88

Host Defenses Against Infection

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HOST VERSUS PATHOGEN: VICTORY, DEATH, OR COEXISTENCE

Many factors determine whether we coexist peacefully with our normal microbial flora and also whether we live or die in an environment filled with a wide spectrum of potentially pathogenic microbes. Factors such as age, nutritional status, underlying medical conditions (e.g., diabetes mellitus, chronic pulmonary disease), and the nature of the exposure (e.g., microbial virulence, inoculum size) may affect our response to infectious disease, with the outcome ultimately determined by our host defenses, which include anatomic (e.g., skin) and physiologic barriers (e.g., stomach acid), innate immune responses (e.g., phagocytes, microbial pattern receptors), and adaptive responses that include specific antibodies and cell–mediated immunity.

Humans are equipped with a multilayered host defense system to counter infectious organisms, and the interaction between a potential pathogen and a human can lead to one of three basic outcomes: death of the human host, elimination of the pathogen (with or without clinical symptoms), or an ongoing symbiotic relationship whose nature may change with time and under additional biologic pressures. For example, while some healthy humans are colonized by *Streptococcus pneumoniae*, pneumonia or meningitis may be caused by virulent strains, leading to death if the host's defenses cannot eliminate the pathogen in time. Most individuals exposed to *Mycobacterium tuberculosis* are asymptomatic because the adaptive immune response contains the organism in a live but nonreplicating (latent) state. Almost one third of the world's population is so infected, but only about 10% progress to active disease. Immunologic impairment (e.g., as a result of human immunodeficiency virus [HIV] infection) and factors such as age-associated immune senescence increase the risk of progressing from latent to active disease.

The asymptomatic nature of an infection should not automatically be equated with latency or dormancy of the pathogen. For example, chronic HIV infection was initially incorrectly characterized as having a prolonged latent or silent stage before the host developed immunodeficiency and opportunistic infections. However, most untreated HIV-infected individuals harbor actively replicating virus that kill $CD4^+$ T lymphocytes on a daily basis, although the aggregate effects are not appreciated until $CD4^+$ T lymphocyte levels are reduced to below 200 cells/mL, typically after 8 to 10 years of infection without antiretroviral treatment. Infected individuals are contagious to others despite their relatively asymptomatic state, thus treatment (when available) is recommended regardless of $CD4^+$ T lymphocyte levels. Treatment halts viral immune destruction and reduces viral burden in blood and genital secretions, thus decreasing an infected individual's risk of transmitting HIV.

CATEGORIES OF HOST DEFENSES AND RISKS OF INFECTION

The relative importance of the innate and adaptive immune defenses is best illustrated by individuals who are deficient in a particular immunological component. For example, cancer chemotherapy may lead to the depletion of innate cells such as neutrophils, rendering the host more susceptible to bacterial and fungal infections. Congenital deficiency of immunoglobulins increases the risk of infections that are usually thwarted by antibody responses such as those associated with *Streptococcus pneumoniae* and *Haemophilus influenzae*. Pharmacologic inhibition of tumor necrosis factor-α (TNF-α) for the treatment of chronic inflammatory disease such as Crohn's or psoriasis increases the risk of developing active tuberculosis among those with latent infection. In 1981 astute clinicians, recognizing the increased incidence of an atypical pneumonia caused by *Pneumocystis jirovecii* (formerly *P. carinii*) among young men, sounded the alarm that a novel acquired immunodeficiency syndrome (eventually shown to primarily affect $CD4^+$ T lymphocytes) had appeared that was later ascribed to HIV.

Host defenses to infection can be classified as nonimmunologic barriers, innate immunity, and specific or adaptive immunity. Immune defenses against microbial pathogens are composed of cells and molecules located in the blood, peripheral sites such as the skin and submucosal regions, and in secondary lymphoid tissues such as the lymph nodes, tonsils, spleen, and Peyer patches.

For a deeper discussion of these topics, please see Chapters 39 through 44 in Section VII, "Principles of Immunology and Inflammation," in *Goldman-Cecil Medicine*, 26th Edition.

Nonimmunologic Host Defenses

Nonimmunologic host defenses include anatomic and physiologic barriers that prevent the entry of pathogens into the body. Injuries or devices that damage or bypass anatomic barriers frequently lead to infection. Examples include burns, intravenous catheters, intubation, urinary tract catheters, surgery, and trauma.

The respiratory tract defenses depend on mucus that entraps pathogens and on ciliary action and cough that continuously clear the mucus and organisms from the lungs and upper airways. Respiratory viruses, including influenza, may inhibit ciliary action or denude the mucous membrane completely, allowing bacteria to colonize and cause secondary infection. Stroke, medications, or other causes of reduced cough reflex may lead to poor clearance of secretions, mucus, and pathogens, leading to lung infection. Smoking and exposure to industrial toxins such as silica may similarly reduce lung host defenses, such as by reducing ciliary action and inhibiting alveolar macrophage function respectively. Alveolar macrophages located in the lung parenchyma play an essential role in the initial clearance and killing of pathogens.

Nonimmune gastrointestinal defenses include gastric acidity, which kills many microorganisms, and vomiting and diarrhea, which help to clear pathogens from the gut. Bacteria vary greatly in their susceptibility to gastrointestinal host defenses. For example, as few as 10 *Shigella* sp bacteria can cause infection, whereas 10^5 to 10^8 *Vibrio cholera* bacteria are required for infection.

The urinary tract is protected physically by regular urine flow, the acidity of the urine, and antimicrobial peptides. Conditions that interfere with these factors (e.g., prostatic hypertrophy, renal stones) may lead to stasis and infection. Mechanical injection of bacteria through the urethra into the bladder, as may occur in women during sexual intercourse, can lead to colonization of the bladder and infection. Urinary tract catheters bypass normal mechanical barriers allowing bacteria to enter the bladder retrograde resulting in urinary tract infections.

The normal microbiologic flora on the skin and in the respiratory and gastrointestinal tracts is an important component of host defenses. Normal florae compete with pathogens for nutrients and have antimicrobial activity of their own. To illustrate, certain commensal bacteria of the skin secrete acid that prevents colonization by species more likely to cause disease. Disruption of the normal flora, such as by antibiotic treatment, allows opportunistic organisms such as *Clostridioides difficile* in the gut and *Candida* sp in the mouth or vagina to colonize and cause disease.

Organs that clear organisms from the bloodstream and lymph, including the liver, spleen, and lymph nodes, play an essential role after a pathogen has breached the primary anatomic barriers. Lack of a spleen increases a person's susceptibility to overwhelming sepsis caused by encapsulated bacteria including *S. pneumoniae, Neisseria meningitidis,* and *H. influenzae.* Cirrhosis of the liver allows portal vein blood to bypass the liver, increasing susceptibility to infection by gut flora.

Innate Immunity

Innate immunity refers to inborn resistance mechanisms that rapidly recognize pathogens and promote inflammation at the site of infection, thus comprising a critical first line of defense against pathogens. Fig. 88.1 compares the major features of innate and adaptive immunity.

