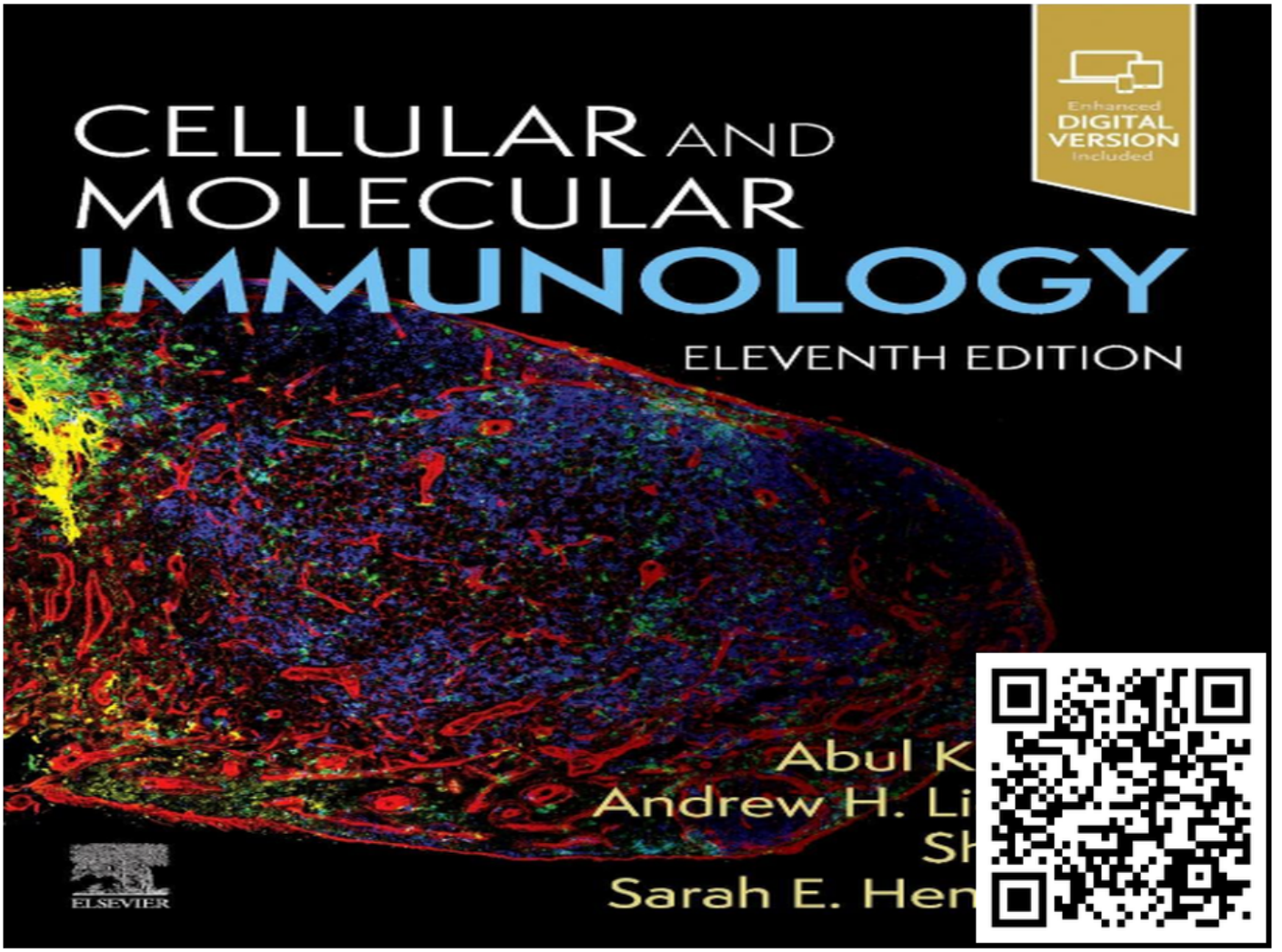

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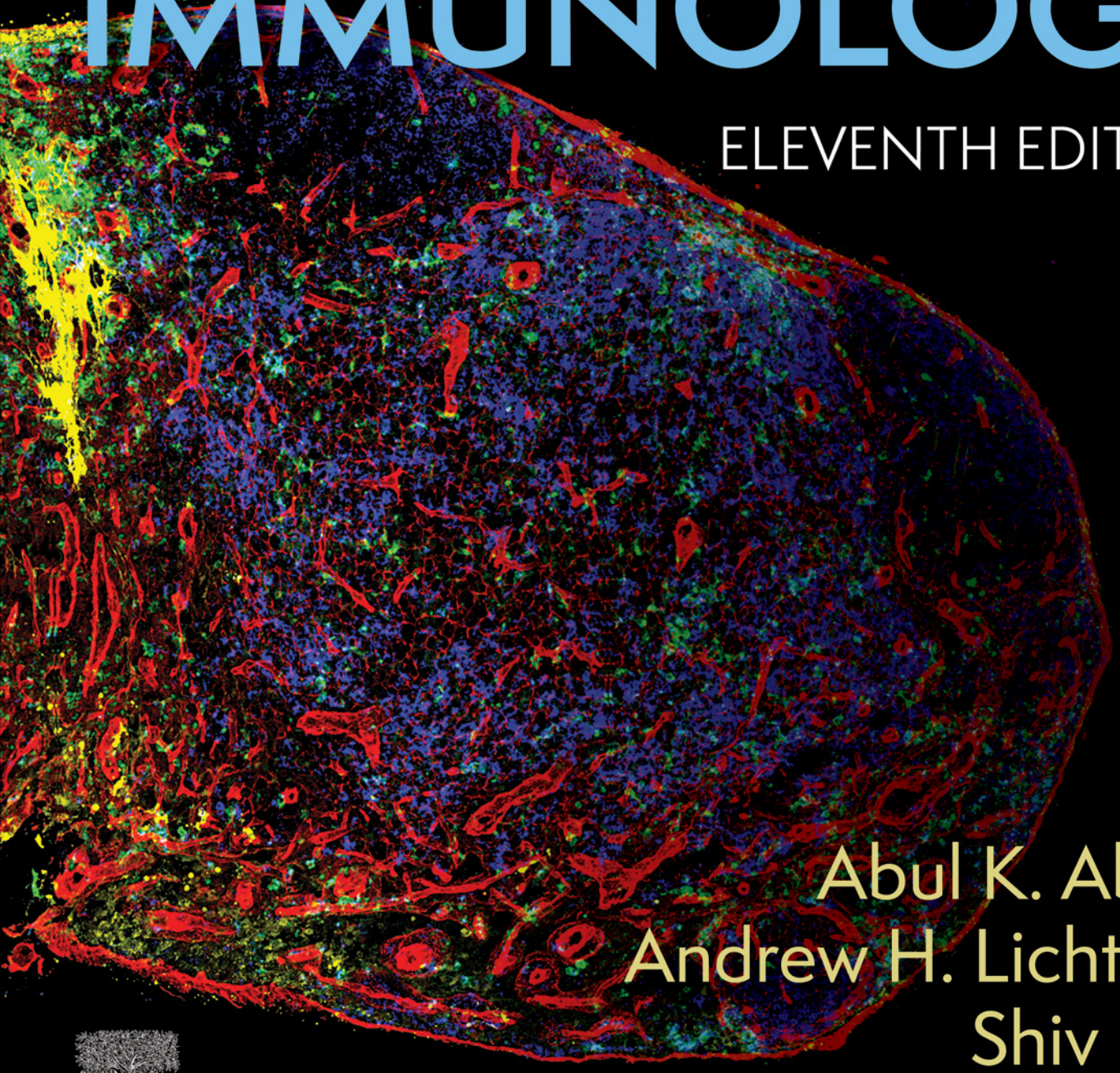

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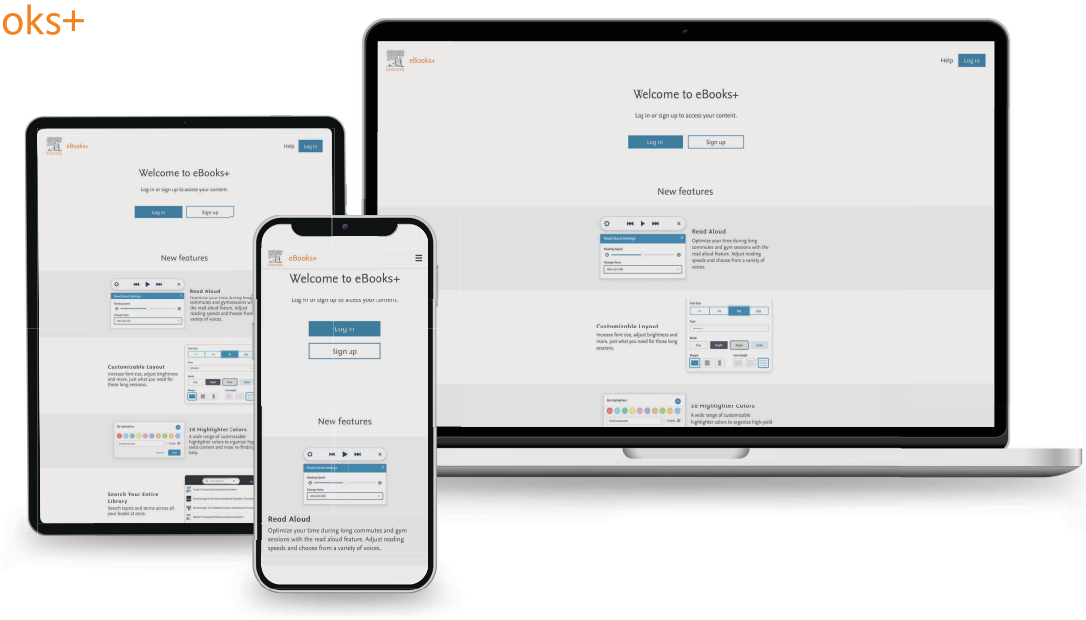

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CELLULAR AND MOLECULAR IMMUNOLOGY

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To Our Students, Our Colleagues, and Our Families

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PREFACE

This 11th edition of *Cellular and Molecular Immunology* includes substantial revisions, reflecting recent scientific advances and clinical applications of the science, while at the same time we have maintained the clear and readable style that has been typical of previous editions. Our presentation of new information focuses primarily on important concepts. We have also rewritten many sections for increased clarity, accuracy, and completeness.

The field of immunology has moved beyond establishing fundamental principles of the mechanisms of immune responses to applying these principles to understand human diseases and develop therapies for them. The revolution in immunological therapies over the last 25 years has been extraordinary. It is especially satisfying for immunologists that some of the most innovative and effective immunotherapies have been developed because the basic science has matured and the complex mechanisms of immune activation and regulation have been elucidated in increasing detail. Throughout the book, we have paid special attention to the clinical relevance of immunology and the scientific underpinnings of human disease and therapies. The links between the basic science of immunology and the remarkable progress we have made in confronting human disease have been amply demonstrated in the recent development of cancer immunotherapies, numerous biological and small molecule drugs to treat inflammatory diseases, and the rapid development of vaccines which greatly reduced mortality during the SARS-CoV2 pandemic.

