system dysfunction in the hypereosinophilic syndromes (Chap. 67). Because the eosinophil granule contains anti-inflammatory types of enzymes (histaminase, arylsulfatase, phospholipase D), eosinophils may also downregulate or terminate ongoing inflammatory responses.

PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders TOX NFIL3 ID2 ETS1 NKP T-BET EOMES T-BET NFIL3 RUNX3 NK A ILC1 ILC2 FIGURE 360-3 Development and function of innate lymphoid cells (ILCs). A. ILC development, mainly based on mouse ILC differentiation paths, is schematized. ILCs develop from common innate lymphoid progenitors (CILPs), which themselves differentiate from common lymphoid progenitors (CLPs). CILPs can differentiate into natural killer (NK) cell precursor (NKP) cells or into common helper innate lymphoid progenitors (CHILPs), which themselves give rise to lymphoid tissue inducer progenitors (LTiPs) and innate lymphoid cell precursors (ILCPs). LTiPs differentiate into lymphoid tissue inducers (LTis) and ILCPs into ILC1, ILC2, or ILC3. Each stage of differentiation is dependent on the expression of the indicated transcription factors: NFIL3 (nuclear factor IL-3 induced), Id2 (inhibitor of DNA binding 2), TOX (thymocyte selection-associated high mobility group box protein), TCF-1 (T-cell factor 1), ETS1 (avian erythroblastosis virus E26 homolog-1), GATA3 (GATA binding protein 3), PLZF (promyelocytic leukemia zinc finger), T-bet (T-box transcription factor), Eomes (eomesodermin), RUNX3 (runt-related transcription factor 3), RORα (RAR-related orphan receptor α), Bcl11b (B cell lymphoma/leukemia 11B), RORγt (RAR-related orphan receptor γt), and AHR (Aryl hydrocarbon receptor). It has been shown in humans that ILC1 subsets may originate from precursors other than ILCPs, but the identity of these precursors remains unknown at this time. B. Some of the most well-known immune functions of each ILC subset are shown: NK cells and ILC1s react to intracellular pathogens, such as viruses, and to tumors; ILC2s respond to large extracellular parasites and allergens; ILC3s combat extracellular microbes, such as bacteria and fungi; and Lutes are involved in the formation of secondary lymphoid structures. For each ILC subset, effector molecules that can be produced upon activation are indicated AREG, amphiregulin; RANK, receptor activation of nuclear factor kB; RANK-L, RANK-ligand. (Reproduced with permission from E Vivier et al: Innate lymphoid cells: 10 years on. Cell 174:1054, 2018.)

Basophils and tissue mast cells are potent reservoirs of cytokines such as IL-4 and can respond to bacteria and viruses with cytokine production through multiple TLRs expressed on their surface. Mast cells and basophils can also mediate antipathogen immunity through the binding of antibodies. This is a particularly important host defense mechanism against parasitic diseases. Basophils express high-affinity surface receptors for IgE (FcεRII) (CD23) and, upon cross-linking of basophil-bound IgE by antigen, can release histamine, eosinophil chemotactic factor of anaphylaxis, and neutral proteases—all media tors of allergic immediate (anaphylaxis) hypersensitivity responses. CLP NFIL3 ID2 TOX TCF-1 ETS1 CILP GATA3 CHILP LTiP PLZF ROR γT TOX ID2 ILCP ROR γT AHR ID2 ROR α Bci11B GATA3 ILC3 LTi

Stimuli Mediators Immune function Tumors, intracellular microbes (virus, bacteria, parasites) NK Large extracellular parasites and allergens Mesenchymal organizer cells (retinoic acid, CXCL13, RANK-L) Extracellular microbes (bacteria, fungi) B FIGURE 360-3 (Continued) In addition, basophils express surface receptors for activated comple ment components (C3a, C5a), through which mediator release can be directly effected. Thus, basophils, like most cells of the immune sys tem, can be activated in the service of host defense against pathogens, or they can be activated for mediator release and cause pathogenic responses in allergic and inflammatory diseases. For further discus sion of tissue mast cells, see Chap. 366. The Complement System The complement system, an impor tant soluble component of the innate immune system, is a series of plasma enzymes, regulatory proteins, and proteins that are activated in a cascading fashion, resulting in cell lysis. There are four pathways of the complement system: the classic activation pathway activated by antigen/antibody immune complexes, the MBL (a serum collectin) activation pathway activated by microbes with terminal mannose groups, the alternative activation pathway activated by microbes or tumor cells, and the terminal pathway that is common to the first three pathways and leads to the membrane attack complex that lyses cells (Fig. 360-5). The series of enzymes of the complement system are serine proteases. Activation of the classic complement pathway via immune complex binding to C1q links the innate and adaptive immune systems via specific antibody in the immune complex. The alternative complement activation pathway is antibody-independent and is activated by bind ing of C3 directly to pathogens and “altered self” such as tumor cells. In the renal glomerular inflammatory disease IgA nephropathy, IgA activates the alternative complement pathway and causes glomerular damage and decreased renal function. Activation of the classic comple ment pathway via C1, C4, and C2 and activation of the alternative path way via factor D, C3, and factor B both lead to cleavage and activation of C3. C3 activation fragments, when bound to target surfaces such as bacteria and other foreign antigens, are critical for opsonization (coat ing by antibody and complement) in preparation for phagocytosis. The MBL pathway substitutes MBL-associated serine proteases (MASPs) 1 and 2 for C1q, C1r, and C1s to activate C4. The MBL activation path way is activated by mannose on the surface of bacteria and viruses.

CHAPTER 360 IFN-γ Granzymes Perforin Type 1 immunity (macrophage activation, cytotoxicity) ILC1 Introduction to the Immune System Type 2 immunity (alternative macrophage activation) IL-4 IL-5 IL-13 IL-9 AREG ILC2 RANK Lymphotoxin TNF IL-17 IL-22 Formation of secondary lymphoid structures LTi Type 3 immunity (phagocytosis, antimicrobial peptides) IL-22 IL-17 GM-CSF Lymphotoxin ILC3 The three pathways of complement activation all converge on the final common terminal pathway. C3 cleavage by each pathway results in activation of C5, C6, C7, C8, and C9, resulting in the membrane attack complex that physically inserts into the membranes of target cells or bacteria and lyses them. Thus, complement activation is a critical component of innate immunity for responding to microbial infection. The functional conse quences of complement activation by the three initiating pathways and the terminal pathway are shown in Fig. 360-5. In general, the cleavage products of complement components facilitate microbe or damaged cell clearance (C1q, C4, C3), promote activation and enhancement of inflammation (anaphylatoxins, C3a, C5a), and promote microbe or opsonized cell lysis (membrane attack complex). ■ ■CYTOKINES Cytokines are soluble proteins produced by a wide variety of cell types (Tables 360-7 and 360-8). They are critical for both normal innate and adaptive immune responses, and their expression may be perturbed in most immune, inflammatory, and infectious disease states. Cytokines are involved in the regulation of the growth, develop ment, and activation of immune

system cells and in the mediation of the inflammatory response. In general, cytokines are characterized by considerable redundancy in that different cytokines have similar functions. In addition, many cytokines are pleiotropic in that they are capable of acting on many different cell types. This pleiotropism results from the expression on multiple cell types of receptors for the same cytokine (see below), leading to the formation of “cytokine networks.” The action of cytokines may be (1) autocrine when the target cell is the same cell that secretes the cytokine, (2) paracrine when the target cell is nearby, and (3) endocrine when the cytokine is secreted into the circulation and acts distal to the source. Cytokines have been named based on presumed targets or based on presumed functions. Those cytokines that are thought to primarily target leukocytes have been named IL-1, -2, -3, etc. Many cytokines that were originally described as having a certain function have retained those names (e.g., granulocyte colony-stimulating factor [G-CSF]). Cytokines

TABLE 360-9 NK-Cell Receptors, Cognate Ligands, and Their Known Signaling Domains/Proximal Adapters SIGNALING DOMAINS AND PROXIMAL ADAPTERS Inhibitory KIR Conserved epitopes on HLA I (“KIR ligands”) ITIM, Src phosphatases KIR2DL1 KIR2DL1 HLA-C2 alleles (Lys80) KIR2DL2 KIR2DL2 HLA-C1 alleles (Asp80); HLA-C2 alleles (Lys80) KIR2DL3 KIR2DL3 HLA-C1 alleles (Asp80) KIR3DL1 KIR3DL1 HLA-B alleles carrying the Bw4 motif; HLA-A alleles carrying the Bw4 motif RECEPTOR GENE LIGAND PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders KIR3DL2 KIR3DL2 HLA-A*03, HLA-A*11 carrying specific peptides KIR2DL4 KIR2DL4 HLA-G KIR2DL5 CD155 Activating KIR HLA-C2, HLA-C1, HLA-F, certain configurations of HLApeptide combinations KIR2DS1 KIR2DS1 HLA-C2 alleles (Lys80) carrying specific peptides KIR2DS2 KIR2DS2 HLA-C1 (Asp80) HLA-A*11 *KIR2DS3 KIR2DS3 Unknown KIR3DS1 HLA-F KIR2DS5 Unknown Natural cytotoxicity receptors (NCRs) NKp30 NCR3 B7-H6, BAT-3, heparan sulfates NKp44 NCR2 PDGF, heparan sulfates, PCNA NKp46 NCR1 Viral hemagglutinins, heparan sulfates, vimentin, ecto-calreticulin SLAM family receptors ITSM, SAP, EAT SLAMF1 (SLAM, CD150, IPO-3) SLAMF1 SLAMF1 SLAMF2 (CD48, BLAST-1) CD48 SLAMF4, CD2 SLAMF3 (CD229, Ly9) LY9 SLAMF3 SLAMF4 (CD244, 2B4, ERT) CD244 SLAMF2 SLAMF6 (NTB-A, Ly108, CD352) SLAMF6 SLAMF6 SLAMF7 (CRACC, CD319) SLAMF7 SLAMF7 SLAMF8 (BLAME, CD353) SLAMF8 Unknown Abbreviations: BAT-3, human leukocyte antigen-B-associated transcript 3; EAT, Ewing sarcoma associated transcript; HLA, human leukocyte antigens; ITAM, immunoreceptor tyrosine-based activation motif; ITIM, immunoreceptor tyrosine-based inhibitory motif; ITSM, immunoreceptor tyrosine-based switch motif; KIR, killer cell immunoglobulin-like receptor; NCRs, natural cytotoxicity receptors; NK, natural killer cell; SAP, SLAM-associated protein; SFK, Src family kinase; SLAM, signalling lymphocyte activating molecule. Source: Reproduced from S Nersesian et al: Killer instincts: Natural killer cells as multifactorial cancer immunotherapy. Front Immunol. 2023; 14:1269614. TABLE 360-10 Association of KIRS with Disease DISEASE KIR ASSOCIATION OBSERVATION Psoriatic arthritis KIR2DS1/KIR2DS2; HLA-Cw group homozygosity Susceptibility Spondylarthritides Increased KIR3DL2 expression Interaction of HLA-B27 homodimers with KIR3DL1/KIR3DL2; independent of peptide Ankylosing spondylitis KIR3DL1/3DS1; HLA-B27 genotypes Susceptibility Rheumatoid vasculitis KIR2DS2; HLA-Cw*03 Increased KIR2L2/2DS2 in patients with extraarticular manifestations Susceptibility Clinical manifestations may have different genetic backgrounds with respect to KIR genotype Rheumatoid arthritis Decreased KIR2DS1/3DS1 in patients without bone erosions KIR2DS4; HLA-Cw4 Susceptibility Susceptibility Scleroderma KIR2DS2+/KIR2DL2– Susceptibility Behçet’s disease Altered KIR3DL1 expression Associated with severe eye disease Psoriasis vulgaris 2DS1; HLA-Cw*06 2DS1; 2DL5; haplotype B Susceptibility Susceptibility IDDM KIR2DS2; HLA-C1 Susceptibility Type 1 diabetes KIR2DS2; HLA-C1 and no HLA-C2, no HLA-Bw4 Increased disease