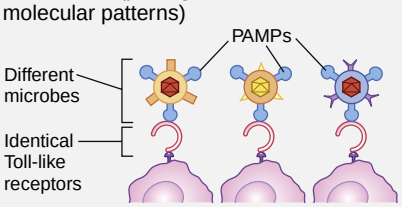
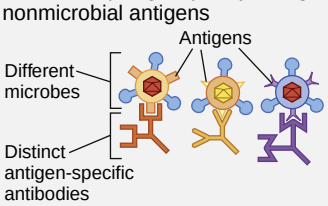
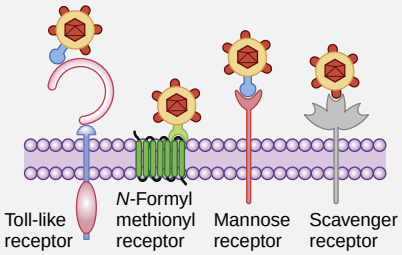
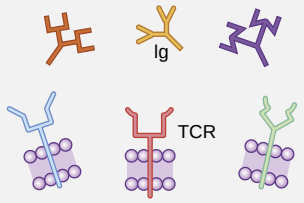
FEATURE	INNATE IMMUNITY	ADAPTIVE IMMUNITY
Specificity	For structures shared by classes of microbes (pathogen-associated molecular patterns) 	For structural detail of microbial molecules (antigens); may recognize nonmicrobial antigens 
Number of microbial molecules recognized	About 1,000 molecular patterns (estimated)	>10^7 antigens
Receptors	Encoded in germline; limited diversity (pattern recognition receptors) 	Encoded by genes produced by somatic recombination of gene segments; greater diversity 
Number and types of receptors	<100 different types of invariant receptors	Only 2 types of receptors (Ig and TCR), with millions of variations of each
Distribution of receptors	Nonclonal: identical receptors on all cells of the same lineage	Clonal: clones of lymphocytes with distinct specificities express different receptors
Genes encoding receptors	Germline encoded, in all cells	Formed by somatic recombination of gene segments only in B and T cells
Discrimination of self and nonself	Yes; healthy host cells are not recognized or they may express molecules that prevent innate immune reactions	Yes; based on elimination or inactivation of self-reactive lymphocytes; may be imperfect (hence the possibility of autoimmunity)

Fig. 88.1 Specificity and receptors of innate immunity and adaptive immunity. This summarizes the important features of the specificity and receptors of innate and adaptive immunity, with select examples illustrated. *Ig,* Immunoglobulin (antibody); *TCR,* T cell receptor. (From Abbas A K, Lichtman A H, Pillai S: Basic immunology: functions and disorders of the immune system, 6th ed. Philadelphia, Elsevier, 2018.)

The response of innate immunity is relatively nonspecific, invariant, rapid, and largely without memory. By contrast, adaptive immunity is highly specific and diverse but relatively slow during a primary infection, typically requiring days or even weeks to reach maximal activation. However, adaptive responses typically lead to the formation of durable memory that can be recalled upon secondary infection with a more rapid, robust response.

The molecules involved in innate immune responses include cytokines, chemokines, integrins, and pattern receptors. Cytokines are soluble proteins that have numerous functions, including promoting cellular growth and activation as well as regulating adaptive immune responses (Table 88.1). Their functions range from stimulating the production of and activating inflammatory cells, including neutrophils, macrophages, and eosinophils, to the direct antiviral action of interferons. Some activate endothelial cells and cause fever, whereas others regulate the inflammatory response.

Concentration gradients of chemokines in tissue attract leukocytes to areas of inflammation. Integrins on the surface of leukocytes allow adhesion to receptors on other types of cells such as vascular endothelium. This is the first step in recruiting and localizing leukocytes to areas of inflammation.

Pathogen pattern recognition receptors on phagocytes include toll-like receptors (TLRs), named for their homology to the toll molecule which was originally identified in the fruit fly, *Drosophila*; nucleotide oligomerization domain–like receptors (often abbreviated as Nod-like receptors, or NLRs); C-type lectin-like receptors (CLRs); and retinoic acid-inducible gene-I-like receptors (RLRs), which are intracellular receptors that detect viral RNA. TLRs, which recognize broad features of microbes such as the lipopolysaccharide (LPS) found in the cell wall of gram-negative bacteria, the peptidoglycan found in the cell walls of gram-positive bacteria, and the nucleic acids of viruses, have been studied extensively. TLRs are located on several immune cell types, including macrophages and dendritic cells. When a pathogen is detected by TLRs on the surface of a cell or associated with endosomes, signaling cascades are initiated that lead to the activation of nuclear transcription factors such as nuclear factor-κB (NF-κB). This stimulates the production of numerous cytokines important in the inflammatory response, including interleukin-1 (IL-1), IL-6, IL-10, IL-15, TNF-α, and growth factors (see Table 88.1). These cytokines amplify the inflammatory response by activating effector cells and by stimulating the production of many other inflammatory factors, including IL-2, interferons, C-reactive protein, complement components, and growth factors.

Complement factors are soluble proteins and enzymes that are produced as inactive precursors in the liver. Complement activation may occur as a result of antigen-antibody immune complex binding by factor C1 (the classical pathway), the binding of mannose-binding lectin (MBL) to microbial glycoproteins containing mannose (the lectin pathway), or the alternative pathway, which can be activated by bacterial cell wall components.

Regardless of how the complement system is activated, the cascade results in the production of C3 convertase, a protein that cleaves C3 into C3a and C3b fragments. This is followed by the production of a C5 convertase, which cleaves C5 into C5a and C5b. C3a and C5a, also known as anaphylatoxins, stimulate histamine release from mast cells leading to vasodilatation, increase vascular permeability and attract activated macrophages. C3b binds to the microbial surface and in conjunction with pathogen-specific immunoglobulin G (IgG) may stimulate phagocytosis. C5b serves as a nucleation point for the assembly of the membrane attack complex (MAC) that consists of C5b, C6, C7, C8 and multiple molecules of C9. MAC assembly results in pore formation that leads to bacterial lysis. Patients deficient in any of the MAC components C5 to C9 appear to be particularly susceptible to organisms such as *Neisseria meningitides* and *N. gonorrhoeae*. The complement system is regulated by numerous factors including soluble C1 inhibitor, which causes breakdown of the C1 complex, as well as the membrane-bound proteins decay-acceleration factor (DAF), which breaks down C3 convertases, and protectin, which inhibits MAC formation. These regulatory factors help to ensure that the complement system is not activated inappropriately against host cells.

The inflammatory response results in the classic clinical signs of inflammation, including erythema, pain, warmth, swelling, and loss of function. It can be initiated by microorganisms in tissue, tissue injury, or dysfunctional adaptive immunity (e.g., autoantibodies). The response includes inflammatory molecules as previously described and tissue and migrating leukocytes. Neutrophils are central to the clinical manifestations of inflammation in tissue, and patients with neutropenia or functional deficits in neutrophil function often lack the signs of inflammation at the site of serious infection.

Neutrophils are bone marrow–derived phagocytes whose production is greatly stimulated by infection through the action of macrophage-produced growth factors, including granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF). Neutrophils circulate in blood (where they are the most abundant white blood cell), are attracted to sites of inflammation, and are activated by chemotactic factors, including formyl peptides derived from bacteria, complement factors C3a and C5a, IL-8, interferon, and leukotrienes, particularly leukotriene B_4. Neutrophils migrate from the endovascular space into inflammatory tissue through an integrin-regulated process that includes receptors on neutrophils and vascular endothelial cells. Activated neutrophils then migrate using a chemoattractive (i.e., chemokine) gradient toward the site of inflammation.

Neutrophils are killing machines containing granules that have up to 100 different antimicrobial molecules. The contents of granules are released intracellularly into phagosomes after phagocytosis of a pathogen or released extracellularly in the vicinity of pathogens. Phagocytosis is greatly enhanced by opsonization (i.e., antibody and complement binding) of pathogens. The major microbicidal mechanism of neutrophils is the superoxide burst (i.e., production of superoxide anion catalyzed by NADPH oxidase) and then the dismutation to hydrogen peroxide (H_2O_2), which may in turn be converted to hypochlorous acid (HClO). Many other granule molecules, such as cathepsins, elastases, defensins, and collagenase contribute to the killing process. Similar mechanisms exist in other phagocytes such as macrophages. More recently it has been found that in addition to phagocytosis and degranulation, activated neutrophils produce neutrophil extracellular traps (NETs), which are webs of chromatin and proteases that can immobilize and kill pathogenic microbes.