In addition to these translational aspects of immunology, we have also updated basic concepts wherever there have been significant new developments. Some examples of these fundamental advances include a better understanding of tissue-resident macrophages and memory T-cell subsets, mechanisms by which inflammasomes and nucleic acid sensors stimulate innate immune responses, the sequence of events in T cell–dependent antibody responses, and mechanisms by which tumor evasion of immune attack can be overcome.

As in previous editions, each chapter is written so that it can be read and understood on its own. To do this, it is often necessary to repeat some basic concepts and general principles that are covered in other chapters. We feel such repetition is valuable because it enables the reader to consolidate learning and understand the content of each chapter independently of the others. We also feel this is helpful for faculty teaching from the book because they can consider each chapter as the topic of one or two lectures.

We have also continued to improve our illustration program. Many illustrations have been revised to provide more visual depth and clarity. New figures have been added, and previously used figures have been reviewed and often changed for accuracy. We have kept design features such as the use of bold italic text to highlight "take-home messages" to make the book easy to read. We have tried to make the nomenclature more consistent by using the conventions for human genes and proteins wherever possible. The lists of Selected Readings continue to emphasize recent review articles that provide in-depth coverage of particular topics for the interested reader. We have divided the lists into sections based on themes to help readers find the most useful articles for their needs. As in the previous edition, we have added some classic primary research publications and links to the lectures of Nobel laureates in immunology.

Individuals who have helped us with specific topics are (in alphabetical order) Drs. Bruce Bochner, Shane Crotty, Jason Cyster, Michael Gerner, Peter Gregersen, Amy Klion, Ari Molofsky, Robert Ohgami, and Andrea Radtke; all were generous with advice and images. Our illustrator, David Baker, remains a full partner in the book and provides invaluable suggestions for clarity and accuracy. Several members of the Elsevier staff played critical roles. Our editor, Jeremy Bowes, has been a source of support and encouragement. Our managing editor, Rebecca Gruliow, shepherded the book through its preparation and into production. Ryan Cook was responsible for managing the design, and Haritha Dharmarajan and Tarana Parveen were invaluable throughout the production stage. We also owe a debt of gratitude to our families for their unflagging support and their tolerance of our absences. Finally, our students were the original inspiration for the first edition of this book, and we remain continually grateful to them because from them we learn how to think about the science of immunology and how to communicate knowledge in the clearest and most meaningful way.

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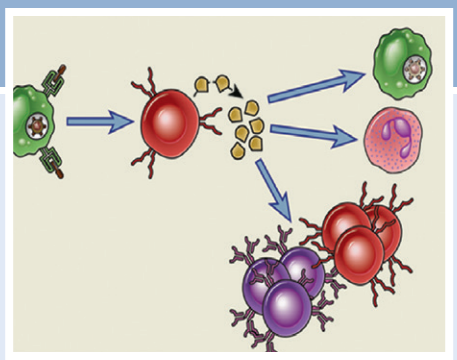

1 Overview of the Immune System

The term **immunity** is derived from the Latin word *immunitas*, which referred to the protection from legal prosecution offered to Roman senators during their tenures in office. In a biological context, immunity has meant protection from disease and, more specifically, against infectious disease. The cells and molecules responsible for immunity constitute the **immune system**, and their collective and coordinated response to the introduction of foreign substances is called the **immune response**.

The major physiologic function of the immune system is defense against microbes (Table 1.1). Our immune systems have evolved over hundreds of millions of years in invertebrate and vertebrate ancestors in response to the selective pressures of diverse biological threats including microbes, multicellular parasites, and toxins of arthropods and reptiles. By far the most numerous and diverse organisms that coinhabit Earth with us are microbes, including viruses, bacteria, fungi, and protozoans. Their impact on mammals is reflected by the fact that the functions of mammalian immune systems are largely directed at protecting against microbial infections. Immune responses act to prevent and control the spread of infections, as well as to stimulate the repair of tissues damaged by infection or by other causes. The devastating consequences of viral pandemics such as COVID-19 and HIV-AIDS have highlighted the importance of learning how to better harness immune responses.

Immune responses can be stimulated by many other cells and molecules besides infectious pathogens and are also the cause of tissue damage and disease. The field of immunology has captured the attention of scientists, physicians, and the lay public for several reasons besides its relevance to infectious diseases (see Table 1.1). Immune responses directed against noninfectious environmental substances, commensal microbes, and self molecules cause inflammatory diseases with serious morbidity and mortality. Allergies and autoimmune diseases are examples of such disorders, and new approaches to treat these diseases continue to be developed based on our evolving understanding of the pathological immune responses involved. Immune responses can damage transplanted tissues and organ grafts, and transplantation as a therapy for many diseases has only become possible because of the development of effective drugs to suppress these immune responses. In light of the many immune responses beyond those that protect against infections, a more inclusive definition of the immune response is a reaction to microbes and molecules that are recognized as foreign or abnormal, regardless of the physiologic or pathologic consequence of such a reaction. Immunology is the study of immune responses in this broader sense and of the cellular and molecular events that occur after an encounter with microbes, microbial products, other foreign cells and molecules, and self molecules and cells.

Historians often credit Thucydides, in the fifth century BCE in Athens, as having first mentioned immunity to an infection that he called "plague" (but was probably not the bubonic plague we recognize today). The concept of protective immunity may have existed long before, as suggested by the ancient Chinese custom of making children resistant to smallpox by having them inhale powders made from the skin lesions of patients recovering from the disease. Immunology, in its modern form, is in large part an experimental science in which explanations of immunologic phenomena are based on experimental observations and the conclusions drawn from them. The development of immunology as an experimental discipline has depended on our ability to manipulate the function of the immune system under controlled conditions.

The first clear example of this manipulation, and one that remains among the most dramatic ever recorded, was Edward

TABLE 1.1 Importance of the Immune System in Health and Disease

Role of the Immune System	Implications
Defense against infections	Deficient immunity results in increased susceptibility to infections; exemplified by AIDS Vaccination boosts immune defenses and protects against infections
Defense against tumors	Potential for immunotherapy
Control of tissue regeneration and scarring	Repair of damaged tissues
Cell injury and pathologic inflammation	Immune responses are the cause of allergic, autoimmune, and other inflammatory diseases, and of some of the harmful consequences of infections
Recognition of and injury to tissue grafts and newly introduced proteins	Immune responses are barriers to transplantation and gene therapy

This table summarizes some of the physiologic functions of the immune system and its role in disease.

TABLE 1.2 Effectiveness of Vaccines for Some Common Infectious Diseases

Disease	Maximum Number of Cases (Year)	Number of Cases in 2019
Diphtheria	206,939 (1921)	2
Measles	894,134 (1941)	1192
Mumps	152,209 (1968)	3780
Pertussis	265,269 (1934)	18,617
Polio (paralytic)	21,269 (1952)	0
Rubella	57,686 (1969)	66
Tetanus	1560 (1923)	26
Haemophilus influenzae type B	~20,000 (1984)	18
Hepatitis B	26,611 (1985)	3563
	Average daily deaths per 100,000 people who tested positive:	
	Unvaccinated	Vaccinated
COVID-19	1.3	0.1

This table illustrates the striking decrease in the incidence of selected infectious diseases in the United States for which effective vaccines have been developed, and the protection against lethal SARS-CoV-2 infection in the United States by COVID-19 vaccination during a 6-month period in 2021. Data from Orenstein WA, Hinman AR, Bart KJ, Hadler SC. Immunization. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practices of Infectious Diseases*. 4th ed. Churchill Livingstone; 1995; *Nationally Notifiable Infectious Diseases and Conditions, United States: 2019 Annual Tables*. Centers fo Disease Control:https://wonder.cdc.gov/nndss/nndss_annual_tables_menu.asp

Jenner's successful vaccination against smallpox. Jenner, an English physician, was aware that milkmaids in rural England who had recovered from cowpox did not contract the more serious smallpox. On the basis of this observation, he injected the material from a cowpox pustule into the arm of an 8-year-old boy. When this boy was later intentionally inoculated with smallpox, the disease did not develop. Jenner's landmark treatise on **vaccination** (Latin *vaccinus*, of or from cows) was published in 1798. The principles of infectious diseases and vaccination were firmly established by the work of Louis Pasteur and Robert Koch a hundred years later. These advances led to the widespread acceptance of the method for inducing protective immunity, and vaccination remains the most effective strategy for preventing infections (Table 1.2). An eloquent testament to the importance of immunology was the announcement by the World Health Organization in 1980 that smallpox was the first disease that had been eradicated worldwide by a program of vaccination. The significance of the immune system has been dramatically and tragically highlighted by the AIDS (acquired immunodeficiency syndrome) epidemic, caused by HIV (human immunodeficiency virus), that started in the 1980s, and the COVID-19 pandemic caused by the coronavirus SARS-CoV-2 that started in 2019. Both have caused severe morbidity and resulted in many deaths and have had devastating impacts on society. The development of effective vaccines for SARS-CoV-2, which have saved millions of lives, is a testament to the importance of research in immunology, but the failure so far to develop an effective HIV vaccine indicates that we still have much to learn.

Since the 1960s there has been a remarkable transformation in our understanding of the immune system and its functions. Advances in cell culture techniques (including monoclonal antibody production), recombinant DNA methodology, next-generation DNA sequencing, analyses of molecular structure, and creation of genetically altered animals (especially transgenic, knockout, and gene-edited mice) have changed immunology from a largely descriptive science into one in which the cellular and molecular basis of diverse immune phenomena are understood. Some of the most important advances in immunology have come since the 1990s, with the development of therapies targeting different components of the immune system that are based on fundamental science and are dramatically altering the progression of human inflammatory diseases and cancers. More recently, rapidly evolving technologies of single-cell phenotypic and transcriptional analyses and spatial-temporal biology are contributing to a more detailed understanding of immune cell subsets and cell–cell interactions during immune responses.

In this chapter we outline the general features of immune responses and introduce the concepts that form the cornerstones of modern immunology and that recur throughout this book.

OVERVIEW OF INNATE AND ADAPTIVE IMMUNITY

Defense against microbes is mediated by the functions of two coordinated and partially overlapping branches of the immune system that are called innate and adaptive immunity (Fig. 1.1 and Table 1.3). **Innate immunity** (also called natural immunity or native immunity) provides continuous barrier defenses to prevent infection and also reacts to invading microbes in the first few hours or days after infection, before adaptive immune responses have developed. The innate immune system is fully functional in individuals even before an infection occurs (hence, innate).