progression Preeclampsia KIR2DL1 with fewer KIR2DS (mother); HLA-C2 (fetus) Increased disease progression AIDS KIR3DS1; HLA-Bw4Ile80 KIR3DS1 homozygous; no HLA-Bw4Ile80 Decreased disease progression Increased disease progression HCV infection KIR2DL3 homozygous; HLA-C1 homozygous Decreased disease progression Cervical neoplasia (HPV induced) KIR3DS1; HLA-C1 homozygous and no HLA-Bw4 Increased disease progression Malignant melanoma KIR2DL2 and/or KIR2DL3; HLA-C1 Increased disease progression Abbreviations: HCV, hepatitis C virus; HLA, human leukocyte antigen; HPV, human papillomavirus; IDDM, insulin-dependent diabetes mellitus; KIR, killer cell immunoglobulin-like receptor. Source: Reproduced with permission from R Diaz-Pena et al: KIR genes and their role in spondyloarthropathies. Adv Exp Med Biol 649:286, 2009.

ITAM, SFK May contribute to disease pathology May contribute to disease pathogenesis

Inhibitory receptor A No response No HLA class I No activating ligands Target NK Activating receptor B No response HLA class I No activating ligands NK Target C NK attacks target cells No HLA class I Activating ligands NK Target D Outcome determined by balance of signals HLA class I Activating ligands NK Target FIGURE 360-4 Encounters between natural killer (NK) cells: Potential targets and possible outcomes. The amount of activating and inhibitory receptors on the NK cells and the amount of ligands on the target cell, as well as the qualitative differences in the signals transduced, determine the extent of the NK response. A. When target cells have no HLA class I or activating ligands, NK cells cannot kill target cells. B. When target cells bear self-HLA, NK cells cannot kill targets. C. When target cells are pathogen-infected and have downregulated HLA and express activating ligands, NK cells kill target cells. D. When NK cells encounter targets with both self-HLA and activating receptors, then the level of target killing is determined by the balance of inhibitory and activating signals to the NK cell. HLA, human leukocyte antigen. (Republished with permission of Annual Review of Immunology, from NK Cell Recognition, L Lanier 23:225,2005: permission conveyed through Copyright Clearance Center, Inc.) belong in general to three major structural families: the hematopoietin family; the TNF, IL-1, platelet-derived growth factor (PDGF), and trans forming growth factor (TGF) β families; and the CXC and C-C chemo kine families. Chemokines are cytokines that regulate cell movement and trafficking; they act through G protein–coupled receptors and have a distinctive three-dimensional structure (Table 360-7). In general, cytokines exert their effects by influencing gene activa tion that results in cellular activation, growth, differentiation, functional cell-surface molecule expression, and cellular effector function. In this regard, cytokines can have dramatic effects on the regulation of immune responses and the pathogenesis of a variety of diseases. Indeed, T cells have been categorized on the basis of the pattern of cytokines that they secrete, which results in either humoral immune response (TH2) or cellmediated immune response (TH1). A third type of T helper cell is the TH17 cell that contributes to host defense against extracellular bacteria and fungi, particularly at mucosal sites (Fig. 360-2). Cytokine receptors can be grouped into five general families based on similarities in their extracellular amino acid sequences and conserved structural domains. The immunoglobulin (Ig) superfamily represents a large number of cell-surface and secreted proteins. The IL-1 receptors (type 1, type 2) are examples of cytokine receptors with extracellular Ig domains. The hallmark of the hematopoietic growth factor (type 1) receptor family is that the extracellular regions of each receptor contain two conserved motifs. One motif, located at the N terminus, is rich in

Mannose-binding Classic activation pathway Bacteria, fungi, virus, or tumor cells Alternative lectin activation pathway activation pathway Microbes with terminal mannose groups Antigen/antibody immune complex CHAPTER 360 C3 (H2O) MBL-MASP1-MASP2 C1q-C1r-C1s C4 B C4 D C2 C2 Introduction to the Immune System P Anaphylatoxin C3 Opsonin Immune complex modification Lymphocyte activation C3b Clearance of apoptotic cells C5 C6 Anaphylatoxin C7 Terminal pathway C8 Lysis poly-C9 Membrane perturbation FIGURE 360-5 The four pathways and the effector mechanisms of the complement system. Dashed arrows indicate the functions of pathway components. (Reproduced with permission from BJ Morley, MJ Walport: The Complement Facts Books. London, Academic Press, 2000.) cysteine residues. The other motif is located at the C terminus proximal to the transmembrane region and comprises five amino acid residues, tryptophan-serine-X-tryptophan-serine (WSXWS). This family can be grouped on the basis of the number of receptor subunits they have and on the utilization of shared subunits. A number of cytokine receptors, i.e., IL-6, IL-11, IL-12, and leukemia inhibitory factor, are paired with gp130. There is also a common 150-kDa subunit shared by IL-3, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF) receptors. The gamma chain (γc) of the IL-2 receptor is common to the IL-2, IL-4, IL-7, IL-9, and IL-15 receptors. Thus, the specific cytokine receptor is responsible for ligand-specific binding, whereas the sub units such as gp130, the 150-kDa subunit, and γc are important in sig nal transduction. The γc gene is on the X chromosome, and mutations in the γc protein result in the X-linked form of severe combined immune deficiency syndrome (X-SCID) (Chap. 362). The members of the interferon (type II) receptor family include the receptors for IFN-γ and -β, which share a similar 210-amino-acid binding domain with conserved cysteine pairs at both the amino and carboxy termini. The members of the TNF (type III) receptor family share a common binding domain composed of repeated cysteine-rich regions. Members of this family include the p55 and p75 receptors for TNF (TNF-R1 and TNF-R2, respectively); CD40 antigen, which is an important B-cell surface marker involved in immunoglobulin isotype switching; fas/Apo-1, whose triggering induces apoptosis; CD27 and CD30, which are found on activated T cells and B cells; and nerve growth factor receptor. The common motif for the seven transmembrane helix family was originally found in receptors linked to GTP-binding proteins. This family includes receptors for chemokines (Table 360-8), β-adrenergic receptors, and retinal rhodopsin. It is important to note that two mem bers of the chemokine receptor family, CXC chemokine receptor type 4 (CXCR4) and β chemokine receptor type 5 (CCR5), have been found to serve as the two major co-receptors for binding and entry of HIV-1 into CD4-expressing host cells (Chap. 208). Significant advances have been made in defining the signaling pathways through which cytokines exert their intracellular effects. The Janus family of protein tyrosine kinases (JAK) is a critical ele ment involved in signaling via the hematopoietin receptors. Four JAK

kinases, JAK1, JAK2, JAK3, and Tyk2, preferentially bind different cytokine receptor subunits. Cytokine binding to its receptor brings the cytokine receptor subunits into apposition and allows a pair of JAKs to transphosphorylate and activate one another. The JAKs then phosphorylate the receptor on the tyrosine residues and allow signal ing molecules to bind to the receptor, whereby the signaling mol ecules become phosphorylated. Signaling molecules bind the receptor because they have domains (SH2, or src homology 2 domains) that can bind phosphorylated tyrosine residues. There are a number of these important signaling molecules that bind the receptor, such as the adapter molecule SHC, which can couple the receptor to the acti vation of the mitogen-activated protein kinase pathway. In addition, an important class of substrate of the JAKs is the signal transducers and activators of transcription (STAT) family of transcription factors. STATs have

SH2 domains that enable them to bind to phosphorylated receptors, where they are then phosphorylated by the JAKs. It appears that different STATs have specificity for different receptor subunits. The STATs then dissociate from the receptor and translocate to the nucleus, bind to DNA motifs that they recognize, and regulate gene expression. The STATs preferentially bind DNA motifs that are slightly different from one another and thereby control transcription of specific genes. The importance of this pathway is particularly relevant to lym phoid development. Mutations of JAK3 itself also result in a disorder identical to X-SCID; however, because JAK3 is found on chromosome 19 and not on the X chromosome, JAK3 deficiency occurs in boys and girls (Chap. 362). A new class of immunosuppressive drugs of JAK inhibitors has been developed that are approved to treat chronic inflammatory diseases such as rheumatoid arthritis (Chap. 370), psoriatic arthritis (Chap. 374), ulcerative colitis (Chap. 337), atopic dermatitis (Chap. 59), and alopecia areata (Chap. 61).

PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders ■ ■THE ADAPTIVE IMMUNE SYSTEM Adaptive immunity is characterized by antigen-specific responses to a foreign antigen or pathogen. A key feature of adaptive immunity is that following the initial contact with antigen (immunologic priming), subsequent antigen exposure leads to more rapid and vigorous immune responses (immunologic memory). The adaptive immune system con sists of dual limbs of cellular and humoral immunity. The principal effectors of cellular immunity are T lymphocytes, whereas the principal effectors of humoral immunity are B lymphocytes. Both B and T lym phocytes derive from a common stem cell (Fig. 360-6). The proportion and distribution of immunocompetent cells in various tissues reflect cell traffic, homing patterns, and functional capabilities. Bone marrow is the major site of maturation of B cells, monocytes-macrophages, DCs, and granulocytes and contains pluripo tent stem cells that, under the influence of various colony-stimulating factors, can give rise to all hematopoietic cell types. T-cell precursors also arise from hematopoietic stem cells and home to the thymus for maturation. Mature T lymphocytes, B lymphocytes, monocytes, and DCs enter the circulation and home to peripheral lymphoid organs (lymph nodes, spleen) and mucosal surface-associated lymphoid tis sue (gut, genitourinary, and respiratory tracts) as well as the skin and mucous membranes and await activation by foreign antigen. T Cells The pool of effector T cells is established in the thymus early in life and is maintained throughout life both by new T-cell production in the thymus and by antigen-driven expansion of virgin peripheral T cells into “memory” T cells that reside in peripheral lymphoid organs. The thymus exports ~2% of the total number of thymocytes per day throughout life, with the total number of daily thymic emigrants decreasing by ~3% per year during the first four decades of life. Mature T lymphocytes constitute 70–80% of normal peripheral blood lymphocytes (only 2% of the total-body lymphocytes are contained in peripheral blood), 90% of thoracic duct lymphocytes, 30–40% of lymph node cells, and 20–30% of spleen lymphoid cells. In lymph nodes, T cells occupy deep paracortical areas around B-cell germinal centers, and in the spleen, they are located in periarteriolar areas of white pulp (Chap. 70). T cells are the primary effectors of cell-mediated immunity, with subsets of T cells maturing into CD8+

cytotoxic T cells capable of lysis of virus-infected or foreign cells (short-lived effector T cells) and CD4+ T cells capable of T-cell help for CD8+ T-cell and B-cell development. Two populations of long-lived memory T cells are triggered by infections: effector memory and cen tral memory T cells. Effector memory T cells reside in nonlymphoid organs and respond rapidly to repeated pathogenic infections with cytokine production and cytotoxic functions to kill virus-infected cells. Central memory T cells home to lymphoid organs where they replenish long- and short-lived and

effector memory T cells as needed. In general, CD4+ T cells are the primary regulatory cells of T and B lymphocyte and monocyte function by the production of cytokines and by direct cell contact (Fig. 360-2). In addition, T cells regulate erythroid cell maturation in bone marrow and, through cell contact (CD40 ligand), have an important role in activation of B cells and induc tion of Ig isotype switching. Considerable evidence now exists that colonization of the gut by commensal bacteria (the gut microbiome) is responsible for expansion of the peripheral CD4+ T-cell compartment in normal children and adults. Human T cells express cell-surface proteins that mark stages of intrathymic T-cell maturation or identify specific functional subpopu lations of mature T cells. Many of these molecules mediate or partici pate in important T-cell functions (Table 360-1, Fig. 360-6, Chap. 361). The earliest identifiable T-cell precursors in bone marrow are CD34+ pro-T cells (i.e., cells in which TCR genes are neither rear ranged nor expressed). In the thymus, CD34+ T-cell precursors begin cytoplasmic (c) synthesis of components of the CD3 complex of TCRassociated molecules (Fig. 360-6). Within T-cell precursors, TCR for antigen gene rearrangement yields two T-cell lineages, expressing either TCR-αβ chains or TCR-γδ chains. T cells expressing the TCR-αβ chains constitute the majority of peripheral T cells in blood, lymph node, and spleen and terminally differentiate into either CD4+ or CD8+ cells. Cells expressing TCR-γδ chains circulate as a minor popu lation in blood; their functions have been postulated to be those of immune surveillance at epithelial surfaces and cellular defenses against mycobacterial organisms and other intracellular bacteria through rec ognition of bacterial lipids. In the thymus, the recognition of self-peptides on thymic epithelial cells, thymic macrophages, and DCs plays an important role in shap ing T-cell repertoire. As immature cortical thymocytes begin to express surface TCR for antigen, thymocytes with TCRs capable of interacting with self-peptides in the context of self-MHC antigens with low affinity are activated and survive (positive selection). Thymocytes with TCRs that are incapable of binding to self-MHC antigens or bind with high affinity die of attrition (no selection) or by apoptosis (negative selec tion). Thymocytes that are positively selected undergo maturation into CD4 or CD8 single positive T cells, and then migrate to the thymus medulla where they interact with self-peptide–self-MHC molecules, where they can again undergo selection. The purpose of negative and positive thymocyte selection is to eliminate potential pathogenic auto reactive T cells, and at the same time, select a repertoire of mature T cells capable of recognizing foreign antigens. Mature TCRab thymocytes that are positively selected are func tional MHC class II–restricted CD4+ T cells (Fig. 360-2), or they are CD8+ T cells destined to become CD8+ MHC class I–restricted cytotoxic T cells. MHC class I or class II restriction means that T cells recognize antigen peptide fragments only when they are presented in the antigen-recognition site of a class I or class II MHC molecule, respectively. After thymocyte maturation and selection, CD4 and CD8 thymocytes leave the thymus and migrate to the peripheral immune system. The thymus can continue to be a contributor to the periph eral immune system well into adult life, both normally and when the peripheral T-cell pool is damaged, such as occurs in AIDS and cancer chemotherapy. MOLECULAR BASIS OF T-CELL RECOGNITION OF ANTIGEN The TCR for antigen is a complex of molecules consisting of an antigen-binding heterodimer of either αβ or γδ chains noncovalently linked with five CD3 subunits (γ, δ, ε, ζ, and η) (Fig. 360-7). The CD3 ζ chains are either disulfide-linked homodimers (CD3-ζ2) or disulfide-linked

Pro-T Pro-T Pro-T Immature T Mature T CD34+ CD7lo+ or - α,β Germline CD34+ Hematopoietic α,β Germline CD7 CD2 CD3 α-Germline β-VDJ Rearranged Hematopoietic stem cell CD34+ Early pro-B cell Late pro-B cell Large pre-B cell Small pre-B cell Immature B cell Mature B cell Heavy-chain genes VDJ rearranging D-J rearranging Light-chain genes Germline Germline Surface Ig Absent

Absent Surface marker proteins CD34 CD10 CD38 CD10 CD19 CD38 CD40 FIGURE 360-6 Development stages of T and B cells. Elements of the developing T- and B-cell receptor for antigen are shown schematically. The classification into the various stages of B-cell development is primarily defined by rearrangement of the immunoglobulin (Ig) heavy (H) and light (L) chain genes and by the absence or presence of specific surface markers. The classification of stages of T-cell development is primarily defined by cell-surface marker protein expression (sCD3, surface CD3 expression; cCD3, cytoplasmic CD3 expression; TCR, T-cell receptor). For B-cell development, the pre-B-cell receptor is shown as a blue-orange B-cell receptor. (Adapted from Janeway's Immunobiology, 9th ed by Kenneth Murphy and Casey Weaver. Copyright © 2017 by Garland Science, Taylor & Francis Group, LLC. Used by permission of W. W. Norton & Company, Inc.) heterodimers composed of one ζ chain and one η chain. TCR-αβ or TCR-γδ molecules must be associated with CD3 molecules to be inserted into the T-cell surface membrane, TCR-α being paired with TCR-β and TCR-γ being paired with TCR-δ. Molecules of the CD3 complex mediate transduction of T-cell activation signals via TCRs, whereas TCR-α and -β or -γ and -δ molecules combine to form the TCR antigen-binding site. The α, β, γ, and δ TCR for antigen molecules have amino acid sequence homology and structural similarities to immunoglobulin heavy and light chains and are members of the immunoglobulin gene superfamily of molecules. The genes encoding TCR molecules are encoded as clusters of gene segments that rearrange during T-cell mat uration. This creates an efficient and compact mechanism for housing the diversity requirements of antigen receptor molecules. The TCR-α chain is on chromosome 14 and consists of a series of V (variable), J (joining), and C (constant) regions. The TCR-β chain is on chromo some 7 and consists of multiple V, D (diversity), J, and C TCR-β loci. The TCR-γ chain is on chromosome 7, and the TCR-δ chain is in the middle of the TCR-α locus on chromosome 14. Thus, molecules of the TCR for antigen have constant (framework) and variable regions, and

Thymus medulla and peripheral T-cell pools CHAPTER 360 CD7 CD2 cCD3, TCRαβ CD1 CD4, CD8 α-VJ Rearranged β-VDJ Rearranged CD7 CD2 CD3, TCRαβ CD4 Mature T Introduction to the Immune System CD7 CD2 CD3, TCRαβ CD8 Mature T CD7 CD2 CD3, TCRγδ CD8 IgM IgD VDJ rearranged VDJ rearranged VDJ rearranged VDJ rearranged VJ rearranged VJ rearranged VJ rearranging Germline μ H-chain in cytoplasm μ H-chain at surface as part of the pre-B receptor (orange) containing surrogate light chain (SLC). Receptor is mainly intracellular IgM expressed on cell surface IgD and IgM made from alternatively spliced H-chain transcripts CD19 CD20 CD19 CD20 CD21 CD19 CD20 CD38 CD19 CD20 CD38 the gene segments encoding the α, β, γ, and δ chains of these molecules are recombined and selected in the thymus, culminating in synthesis of the completed molecule. In both T- and B-cell precursors (see below), DNA rearrangements of antigen receptor genes involve the same enzymes, recombinase activating gene RAG1 and RAG2, both DNAdependent protein kinases. TCR diversity is created by the different V, D, and J segments that are possible for each receptor chain by the many permutations of V, D, and J segment combinations, by "N-region diversification" due to the addition of nucleotides at the junction of rearranged gene seg ments, and by the pairing of individual chains to form a TCR dimer. As T cells mature in the thymus, the repertoire of antigen-reactive T cells is modified by selection processes that eliminate many autoreactive T cells, enhance the proliferation of cells that function appropriately with self-MHC molecules and antigen, and allow T cells with nonpro ductive TCR rearrangements to die. TCR-αβ cells do not recognize native protein or carbohydrate anti gens. Instead, T cells recognize only short (~9–13 amino acids) peptide fragments derived from protein antigens taken up or produced in APCs. Foreign antigens may be taken up by endocytosis into acidified

PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders PtdIns (4,5)P3 Lipid raft InsP3 Release of Ca2+ Translocation of NFAT to the nucleus DAG PKC RASGRP Activation of downstream effectors such as NFkB, AP1, and NFAT to induce specific gene transcription leading to cell proliferation and differentiation MAPK activation FIGURE 360-7 Signaling through the T-cell receptor. Activation signals are mediated via immunoreceptor tyrosine-based activation (ITAM) sequences in LAT and CD3 chains (blue bars) that bind to enzymes and transduce activation signals to the nucleus via the indicated intracellular activation pathways. Ligation of the T-cell receptor (TCR) by MHC complexed with antigen results in sequential activation of LCK and γ-chain-associated protein kinase of 70 kDa (ZAP70). ZAP70 phosphorylates several downstream targets, including LAT (linker for activation of T cells) and SLP76 (SCR homology 2 [SH2] domain-containing leukocyte protein of 76 kDa). SLP76 is recruited to membrane-bound LAT through its constitutive interaction with GADS (GRB2-related adaptor protein). Together, SLP76 and LAT nucleate a multimolecular signaling complex, which induces a host of downstream responses, including calcium flux, mitogen-activated protein kinase (MAPK) activation, integrin activation, and cytoskeletal reorganization. APC, antigen-presenting cell; NFAT, nuclear factor of activated T cells. (Reproduced with permission from GA Koretzky, F Abtahian, MA Silverman. SLP76 and SLP65: Complex regulation of signalling in lymphocytes and beyond. Nat Rev Immunol 6:67, 2006.) intracellular vesicles or by phagocytosis and degraded into small pep tides that associate with MHC class II molecules (exogenous antigenpresentation pathway). Other foreign antigens arise endogenously in the cytosol (such as from replicating viruses) and are broken down into small peptides that associate with MHC class I molecules (endogenous antigen-presenting pathway). Thus, APCs proteolytically degrade for eign proteins and display peptide fragments embedded in the MHC class I or II antigen-recognition site on the MHC molecule surface, where foreign peptide fragments are available to bind to TCR-αβ or TCR-γδ chains of reactive T cells. CD4 molecules act as adhesives and, by direct binding to MHC class II (DR, DQ, or DP) molecules, stabilize the interaction of TCR with peptide antigen (Fig. 360-7). Similarly, CD8 molecules also act as adhesives to stabilize the TCR-antigen inter action by direct CD8 molecule binding to MHC class Ia (HLA A, B, or C) molecules or to MHC class Ib (HLA E). Antigens that arise in the cytosol and are processed via the endog enous antigen-presentation pathway are cleaved into small peptides by a complex of proteases called the proteasome. From the proteasome, antigen peptide fragments are transported from the cytosol into the lumen of the endoplasmic reticulum by a heterodimeric complex termed transporters associated with antigen processing or TAP proteins. There, MHC class I molecules in the endoplasmic reticulum mem brane physically associate with processed cytosolic peptides. Following peptide association with class I molecules, peptide–class I complexes are exported to the Golgi apparatus, and then to the cell surface, for recognition by CD8+ T cells. Antigens taken up from the extracellular space via endocytosis into intracellular acidified vesicles are degraded by vesicle proteases into peptide fragments. Intracellular vesicles containing MHC class II molecules fuse with peptide-containing vesicles, thus allowing peptide fragments to physically bind to MHC class II molecules. Peptide–MHC

APC ICAM-1 LFA-3 CD28 B7-1 β α CD3 TCR LFA-1 CD2 RAS LCK Cytoskeletal reorganization ZAP70 LAT GRB2 SOS ITK VAV1 PLCγ NCK GADS HPK1 ADAP Integrin activation class II complexes are then transported to the cell surface for recogni tion by CD4+ T cells. Whereas it is generally agreed that the TCR-αβ receptor recognizes peptide antigens in the context of MHC class I or class II molecules, lipids in the cell wall of intracellular bacteria such as M. tuberculosis can also be presented to a wide variety of T cells, including subsets of TCR-γδ T cells, and a subset of CD8+ TCR-αβ T cells.

Importantly, bacterial lipid antigens are not presented in the context of MHC class I or II molecules, but rather are presented in the context of MHC-related CD1 molecules. Some γδ T cells that recognize lipid antigens via CD1 molecules have very restricted TCR usage, do not need antigen prim ing to respond to bacterial lipids, and may be a form of innate rather than acquired immunity to intracellular bacteria. Just as foreign antigens are degraded and their peptide fragments presented in the context of MHC class I or class II molecules on APCs, endogenous self-proteins also are degraded, and self-peptide frag ments are presented to T cells in the context of MHC class I or class II molecules on APCs. In peripheral lymphoid organs, there are T cells that are capable of recognizing self-protein fragments but normally are anergic or tolerant, i.e., nonresponsive to self-antigenic stimulation, due to lack of self-antigen upregulating APC co-stimulatory molecules such as B7-1 (CD80) and B7-2 (CD86) (see below and Chap. 361). Once engagement of mature T-cell TCR by foreign peptide occurs in the context of self-MHC class Ia (A, B, or C), class 1b (E), or class II molecules, binding of non-antigen-specific adhesion ligand pairs such as CD54-CD11/CD18 and CD58-CD2 stabilizes MHC peptide-TCR binding, and the expression of these adhesion molecules is upregu lated. Once antigen ligation of the TCR occurs, the T-cell membrane is partitioned into lipid membrane microdomains, or lipid rafts, that coalesce the key signaling molecules TCR/CD3 complex, CD28, CD2, LAT (linker for activation of T cells), intracellular activated

(dephosphorylated) src family protein tyrosine kinases (PTKs), and the key CD3ζ-associated protein-70 (ZAP-70) PTK (Fig. 360-7). Impor tantly, during T-cell activation, the CD45 molecule, with protein tyro sine phosphatase activity, is partitioned away from the TCR complex to allow activating phosphorylation events to occur. The coalescence of signaling molecules of activated T lymphocytes in microdomains has suggested that T cell–APC interactions can be considered immunologic synapses, analogous in function to neuronal synapses. After TCR-MHC binding is stabilized, activation signals are trans mitted through the cell to the nucleus and lead to the expression of gene products important in mediating the wide diversity of T-cell func tions such as the secretion of IL-2. The TCR does not have intrinsic signaling activity but is linked to a variety of signaling pathways via ITAMs expressed on the various CD3 chains that bind to proteins that mediate signal transduction. Each of the pathways results in the activa tion of particular transcription factors that control the expression of cytokine and cytokine receptor genes. Thus, antigen-MHC binding to the TCR induces the activation of the src family of PTKs, Fyn and Lck (Lck is associated with CD4 or CD8 co-stimulatory molecules); phos phorylation of CD3ζ chain; activation of the related tyrosine kinases ZAP-70 and Syk; and downstream activation of the calcium-dependent calcineurin pathway, the ras pathway, and the protein kinase C path way. Each of these pathways leads to activation of specific families of transcription factors (including NF-AT, fos and jun, and rel/NF-κB) that form heteromultimers capable of inducing expression of IL-2, IL-2 receptor, IL-4, TNF-α, and other T-cell mediators. In addition to the signals delivered to the T cell from the TCR complex and CD4 and CD8, molecules on the T cell, such as CD28 and inducible co-stimulator (ICOS), and molecules on DCs, such as B7-1 (CD80) and B7-2 (CD86), also deliver important co-stimulatory signals that upregulate T-cell cytokine production and are essential for T-cell activation. If signaling through CD28 or ICOS does not occur, or if CD28 is blocked, the T cell becomes anergic rather than activated (see “Immune Tolerance and Autoimmunity” below and Chap. 361). CTLA-4 (CD152) is similar to CD28 in its ability to bind CD80 and CD86. Unlike CD28, CTLA-4 transmits an inhibitory signal to T cells, acting as an off switch. T-CELL EXHAUSTION IN VIRAL INFECTIONS AND CANCER In chronic viral infections such as HIV-1, hepatitis C virus, and hepatitis B virus and in chronic malignancies, the persistence of antigen disrupts mem ory T-cell function, resulting in

defects in memory T-cell responses. This has been defined as T-cell exhaustion and is associated with T-cell programmed cell death protein 1 (PD-1) (CD279) expression. Exhausted T cells have compromised proliferation and lose the ability to produce effector molecules, like IL-2, TNF-α, and IFN-γ. PD-1 and CTLA-4 activation downregulates T-cell responses and is associated with T-cell exhaustion and tumor progression. Inhibition of T-cell PD-1 or CTLA-4 activity to enhance effector T-cell killing of tumor cells has become a critical component of therapy for certain malignan cies (Chap. 361). T-CELL SUPERANTIGENS Conventional antigens bind to MHC class I or II molecules in the groove of the αβ heterodimer and bind to T cells via the V regions of the TCR-α and -β chains. In contrast, superantigens bind directly to the lateral portion of the TCR-β chain and MHC class II β chain and stimulate T cells based solely on the Vβ gene segment used independent of the D, J, and Vα sequences present. Superantigens are protein molecules capable of activating up to 20% of the peripheral T-cell pool, whereas conventional antigens activate <1 in 10,000 T cells. T-cell superantigens include staphylococcal enterotox ins and other bacterial products. Superantigen stimulation of human peripheral T cells occurs in the clinical setting of staphylococcal toxic shock syndrome, leading to massive overproduction of T-cell cytokines that leads to hypotension and shock (Chap. 152). B CELLS Mature B cells constitute 5–10% of human peripheral blood lymphocytes, 20–30% of lymph node cells, 50% of splenic lympho cytes, and ~10% of bone marrow lymphocytes. B cells express on their surface intramembrane immunoglobulin (Ig) molecules that function as BCRs for antigen in a complex of Ig-associated α and β signaling

molecules with properties similar to those described in T cells (Fig. 360-8). Unlike T cells, which recognize only processed peptide fragments of conventional antigens embedded in the notches of MHC class I and class II antigens of APCs, B cells are capable of recognizing and proliferating to whole unprocessed native antigens via antigen binding to B-cell surface Ig (sIg) receptors. B cells also express surface receptors for the Fc region of IgG molecules (CD32) as well as receptors for activated complement components (C3d or CD21, C3b or CD35). The primary function of B cells is to produce antibodies. B cells also serve as APCs and are highly efficient at antigen processing. Their antigen-presenting function is enhanced by a variety of cytokines. Mature B cells are derived from bone marrow precursor cells that arise continuously throughout life (Fig. 360-6).