Eosinophils, which are found more in tissue than the circulation, are primarily important in host defenses against multicellular parasites such as parasitic worms. Growth and differentiation of eosinophils is promoted by IL-5. Eosinophils are activated and recruited by a variety of mediators, including complement factors and leukotrienes. Eosinophil granules contain specific cationic proteins that are toxic to parasites. Eosinophils also play key roles in the pathogenesis of allergic reactions and diseases such as asthma.

Basophils in blood and mast cells in tissue contain granules with high concentrations of histamine and other inflammatory mediators. Basophils and mast cells express receptors for complement factors and others that bind immunoglobulin E (IgE) produced by B cells. They can be activated by complement factors C3a and C5a and by cross-linking of IgE by antigen on the surface of mast cells. Histamine is a short-acting, low-molecular-weight amine that acts through four

TABLE 88.1 Cytokines

Cytokine and Subunits	Principal Cell Source	Cytokine Receptor and Subunits[a]	Principal Cellular Targets and Biologic Effects
Type I Cytokine Family Members			
Interleukin-2 (IL-2)	T cells	CD25 (IL-2Rα) CD122 (IL-2Rβ) CD132 (γc)	T cells: proliferation and differentiation into effector and memory cells; promotes regulatory T cell development, survival, and function NK cells: proliferation, activation B cells: proliferation, antibody synthesis (in vitro)
Interleukin-3 (IL-3)	T cells	CD123 (IL-3Rα) CD131 (βc)	Immature hematopoietic progenitors: induced maturation of all hematopoietic lineages
Interleukin-4 (IL-4)	$CD4^+$ T cells (Th2, Tfh), mast cells	CD124 (IL-4Rα) CD132 (γc)	B cells: isotype switching to IgE T cells: Th2 differentiation, proliferation Macrophages: alternative activation and inhibition of IFN-γ–mediated classical activation
Interleukin-5 (IL-5)	$CD4^+$ T cells (Th2), group 2 ILCs	CD125 (IL-5Rα) CD131 (βc)	Eosinophils: activation, increased generation
Interleukin-6 (IL-6)	Macrophages, endothelial cells, T cells	CD126 (IL-6Rα) CD130 (gp130)	Liver: synthesis of acute-phase protein B cells: proliferation of antibody-producing cells T cells: Th17 differentiation
Interleukin-7 (IL-7)	Fibroblasts, bone marrow stromal cells	CD127 (IL-7R) CD132 (γc)	Immature lymphoid progenitors: proliferation of early T and B cell progenitors T lymphocytes: survival of naïve and memory cells
Interleukin-9 (IL-9)	$CD4^+$ T cells	CD129 (IL-9R) CD132 (γc)	Mast cells, B cells, T cells, and tissue cells: survival and activation
Interleukin-11 (IL-11)	Bone marrow stromal cells	IL-11Rα CD130 (gp130)	Production of platelets
Interleukin-12 (IL-12): IL-12A (p35) IL-12B (p40)	Macrophages, dendritic cells	CD212 (IL-12Rβ1) IL-12Rβ2	T cells: Th1 differentiation NK cells and T cells: IFN-γ synthesis, increased cytotoxic activity
Interleukin-13 (IL-13)	$CD4^+$ T cells (Th2), NKT cells, group 2 ILCs, mast cells	CD213a1 (IL-13Rα1) CD213a2 (IL-13Rα2) CD132 (γc)	B cells: isotype switching to IgE Epithelial cells: increased mucus production Macrophages: alternative activation
Interleukin-15 (IL-15)	Macrophages, other cell types	IL-15Rα CD122 (IL-2Rβ) CD132 (γc)	NK cells: proliferation T cells: survival and proliferation of memory $CD8^+$ cells
Interleukin-17A (IL-17A) Interleukin-17F (IL-17F)	$CD4^+$ T cells (Th17), group 3 ILCs	CD217 (IL-17RA) IL-17RC	Epithelial cells, macrophages and other cell types: increased chemokine and cytokine production; GM-CSF and G-CSF production
Interleukin-21 (IL-21)	Th2 cells, Th17 cells, Tfh cells	CD360 (IL-21R) CD132 (γc)	B cells: activation, proliferation, differentiation Tfh cells: development Th17 cells: increased generation
Interleukin-23 (IL-23): IL-23A (p19) IL-12B (p40)	Macrophages, dendritic cells	IL-23R CD212 (IL-12Rβ1)	T cells: differentiation and expansion of Th17 cells
Interleukin-25 (IL-25; IL-17E)	T cells, mast cells, eosinophils, macrophages, mucosal epithelial cells	IL-17RB	T cells and various other cell types: expression of IL-4, IL-5, IL-13
Interleukin-27 (IL-27): IL-27 (p28) EBI3 (IL-27B)	Macrophages, dendritic cells	IL-27Rα CD130 (gp130)	T cells: enhancement of Th1 differentiation; inhibition of Th17 differentiation NK cells: IFN-γ synthesis?

Continued

TABLE 88.1 Cytokines—cont'd

Cytokine and Subunits	Principal Cell Source	Cytokine Receptor and Subunits[a]	Principal Cellular Targets and Biologic Effects
Stem cell factor (c-Kit ligand)	Bone marrow stromal cells	CD117 (KIT)	Pluripotent hematopoietic stem cells: induced maturation of all hematopoietic lineages
Granulocyte-monocyte CSF (GM-CSF)	T cells, macrophages, endothelial cells, fibroblasts	CD116 (GM-CSFRα) CD131 (βc)	Immature and committed progenitors, mature macrophages: induced maturation of granulocytes and monocytes, macrophage activation
Monocyte CSF (M-CSF, CSF1)	Macrophages, endothelial cells, bone marrow cells, fibroblasts	CD115 (CSF1R)	Committed hematopoietic progenitors: induced maturation of monocytes
Granulocyte CSF (G-CSF, CSF3)	Macrophages, fibroblasts, endothelial cells	CD114 (CSF3R)	Committed hematopoietic progenitors: induced maturation of granulocytes
Thymic stromal lymphopoietin (TSLP)	Keratinocytes, bronchial epithelial cells, fibroblasts, smooth muscle cells, endothelial cells, mast cells, macrophages, granulocytes and dendritic cells	TSLP-receptor CD127 (IL-7R)	Dendritic cells: activation Eosinophils: activation Mast cells: cytokine production T cells: Th2 differentiation
Type II Cytokine Family Members			
IFN-α (multiple proteins)	Plasmacytoid dendritic cells, macrophages	IFNAR1 CD118 (IFNAR2)	All cells: antiviral state, increased class I MHC expression NK cells: activation
IFN-β	Fibroblasts, plasmacytoid dendritic cells	IFNAR1 CD118 (IFNAR2)	All cells: antiviral state, increased class I MHC expression NK cells: activation
Interferon-γ (IFN-γ)	T cells (Th1, $CD8^+$ T cells), NK cells	CD119 (IFNGR1) IFNGR2	Macrophages: classical activation (increased microbicidal functions) B cells: isotype switching to opsonizing and complement-fixing IgG subclasses (established in mice) T cells: Th1 differentiation Various cells: increased expression of class I and class II MHC molecules, increased antigen processing and presentation to T cells
Interleukin-10 (IL-10)	Macrophages, T cells (mainly regulatory T cells)	CD210 (IL-10Rα) IL-10Rβ	Macrophages, dendritic cells: inhibition of expression of IL-12, co-stimulators, and class II MHC
Interleukin-22 (IL-22)	Th17 cells	IL-22Rα1 *or* IL-22Rα2 IL-10Rβ2	Epithelial cells: production of defensins, increased barrier function Hepatocytes: survival
Interleukin-26 (IL-26)	T cells, monocytes	IL-20R1IL-10R2	Not established
Interferon-λs (type III interferons)	Dendritic cells	IFNLR1 (IL-28Rα) CD210B (IL-10Rβ2)	Epithelial cells: antiviral state
Leukemia inhibitory factor (LIF)	Embryonic trophectoderm, bone marrow stromal cells	CD118 (LIFR) CD130 (gp130)	Stem cells: block in differentiation
Oncostatin M	Bone marrow stromal cells	OSMR CD130 (gp130)	Endothelial cells: regulation of hematopoietic cytokine production Cancer cells: inhibition of proliferation
TNF Superfamily Cytokines[b]			
Tumor necrosis factor (TNF, TNFSF1)	Macrophages, NK cells, T cells	CD120a (TNFRSF1) *or* CD120b (TNFRSF2)	Endothelial cells: activation (inflammation, coagulation) Neutrophils: activation Hypothalamus: fever Muscle, fat: catabolism (cachexia)
Lymphotoxin-α (LTα, TNFSF1)	T cells, B cells	CD120a (TNFRSF1) or CD120b (TNFRSF2)	Same as TNF