In contrast to innate immunity, **adaptive immunity** (also called specific immunity or acquired immunity) relies on immune responses that are stimulated by exposure to infectious agents and increase in magnitude and defensive capabilities with repeated exposures to a particular microbe. In other words, this form of immunity adapts to the infection. The adaptive immune system can recognize and react to a large number of microbial and nonmicrobial substances called **antigens**. Although pathogens frequently evolve to resist the innate immune response, the stronger and more specialized adaptive immune responses are capable of eradicating many of these infections. There are numerous connections between innate and adaptive immune responses. The innate immune response to microbes provides early danger signals that stimulate adaptive immune responses. Conversely, adaptive immune responses often work by enhancing the protective mechanisms of innate immunity, making them more capable of effectively combating microbes.

Mechanisms for defending the host against microbes are present in all multicellular organisms. The phylogenetically oldest mechanisms of host defense are those of innate immunity, which are present even in plants and insects. Approximately 500 million years ago, jawless fish, such as lampreys and hagfish, developed an immune system containing lymphocyte-like cells that may function like lymphocytes in more advanced species and even respond to immunization. The antigen receptors on these cells are proteins with limited variability that are capable of recognizing many antigens but are distinct from the highly variable antibodies and T-cell receptors that appeared later in evolution. The more specialized defense mechanisms that constitute adaptive immunity are found only in vertebrates. Most of the components of the adaptive immune system, including lymphocytes with diverse antigen receptors, antibodies, and specialized lymphoid tissues, evolved coordinately within a short time in jawed vertebrates (e.g., sharks) approximately 360 million years ago.

Every individual's immune system is able to recognize, respond to, and eliminate many foreign (nonself) antigens but does not usually react against that individual's own (self) antigens and tissues. In the adaptive immune system of all individuals, cells with antigen receptors capable of recognizing self antigens are produced but are either eliminated or inactivated before they can make harmful responses against self tissues. Different mechanisms are used by the innate and

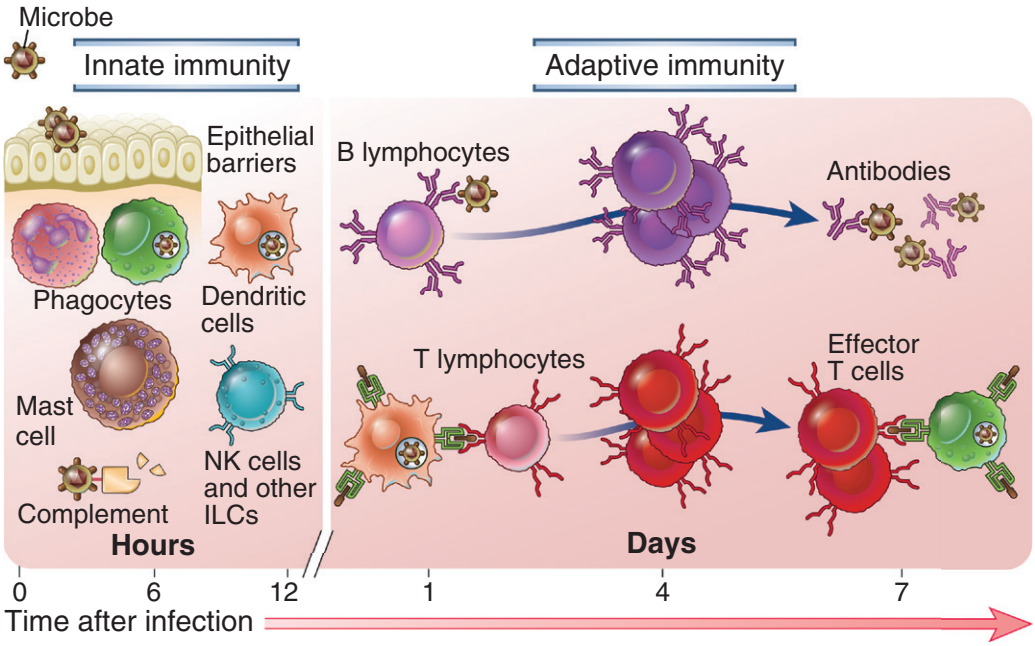

Fig. 1.1 Innate and adaptive immunity. The mechanisms of innate immunity provide the initial defense against microbial infections. Adaptive immune responses to the first exposure of a microbe develop later because they require the activation, expansion, and differentiation of lymphocytes specific for the microbe. The kinetics of the innate and adaptive immune responses are approximations and may vary in different infections. Only selected cell types are shown. *ILCs*, Innate lymphoid cells; *NK*, natural killer.

TABLE 1.3 Features of Innate and Adaptive Immunity

	Innate	Adaptive
Characteristics		
Specificity	For molecules shared by groups of related microbes and molecules produced by damaged host cells	For many different microbial and nonmicrobial antigens
Diversity	Low; recognition molecules encoded by inherited (germline) genes	Very high; antigen receptors are generated by somatic recombination of gene segments in lymphocytes
Memory	Limited	Yes
Nonreactivity to self	Yes	Yes
Components		
Cellular and chemical barriers	Skin, mucosal epithelia; antimicrobial molecules	Lymphocytes in epithelia; antibodies secreted at epithelial surfaces
Secreted proteins	Complement, various lectins	Antibodies
Cells	Phagocytes (macrophages, neutrophils), dendritic cells, natural killer cells, mast cells, eosinophils, innate lymphoid cells	Lymphocytes (B and T)

Many of the components of innate immunity also serve important functions in adaptive immune responses, as we will discuss in later chapters.

adaptive immune systems to prevent reactions against self molecules, cells, and tissues in the healthy host.

INTRODUCTION TO INNATE IMMUNITY

The innate immune system provides continuously present defense against potential infection, and responds rapidly to microbes and injured cells. Many different microbes or types of tissue injury induce similar responses, and the kinetics, magnitude, and qualities of innate responses to repeated exposures of the same microbe are usually the same as after the first exposure. The receptors of innate immunity are specific for structures that are common to groups of related microbes and do not distinguish fine differences among microbes. The principal components of innate immunity are (1) physical and chemical barriers, such as epithelia and antimicrobial chemicals produced at epithelial surfaces; (2) phagocytic cells (neutrophils, macrophages), dendritic cells (DCs), mast cells, natural killer cells, and other innate lymphoid cells; and (3) blood proteins, including components of the complement system and other mediators of inflammation. Innate immune cells, including DCs, some macrophages, and mast cells, are resident in most tissues, and they function as sentinels to keep watch for invading microbes. The innate immune response combats microbes by two main strategies: by recruiting phagocytes and other leukocytes that destroy the microbes, in the process called **inflammation**, and by blocking viral replication or killing virus-infected cells by mechanisms distinct from inflammatory reactions. We will discuss the features, mechanisms, and components of innate immunity in Chapter 4.

INTRODUCTION TO ADAPTIVE IMMUNITY

The adaptive immune response is mediated by cells called lymphocytes and their products. Each lymphocyte expresses antigen receptors that are specific for a single antigen, but among all the lymphocytes in an individual's immune system, these receptors are highly diverse and are capable of recognizing a vast number of antigens. There are two major populations of lymphocytes, called **B lymphocytes** and **T lymphocytes**, which mediate different types of adaptive immune responses. We will first summarize the important properties of the adaptive immune system and then describe the different types of adaptive immune responses.

Fundamental Properties of Adaptive Immune Responses

The fundamental properties of the adaptive immune system reflect the properties of the lymphocytes that mediate adaptive immune responses.

- ***Specificity and diversity.*** Immune responses are specific for distinct antigens and often for different portions of a single complex protein, polysaccharide, or other macromolecule (Fig. 1.2). The parts of complex antigens that are specifically recognized by lymphocytes are called **determinants** or **epitopes**. This fine specificity exists because individual lymphocytes express membrane receptors that can distinguish subtle structural differences between distinct epitopes. Clones of lymphocytes with different specificities are present in unimmunized individuals and are able to recognize and respond to foreign antigens (Fig. 1.3). This fundamental concept is called **clonal selection**. It was postulated by Macfarlane

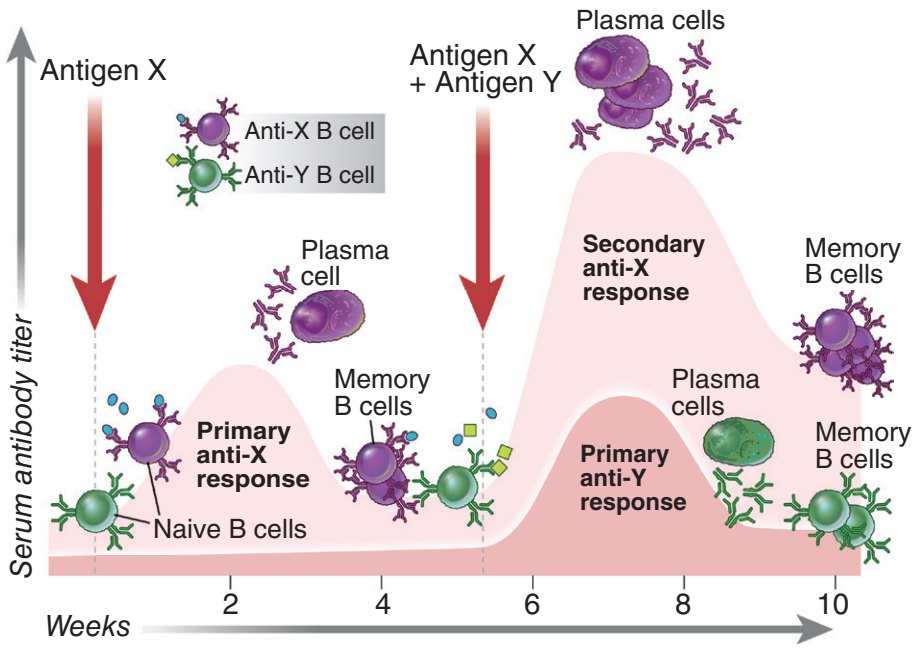

Fig. 1.2 Specificity, memory, and contraction of adaptive immune responses. Antigens X and Y activate different clones of B cells and induce the production of different antibodies (specificity). The secondary response to antigen X is more rapid and larger than the primary response (memory). Antibody levels decline with time after each immunization (contraction, the process that maintains homeostasis). The same features are seen in T cell-mediated immune responses.