CHAPTER 360 Introduction to the Immune System B lymphocyte development can be separated into antigen-inde pendent and antigen-dependent phases. Antigen-independent B-cell development occurs in primary lymphoid organs and includes all stages of B-cell maturation up to the sIg+ mature B cell. Antigendependent B-cell maturation is driven by the interaction of antigen with the mature B-cell sIg, leading to memory B-cell induction, Ig class switching, and plasma cell formation. Antigen-dependent stages of B-cell maturation occur in secondary lymphoid organs, including lymph node, spleen, and gut Peyer’s patches. In contrast to the T-cell repertoire that is generated intrathymically before contact with foreign antigen, the repertoire of B cells expressing diverse antigen-reactive sites is modified by further alteration of Ig genes by the enzyme acti vation-induced cytidine deaminase after stimulation by antigen—a process called somatic hypermutation—that occurs in lymph node germinal centers. During B-cell development, diversity of the antigen-binding variable region of Ig is generated by an ordered set of Ig gene rearrangements that are similar to the rearrangements undergone by TCR α, β, γ, and δ genes. For the heavy chain, there is first a rearrangement of D segments to J segments, followed by a second rearrangement between a V gene segment and the newly formed D-J sequence; the C segment is aligned to the V-D-J complex to yield a functional Ig heavy chain gene (V-D-JC). During later stages,

a functional κ or γ light chain gene is generated by rearrangement of a V segment to a J segment, ultimately yielding an intact Ig molecule composed of heavy and light chains. The process of Ig gene rearrangement is regulated and results in a single antibody specificity produced by each B cell, with each Ig molecule comprising one type of heavy chain and one type of light chain. Although each B cell contains two copies of Ig light and heavy chain genes, only one gene of each type is productively rearranged and expressed in each B cell, a process termed allelic exclusion. There are ~300 Vκ genes and 5 Jκ genes, resulting in the pairing of Vκ and Jκ genes to create >1500 different kappa light chain combinations. There are ~70 Vλ genes and 4 Jλ genes for >280 different lambda light chain combinations. The number of distinct light chains that can be generated is increased by somatic mutations within the V and J genes, thus creating large numbers of possible specificities from a limited amount of germline genetic information. As noted above, in heavy chain Ig gene rearrangement, the VH domain is created by the joining of three types of germline genes called VH, DH, and JH, thus allowing for even greater diversity in the variable region of heavy chains than of light chains. The most immature B-cell precursors (early pro-B cells) lack cyto plasmic Ig (cIg) and sIg (Fig. 360-6). The large pre-B cell is marked by the acquisition of the surface pre-BCR composed of μ heavy (H) chains and a pre-B light chain, termed V pre-B. V pre-B is a surrogate light chain receptor encoded by the non-rearranged V pre-B and the γ5 light chain locus (the pre-BCR). Pro- and pre-B cells are driven to proliferate and mature by signals from bone marrow stroma—in particular, IL-7. Light chain rearrangement occurs in the small pre-B-cell stage such that the full BCR is expressed at the immature B-cell stage. Imma ture B cells have rearranged Ig light chain genes and express sIgM. As immature B cells develop into mature B cells, sIgD is expressed as well as sIgM. At this point, B lineage development in bone marrow is complete, and B cells exit into the peripheral circulation and migrate to secondary lymphoid organs to encounter specific antigens.

Heavy chain Fab region PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders BCR RAS LYN Igβ MAPK activation Cytoskeletal reorganization a VAV1 PLCγ NCK SOS FIGURE 360-8 B-cell receptor (BCR) activation results in the sequential activation of protein tyrosine kinases, which results in the formation of a signaling complex and activation of downstream pathways as shown. Whereas SLP76 is recruited to the membrane through GADS and LAT, the mechanism of SLP65 recruitment is unclear. Studies have indicated two mechanisms: (a) direct binding by the SH2 domain of SLP65 to immunoglobulin (Ig) of the BCR complex or (b) membrane recruitment through a leucine zipper in the amino terminus of SLP65 and an unknown binding partner. ADAP, adhesion- and degranulation-promoting adaptor protein; AP1, activator protein 1; BTK, Bruton’s tyrosine kinase; DAG, diacylglycerol; GRB2, growth factor receptor-bound protein 2; HPK1, hematopoietic progenitor kinase 1; InsP3, inositol-1,4,5-trisphosphate; ITK, interleukin-2-inducible T-cell kinase; NCK, noncatalytic region of tyrosine kinase; NF-B, nuclear factor B; PKC, protein kinase C; PLC, phospholipase C; PtdIns(4,5)P2, phosphatidylinositol-4,5-bisphosphate; RASGRP, RAS guanyl-releasing protein; SOS, son of sevenless homologue; SYK, spleen tyrosine kinase. (Reproduced with permission from GA Koretzky et al: SLP76 and SLP65: Complex regulation of signalling in lymphocytes and beyond. Nat Rev Immunol 6:67, 2006.) Random rearrangements of Ig genes occasionally generate selfreactive antibodies, and mechanisms must be in place to correct these mistakes. One such mechanism is BCR editing, whereby autoreactive BCRs are mutated to not react with self-antigens. If receptor editing is unsuccessful in eliminating autoreactive B cells, then autoreactive B cells may undergo negative selection in the bone marrow through induction of apoptosis after BCR engagement of self-antigen. After leaving the bone marrow, B cells populate

peripheral B-cell sites, such as lymph node and spleen, and await contact with foreign antigens that react with each BCR. Antigen-driven B-cell activation occurs through the BCR, and somatic hypermutation takes place whereby point mutations in rearranged H- and L-genes give rise to mutant sIg molecules, some of which bind antigen better than the original sIg molecules. Somatic hypermutation, therefore, is a process whereby memory B cells in peripheral lymph organs have the best binding or the highest-affinity antibodies. This overall process of generating the best antibodies is called affinity maturation of antibody. Lymphocytes that synthesize IgG, IgA, and IgE are derived from sIgM+, sIgD+ mature B cells. Ig class switching occurs in lymph node and other peripheral lymphoid tissue germinal centers. CD40 on B cells and CD40 ligand on T cells constitute a critical co-stimulatory receptorligand pair of immune-stimulatory molecules. Pairs of CD40+ B cells and CD40 ligand+ T cells bind and drive B-cell Ig class switching via

T cell–produced cytokines such as IL-4 and TGF-β. IL-1, -2, -4, -5, and -6 synergize to drive mature B cells to proliferate and differentiate into Ig-secreting cells. Humoral Mediators of Adaptive Immunity: Immunoglobulins

Immunoglobulins are the products of differentiated B cells and mediate

Light chain Igα PtdIns(4,S)P3 SYK b InsP3 Release of Ca2+ DAG BTK SLP65 PKCβ RASGRP GRB2 Activation of downstream effectors the humoral arm of the immune response. The primary functions of antibodies are to bind specifically to antigen and bring about the inac tivation or removal of the offending toxin, microbe, parasite, or other foreign substance from the body. The structural basis of Ig molecule function and Ig gene organization has provided insight into the role of antibodies in normal protective immunity, pathologic immunemediated damage by immune complexes, and autoantibody formation against host determinants. All immunoglobulins have the basic structure of two heavy and two light chains (Fig. 360-8). Immunoglobulin isotype (i.e., G, M, A, D, E) is determined by the type of Ig heavy chain present. IgG and IgA iso types can be divided further into subclasses (G1, G2, G3, G4, and A1, A2) based on specific antigenic determinants on Ig heavy chains. The characteristics of human immunoglobulins are outlined in Table 360-11. The four chains are covalently linked by disulfide bonds. Each chain is made up of a V region and C regions (also called domains), themselves made up of units of ~110 amino acids. Light chains have one variable (VL) and one constant (CL) unit; heavy chains have one variable unit (VH) and three or four constant (CH) units, depending on isotype. As the name suggests, the constant, or C, regions of Ig molecules are made up of homologous sequences and share the same primary structure as all other Ig chains of the same isotype and subclass. Constant regions are involved in biologic functions of Ig molecules. The CH2 domain of IgG and the CH4 units of IgM are involved with the binding of the C1q portion of C1 during complement activation. The CH region at the carboxy-terminal end of the IgG molecule, the Fc region, binds to surface Fc receptors (CD16, CD32, CD64) of macrophages, DCs, NK cells, B cells, neutrophils, and eosinophils. The Fc of IgA binds to FcαR (CD89), and the Fc of IgE binds to FcεR (CD23).

TABLE 360-11 Physical, Chemical, and Biologic Properties of Human Immunoglobulins PROPERTY IgG IgA IgM IgD IgE Usual molecular form Monomer Monomer, dimer Pentamer, hexamer Monomer Monomer Other chains None J chain, SC J chain None None Subclasses G1, G2, G3, G4 A1, A2 None None None Heavy chain allotypes Gm (=30) No A1, A2m (2) None None None Molecular mass, kDa

160, 400 950, 1150

Serum level in average adult, mg/mL 9.5–12.5 1.5–2.6 0.7–1.7 0.04 0.0003 Percentage of total serum Ig 75–85 7–15 5–10 0.3 0.019 Serum half-life, days

2.5 Synthesis rate, mg/kg per day

0.4 0.016 Antibody valence

2, 4 10, 12

Classical complement activation +(G1, 2?, 3) – ++ – – Alternate complement activation +(G4) + – + – Binding cells via Fc Macrophages, neutrophils, large granular lymphocytes Biologic properties Placental transfer, secondary antibody for most antipathogen responses Source: Reproduced with permission from L Carayannopoulos, JD Capra, in WE Paul (ed): Fundamental Immunology, 3rd ed. New York, Raven, 1993. Variable regions (VL and VH) constitute the antibody-binding (Fab) region of the molecule. Within the VL and VH regions are hypervari able regions (extreme sequence variability) that constitute the antigenbinding site unique to each Ig molecule. The idiotype is defined as the specific region of the Fab portion of the Ig molecule to which antigen binds. Antibodies against the idiotype portion of an antibody molecule are called anti-idiotype antibodies. The formation of such antibodies in vivo during a normal B-cell antibody response may generate a negative (or “off”) signal to B cells to terminate antibody production. IgG constitutes ~75–85% of total serum immunoglobulin. The four IgG subclasses are numbered in order of their level in serum, IgG1 being found in greatest amounts and IgG4 the least. IgG subclasses have clinical relevance in their varying ability to bind macrophage and neutrophil Fc receptors and to activate complement (Table 360-11). Moreover, selective deficiencies of certain IgG subclasses give rise to clinical syndromes in which the patient is inordinately susceptible to bacterial infections. IgG antibodies are frequently the predominant antibody made after rechallenge of the host with antigen (secondary antibody response). IgM antibodies normally circulate as a 950-kDa pentamer with 160-kDa bivalent monomers joined by a molecule called the J chain, a 15-kDa nonimmunoglobulin molecule that also effects polymerization of IgA molecules. IgM is the first immunoglobulin to appear in the immune response (primary antibody response) and is the initial type of antibody made by neonates. Membrane IgM in the monomeric form also functions as a major antigen receptor on the surface of mature B cells (Table 360-11). IgM is an important component of immune com plexes in autoimmune diseases. For example, IgM antibodies against IgG molecules (rheumatoid factors) are present in high titers in rheu matoid arthritis, other collagen diseases, and some infectious diseases (subacute bacterial endocarditis). IgA constitutes only 7–15% of total serum immunoglobulin but is the predominant class of immunoglobulin in secretions. IgA in secretions (tears, saliva, nasal secretions, gastrointestinal tract fluid, and human milk) is in the form of secretory IgA (sIgA), a polymer consisting of two IgA monomers, a joining molecule, again termed the J chain, and a glycoprotein called the secretory protein. Of the two IgA subclasses, IgA1 is primarily found in serum, whereas IgA2 is more prevalent in secretions. IgA fixes complement via the alternative complement pathway and has potent antiviral activity in humans by prevention of virus binding to respiratory and gastrointestinal epithe lial cells. IgD is found in minute quantities in serum and, together with IgM, is a major receptor for antigen on the naïve B-cell surface. IgE, which is present in serum in very low concentrations, is the major class of