TABLE 88.1 Cytokines—cont'd

Cytokine and Subunits	Principal Cell Source	Cytokine Receptor and Subunits[a]	Principal Cellular Targets and Biologic Effects
Lymphotoxin-αβ (LTαβ)	T cells, NK cells, follicular B cells, lymphoid inducer cells	LTβR	Lymphoid tissue stromal cells and follicular dendritic cells: chemokine expression and lymphoid organogenesis
BAFF (CD257, TNFSF13B)	Dendritic cells, monocytes, follicular dendritic cells, B cells	BAFF-R (TNFRSF13C) *or* TACI (TNFRSF13B) *or* BCMA (TNFRSF17)	B cells: survival, proliferation
APRIL (CD256, TNFSF13)	T cells, dendritic cells, monocytes, follicular dendritic cells	TACI (TNFRSF13B) *or* BCMA (TNFRSF17)	B cells: survival, proliferation
Osteoprotegerin (OPG, TNFRSF11B)	Osteoblasts	RANKL	Osteoclast precursor cells: inhibits osteoclast differentiation
IL-1 Family Cytokines			
Interleukin-1α (IL-1α)	Macrophages, dendritic cells, fibroblasts, endothelial cells, keratinocytes, hepatocytes	CD121a (IL-1R1) IL-1RAP *or* CD121b (IL-1R2)	Endothelial cells: activation (inflammation, coagulation) Hypothalamus: fever
Interleukin-1β (IL-1β)	Macrophages, dendritic cells, fibroblasts, endothelial cells, keratinocyte	CD121a (IL-1R1) IL-1RAP *or* CD121b (IL-1R2)	Endothelial cells: activation (inflammation, coagulation) Hypothalamus: fever Liver: synthesis of acute-phase proteins T cells: Th17 differentiation
Interleukin-1 receptor antagonist (IL-1RA)	Macrophages	CD121a (IL-1R1) IL-1RAP	Various cells: competitive antagonist of IL-1
Interleukin-18 (IL-18)	Monocytes, macrophages, dendritic cells, Kupffer cells, keratinocytes, chondrocytes, synovial fibroblasts, osteoblasts	CD218a (IL-18Rα) CD218b (IL-18Rβ)	NK cells and T cells: IFN-γ synthesis Monocytes: expression of GM-CSF, TNF, IL-1β Neutrophils: activation, cytokine release
Interleukin-33 (IL-33)	Endothelial cells, smooth muscle cells, keratinocytes, fibroblasts	ST2 (IL1RL1) IL-1 Receptor Accessory Protein (IL1RAP)	T cells: Th2 development ILCs: activation of group 2 ILCs
Other Cytokines			
Transforming growth factor-β (TGF-β)	T cells (mainly Tregs), macrophages, other cell types	TGF-β R1 TGF-β R2 TGF-β R3	T cells: inhibition of proliferation and effector functions; differentiation of Th17 and Treg B cells: inhibition of proliferation; IgA production Macrophages: inhibition of activation; stimulation of angiogenic factors Fibroblasts: increased collagen synthesis

APRIL, A proliferation-inducing ligand; *BAFF,* B cell–activating factor belonging to the TNF family; *BCMA,* B cell maturation protein; *CSF,* colony-stimulating factor; *IFN,* interferon; *IgE,* immunoglobulin E; *ILCs,* innate lymphoid cells; *MHC,* major histocompatibility complex; *NK cell,* natural killer cell; *NKT cell,* natural killer T cell; *OSMR,* oncostatin M receptor; *RANK,* receptor activator for nuclear factor κB ligand; *RANKL,* RANK ligand; *TACI,* transmembrane activator and calcium modulator and cyclophilin ligand interactor; *Th,* T helper; *Tfh,* T follicular helper; *TNF,* tumor necrosis factor; *TNFSF,* TNF superfamily; *TNFRSF,* TNF receptor superfamily; *Treg,* regulatory T cell.

[a]Most cytokine receptors are dimers or trimers composed of different polypeptide chains, some of which are shared between receptors for different cytokines. The set of polypeptides that compose a functional receptor (cytokine binding plus signaling) for each cytokine is listed. The functions of each subunit polypeptide are not listed.

[b]All TNF superfamily (TNFSF) members are expressed as cell surface transmembrane proteins, but only the subsets that are predominantly active as proteolytically released soluble cytokines are listed in the table. Other TNFSF members that function predominantly in the membrane-bound form and are not, strictly speaking, cytokines are not listed in the table. These membrane-bound proteins and the TNFRSF receptors they bind to include OX40L (CD252, TNFSF4):OX40 (CD134, TNFRSF4); CD40L (CD154, TNFSF5):CD40 (TNFRSF5); FasL (CD178, TNFSF6):Fas (CD95, TNFRSF6); CD70 (TNFSF7):CD27 (TNFRSF27); CD153 (TNFSF8):CD30 (TNFRSF8); TRAIL (CD253, TNFSF10):TRAIL-R (TNFRSF10A-D); RANKL (TNFSF11):RANK (TNFRSF11); TWEAK (CD257, TNFSF12):TWEAKR (CD266, TNFRSF12); LIGHT (CD258, TNFSF14):HVEM (TNFRSF14); GITRL (TNFSF18):GITR (CD357 TNFRSF18); and 4-IBBL:4-IBB (CD137).

From Abbas A K, Lichtman A H, Pillai S: Basic immunology: functions and disorders of the immune system, 6th ed. Philadelphia, Elsevier, 2018.

different histamine receptors. Its actions include bronchoconstriction and bronchial smooth muscle contraction, itching, pain, vasodilation, and increased vascular permeability. Histamine also plays a role in gastric acid secretion, motion sickness, and sleep suppression. Commonly used antihistamines counter these effects.

Blood monocytes are produced in the bone marrow and circulate for several days in the blood. Some may migrate into tissues, where they may develop into macrophages that phagocytize pathogens and debris and kill microorganisms when activated by bacterial products such as lipopolysaccharide (LPS), interferon-γ, and other cytokines.

The properties and function of macrophages depend on the tissue. Alveolar macrophages in the lung are continuously exposed to airborne particles and pathogens, whereas microglia in the brain have a very different environment and function. Macrophages clear cellular debris after acute inflammation and thus are the custodians of peripheral tissue. Macrophages produce a variety of cytokines important in the inflammatory process, including IL-1, TNF-α, IL-6, IL-15, and leukocyte growth factors.