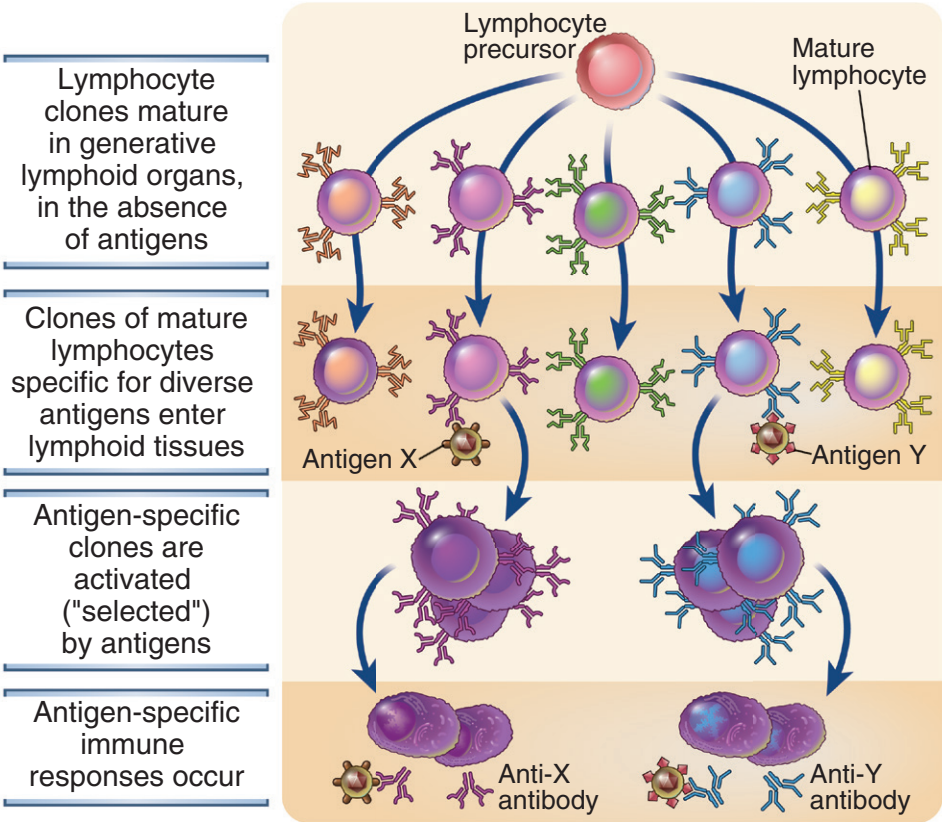

Fig. 1.3 Clonal selection. Each antigen (X, Y) selects a preexisting clone of specific lymphocytes and stimulates the proliferation and differentiation of that clone. The diagram shows only B lymphocytes giving rise to antibody-secreting effector cells, but the same principle applies to T lymphocytes.

Burnet in 1957 to explain how the immune system could respond to a large number and variety of antigens. According to this hypothesis, which is now a proven feature of adaptive immunity, antigen-specific clones of lymphocytes develop before and independent of exposure to an antigen. An introduced antigen binds to (selects) the cells of the preexisting antigen-specific clone and activates them, leading to an immune response specific for that antigen. The total number of antigenic specificities of the lymphocytes in an individual, called the lymphocyte repertoire, is extremely large. It is estimated that the immune system of an individual can recognize and discriminate between 10^7 and 10^9 distinct antigenic determinants. This ability of the lymphocyte repertoire to recognize a very large number of antigens, called **diversity**, is the result of variability in the structures of the antigen-binding sites of lymphocyte receptors for antigens. In other words, there are many different clones of lymphocytes and each clone has a unique antigen receptor and therefore a single antigen specificity, contributing to a total repertoire that is extremely diverse. The expression of different antigen receptors in different clones of T and B cells is the reason why these receptors are said to be clonally distributed. The molecular mechanisms that generate such diverse antigen receptors are discussed in Chapter 8. Diversity is essential if the immune system is to defend individuals against the enormous number of potential pathogens in the environment.

- ***Memory***. Exposure of the immune system to a foreign antigen enhances its ability to respond again to that antigen. Responses to second and subsequent exposures to the same antigen, called secondary immune responses, are usually more rapid, greater in magnitude, and often qualitatively different from the first, or primary, immune response to that antigen (see Fig. 1.2). Immunologic memory exists because each exposure to an antigen generates long-lived memory cells specific for the antigen. Two properties of memory cells account for why secondary responses are typically stronger than primary immune responses—memory cells accumulate and become more numerous than the naive lymphocytes specific for the antigen that exist at the time of initial antigen exposure, and memory cells react more rapidly and vigorously to antigen challenge than do naive lymphocytes. Memory enables the immune system to mount heightened responses to persistent or recurring exposure to the same antigen and thus to combat infections by microbes that are prevalent in the environment and are encountered repeatedly. Immunologic memory is one mechanism by which vaccines confer long-lasting protection against infections.
- ***Nonreactivity to self (self-tolerance)***. One of the most remarkable properties of every individual's immune system is its ability to recognize, respond to, and eliminate many foreign (nonself) antigens while not reacting harmfully to that individual's own (self) antigens. Immunologic unresponsiveness is also called **tolerance**. Tolerance to self antigens, or self-tolerance, is maintained by several mechanisms. These include eliminating lymphocytes that express receptors specific for some self antigens, inactivating self-reactive lymphocytes, or suppressing these cells by the actions of other (regulatory) cells. Abnormalities in the induction or maintenance of self-tolerance lead to immune responses against self (autologous) antigens, which may result in disorders called **autoimmune diseases**. The mechanisms of self-tolerance and its failure are discussed in Chapter 15.

In addition to these fundamental features of adaptive immunity, these responses have some other important properties.

- ***Because of the ability of lymphocytes and other immune cells to circulate among tissues, adaptive immunity is systemic***, meaning that even if an immune response is initiated at one site it can provide protection at distant sites. This feature is, of course, essential for the success of vaccination—a vaccine administered in the subcutaneous or muscle tissue of the arm can protect from infections in any tissue.
- ***Immune responses are regulated by a system of positive feedback loops that amplify the reaction and by control mechanisms that prevent inappropriate, overly prolonged or pathologic reactions***. When lymphocytes are activated, they trigger mechanisms that further increase the magnitude of the response. This positive feedback is important to enable the small number of lymphocytes that are specific for any microbe to generate the large response needed to eradicate that infection. Many control mechanisms become active during immune responses, which prevent excessive activation of lymphocytes that could cause collateral damage to normal tissues and also prevent responses against self antigens.

Overview of Humoral and Cell-Mediated Immunity

There are two types of adaptive immunity, called humoral immunity and cell-mediated immunity, which are mediated by different types of lymphocytes and function to eliminate different types of microbes (Figs. 1.4 and 1.5). **Humoral immunity** is mediated by molecules in the blood and mucosal secretions, called **antibodies** (also called immunoglobulins), which are produced by **B lymphocytes**. Antibodies recognize microbial antigens, neutralize the infectivity of the microbes, and target microbes for elimination by phagocytes and the complement system. Humoral immunity is the principal defense mechanism against microbes and their toxins located outside cells (e.g., in the lumens of the gastrointestinal and respiratory tracts and in the blood and extracellular tissue spaces) because secreted antibodies can bind to these microbes and toxins, neutralize them, and assist in their elimination.

Cell-mediated immunity, also called cellular immunity, is mediated by **T lymphocytes**. Many microbes are ingested by but survive within phagocytes, and some microbes, notably viruses, infect and replicate in various host cells. In these locations the microbes are inaccessible to circulating antibodies. Defense against such infections is a function of cell-mediated immunity, which promotes the destruction of microbes inside phagocytes and the killing of infected cells to eliminate reservoirs of infection.

Different classes of lymphocytes may be distinguished by the expression of membrane proteins, many of which are designated by Cluster of Differentiation (CD) numbers. CD molecules are also involved in the functions of the lymphocytes. We will introduce some of the surface molecules that are used to identify lymphocyte classes in Chapter 2 and discuss them further in later

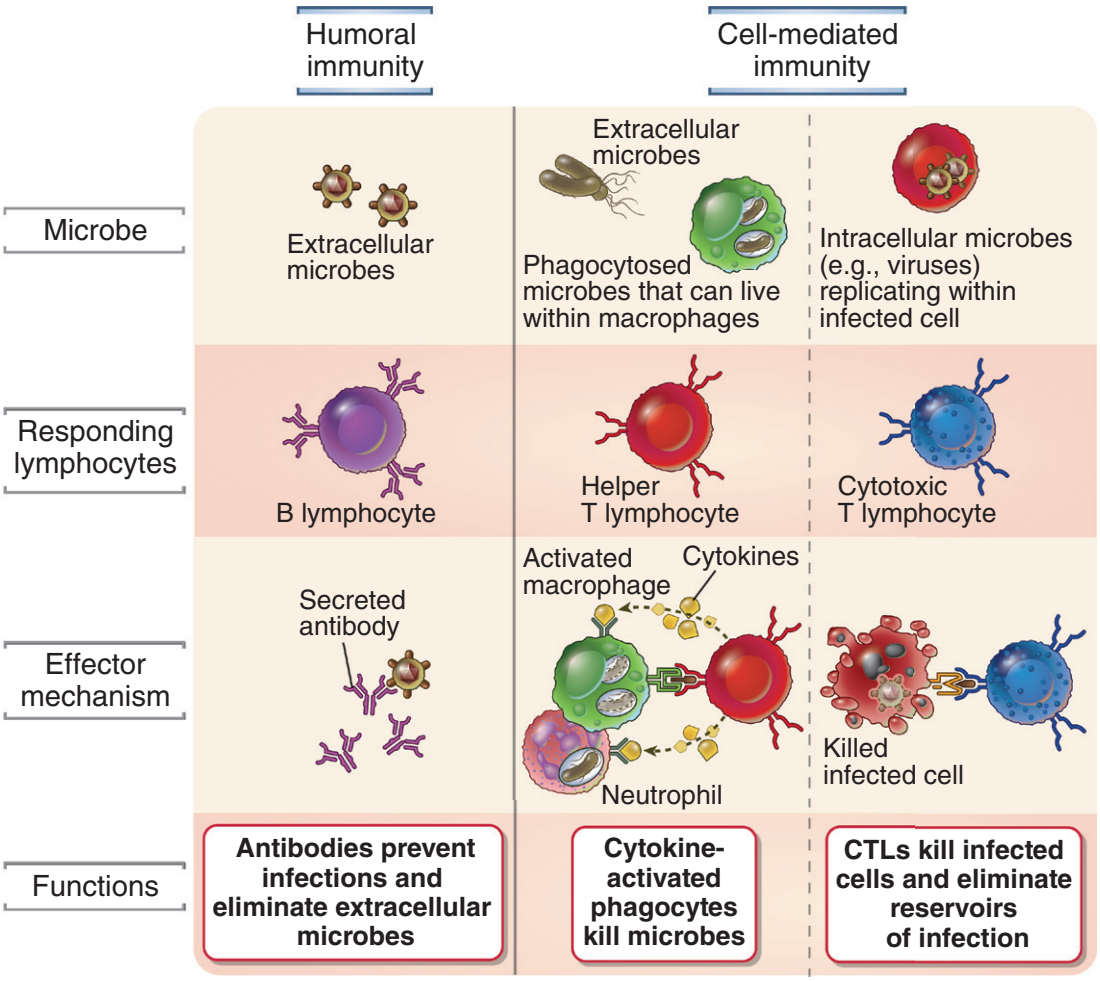

Fig. 1.4 Types of adaptive immunity. In humoral immunity, B lymphocytes secrete antibodies that prevent infections and eliminate extracellular microbes. In cell-mediated immunity, helper T lymphocytes activate macrophages and neutrophils to kill phagocytosed microbes or cytotoxic T lymphocytes (*CTLs*) to directly destroy infected cells.

chapters. A summary of the molecules designated by CD numbers mentioned in the book is provided in Appendix I.