CHAPTER 360 Introduction to the Immune System Lymphocytes Lymphocytes None Mast cells, basophils, B cells Secretory immunoglobulin Primary antibody responses Marker for mature B cells Allergy, antiparasite responses immunoglobulin involved in arming mast cells and basophils by bind ing to these cells via the Fc region. Antigen cross-linking of IgE mol ecules on basophil and mast cell surfaces results in release of mediators of the immediate hypersensitivity (allergic) response (Table 360-11). ■ ■CELLULAR INTERACTIONS IN REGULATION OF NORMAL IMMUNE RESPONSES The net result of activation of the humoral (B-cell) and cellular (T-cell) arms of the adaptive immune system by foreign antigen is the elimina tion of antigen directly by specific effector T cells or in concert with specific antibody. The expression of adaptive immune cell function is the result of a complex series of immunoregulatory events that occur in phases. Both T and B lymphocytes mediate immune functions, and each of these cell types, when given appropriate signals, passes through stages, from activation and induction through proliferation, differentiation, and ultimately effector functions. The effector function expressed may be at the end point of a response, such as secretion of antibody by a differentiated plasma cell, or it might serve a regulatory function that modulates other functions, such as is seen with CD4 and CD8 T lym phocytes that modulate both differentiation of B cells and activation of CD8 cytotoxic T cells. TH1 CD4+ T cells, through elaboration of IFN-γ, have a central role in mediating intracellular killing by a variety of pathogens. TH1 CD4+ T cells also provide T-cell help for generation of cytotoxic T cells and some types of opsonizing antibody, and they generally respond to antigens that lead to delayed hypersensitivity types of immune responses for many intracellular viruses and bacteria (such as HIV-1 or

M. tuberculosis). In contrast, TH2 cells have a primary role in regula tory humoral immunity and isotype switching. TH2 cells, through production of IL-4 and IL-10, have a regulatory role in limiting proin flammatory responses mediated by TH1 cells (Fig. 360-2). In addition, TH2 CD4+ T cells provide help to B cells for specific Ig production and respond to antigens that require high antibody levels for foreign antigen elimination (extracellular encapsulated bacteria such as Strep tococcus pneumoniae and certain parasite infections). TH17 cells secrete cytokines IL-17, -22, and -26 and have been shown to play a role in autoimmune inflammatory disorders in addition to defense against extracellular bacteria and fungi, particularly at mucosal surfaces. TH9 cells are defined by their secretion of IL-9 and have been shown to play a role in atopic disease, inflammatory bowel disease, and antitumor immunity. Moreover, the TFH subset of helper T cells secrete IL-21 and is crucial for providing the necessary signals to B cells in germinal centers to undergo affinity maturation. TFH13 cells secrete IL-4, IL-5, and IL-13 in response to allergens and and have been postulated to

mediate anaphylaxis reactions (Fig. 360-2). In summary, the type of T-cell response generated in an immune response is determined by the microbe PAMPs presented to the DCs, the TLRs on the DCs that become activated, the types of DCs that are activated, and the cytokines that are produced (Table 360-7). Commonly, myeloid DCs produce IL-12 and activate TH1 T-cell responses that result in IFN-γ and cytotoxic T-cell induction, and plasmacytoid DCs produce IFN-α and lead to TH2 responses that result in IL-4 production and enhanced antibody responses.

PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders As shown in Fig. 360-2, upon activation by DCs, T-cell subsets that produce IL-2, IL-3, IFN-γ, and/or IL-4, -5, -6, -10, and -13 are gener ated and exert positive and negative influences on effector T and B cells. For B cells,

trophic effects are mediated by a variety of cytokines, particularly T cell–derived IL-3, -4, -5, and -6, that act at sequential stages of B-cell maturation, resulting in B-cell proliferation, differentia tion, and ultimately antibody secretion. For cytotoxic T cells, trophic factors include inducer T-cell secretion of IL-2, IFN-γ, and IL-12. Important types of immunomodulatory T cells that control immune responses are CD4 and CD8 Treg cells. These cells express the α chain of the IL-2 receptor (CD25), produce IL-10, and suppress both T- and B-cell responses. T regulatory cells (Tregs) are induced by immature DCs and play key roles in maintaining tolerance to self-antigens. Loss of Treg cells is the cause of organ-specific autoimmune disease in mice such as autoimmune thyroiditis, adrenalitis, and oophoritis and plays a role in inflammatory bowel disease (see “Immune Tolerance and Auto immunity” below, Chap. 361). Tregs also play key roles in controlling the magnitude and duration of immune responses to microbes. Nor mally, after the initial immune response to a microbe has eliminated the invader, Tregs are activated to suppress the antimicrobe response and prevent host injury. Some microbes have adapted to induce Treg activation at the site of infection to promote parasite infection and sur vival. In Leishmania infection, the parasite induces Treg accumulation at skin infection sites that dampens anti-Leishmania T-cell responses and prevents parasite elimination. Although B cells recognize native antigen via B-cell surface Ig receptors, B cells require T-cell help to produce high-affinity antibody of multiple isotypes that are the most effective in eliminating foreign antigen. In B-cell germinal centers, CD4 T cells that promote B-cell maturation and affinity maturation are termed T follicular helper (TFH) cells. T cell–B cell interactions that lead to high-affinity antibody production require (1) processing of native antigen by B cells and expression of peptide fragments on the B-cell surface for presentation to TH cells, (2) the ligation of B cells by both the TCR complex and the CD40 ligand, (3) induction of the pro cess termed antibody isotype switching in antigen-specific B-cell clones, and (4) induction of the process of affinity maturation of antibody in the germinal centers of B-cell follicles of lymph node and spleen. Naïve B cells express cell-surface IgD and IgM, and initial contact of naïve B cells with antigen is via binding of native antigen to B-cell surface IgM. T-cell cytokines, released following TH2 cell contact with B cells or by a “bystander” effect, induce changes in Ig gene conforma tion that promote recombination of Ig genes. These events then result in the switching of expression of heavy chain exons in a triggered B cell, leading to the secretion of IgG, IgA, or, in some cases, IgE antibody with the same V region antigen specificity as the original IgM antibody, for response to a wide variety of extracellular bacteria, protozoa, and helminths. CD40 ligand expression by activated T cells is critical for induction of B-cell antibody isotype switching and for B-cell respon siveness to cytokines. Patients with mutations in T-cell CD40 ligand have B cells that are unable to undergo isotype switching, resulting in lack of memory B-cell generation and the immunodeficiency syn drome of X-linked hyper-IgM syndrome (Chaps. 361 and 362). ■ ■IMMUNE TOLERANCE AND AUTOIMMUNITY Immune tolerance is defined as the absence of activation of pathogenic autoreactivity to self-antigens. Mechanisms of immune tolerance can be classified as cell intrinsic or cell extrinsic. Cell intrinsic mechanisms of tolerance include apoptosis and induction of cell unresponsiveness (anergy). Mechanisms of cell extrinsic tolerance include suppression of immune responses by immunomodulatory cells such as Tregs.

Autoimmune diseases are syndromes caused by the activation of T or B cells or both, with no evidence of other causes such as infections or malignancies (Chaps. 361 and 367). Low levels of autoreactivity of T and B cells with self-antigens in the periphery are critical to T- and B-cell survival. Similarly, low levels of autoreactivity and thymocyte recognition of self-antigens in the thymus are the mechanisms whereby normal T cells are positively selected to survive and leave

the thymus to respond to foreign microbes in the periphery and T cells highly reac tive to self-antigens are negatively selected and die to prevent overly self-reactive T cells from migrating to the periphery (central toler ance). Unlike the presentation of microbial antigens by mature DCs, the presentation of self-antigens by immature DCs neither activates nor matures the DCs to express high levels of co-stimulatory molecules such as B7-1 (CD80) or B7-2 (CD86). When peripheral T cells are stimulated by DCs expressing self-antigens in the context of HLA mol ecules, sufficient stimulation of T cells occurs to keep them alive, but otherwise, they remain anergic, or nonresponsive, until T cells contact a DC with high levels of co-stimulatory molecules expressing microbial antigens and become activated to respond to the microbe. If B cells have high self-reactive BCRs, they normally undergo either deletion in the bone marrow or receptor editing to express a less autoreactive receptor. Although many autoimmune diseases are characterized by abnormal or pathogenic autoantibody production (see Chap. 361, Table 361-4), most autoimmune diseases are caused by a combination of excess T- and B-cell reactivity. Multiple factors contribute to the genesis of autoimmune disease syndromes, including genetic susceptibility (e.g., HLA-B27 with anky losing spondylitis), environmental immune stimulants such as drugs (e.g., procainamide and phenytoin [Dilantin] with drug-induced systemic lupus erythematosus), infectious agent triggers (e.g., EpsteinBarr virus and autoantibody production against red blood cells and platelets), and loss of Treg cells (leading to thyroiditis, adrenalitis, and oophoritis). Immunity at Mucosal Surfaces Mucosa covering the respiratory, digestive, and urogenital tracts; the eye conjunctiva; the inner ear; and the ducts of all exocrine glands contain cells of the innate and adaptive mucosal immune system that protect these surfaces against pathogens. In the healthy adult, mucosa-associated lymphoid tissue (MALT) contains 80% of all immune cells within the body and constitutes the largest mammalian lymphoid organ system. MALT has three main functions: (1) to protect the mucous mem branes from invasive pathogens; (2) to prevent uptake of foreign anti gens from food, commensal organisms, and airborne pathogens and particulate matter; and (3) to prevent pathologic immune responses from foreign antigens if they do cross the mucosal barriers of the body. MALT is a compartmentalized system of immune cells that func tions independently from systemic immune organs. Whereas the systemic immune organs are essentially sterile under normal condi tions and respond vigorously to pathogens, MALT immune cells are continuously bathed in foreign proteins and commensal bacteria, and they must select those pathogenic antigens that must be eliminated. MALT contains anatomically defined foci of immune cells in the intestine, tonsil, appendix, and peribronchial areas that are inductive sites for mucosal immune responses. From these sites, immune T and B cells migrate to effector sites in mucosal parenchyma and exocrine glands where mucosal immune cells eliminate pathogen-infected cells. In addition to mucosal immune responses, all mucosal sites have strong mechanical and chemical barriers and cleansing functions to repel pathogens. Key components of MALT include specialized epithelial cells called “membrane” or “M” cells that take up antigens and deliver them to DCs or other APCs. Regulatory cells that maintain gut homeostasis include ILC APCs, likely ILC3, that drive the development of CD4 Tregs that suppress pathogenic immune responses to benign commensal micro biota. Effector cells in MALT include B cells producing antipathogen neutralizing antibodies of secretory IgA as well as IgG isotype, T cells producing similar cytokines as in systemic immune responses, and T helper and cytotoxic T cells that respond to pathogen-infected cells.