Fever during inflammation and infection results from cytokines such as IL-1 and TNF-α that are released by macrophages into the circulation. These molecules increase the level of prostaglandins in the hypothalamus, which elevates the normal temperature set point. This stimulates thermoregulatory mechanisms to elevate the core body temperature, which has antimicrobial effects.

Macrophages play a central role in granuloma formation. For example, macrophages are critical in controlling difficult-to-kill acid-fast mycobacteria such as *M. tuberculosis* or fungi by walling off viable organisms in granulomas. Macrophages also present antigen derived from microbial pathogens to T cells, helping to initiate the adaptive immune response.

Dendritic cells (DCs) are derived from myeloid or lymphocytic precursors. Dendritic cells of the myeloid lineage (also known as conventional DCs or cDCs) are found primarily in tissues where pathogens are likely to enter the body, such as the skin, gastrointestinal tract, spleen, and respiratory tract. These cells have branchlike cytoplasmic extensions (for which they are named), and they phagocytize pathogens in a manner similar to macrophages, then migrate to lymphoid organs where they interact with T cells. They are the major antigen-presenting cells (APCs) in the body and are critical for the initial activation of adaptive immune responses. Dendritic cells of the lymphoid lineage are known as plasmacytoid dendritic cells (pDCs). Like cDCs, pDCs may also present antigen to T cells; however, their major role is to produce copious amounts of interferon-α upon viral infection, providing a critical first line of defense.

Natural killer (NK) cells are large granular lymphocytes that kill abnormal cells, including virus-infected cells and certain tumor cells. NKs do not express immunoglobulins or T-cell receptors but rather employ a system of activating and inhibitory receptors to detect features of stressed cells such as reduction in the expression of major histocompatibility complex (MHC) molecules. Upon activation, NKs kill their targets by releasing granule contents that include the pore-forming protein perforin and various proteases known as granzymes, which may induce target cell death via lysis or apoptosis. NKs are part of the first line of defense against viral infections while adaptive immunity is developing. Patients with NK deficiencies have been shown to be highly susceptible to herpesvirus infection such as varicella-zoster virus.

Adaptive Immunity

The adaptive immune response is capable of producing exquisitely specific protective mechanisms against microbial pathogens (see Fig. 88.1). Adaptive responses to most protein-containing antigens produced by pathogens during a primary exposure leads to the formation of memory B and T cells; secondary exposure to that antigen may recall the memory, leading to adaptive responses that are more rapid, of much greater magnitude, and of higher affinity than before (Fig. 88.2). The capacity of the adaptive immune system to protect against different pathogens is truly astounding. Through a process known as gene rearrangement it has been estimated that B cells can produce 10^{12} different immunoglobulin molecules and that T cells can have up to 10^{18} different T-cell receptors (TCRs) for specific antigens.

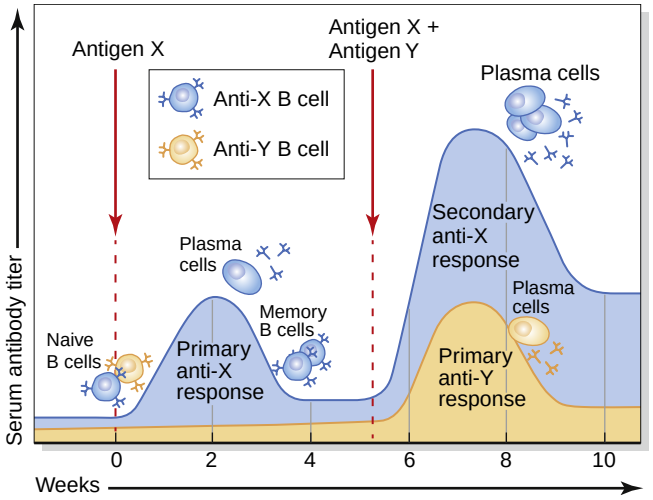


Fig. 88.2 Primary and secondary immune responses. The properties of memory and specificity can be demonstrated by repeated immunizations with defined antigens in animal experiments. Antigens X and Y induce the production of different antibodies (a reflection of specificity). The secondary response to antigen X is more rapid and larger than the primary response (illustrating memory) and is different from the primary response to antigen Y (again reflecting specificity). Antibody levels decline with time after each immunization. The level of antibody produced is shown as arbitrary values and varies with the type of antigen exposure. Only B cells are shown, but the same features are seen with T cell responses to antigens. The time after immunization may be 1 to 3 weeks for a primary response and 2 to 7 days for a secondary response, but the kinetics vary, depending on the antigen and the nature of immunization. (From Abbas A K, Lichtman A H, Pillai S: Basic immunology: functions and disorders of the immune system, 6th ed. Philadelphia, Elsevier, 2018.)

Antibodies and B Lymphocytes

Antibodies, also known as immunoglobulins (Igs), are variable glycoproteins produced by B cells that recognize specific structural motifs (epitopes) on the molecules (antigens) produced by microbial pathogens. In antimicrobial defense, binding of an antibody to a pathogen may inhibit (neutralize) the ability of the pathogen to infect a cell (e.g., influenza virus) or the ability of a toxin (e.g., tetanus toxin) to be effective; prompt phagocytosis by phagocytic cells such as neutrophils and macrophages (i.e., opsonization); activate the complement cascade; or kill an infected cell through the process known as antibody-dependent cellular cytotoxicity (ADCC), in which otherwise nonspecific immune cells such as neutrophils or macrophages are able to recognize antibodies bound to target cell surfaces and release cytolytic factors.

Antibody-mediated host defense occurs mainly in the extracellular space, as opposed to T cell–mediated host defenses that act primarily on intracellular pathogens (i.e., those that enter cells and survive intracellularly). The five major isotypes (also known as classes) of antibodies are summarized in Fig. 88.3 (note that IgG and IgA are further divided into subtypes). Effector functions mediated by antibodies include complement activation (IgM and IgG1/2/3),

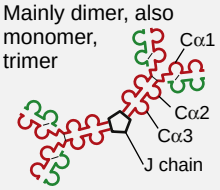
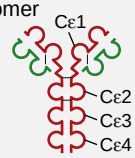
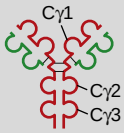
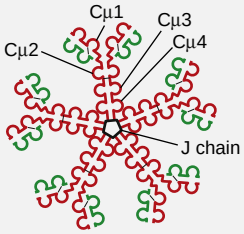
ISOTYPE OF ANTIBODY	SUBTYPES (H CHAIN)	PLASMA CONCENTRATION (mg/ml)	PLASMA HALF-LIFE (DAYS)	SECRETED FORM	FUNCTIONS
IgA	IgA 1,2 (α1 or α2)	3.5	6	Mainly dimer, also monomer, trimer 	Mucosal immunity
IgD	None (δ)	Trace	3	Monomer	Naive B cell antigen receptor
IgE	None (ε)	0.05	2	Monomer 	Defense against helminthic parasites, immediate hypersensitivity
IgG	IgG 1-4 (γ1, γ2, γ3 or γ4)	13.5	23	Monomer 	Opsonization, complement activation, antibody-dependent cell-mediated cytotoxicity, neonatal immunity, feedback inhibition of B cells
IgM	None (μ)	1.5	5	Pentamer 	Naive B cell antigen receptor (monomeric form), complement activation

Fig. 88.3 Features of the major isotypes (classes) of antibodies. This figure summarizes some important features of the major antibody isotypes of humans. Isotypes are classified on the basis of their heavy (H) chains; each isotype may contain either κ or λ light chain. The schematic diagrams illustrate the distinct shapes of the secreted forms of these antibodies. Note that IgA consists of two subclasses, called IgA1 and IgA2, and IgG consists of four subclasses, called IgG1, IgG2, IgG3, and IgG4. Most of the opsonizing and complement fixation functions of IgG are attributable to IgG1 and IgG3. The domains of the heavy chains in each isotype are labeled. The plasma concentrations and half-lives are average values in normal individuals. *Ig,* Immunoglobulin. (From Abbas A K, Lichtman A H, Pillai S: Basic immunology: functions and disorders of the immune system, 6th ed. Philadelphia, Elsevier, 2018.)

opsonization (IgG), neutralization (IgM, IgG, and IgA) and mast cell degranulation (IgE) which mediates type I hypersensitivity. IgG antibodies cross the placenta, providing protective immunity to newborns for months after birth. IgA molecules are secretory antibodies that act at mucosal surfaces and are the predominant antibody in external secretions such as mucus, saliva, and breast milk. IgE is responsible for allergic responses and host defenses against parasites. IgM (in monomeric form) and IgD are found on the surface of naïve B cells and function in the initial antigen-mediated activation of these cells.