Protective immunity against a microbe may be provided either by the host's response to the microbe or by the transfer of antibodies from another individual (of the same or different species) that defend against the microbe (Fig. 1.6). The form of immunity that is induced by the host's response to a foreign antigen is called **active immunity**. Individuals and lymphocytes that have not encountered a particular antigen are said to be naive, implying that they are immunologically inexperienced. Individuals who have responded to a microbial antigen and are protected from subsequent exposures to that microbe are said to be immune.

Immunity also can be conferred on an individual by transferring antibodies from an individual who had previously made an active immune response to an antigen into an individual who has not encountered the antigen (see Fig. 1.6). The recipient of such a transfer becomes immune to the particular antigen without ever having been exposed to or having responded to that antigen. This form of immunity is called **passive immunity**. A physiologically important example of passive immunity is the transfer of maternal antibodies through the placenta to the fetus, which enables newborns to combat infections for several months before they develop the ability to produce antibodies themselves. Passive immunization is also a medically useful method for conferring resistance rapidly without having to wait for an active immune response to develop. Passive immunization against potentially lethal toxins by the administration of antibodies from animals or people previously exposed to the toxins is a lifesaving treatment for rabies infection and snake bites. Patients with some genetic immunodeficiency diseases who cannot make their own antibodies are passively immunized by the transfer of pooled antibodies from healthy donors.

The first demonstration of humoral immunity was provided by Emil von Behring and Shibasaburo Kitasato in 1890, using a passive immunization strategy. They showed that if serum from animals that had been immunized with an attenuated form of diphtheria toxin was transferred to naive individuals, the recipients became resistant to diphtheria infection. The active components of the serum were called antitoxins because they neutralized the pathologic effects of the diphtheria toxin.

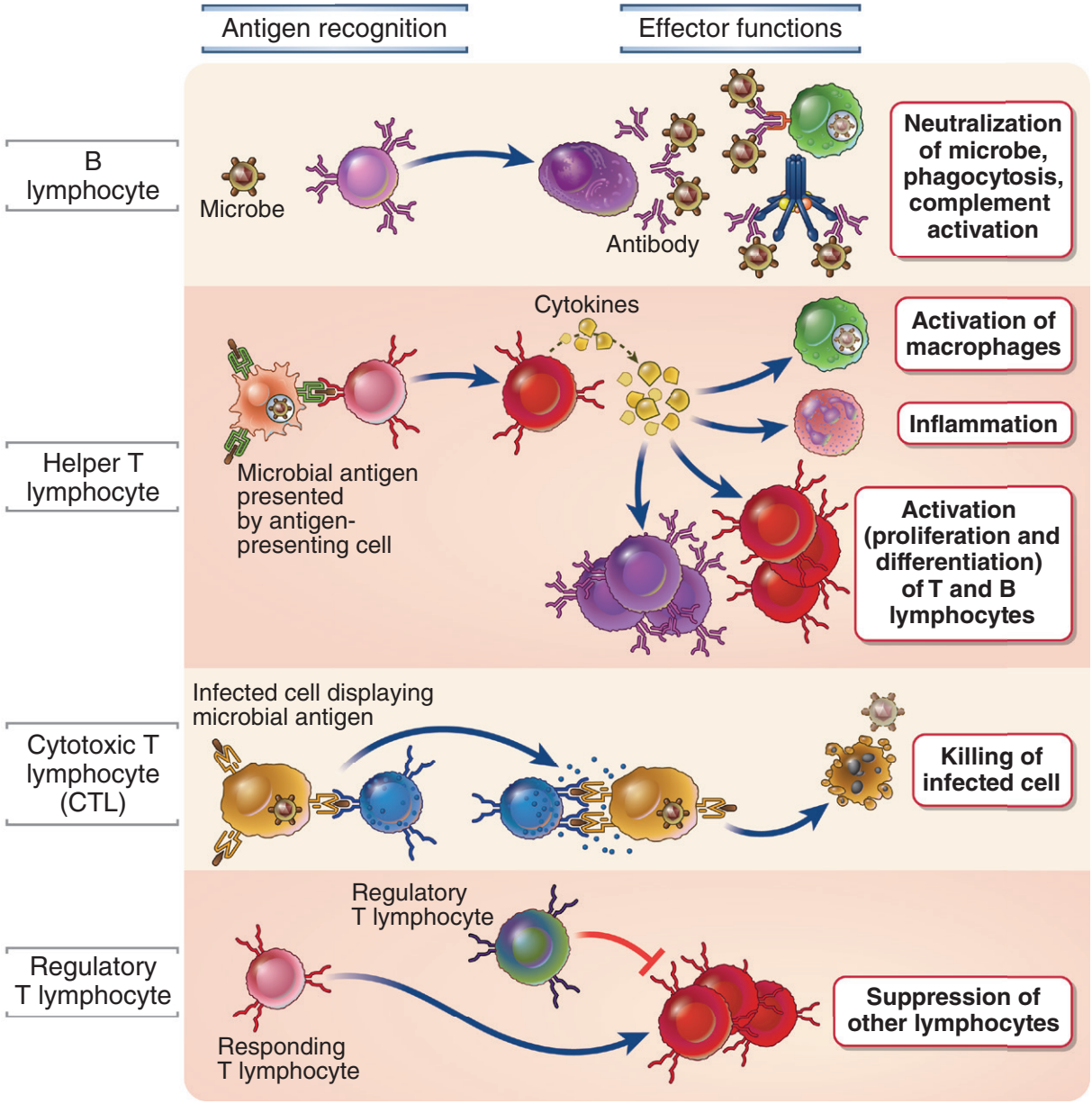

Fig. 1.5 Classes of lymphocytes. B lymphocytes recognize many different types of antigens and develop into antibody-secreting cells. Helper T lymphocytes recognize peptide fragments of protein antigens displayed on the surfaces of antigen-presenting cells and in response secrete cytokines, which stimulate different mechanisms of immunity and inflammation. Cytotoxic T lymphocytes recognize peptide fragments of protein antigens displayed on the surfaces of infected cells and kill these cells. Regulatory T cells suppress immune responses (e.g., to self antigens).

This result led to the treatment of otherwise lethal diphtheria infection by the administration of antitoxin, an achievement that was recognized by the award of the first Nobel Prize in Physiology or Medicine to von Behring. In the 1890s Paul Ehrlich postulated that immune cells use receptors, which he called side chains, to recognize microbial toxins and, subsequently, secrete these receptors to combat microbes. He coined the term *antibodies* (*antikörper* in German) for the serum proteins that bound foreign substances, such as toxins, and the substances that generated antibodies were called antigens. The modern definition of *antigens* includes molecules that bind to specific lymphocyte receptors, whether or not they stimulate immune responses. According to strict definitions, substances that stimulate immune responses are called immunogens, but antigen is often used interchangeably with immunogen. The properties of antibodies and antigens are described in Chapter 5. Ehrlich's concepts were a remarkably prescient model for the specificity of adaptive immunity. These early studies of antibodies led to the general acceptance of the humoral theory of immunity, according to which host defense against infections is mediated by substances present in body fluids (once called humors).

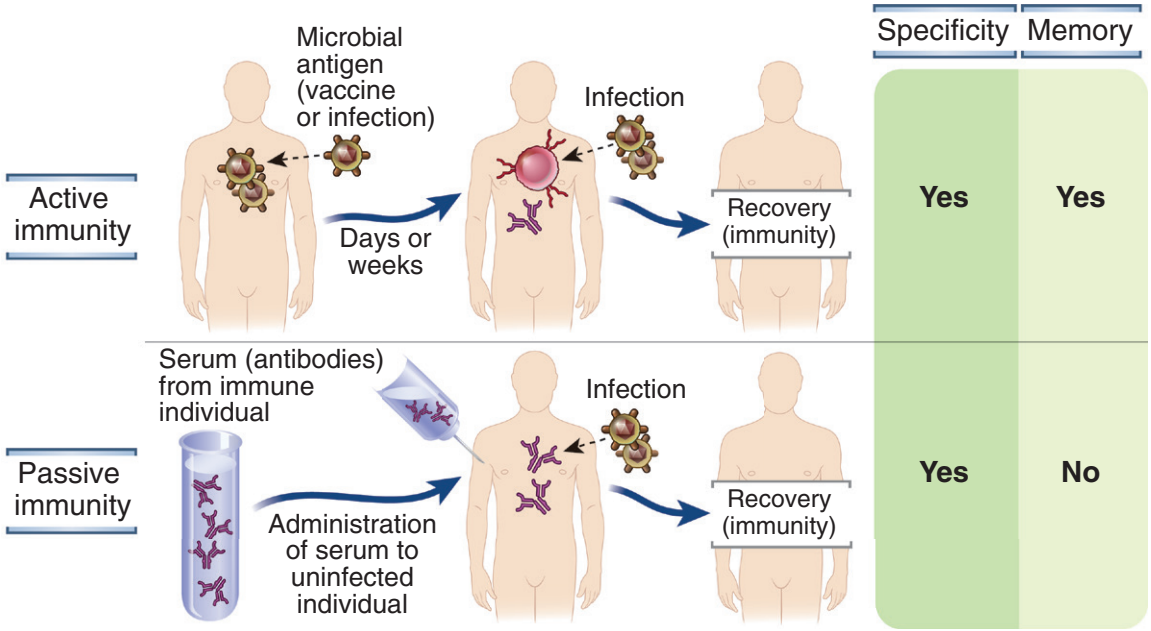

Fig. 1.6 **Active and passive immunity.** Active immunity is conferred by a host response to a microbe or microbial antigen, whereas passive immunity is conferred by adoptive transfer of antibodies specific for the microbe. Both forms of immunity provide resistance to infection and are specific for microbial antigens, but only active immune responses generate immunologic memory. Passive transfer of antibodies occurs during pregnancy (from mother to fetus), and injection of antibodies is used therapeutically to rapidly confer passive protective immunity against lethal toxins. Lymphocytes can be transferred only among genetically identical animals; in humans, lymphocytes from another individual would be recognized as foreign and rejected.

Ilya Metchnikoff initially championed the cellular theory of immunity, which stated that host cells are the principal mediators of immunity. His demonstration of phagocytes surrounding a thorn stuck into a translucent starfish larva, published in 1883, was perhaps the first experimental evidence that cells respond to foreign invaders. Ehrlich and Metchnikoff shared the Nobel Prize in 1908, in recognition of their contributions to establishing these fundamental principles of immunity. Sir Almroth Wright's observation in the early 1900s that factors in immune serum enhanced the phagocytosis of bacteria by coating the bacteria, a process known as **opsonization**, lent support to the belief that antibodies prepare microbes for ingestion by phagocytes. These early cellularists were unable to prove that specific immunity to microbes could be mediated by cells. The importance of cellular immunity in host defense became firmly established in the 1950s, when it was shown that resistance to an intracellular bacterium, *Listeria monocytogenes*, could be transferred to animals with cells but not with serum. We now know that the specificity of cell-mediated immunity is due to T lymphocytes, which often function in concert with other cells, such as phagocytes, to eliminate microbes.