Secretory IgA is produced in amounts of >50 mg/kg of body weight per 24 h and functions to inhibit bacterial adhesion, inhibit macromol ecule absorption in the gut, neutralize viruses, and enhance antigen elimination in tissue through binding to IgA and receptor-mediated transport of

immune complexes through epithelial cells. Recent studies have demonstrated the importance of commensal gut and other mucosal bacteria to the health of the human immune system. Normal commensal flora induces anti-inflammatory events in the gut and protects epithelial cells from pathogens through TLRs and other PRR signaling. When the gut is depleted of normal com mensal flora, the immune system becomes abnormal, with loss of TH1 T-cell function. Restoration of the normal gut flora can reestablish the balance in Treg and T helper cell ratios characteristic of the normal immune system. Diet also has an impact on the gut microbiome. Altered microbiome composition has been etiologically related to obesity, insulin resistance, inflammatory bowel disease, and diabetes. When the gut barrier is intact, either antigens do not transverse the gut epithelium or, when pathogens are present, a self-limited, protec tive MALT immune response eliminates the pathogen. However, when the gut barrier breaks down, immune responses to commensal flora antigens can contribute to Crohn's disease and, perhaps, ulcerative colitis (Chap. 337). Uncontrolled MALT immune responses to food antigens, such as gluten, can cause celiac disease (Chap. 337). ■ ■THE CELLULAR AND MOLECULAR CONTROL OF PROGRAMMED CELL DEATH The process of apoptosis (programmed cell death) plays a crucial role in regulating normal immune responses to antigen. In general, a wide variety of stimuli trigger one of several apoptotic pathways to eliminate microbe-infected cells, eliminate cells with damaged DNA, or eliminate activated immune cells that are no longer needed. The largest known family of "death receptors" is the TNF receptor (TNF-R) family (TNF-R1, TNF-R2, Fas [CD95], death receptor 3 [DR3], death receptor 4 [DR4; TNF-related apoptosis-including ligand receptor 1, or TRAIL-R1], and death receptor 5 [DR5, TRAIL-R2]); their ligands are all in the TNF-α family. Binding of ligands to these death recep tors leads to a signaling cascade that involves activation of the caspase family of molecules that leads to DNA cleavage and cell death. Two other pathways of programmed cell death involve nuclear p53 in the elimination of cells with abnormal DNA and mitochondrial cytochrome c to induce cell death in damaged cells. A number of human diseases have now been described that result from, or are associated with, mutated apoptosis genes. These include mutations in the Fas and Fas ligand genes in autoimmune and lymphoproliferation syndromes, and multiple associations of mutations in genes in the apoptotic pathway with malignant syndromes (Chap. 361). ■ ■MECHANISMS OF IMMUNE-MEDIATED DAMAGE TO MICROBES OR HOST TISSUES Several responses by the host innate and adaptive immune systems to foreign microbes culminate in rapid and efficient elimination of microbes. In these scenarios, the classic weapons of the adaptive immune system (T cells, B cells) interface with cells (macrophages, DCs, NK cells, neutrophils, eosinophils, basophils) and soluble prod ucts (microbial peptides, pentraxins, complement and coagulation systems) of the innate immune system (Chaps. 67 and 363). There are five general phases of host defenses: (1) migration of leukocytes to sites of antigen localization; (2) antigen-nonspecific rec ognition of pathogens by macrophages and other cells and systems of the innate immune system; (3) specific recognition of foreign antigens mediated by T and B lymphocytes; (4) amplification of the inflamma tory response with recruitment of specific and nonspecific effector cells by complement components, cytokines, kinins, arachidonic acid metabolites, and mast cell–basophil products; and (5) macrophage, neutrophil, and lymphocyte participation in destruction of antigen with ultimate removal of antigen particles by phagocytosis (by macro phages or neutrophils) or by direct cytotoxic mechanisms (involving macrophages, neutrophils, DCs, or lymphocytes). Under normal cir cumstances, orderly progression of host defenses through these phases

results in a well-controlled immune and inflammatory response that protects the host from the offending antigen. However, dysfunction of any of the host defense systems can damage host tissue and produce clinical disease. Furthermore, for certain pathogens or antigens, the nor mal immune response itself might contribute substantially to the tissue damage. For example, the immune and inflammatory response in the brain to certain pathogens such as M. tuberculosis may be responsible for much of the morbidity rate of this disease in that organ system (Chap. 183). In addition, the morbidity rate associated with certain pneumonias such as that caused by Pneumocystis jirovecii may be associated more with inflammatory infiltrates than with the tissuedestructive effects of the microorganism itself (Chap. 227).

CHAPTER 360 Introduction to the Immune System Molecular Basis of Lymphocyte–Endothelial Cell Interac tions The control of lymphocyte circulatory patterns between the bloodstream and peripheral lymphoid organs operates at the level of lymphocyte–endothelial cell interactions to control the specificity of lymphocyte subset entry into organs. Similarly, lymphocyte–endothelial cell interactions regulate the entry of lymphocytes into inflamed tissue. Adhesion molecule expression on lymphocytes and endothelial cells regulates the retention and subsequent egress of lymphocytes within tissue sites of antigenic stimulation, delaying cell exit from tissue and preventing reentry into the circulating lymphocyte pool (Fig. 360-9). All types of lymphocyte migration begin with lymphocyte attachment to specialized regions of vessels, termed high endothelial venules (HEVs). An important concept is that adhesion molecules do not generally bind their ligand until a conformational change (ligand activation) occurs in the adhesion molecule that allows ligand binding. Induction of a conformation-dependent determinant on an adhesion molecule can be accomplished by cytokines or via ligation of other adhesion molecules on the cell. The first stage of lymphocyte–endothelial cell interactions, attach ment and rolling, occurs when lymphocytes leave the stream of flowing blood cells in a postcapillary venule and roll along venule endothelial cells (Fig. 360-9). Lymphocyte rolling is mediated by the l-selectin molecule (LECAM-1, LAM-1, CD62L) and slows cell transit time through venules, allowing time for activation of adherent cells. The second stage of lymphocyte–endothelial cell interactions, firm adhesion with activation-dependent stable arrest, requires stimulation of lymphocytes by chemoattractants or by endothelial cell–derived cytokines. Cytokines thought to participate in adherent cell activa tion include members of the IL-8 family, platelet-activation factor, leukotriene B4, and C5a. In addition, HEVs express chemokines, SLC (CCL21) and ELC (CCL19), which participate in this process. Fol lowing activation by chemoattractants, lymphocytes shed l-selectin from the cell surface and upregulate cell CD11b/18 (MAC-1) or CD11a/18 (LFA-1) molecules, resulting in firm attachment of lym phocytes to HEVs. Lymphocyte homing to peripheral lymph nodes involves adhesion of l-selectin to glycoprotein HEV ligands collectively referred to as peripheral node addressin (PNAd), whereas homing of lymphocytes to intestine Peyer’s patches primarily involves adhesion of the a4β7 integrin to mucosal addressin cell adhesion molecule-1 (MAdCAM-1) on the Peyer’s patch HEVs. However, for migration to mucosal Peyer’s patch lymphoid aggregates, naïve lymphocytes primarily use l-selectin, whereas memory lymphocytes use α4β7 integrin. α4β1 integrin (CD49d/CD29, VLA-4)–VCAM-1 interactions are important in the initial interaction of memory lymphocytes with HEVs of multiple organs in sites of inflammation. The third stage of leukocyte emigration in HEVs is sticking and arrest. Sticking of the lymphocyte to endothelial cells and arrest at the site of sticking are mediated predominantly by ligation of a1β2 integrin LFA-1 to the integrin ligand ICAM-1 on HEVs. Whereas the first three stages of lymphocyte attachment to HEVs take only a few seconds, the fourth stage of lymphocyte emigration, transendothelial migration, takes ~10

min. Although the molecular mechanisms that control lymphocyte transendothelial migration are not fully character ized, the HEV CD44 molecule and molecules of the HEV glycocalyx (extracellular matrix) are thought to play important regulatory roles in

Blood vessel lumen

1. Tethering and rolling
2. Chemokine signal
3. Arrest
4. Polarization and diapedesis PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders Basement membrane DC Lymph vessel
5. DC migration to draining LN Inflammatory chemoattractants Selectin sialomucin Resting actve integrins Collagen FIGURE 360-9 Key migration steps of immune cells at sites of inflammation. Inflammation due to tissue damage or infection induces the release of cytokines (not shown) and inflammatory chemoattractants (red arrowheads) from distressed stromal cells and “professional” sentinels, such as mast cells and macrophages (not shown). The inflammatory signals induce upregulation of endothelial selectins and immunoglobulin “superfamily” members, particularly ICAM-1 and/or VCAM-1. Chemoattractants, particularly chemokines, are produced by or translocated across venular endothelial cells (red arrow) and are displayed in the lumen to rolling leukocytes. Those leukocytes that express the appropriate set of trafficking molecules undergo a multistep adhesion cascade (steps 1–3) and then polarize and move by diapedesis across the venular wall (steps 4 and 5). Diapedesis involves transient disassembly of endothelial junctions and penetration through the underlying basement membrane (step 6). Once in the extravascular (interstitial) space, the migrating cell uses different integrins to gain “footholds” on collagen fibers and other ECM molecules, such as laminin and fibronectin, and on inflammation-induced ICAM-1 on the surface of parenchymal cells (step 7). The migrating cell receives guidance cues from distinct sets of chemoattractants, particularly chemokines, which may be immobilized on glycosaminoglycans (GAG) that “decorate” many ECM molecules and stromal cells. Inflammatory signals also induce tissue dendritic cells (DCs) to undergo maturation. Once DCs process material from damaged tissues and invading pathogens, they upregulate CCR7, which allows them to enter draining lymph vessels that express the CCR7 ligand CCL21 (and CCL19). In lymph nodes (LNs), these antigen-loaded mature DCs activate naïve T cells and expand pools of effector lymphocytes, which enter the blood and migrate back to the site of inflammation. T cells in tissue also use this CCR7-dependent route to migrate from peripheral sites to draining lymph nodes through afferent lymphatics. (Reproduced with permission from AD Luster et al: Immune cell migration in inflammation: present and future therapeutic targets. Nat Immunol 6:1182, 2005.) this process (Fig. 360-10). Finally, expression of matrix metalloprote ases capable of digesting the subendothelial basement membrane, rich in nonfibrillar collagen, appears to be required for the penetration of lymphoid cells into the extravascular sites. Abnormal induction of HEV formation and use of the molecules discussed above have been implicated in the induction and mainte nance of inflammation in a number of chronic inflammatory diseases. In animal models of type 1 diabetes mellitus, MAdCAM-1 and GlyCAM-1 have been shown to be highly expressed on HEVs in inflamed pancre atic islets, and treatment of these animals with inhibitors of l-selectin and