The basic structural unit of an antibody is composed of two identical "heavy" (H) chains and two identical "light" (L) chains (Fig. 88.4). Each heavy and light chain has constant and variable regions, the latter mediating antigen specificity. The five major types of heavy chains are designated mu, delta, gamma, epsilon and alpha (μ, δ, γ, ε, and α) and define the antibody isotype (IgM, IgD, IgG, IgE and IgA). There are two types of light chains, kappa and lambda (κ and λ), that may associate with any of the heavy chains. The antigen-binding site of each molecule is composed partly of the variable region of a heavy chain and partly of the variable region of a light chain. There are two such binding sites for each antibody monomer, although secreted antibodies may contain 2, 4, or 10 identical antigen binding sites depending on if they are secreted as a monomer (IgG, IgD, IgE), a dimer (IgA) or a pentamer (IgM) (see Fig. 88.3).

The B-cell receptor (BCR) is composed of the specific immunoglobulin produced by that B cell associated with signaling molecules on the cell surface. Naïve B cells simultaneously express BCRs that contain monomeric IgM or IgD, each with identical antigen specificity. When initially stimulated, B cells typically secrete pentameric IgM antibodies. Later in the immune response, a B cell may undergo a process that allows the isotype of immunoglobulin produced to switch (e.g., from IgM to IgG; see later).

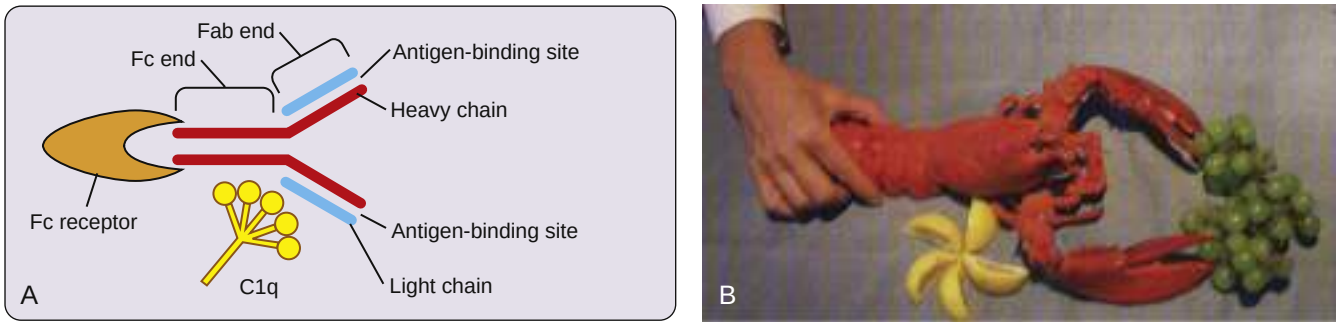


Fig. 88.4 Structure of antibodies. Antibody molecules are composed of two heavy chains *(red lines)* and two light chains *(blue lines)* held together by disulfide bonds. The two heavy chains join to form a tail (Fc end), which can interact with receptors (FcR) on a variety of cells. The heavy and light chains contribute to the Fab end. At the 5′ or amino-terminal end, these chains form two identical antigen-binding sites, much like two lobster claws. Near the hinge region of the antibody, there is a binding site for C1q, the first component of the complement cascade. (From Birdsall H: Adaptive immunity: antibodies and immunodeficiencies. In Bennett JE, Dolin R, Blaser M, editors: Mandell, Douglas, and Bennett's principles and practice of infectious diseases, ed 8, Philadelphia, 2015, Saunders.)

The constant region of the two antibody heavy chains comprises the Fc portion, which can be bound by various Fc receptors (FcRs) on the surface of immune cells (Fig. 88.4), mediating effector functions such as opsonization, ADCC, and degranulation, depending on the isotype and cell type. Soluble complement factors may also bind the Fc portion of antibodies that have bound soluble or surface-associated antigens, activating the classic complement pathway.

Much as a child might produce a large number of unique structures from a small set of building blocks, using a relatively small amount of DNA humans can generate billions of different antibodies. The two major genetic strategies that allow humans to produce antibodies specific to virtually any antigen are known as immunoglobulin gene rearrangement and somatic hypermutation. Immunoglobulin gene rearrangement involves recombination of individual variable (V), diversity (D), and joining (J) gene segments to produce functional genes that encode the immunoglobulin light and heavy chains.

Humans have about 130 functional V segments distributed among the three immunoglobulin gene clusters (heavy chain, kappa light chain, and lambda light chain); each cluster contains four to six functional J segments, with the heavy chain cluster also containing about 25 functional D segments. During B-cell development proteins known as recombination activating genes 1 and 2 (RAG-1/2) mediate random recombination of V, D, and J segments on heavy chain alleles and V and J segments on light chain alleles in a stepwise process. The combinational diversity of V(D)J rearrangement is greatly augmented by flexible joining events that can lead to insertion or deletion of nucleotides at each junction. In this manner, an enormously diverse set of variable chains—perhaps as many as 10^{12}—may be assembled. Further genetic variation arises through a process known as somatic hypermutation, which occurs in proliferating B cells following activation by foreign antigen in lymphoid tissues.

The adaptive humoral response begins with recognition of foreign antigen by specific B cells in secondary lymphoid organs. Before activation, B cells express IgM and IgD with a particular specificity on their membranes; following binding of a protein antigen the B cells internalize and process the antigen, then present peptides derived from it to $CD4^+$ helper T (Th) cells. Interaction with a Th that expresses a TCR specific for peptide derived from the foreign antigen allows a B cell to become activated, proliferate, and differentiate into antibody-secreting plasma cells or memory B cells. Proliferating B cells may begin to express antibody isotypes other than IgM and IgD (e.g., IgG, IgA, IgE) through a process known as isotype switching that is driven by cytokines such as IL-4, IL-10, IL-5 and others produced by T cells. Isotype switching, which does not affect the specificity of the antibody, allows the host to take advantage of the various effector functions mediated by the different isotypes (e.g., complement fixation for IgM, opsonic activity for IgG). As mentioned previously, proliferating B cells may also undergo somatic hypermutation, a process by which point mutations are randomly inserted into the immunoglobulin DNA. While most such mutations are deleterious, those B cells bearing mutations that enhance antigen binding activity (affinity) are selected and expanded, leading to an overall increase in the quality of the antibody response over time—this is known as affinity maturation. Furthermore, T-cell interaction typically drives the generation of a pool of memory B cells that persist for the life of the individual. Such memory cells have the capacity to be reactivated upon subsequent exposure to foreign antigen, leading to secondary antibody responses that are faster, of greater magnitude, and of higher affinity than the primary response (see Fig. 88.2).