In the clinical setting, immunity to a previously encountered microbe is measured indirectly, either by assaying for the presence of products of immune responses (such as serum antibodies specific for microbial antigens) or by administering substances purified from the microbe and measuring reactions to these substances. A reaction to an antigen is detectable only in individuals who have previously encountered the antigen, reflecting memory for that antigen. These individuals are said to be sensitized to the antigen, and the reaction is an indication of sensitivity. Such a reaction to a microbial antigen implies that the sensitized individual is capable of mounting a protective immune response to the microbe.

Initiation and Development of Adaptive Immune Responses

Adaptive immune responses develop in several steps, starting with the capture of antigen, followed by the activation of specific lymphocytes (Fig. 1.7).

Most microbes and other antigens enter through epithelial barriers and may colonize tissues, and adaptive immune responses to these antigens develop in secondary (peripheral) lymphoid organs. The initiation of adaptive immune responses requires that antigens be captured and displayed to specific lymphocytes. The cells that serve this role are called **antigen-presenting cells** (APCs). The most specialized APCs are **dendritic cells** (DCs), which capture microbial antigens that enter from the external environment, transport these antigens to secondary lymphoid organs called lymph nodes, and present the antigens to naive T lymphocytes to initiate immune responses. Cells other than DCs may function as APCs at different stages of cell-mediated and humoral immune responses. We will describe lymph nodes in Chapter 2 and the functions of APCs in Chapter 6.

Naive lymphocytes express antigen receptors but have not responded to antigen. The activation of these lymphocytes by an antigen leads to the proliferation of these cells, resulting in an

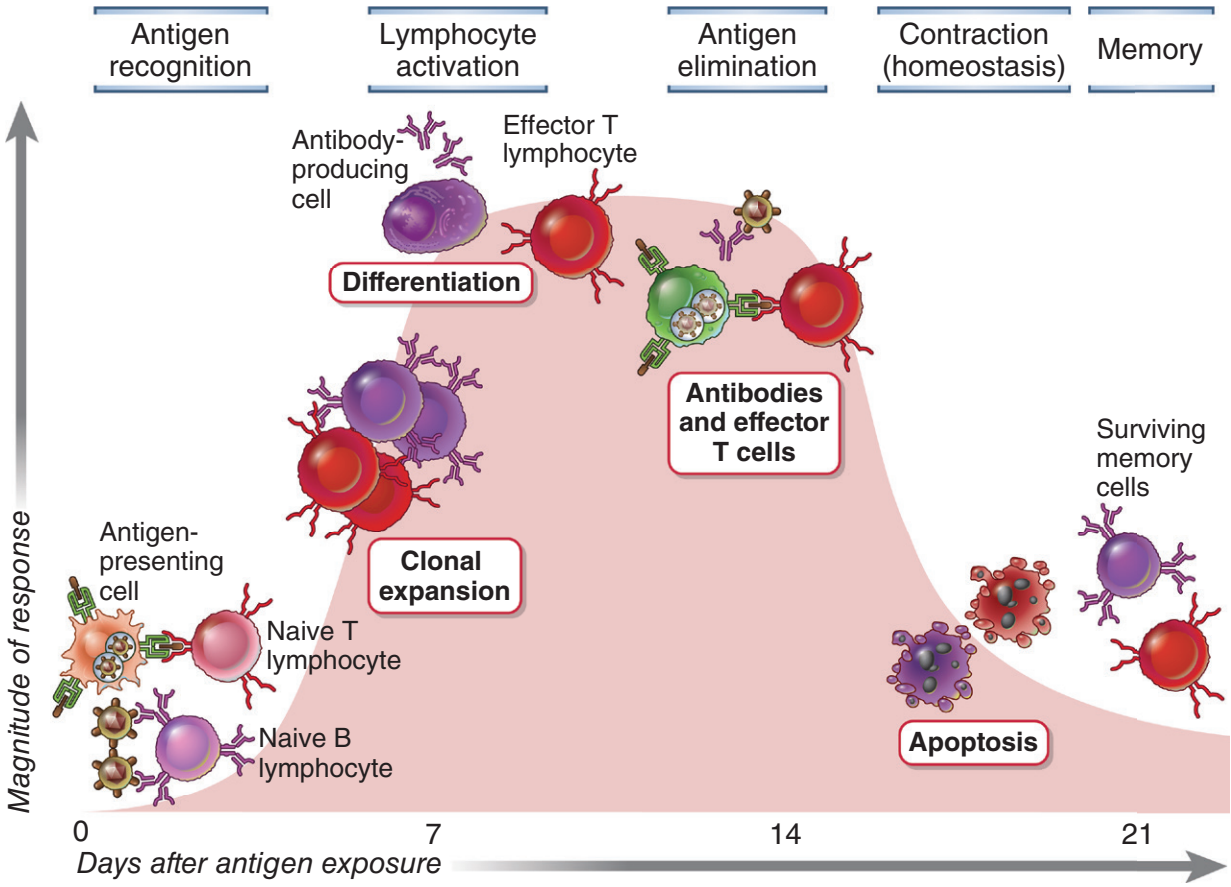

Fig. 1.7 Development of adaptive immune responses. Adaptive immune responses consist of distinct steps, the first three being the recognition of antigen, the activation of lymphocytes, and the elimination of the antigen (the effector phase). The response contracts (declines) as antigen-stimulated lymphocytes die by apoptosis, restoring homeostasis, but many antigen-specific cells survive for a long time and differentiate into memory cells. The duration of each phase may vary in different immune responses. The *y*-axis represents an arbitrary measure of the magnitude of the response. These principles apply to humoral immunity (mediated by B lymphocytes) and cell-mediated immunity (mediated by T lymphocytes).

increase in the number of lymphocytes with identical antigen receptors. The population of lymphocytes derived from a single naive lymphocyte is called a clone. In response to antigen recognition (and other signals discussed in later chapters), lymphocytes proliferate, leading to an increase in the clone, a process called **clonal expansion**. Concurrent with clonal expansion is the differentiation of the antigen-stimulated lymphocytes into cells capable of eliminating the antigen, called **effector cells** because they mediate the ultimate effect of the immune response, and the differentiation of some of the activated lymphocytes into **memory cells** that survive for long periods and mount strong responses upon repeat antigen encounter. Antigen elimination often requires the participation of other, nonlymphoid cells, such as macrophages and neutrophils, which are also sometimes called effector cells. These steps in lymphocyte activation and differentiation into effector cells typically take several days, which explains why the adaptive response is slow to develop and innate immunity has to provide protection initially.

After the adaptive immune response has eradicated the infection, the stimuli for lymphocyte activation dissipate and most of the effector cells die, resulting in the decline of the response. Memory cells remain, ready to respond vigorously if the same infection recurs.

The cells of the immune system interact with one another and with other host cells via secreted proteins called cytokines. Such interactions are essential during both the initiation and effector stages of innate and adaptive immune responses. **Cytokines** are a large group of secreted proteins with diverse structures and functions, which regulate and coordinate many activities of the cells of innate and adaptive immunity. All cells of the immune system secrete at least some cytokines and express specific signaling receptors for several cytokines. Some of the many functions of cytokines we will discuss throughout this book include promoting the growth and differentiation of immune cells, activating the functions of lymphocytes and phagocytes that eliminate microbes (called effector functions), and stimulating directed movement of immune cells from blood into tissues and within tissues. A large subset of structurally related cytokines that regulate cell adhesion and migration are called **chemokines**. Cytokines are also involved in immunological diseases, and some of the most effective drugs developed to treat these diseases target cytokines. We

will describe the functions of individual cytokines when we discuss immune responses in which these proteins play important roles. A list of cytokines and a brief summary of their properties are provided in Appendix II.

Major Features of Humoral Immunity

B lymphocytes that recognize antigens proliferate and differentiate into plasma cells that secrete different classes of antibodies with distinct functions. Each clone of B cells expresses a cell surface antigen receptor, which is a membrane-bound form of antibody with a unique antigen specificity. Humoral immune responses may be specific for many different types of antigens, including proteins, polysaccharides, lipids, and small molecules. The response of B cells to protein antigens requires activating signals (help) from $CD4^+$ T cells (which is the historical reason for calling these T cells helper cells). B cells can respond to nonprotein antigens without the participation of helper T cells. Each plasma cell secretes antibodies that have the same antigen-binding site as the B cell surface antigen receptor that first recognized the antigen. Polysaccharides and lipids stimulate secretion of antibodies mainly of the class (isotype) called immunoglobulin M (IgM). Protein antigens also induce the production of IgM antibodies in the early stages of an immune response but may later induce antibodies of different classes (IgG, IgA, and IgE) from a single clone of B cells, a process called heavy-chain class (or isotype) switching. These different antibody classes serve distinct functions, mentioned later. Helper T cells also stimulate the production of antibodies with increased affinity for the antigen. This process, called affinity maturation, improves the effectiveness of the humoral immune response.

The humoral immune response combats microbes in many ways. Antibodies bind to microbes and prevent them from infecting cells, thus neutralizing the microbes. Antibody-mediated neutralization is the only mechanism of adaptive immunity that stops an infection before it is established; this is why eliciting the production of potent neutralizing antibodies is a key goal of vaccination. IgG antibodies coat microbes and target them for phagocytosis because phagocytes (neutrophils and macrophages) express receptors for parts of IgG molecules and are able to bind and ingest microbes coated with these antibodies. IgG and IgM activate the complement system, and complement products promote phagocytosis and destruction of microbes. IgA is secreted from mucosal epithelia and neutralizes microbes in the lumens of mucosal tissues, such as the respiratory and gastrointestinal tracts, thus preventing inhaled and ingested microbes from infecting the host. Maternal IgG is actively transported across the placenta and protects the newborn until the baby's immune system becomes mature. Most IgG antibodies have plasma half-lives in the circulation of approximately 3 weeks, whereas other classes of antibodies have half-lives of just a few days. Some antibody-secreting plasma cells migrate to the bone marrow or mucosal tissues and live for years, continuing to produce low levels of antibodies. The antibodies that are secreted by these long-lived plasma cells provide immediate protection if the microbe returns to infect the individual. Additional protection is provided by memory B cells that are activated by the microbe and rapidly differentiate to generate large numbers of plasma cells.

Major Features of Cell-Mediated Immunity

T lymphocytes, the cells of cell-mediated immunity, recognize the antigens of microbes that are inside other cells, and different types of T cells help phagocytes to destroy these microbes or kill the infected cells. T cells do not produce antibody molecules. Their antigen receptors are membrane molecules distinct from, but structurally related to, antibodies (see Chapter 7). The antigen receptors on most T lymphocytes only recognize peptides derived from foreign proteins present inside other cells that are bound to host proteins called **major histocompatibility complex (MHC)** molecules. The peptide-MHC complexes must be displayed on the surface of the other cells in order for T cells to see them. The MHC molecules bind the peptides inside the cell and then move to the cell surface. As a result, T cells recognize and respond to cell-associated, but not soluble, antigens (see Chapter 6).