a4 integrin function blocked the development of type 1 diabetes mellitus (Chap. 415). A similar role for abnormal induction of the adhesion molecules of lymphocyte emigration has been suggested in rheumatoid arthritis (Chap. 370), Hashimoto's thyroiditis (Chap. 394), Graves' disease (Chap. 394), multiple sclerosis (Chap. 455), Crohn's disease (Chap. 337), and ulcerative colitis (Chap. 337). Immune-Complex Formation Clearance of antigen by immunecomplex formation between antigen, complement, and antibody is a highly effective mechanism of host defense. However, depending

6. Junctional rearrangement
7. Proteolysis Cytokinestimulated parenchymal cell Damaged or inflamed tissue
8. Interstitial migration ECM with GAG GPCR CCL19 CCL21 CCR7 ICAM-1 or VCAM-1 on the level of immune complexes formed and their physicochemi cal properties, immune complexes may or may not result in host and foreign cell damage. After antigen exposure, certain types of soluble antigen-antibody complexes freely circulate and, if not cleared by the reticuloendothelial system, can be deposited in blood vessel walls and in other tissues such as renal glomeruli and cause vasculitis or glomerulonephritis syndromes (Chaps. 326 and 375). Deficiencies of early complement components are associated with inefficient clearance of immune complexes and immune complex–mediated autoimmune syndromes or encapsulated bacterial infections such as S. pneumoniae, whereas deficiencies of the later complement components are associ ated with susceptibility to recurrent Neisseria infections (Table 360-12). Immediate-Type Hypersensitivity Helper T cells that drive antiallergen IgE responses are usually TH2-type inducer T cells that secrete IL-4, IL-5, IL-6, and IL-10. A subset of TFH, TFH13, cells have been identified that produce IL-4, IL-5, and IL-13, which play a key role in responses to allergens that induce IgE and mediate ana phylaxis. Mast cells and basophils have high-affinity receptors for the Fc portion of IgE (FcRI), and cell-bound antiallergen IgE effectively

TABLE 360-12 Complement Deficiencies and Associated Diseases COMPONENT ASSOCIATED DISEASES Classic Pathway Clq, Clr, Cls, C4 Immune-complex syndromes,a pyogenic infections C2 Immune-complex syndromes,a few with pyogenic infections C1 inhibitor Rare immune-complex disease, few with pyogenic infections C3 and Alternative Pathway C3 C3 Immune-complex syndromes,a pyogenic infections D Pyogenic infections Properdin Neisseria infections I Pyogenic infections H Hemolytic-uremic syndrome Membrane Attack Complex C5, C6, C7, C8 Recurrent Neisseria infections, immune-complex disease C9 Rare Neisseria infections aImmune-complex syndromes include systemic lupus erythematosus (SLE) and

SLE-like syndromes, glomerulonephritis, and vasculitis syndromes. Source: After JA Schifferli, DK Peters: Lancet 322:957, 1983. Copyright 1983. "arms" basophils and mast cells. Mediator release is triggered by antigen (allergen) interaction with Fc receptor-bound IgE, and the mediators released are responsible for the pathophysiologic changes of allergic diseases. Mediators released from mast cells and basophils can be divided into three broad functional types: (1) those that increase vascular permeability and contract smooth muscle (histamine, plateletactivating factor, SRS-A, BK-A), (2) those that are chemotactic for or activate other inflammatory cells (ECF-A, NCF, leukotriene B4), and (3) those that modulate the release of other mediators (BK-A, plateletactivating factor) (Chap. 363). Cytotoxic Reactions of Antibody In this type of immunologic injury, complement-fixing (C1-binding) antibodies against normal or foreign cells or tissues (IgM, IgG1, IgG2, IgG3) bind complement via the classic pathway and initiate a sequence of events similar to that initiated by

immune-complex deposition, resulting in cell lysis or tissue injury. Examples of antibody-mediated cytotoxic reactions include red cell lysis in transfusion reactions, Goodpasture's syndrome with anti–glomerular basement membrane antibody formation, and pemphigus vulgaris with anti-epidermal antibodies inducing blistering skin disease. Delayed-Type Hypersensitivity Reactions Inflammatory reactions initiated by mononuclear leukocytes and not by antibody alone have been termed delayed-type hypersensitivity reactions. The term delayed has been used to contrast a secondary cellular response that appears 48–72 h after antigen exposure with an immediate hyper sensitivity response generally seen within 12 h of antigen challenge and initiated by basophil mediator release or preformed antibody. For example, in an individual previously infected with M. tuberculo sis organisms, intradermal placement of tuberculin purified protein derivative as a skin test challenge results in an indurated area of skin at 48–72 h, indicating previous exposure to tuberculosis. The cellular events that result in classic delayed-type hypersensitiv ity responses are centered on T cells (predominantly, although not exclusively, IFN-γ, IL-2, and TNF-α-secreting TH1-type helper T cells) and macrophages. Recently, NK cells have been suggested to play a major role in the form of delayed hypersensitivity that occurs follow ing skin contact with immunogens. First, local immune and inflam matory responses at the site of foreign antigen upregulate endothelial cell adhesion molecule expression, promoting the accumulation of lymphocytes at the tissue site. In the scheme outlined in Fig. 360-2, antigen is processed by DCs and presented to small numbers of CD4+ T cells expressing a TCR specific for the antigen. IL-12 produced by APCs induces T cells to produce IFN-γ (TH1 response). Macrophages frequently undergo epithelioid cell transformation and fuse to form multinucleated giant cells in response to IFN-γ. This type of mono nuclear cell infiltrate is termed granulomatous inflammation. Examples

of diseases in which delayed-type hypersensitivity plays a major role are fungal infections (histoplasmosis; Chap. 218), mycobacterial infec tions (tuberculosis, leprosy; Chaps. 183 and 184), chlamydial infections (lymphogranuloma venereum; Chap. 194), helminth infections (schis tosomiasis; Chap. 241), reactions to toxins (berylliosis; Chap. 300), and hypersensitivity reactions to organic dusts (hypersensitivity pneumoni tis; Chap. 299). In addition, delayed-type hypersensitivity responses play important roles in tissue damage in autoimmune diseases such as rheumatoid arthritis, temporal arteritis, and granulomatosis with poly angiitis (Chaps. 370 and 375).

CHAPTER 360 Introduction to the Immune System Autophagy Autophagy is a process that involves a lysosomal deg radation pathway mechanism of cells to dispose of intracellular debris and damaged organelles. Autophagy by cells of the innate immune sys tem is used to control intracellular infectious agents such as M. tuber culosis, in part by initiation of phagosome maturation and enhancing MHC class II antigen presentation to CD4 T cells. ■ ■CLINICAL EVALUATION OF IMMUNE FUNCTION Clinical assessment of immunity requires investigation of the four major components of the immune system that participate in host defense and in the pathogenesis of autoimmune diseases: (1) humoral immunity (B cells); (2) cell-mediated immunity (T cells, monocytes); (3) phagocytic cells of the reticuloendothelial system (macrophages), as well as polymorphonuclear leukocytes; and (4) complement. Clini cal problems that require an evaluation of immunity include chronic infections, recurrent infections, unusual infecting agents, and certain autoimmune syndromes. The type of clinical syndrome under evalu ation can provide information regarding possible immune defects (Chap. 362). Defects in cellular immunity generally result in viral, mycobacterial, and fungal infections. An extreme example of defi ciency in cellular immunity is AIDS (Chap. 208). Antibody deficien cies result in recurrent bacterial infections,

frequently with organisms such as S. pneumoniae and Haemophilus influenzae (Chap. 362). Dis orders of phagocyte function are frequently manifested by recurrent skin infections, often due to Staphylococcus aureus (Chap. 67). Finally, deficiencies of early and late complement components are associated with autoimmune phenomena and recurrent Neisseria infections (Table 360-12). Artificial intelligence/machine learning algorithms are now being tested for improving the diagnosis of infectious, immune deficiency, and autoimmune diseases. For further discussion of useful initial screening tests of immune function, see Chap. 362. ■ ■IMMUNOTHERAPY Many therapies for autoimmune and inflammatory diseases involve the use of nonspecific immune-modulating or immunosuppressive agents such as glucocorticoids or cytotoxic drugs. The goal of development of new treatments for immune-mediated diseases is to design ways to specifically interrupt pathologic immune responses, leaving nonpatho logic immune responses intact (Chap. 361). Novel ways to interrupt pathologic immune responses that are under investigation include the use of anti-inflammatory cytokines or specific cytokine inhibitors as anti-inflammatory agents, the use of monoclonal antibodies against T or B lymphocytes as therapeutic agents, the use of intravenous Ig for certain infections and immune complex–mediated diseases, the use of specific cytokines to reconstitute components of the immune system, and bone marrow transplantation to replace the pathogenic immune system with a more normal immune system (Chaps. 67, 208, 361, and 362). CTLA-4 inhibitors such as ipilimumab and tremelimumab and anti-PD-1 antibodies such as nivolumab are termed checkpoint inhibitors and have been shown to reverse CD8 T-cell exhaustion in melanoma and other solid tumors and induce immune cell control of tumor growth (Chap. 361). A technique that engineers autologous T cells to express antibody receptors that target leukemic cells, termed chimeric antigen receptor T cells (CAR T cells), has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of certain types of leukemias and lymphomas (Chap. 361). Cell-based therapies have been studied for many years, includ ing ex vivo activation of NK cells for reinfusion into patients with

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