Although most protein antigens are said to be T-dependent (i.e., require Th cells for optimal B-cell activation), some antigens can stimulate B cells to proliferate and produce antibody directly without the presence of Th cells (T-independent). T-independent antigens include microbial-derived molecules such as LPS, which bind pattern receptors (e.g., TLRs) on B cells and may stimulate them without regard to antigen specificity. Others, such as microbial-derived polysaccharides that contain repeating epitopes, specifically engage B cells with sufficient strength to bypass the requirement for Th cell interaction. More commonly, however, B cells are stimulated through synergistic action with Th cells. Specific antigen is bound to the surface immunoglobulin of the B cell, triggering endocytosis, degradation of the antigen, and presentation of peptide fragments in association with MHC class II molecules on the cell surface. Th cells with TCRs specific for the MHC-peptide complex interact with the B cell; this interaction is stabilized and strengthened through cell adhesion molecules and costimulatory activation molecules such as CD28 on the T cell and B7-1/2 (also known as CD80/86) on the B cell. Th cells then produce costimulatory molecules such as CD40L (which engages CD40 on the B cell) and cytokines such as IL-4 that drive activation and antibody production by the B cells.

T Lymphocytes

T cell precursors are produced in the bone marrow and migrate to the thymus where they undergo development and selection. At the conclusion of their development most T lymphocytes express either

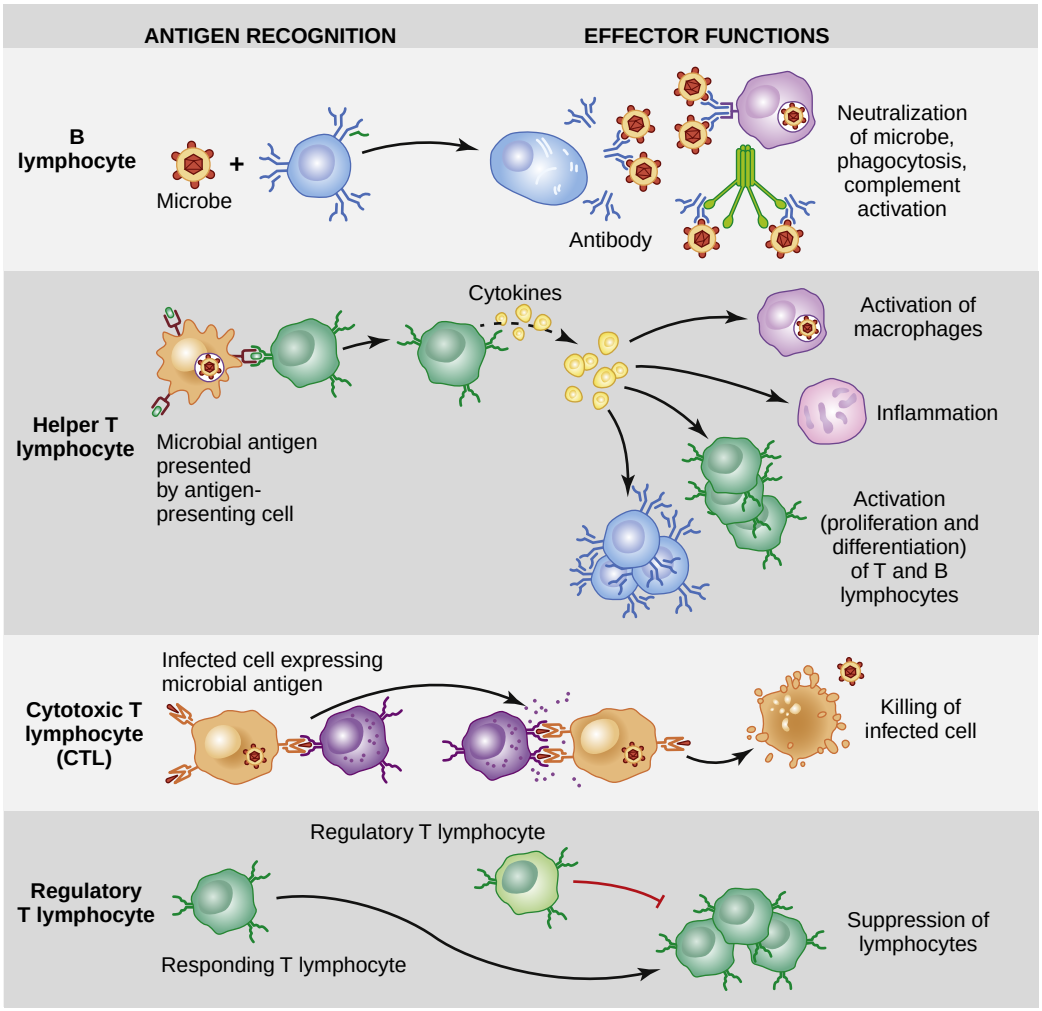


Fig. 88.5 Classes of lymphocytes. B lymphocytes recognize many different types of antigens and develop into antibody-secreting cells. Helper T lymphocytes recognize antigens on the surfaces of antigen-presenting cells and secrete cytokines, which stimulate different mechanisms of immunity and inflammation. Cytotoxic T lymphocytes recognize antigens on infected cells and kill these cells. Regulatory T cells suppress immune responses (e.g., to self antigens). (From Abbas A K, Lichtman A H, Pillai S: Basic immunology: functions and disorders of the immune system, 6th ed. Philadelphia, Elsevier, 2018.)

CD4 or CD8 molecules on their surface along with TCRs specific for a particular combination of antigenic peptide and self MHC. During development, the TCR is produced in a process involving V(D)J gene rearrangement mediated by RAG-1/2 in a manner broadly analogous to that of B cells. Most conventional T cells express TCRs that are a combination of alpha and beta TCR chains, each with constant and variable regions; others express TCRs consisting of gamma and delta TCR chains.

As maturation takes place in the thymus, T cells undergo selection processes that eliminate those whose TCRs have low affinity for self MHC (positive selection) or too high an affinity for self molecules (negative selection). The combination of positive and negative selection thus ensures that T-cell activation requires a combination of self MHC and foreign antigen. Naïve T cells, usually in regional lymph nodes or similar tissues such as Peyer patches in the gut, are sensitized by interaction with an APC such as a dendritic cell or memory B cell. The APC internalizes and processes microbial antigen and then presents peptides derived from that antigen to the associated T cell. Presentation of antigen occurs in association with MHC (also known as human leukocyte antigens, or HLA) class II molecules for $CD4^+$ cells or MHC class I molecules for $CD8^+$ cells. $CD4^+$ cells are called helper T cells (Th) and develop into Th1, Th2, and Th17 subsets. $CD8^+$ cells are cytotoxic T cells (CTLs; see Fig. 88.5).

$CD4^+$ T cells play a central role in the activation of B lymphocytes, other $CD4^+$ T cells, $CD8^+$ T cells, and phagocytic cells such as macrophages. $CD4^+$ T cells orchestrate host defenses against pathogens that are initially acquired by phagocytic cells during phagocytosis or pinocytosis. Dendritic cells, for example, take up pathogens or antigens by phagocytosis or pinocytosis and then degrade them within phagosomes.

Antigenic peptides, which are produced by proteolytic degradation of protein antigens in phagolysosomes, bind noncovalently to a grove in MHC class II molecules. The complex is then transported to the cell surface for presentation to T cells expressing CD4 molecules on their surface. $CD4^+$ T cells with specificity for the antigen then bind via their TCRs to the MHC class II/antigen complex on the surface of the APC. CD4 also associates with MHC II, stabilizing the interaction between T cell and APC. Accessory molecules, such as the adhesion molecule lymphocyte function–associated antigen 1 (LFA-1) on T cells, which interacts with intercellular adhesion molecule 1 (ICAM-1)

on the APC, are necessary to stabilize the interaction. Activating adhesion complexes such as CD28 on T cells and B7-1/2 (also known as CD80/86) on APCs are necessary for activation, proliferation, and activation of T cells. Following activation, T cell proliferation is driven by IL-2, which is produced by the activated T cell and stimulates it in an autocrine loop.