T lymphocytes consist of functionally distinct populations, the best defined of which are **helper T cells** and **cytotoxic** (or **cytolytic**) **T lymphocytes** (CTLs). Helper T-cell functions are mainly mediated by secreted cytokines and membrane molecules, which activate other cells such as B lymphocytes and macrophages, whereas CTLs produce molecules that directly kill infected host cells. Some T lymphocytes, which are called **regulatory T cells**, function mainly to inhibit immune responses. We will return to a more detailed discussion of the properties of lymphocytes in Chapter 2 and in later chapters.

Upon activation in secondary lymphoid organs, naive T lymphocytes differentiate into effector cells, and many of them leave the lymphoid organs and migrate to the sites of infection. When these effector T cells again encounter cell-associated microbes, they are activated to perform the functions that are responsible for elimination of the microbes. Cytokines produced by $CD4^+$ helper T cells recruit leukocytes, and both cytokines and plasma membrane proteins stimulate the production of microbicidal substances in phagocytes. Thus, these T cells help phagocytes kill the infectious pathogens. Other $CD4^+$ helper T cells secrete cytokines that activate leukocytes called eosinophils, which are able to kill helminths that may be too large to be phagocytosed. Some $CD4^+$ T cells stay in the lymphoid organs and express membrane molecules and cytokines that stimulate B cells to make highly effective and functionally specialized antibodies.

$CD8^+$ CTLs kill cells harboring intracellular microbes. These microbes may be viruses that infect many cell types or bacteria that are ingested by macrophages but escape from phagocytic vesicles into the cytosol (where they are inaccessible to the killing machinery of phagocytes, which is largely confined to vesicles). By destroying the infected cells, CTLs eliminate the reservoirs of infection. CTLs also kill tumor cells that express antigens that are recognized as foreign.

In the remainder of the book, we describe the recognition, activation, regulation, and effector phases of innate and adaptive immune responses in detail. The principles introduced in this chapter recur throughout this book.

SUMMARY

- The innate immune system provides continuous protection against microbes before infection and also rapidly responds to infectious pathogens, while the adaptive immune system provides more effective protection within a few days after exposure to a newly encountered microbe or more quickly to a previously encountered microbe.
- Innate immune responses are stimulated by molecular structures shared by groups of microbes and molecules expressed by damaged host cells. Adaptive immunity is specific for different microbial and nonmicrobial antigens and is increased by repeated exposures to an antigen (immunologic memory).
- Many features of adaptive immunity are of fundamental importance for its normal functions. These include specificity for different antigens, a diverse repertoire capable of recognizing a wide variety of antigens, memory of antigen exposure, and the ability to discriminate between foreign antigens and self antigens.
- Immunity may be acquired by a response to antigens (active immunity) or conferred by the transfer of antibodies or effector cells (passive immunity).
- Lymphocytes are the only cells capable of specifically recognizing antigens and are thus the principal cells of adaptive immunity. The total population of lymphocytes consists of many clones, each with a unique antigen receptor and specificity. The two major subsets of lymphocytes are B cells and T cells, and they differ in their antigen receptors and functions.
- The adaptive immune response is initiated by the recognition of foreign antigens by specific lymphocytes. Specialized antigen-presenting cells (APCs) capture microbial antigens and display these antigens for recognition by lymphocytes. Lymphocytes respond by proliferating and by differentiating into effector cells, whose function is to eliminate the antigen, and into memory cells, which show rapid and enhanced responses on subsequent encounters with the antigen. The elimination of antigens often requires the participation of various effector cells.
- Humoral immunity is mediated by antibodies secreted by B lymphocytes and their differentiated progeny, plasma cells, and is the mechanism of defense against extracellular microbes. Antibodies neutralize the infectivity of microbes and promote the elimination of microbes by phagocytes and by activation of the complement system.
- Cell-mediated immunity is mediated by T lymphocytes and their products, such as cytokines, and is important for defense against intracellular microbes. $CD4^+$ helper T lymphocytes help macrophages to eliminate ingested microbes and help B cells to produce antibodies. $CD8^+$ cytotoxic T lymphocytes kill cells harboring intracellular pathogens, thus eliminating reservoirs of infection.

SELECTED READINGS

∗Indicates publications of historical interest, generally reporting the discovery of a phenomenon or process that was later shown to be of fundamental importance in the immune system. Many (but not all) of these discoveries led to Nobel Prizes for the discoverer(s). The nature of the discovery is summarized briefly in each of these references.

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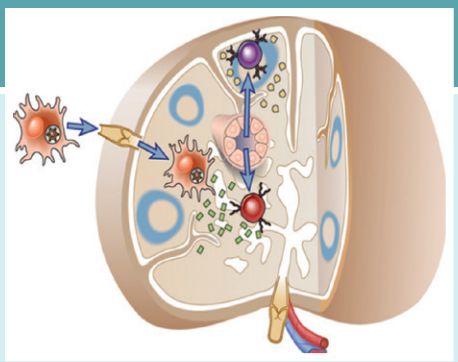

2

Cells and Tissues of the Immune System

The cells of the innate and adaptive immune system are normally present as circulating cells in the blood and lymph and as extravascular cells in lymphoid organs and scattered in virtually all tissues. The anatomic organization of these cells in lymphoid tissues and their ability to circulate and exchange among blood, lymph, and tissues are of critical importance for immune responses. The immune system faces numerous challenges to generate effective protective responses against infectious pathogens. First, the system must be able to respond rapidly to small numbers of many different microbes that may be introduced at any site in the body. Second, in the adaptive immune response, there are very few naive lymphocytes that can specifically recognize and respond to any one antigen. Third, the effector mechanisms of the adaptive immune system (antibodies and effector T cells) may have to locate and destroy microbes at sites that are distant from the site where the immune response was induced. The capacity of the immune system to meet these challenges and to optimally perform its protective functions is dependent on the remarkably rapid and varied responses of immune cells, the way these cells are organized in lymphoid tissues, and their ability to migrate from one tissue to another.

This chapter describes the cells and tissues that make up the immune system. In Chapter 3, we describe the traffic patterns of lymphocytes throughout the body and the mechanisms of migration of lymphocytes and other leukocytes.

CELLS OF THE IMMUNE SYSTEM

The cells that serve specialized roles in innate and adaptive immune responses include phagocytes, dendritic cells (DCs), antigen-specific lymphocytes, and various other leukocytes that function to eliminate antigens. These cells were introduced briefly in Chapter 1. Most of them are derived from hematopoietic stem cells (HSCs) in the bone marrow, which differentiate along branching lineages. Based on their common precursors, immune cells are broadly classified as either **myeloid cells**, which include phagocytes and DCs, or **lymphoid cells**, which include all lymphocytes. The counts of some of these cell types in the blood are listed in Table 2.1. These cells are found in the blood and in tissues. The responses of lymphocytes to antigens usually occur in secondary lymphoid organs and therefore may not be reflected by changes in the numbers of blood lymphocytes. In addition to lymphoid and myeloid cells, various cell types not derived from the bone marrow play crucial roles in immune responses. These include barrier epithelial cells, such as skin keratinocytes and intestinal epithelial cells, endothelial

TABLE 2.1 Normal Blood Cell Counts

	Mean Number (per μL)	Normal Range
White blood cells (leukocytes)	7400	4500–11,000/μL
Neutrophils	4400	40%–60%
Eosinophils	200	1%–4%
Basophils	40	<1%
Lymphocytes	2500	20%–40%
Monocytes	300	2%–8%

cells lining blood vessels throughout the body, and stromal cells in lymphoid tissues, such as fibroblast reticular cells.

The expression of various membrane proteins is used to distinguish distinct populations of cells in the immune system. For instance, most helper T cells express a surface protein called CD4, and most cytotoxic T lymphocytes (CTLs) express a different surface protein called CD8. These and many other surface proteins are often called markers because they are used to identify and distinguish (mark) different cell populations. The most common way to determine if a particular marker is expressed on a cell is to test if antibodies specific for the marker bind to the cell. In this context, the antibodies are used by investigators or clinicians as analytical tools. Thousands of different pure antibody preparations, called monoclonal antibodies, are available, each specific for a different molecule and labeled with chemicals that can be readily detected on cell surfaces by the use of appropriate instruments. (Monoclonal antibodies are described in Chapter 5, and methods to detect labeled antibodies bound to cells are discussed in Appendix III.) The cluster of differentiation (CD) nomenclature is a widely adopted uniform method for naming cell surface molecules that may be characteristic of a particular cell lineage or differentiation stage and recognized by a group (cluster) of monoclonal antibodies. Thus, all antigenically distinguishable cell surface proteins and some carbohydrates are given a CD number designation (e.g., CD1, CD2). Although originally devised to define circulating immune cell (leukocyte) subtypes, CD markers are found on all cell types in the body. Surface molecules (now identified by CD numbers) are not only markers of different cell types but also have important roles in immune responses and are the targets of many therapeutic antibodies used in the treatment of inflammatory diseases and cancer. Appendix I provides a current list of leukocyte CD markers that are mentioned in this book.

Phagocytes

Phagocytes, including neutrophils and macrophages, are cells whose primary function is to ingest and destroy microbes and remove damaged tissues. The functional responses of phagocytes in host defense consist of sequential steps: recruitment of the cells to the sites of infection, recognition of and activation by microbes, ingestion of the microbes by the process of phagocytosis, and destruction of ingested microbes. In addition, through direct contact and by secreting cytokines, phagocytes communicate with other cells in ways that promote or regulate immune responses.

Neutrophils and monocytes are produced in the bone marrow, circulate in the blood, and are recruited to sites of inflammation. Monocytes differentiate into macrophages after entering tissues. Although both are actively phagocytic, neutrophils and macrophages differ in significant ways (Table 2.2). The neutrophil response is more rapid and the life span of these cells after they enter tissues is short, whereas macrophages can live for long periods so that the macrophage response may last for a prolonged time. Neutrophils mainly use cytoskeletal rearrangements and enzyme activation to mount rapid, transient responses, whereas macrophage responses rely more on induced gene transcription and protein expression. In addition, as we discuss later, there are populations of macrophages that normally reside in healthy tissues, but neutrophils do not. The functions of phagocytes are important in innate immunity (see Chapter 4) and also in the effector phase of some adaptive immune responses (see Chapters 10 and 13). As a prelude to more detailed discussions of the role of phagocytes in immune responses in later chapters, here we will describe the development and morphologic features of neutrophils and macrophages and briefly introduce their functional responses.