Activated $CD4^+$ Th cells (initially called Th0 cells) can be driven by IL-12 and other cytokines to become Th1 cells or by IL-4 and IL-10 to become Th2 cells. Th17 cell differentiation is driven by transforming growth factor-β (TGF-β), IL-6, and IL-23. Th1 cells mediate host defenses against intracellular pathogens such as viruses, bacteria (e.g., *M. tuberculosis*) or parasites (e.g., *Toxoplasma gondii*). They do so by producing γ-interferon, which activates phagocytic cells such as macrophages that then destroy the invading intracellular pathogen, and IL-2, which activates CTLs to lyse infected cells.

Alternatively, activated $CD4^+$ T cells can be driven by IL-4 to become Th2 cells that mediate processes such as antiparasitic immunity. Th2 cells stimulate B cells to produce antibodies against extracellular pathogens through the production of IL-4, and they stimulate proliferation of eosinophils for activity against parasites (e.g., worms) through the production of IL-5.

Th17 cells are stimulated by IL-23 and produce IL-17, which plays an important role in amplifying the inflammatory response by attracting neutrophils to sites of infection caused by extracellular bacteria and possibly fungi. The complexity of these $CD4^+$ T-cell subsets is still being explored.

$CD8^+$ T cells respond to pathogens that initially enter host cells directly, such as viruses. During intracellular replication, viral proteins are degraded in the cytosol by the immunoproteasome, a variant of the proteasome enzyme complex that is typically involved in cellular protein turnover. Resulting peptide chains of 8 to 10 amino acids are transported into the endoplasmic reticulum where they associate with newly synthesized MHC class I molecules and are routed via the Golgi complex to the cell surface. $CD8^+$ CTLs may then bind to the presented MHC class I/antigen complex and lyse the infected cell through release of the pore-forming molecule perforin and apoptosis-inducing enzymes known as granzymes, or through ligation of Fas ligand on the CTL with Fas on the target cell, which also may induce apoptosis. CTLs are generated from naïve CTL precursors through specific association with a dendritic cell (DC) that has been "licensed" through interaction with a $CD4^+$ Th1 cell. Interaction with the DC stimulates the production of IL-2 by the $CD4^+$ Th1 cell and increases B7-1/2 (CD80/86) expression by the DC. The combination of antigen-specific signaling through the TCR, engagement of CD28 on the $CD8^+$ cell by B7-1/2 on the DC, and Th1-derived IL-2 stimulates the $CD8^+$ T cell to proliferate and differentiate into CTLs, which may then lyse infected target cells as described above.

In addition to effector T cells, populations of regulatory T cells modulate the immune response. Most regulatory T cells (Tregs) express CD4, CD25, and the FOXP3 transcription factor and help to temper immune responses, particularly those related to autoimmune diseases but also some infectious diseases.

HOST DEFENSE RESPONSE TO PATHOGENS

Humans are constantly exposed to microbial pathogens. Organisms such as *Streptococcus pneumoniae*, group A streptococci, and respiratory viruses may colonize the respiratory tract. *Staphylococcus aureus*, fungi, and many other organisms live on the skin. Thousands of microbial species have been identified in the gastrointestinal tract; most are benign, many are beneficial, and some are dangerous.

Host defenses need to react continuously and appropriately to breaches in nonimmunologic host defenses. For example, if a person suffers a puncture wound the skin barrier is breached, and pathogens may be inoculated into the subcutaneous tissues. This stimulates inflammatory responses in which cytokines stimulate the expression of adhesion molecules and chemokines on vascular endothelium. Neutrophils in the bloodstream then bind to the endothelium, traverse the vessel walls, and migrate into tissues, where they are attracted by a chemokine gradient to the site of tissue damage and infection.

A second process that breaches nonimmune host defenses results from infection by respiratory viruses. For example, influenza virus may compromise upper and lower respiratory host defenses by damaging the respiratory epithelium, inhibiting ciliary action and mucus production. Bacterial pathogens, most commonly *S. pneumoniae*, that colonize the respiratory tract in normal hosts may then colonize and invade the lower respiratory tract, leading to pneumonia. Organisms such as *M. tuberculosis* may evade upper respiratory and lower respiratory defenses and lodge in alveolar macrophages in the lung, where they can survive and multiply. Interference with alveolar macrophage function (e.g., silica exposure) may increase susceptibility to tuberculosis.

The innate immune system is critical during the early phases of infection. The response is rapid, albeit relatively nonspecific, and eliminates the pathogen or holds it in check until the adaptive immune system has time to respond. Phagocytes such as tissue macrophages patrol the periphery and detect pathogens through pattern receptors such as TLRs. This activates the phagocyte, induces phagocytosis and killing, and stimulates the production of cytokines and chemokines that initiate the inflammatory response and influence the development of the adaptive response.

Complement may be activated innately by pathogens through the alternative and lectin pathways and produce products to attract neutrophils, opsonize pathogens, lyse pathogens, and degranulate mast cells. Vasodilation results from histamine release, and circulating neutrophils are localized to the vascular endothelium nearest the site of invasion by integrins, pass through the vascular wall, and move down a chemokine gradient to the site of infection. Opsonization helps neutrophils, macrophages, and other immune cells ingest and kill the pathogen. These immediate inflammatory and innate immune responses are initiated immediately and increase over hours to days. These responses are highly effective, buying survival time for the host while more specific responses of the adaptive immune system develop.

Immature dendritic cells in peripheral tissues are sentinels for foreign molecules. Through pinocytosis and phagocytosis initiated by TLRs and other receptors, DCs detect pathogens; once they have acquired foreign antigen, DCs migrate to regional lymph nodes. There the DCs mature, process, and present antigen to T cells, initiating the specific adaptive immune response. The type of response depends on the type of pathogen. Intracellular pathogens such as *M. tuberculosis* stimulate a T cell–mediated response, whereas *S. pneumoniae* stimulates primarily a B-cell, antibody-mediated (humoral) response. Most infections produce components of cellular and humoral responses in various degrees that often act in concert. For example, influenza virus induces B-cell and T-cell responses; antibodies neutralize free virus and prevent further infection of respiratory epithelium and CTLs lyse infected epithelial cells.

Humoral Response

Early in infection, preexisting antibodies and complement factors react to pathogens directly and can initiate lysis, opsonization, and neutralization of pathogens. B cells may be activated by T cell–independent antigens or through interaction with $CD4^+$ T cells for T cell–dependent antigens. B-cell populations proliferate and produce IgM antibodies

initially and then with isotype switching produce other types of antibodies, including IgG, IgE, and IgA. Antibodies acting in the extracellular space bind to pathogens or their products, potentially leading to neutralization, agglutination, opsonization, complement fixation, ADCC, and mast cell degranulation.

Cell-Mediated Response

Naïve T cells with specificity for the invading pathogen are activated, proliferate, and produce cytokines. $CD4^+$ T cells produce cytokines that stimulate other T cells such as CTLs, enhance the overall inflammatory response, activate phagocytes for killing, and stimulate antibody production. Previously sensitized memory $CD4^+$ and $CD8^+$ T cells may react rapidly with activation and proliferation on exposure to previously recognized pathogens.

SUGGESTED READINGS

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Medzhitov R, Shevach EM, Trinchieri G, et al: Highlights of 10 years of immunology in nature reviews immunology, Nat Rev Immunol 11:693–702, 2011.