Neutrophils

Neutrophils are the most abundant population of circulating white blood cells and the principal cell type in acute inflammatory reactions. Neutrophils circulate as spherical cells approximately 12 to 15 μm in diameter with numerous membranous projections. The nucleus is segmented into three to five connected lobules (Fig. 2.1A). Because of their nuclear morphology, neutrophils are also called polymorphonuclear leukocytes (PMNs) to contrast them with mononuclear cells (macrophages and lymphocytes), whose nuclei are not multilobed. Neutrophil cytoplasm contains two types of membrane-bound granules. The majority of these, called specific granules, are filled with enzymes, such as lysozyme, collagenase, and elastase. Specific granules do not stain strongly with either basic or acidic dyes (hematoxylin and eosin, respectively), which distinguishes neutrophils from two other types of circulating leukocytes with cytoplasmic granules, called **basophils** and **eosinophils**. The remainder of the granules of neutrophils, called azurophilic granules because they are stained by dye called azure A, contain enzymes (e.g., myeloperoxidase) and microbicidal substances, including defensins and cathelicidins, which we will discuss in Chapter 4. Neutrophils arise from precursors in the bone marrow that also give rise to circulating monocytes. Production of neutrophils is stimulated by granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF). An adult human produces more than 1×10^{11} neutrophils per day, each of which circulates in the blood from a few hours to up to 5 days before dying. Neutrophils may migrate to sites of infection rapidly after the entry of microbes. After entering tissues, neutrophils function for only a few days before most of them then die.

TABLE 2.2 Distinguishing Properties of Neutrophils and Macrophages

	Neutrophils	Macrophages
Origin	HSCs in bone marrow	Blood monocytes: derived from HSCs in bone marrow (in inflammatory reactions) Many tissue-resident macrophages: derived from stem cells in a yolk sac or fetal liver (early in development)
Surface markers (human)	CD11b, CD18, CD15, CD66b, CD10	CD11b, CD14, CD68, CD16, CD64, CCR5
Life span in tissues	1–2 days	Inflammatory macrophages: days or weeks Tissue-resident macrophages: years
Responses to activating stimuli	Rapid, short-lived, activation of preformed enzymes	More prolonged, slower, often dependent on new gene transcription
Phagocytosis	Rapid ingestion of microbes	Prolonged ability to ingest microbes, apoptotic cells, tissue debris, foreign material
Reactive oxygen species	Rapidly induced by assembly of phagocyte oxidase (respiratory burst)	Less prominent
Nitric oxide	Low levels or none	Induced after transcriptional activation of iNOS
Degranulation	Major response; induced by cytoskeletal rearrangement	Not prominent
Cytokine production	Low levels per cell	Major functional activity, large amounts per cell, requires transcriptional activation of cytokine genes
NET formation	Rapidly induced by extrusion of nuclear contents	No
Pyroptosis	No	Prominent: caspase-1 activation

HSC, Hematopoietic stem cell; *iNOS*, inducible nitric oxide synthase; *NET*, neutrophil extracellular trap.
This table lists the major differences between neutrophils and macrophages. The reactions summarized above are described in the text. Note that the two cell types share many features, such as phagocytosis, chemotaxis, and ability to migrate through blood vessels into tissues.

The major function of neutrophils is to phagocytose microbes, especially opsonized microbes, and products of necrotic cells and destroy these in phagolysosomes. In addition, neutrophils may secrete granule contents and can extrude their nuclear contents, forming neutrophil extracellular traps (NETs), which serve to immobilize and kill extracellular microbes but also may damage healthy tissues (see Chapter 4).

Mononuclear Phagocytes

The mononuclear phagocyte system includes circulating bone marrow–derived cells called monocytes, many of which become macrophages when they migrate into tissues, and tissue-resident macrophages, which are initially derived from a yolk sac or hematopoietic precursors during fetal life.

Development of Monocytes and Macrophages. After birth, cells of the monocyte-macrophage lineage arise from committed precursor cells in the bone marrow, driven by a cytokine called a monocyte (or macrophage) colony-stimulating factor (M-CSF). These precursors mature into monocytes, which enter and circulate in the blood (Fig. 2.2A), where they have a short life span of approximately 1 to 7 days. Blood monocytes are efficiently recruited into tissue sites of infection or injury, where they differentiate (mature) into macrophages and therefore most macrophages at sites of inflammation are derived from monocytes.

Most tissue-resident macrophages are long-lived and are derived not from the bone marrow but from yolk sac or fetal liver precursors during fetal development. These cells have self-renewal capacity, so they can maintain stable numbers. Some examples of tissue-resident macrophages are Kupffer cells lining the sinusoids in the liver, alveolar macrophages in the lung, and microglial cells in the brain (Fig. 2.2B). In the steady state, blood monocytes are recruited at a low rate into healthy tissues, where they may differentiate into tissue-resident macrophages. This pathway of monocyte differentiation into tissue macrophages supplements the self-renewal of the fetally derived cells, and accounts for varying fractions of resident macrophages in different tissues.

Subsets of Monocytes. Monocytes are 10 to 15 μm in diameter, and they have bean-shaped nuclei and a finely granular cytoplasm containing lysosomes, phagocytic vacuoles, and

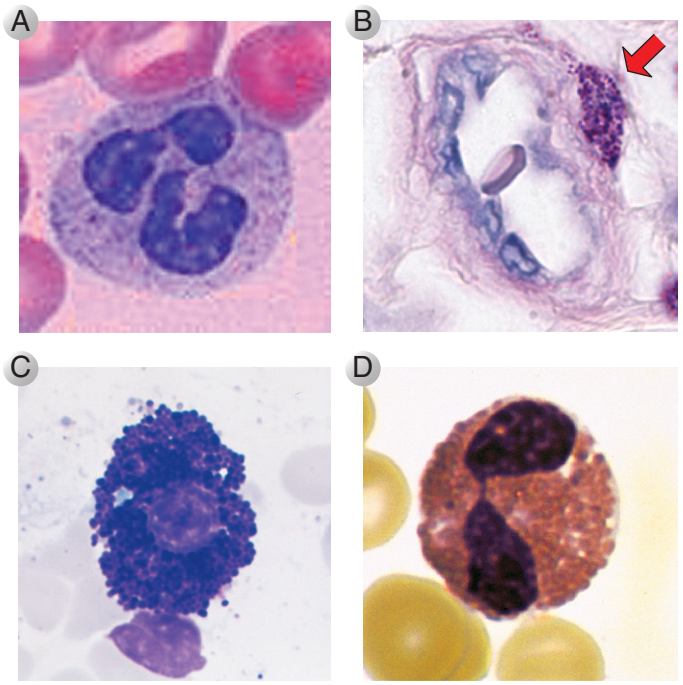

Fig. 2.1 Morphology of neutrophils, mast cells, basophils, and eosinophils. (A) The light micrograph of a Wright-Giemsa–stained blood neutrophil shows the multilobed nucleus, because of which these cells are also called polymorphonuclear leukocytes, and the faint cytoplasmic granules. (B) The light micrograph of a Wright-Giemsa–stained section of skin shows a mast cell *(arrow)* adjacent to a small blood vessel, identifiable by the red blood cell in the lumen. The cytoplasmic granules in the mast cell, which are stained purple, are filled with histamine and other mediators that act on adjacent blood vessels to promote increased blood flow and delivery of plasma proteins and leukocytes into the tissue. (C) The light micrograph of a Wright-Giemsa–stained blood basophil shows the characteristic blue-staining cytoplasmic granules. (D) The light micrograph of a Wright-Giemsa–stained blood eosinophil shows the characteristic segmented nucleus and red staining of the cytoplasmic granules. B, Courtesy Dr. George Murphy, Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts. C, Courtesy Dr. Jonathan Hecht, Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts.

cytoskeletal filaments (Fig. 2.3). All human monocytes express major histocompatibility complex (MHC) class II molecules, CD11b, and CD86, and all mouse monocytes express CD115, CD11b, and CD64. However, monocytes are heterogeneous and consist of different subsets distinguishable by cell surface markers and functions, but not by morphology. In both humans and mice, the most numerous monocytes, called classical or inflammatory monocytes (comprising 90%–95% of blood monocytes in humans), produce inflammatory mediators, are phagocytic, and are rapidly recruited to sites of infection or tissue injury. A second type of circulating monocyte, called nonclassical monocytes (5%–10% of blood monocytes), are recruited into tissues after infection or injury and engage in phagocytosis of microbes and may contribute to repair of damaged tissues. Some nonclassical monocytes are known to crawl along endothelial surfaces (described as patrolling), where they scavenge luminal microparticles and may play a role in eliminating circulating microbes and in repairing endothelial barrier defects.

Functions of Macrophages. Macrophages play crucial roles in innate and adaptive immune responses to infections and in the repair of damaged tissues (Fig. 2.4).

- A major function of monocyte-derived macrophages in host defense is to ingest microbes by the process of phagocytosis and then to kill the ingested microbes. The mechanisms of phagocytosis and killing, which we will discuss in Chapter 4, include the formation of cytoplasmic membrane-bound organelles that contain the microbes, the fusion of these organelles with lysosomes, the enzymatic generation of reactive oxygen and nitrogen species in the lysosome that are toxic to microbes, and the digestion of microbial proteins by proteolytic enzymes.
- Tissue-resident macrophages function as sentinel cells that sense the presence of microbes and respond by secreting cytokines that initiate and then amplify the protective response against the microbes. Some of these cytokines act on endothelial cells lining blood vessels to enhance the recruitment of monocytes and other leukocytes from the blood into sites of infections. Other cytokines made by activated macrophages act on leukocytes and stimulate their migration to tissue sites of infection or damage. Some important macrophage-derived cytokines are discussed in Chapter 4.
- Macrophages that have engulfed microbes can be induced by microbial molecules to undergo an inflammatory form of death called pyroptosis, which usually results from the activation of a cytoplasmic enzyme complex called the inflammasome, discussed in Chapter 4. Pyroptosis leads to the release of cytokines that enhance the host's inflammatory response to the infection.
- In addition to ingesting microbes, macrophages ingest necrotic host cells, including cells that die in tissues because of the effects of toxins, trauma, or interrupted blood supply, and neutrophils that die after accumulating at sites of infection. This is part of the cleaning-up process after infection or sterile tissue injury. Macrophages also can specifically recognize and engulf cells that die by apoptosis before the dead cells can release their contents and induce inflammatory responses. This clearance of apoptotic cells by macrophages is called efferocytosis. Throughout the body and throughout the life of an individual, unwanted cells die by apoptosis as part of many physiologic processes, such as development and renewal of healthy tissues and maintenance of cell numbers (tissue homeostasis), and the dead cells are eliminated by macrophages.
- Macrophages serve as antigen-presenting cells (APCs) that display fragments of protein antigens to T lymphocytes and activate T cells recruited to sites of injury or infection. This function is important in the effector phase of T cell–mediated immune responses (see Chapters 6 and 10).
- Subcapsular sinus macrophages and marginal zone macrophages in lymphoid tissues can bind antigens and then hand them over to B cells and follicular dendritic cells. This is important for intitiation of humoral immune responses (see Chapter 12).
- Macrophages promote the repair of damaged tissues by stimulating new blood vessel growth (angiogenesis) and the synthesis of collagen-rich extracellular matrix (fibrosis). These

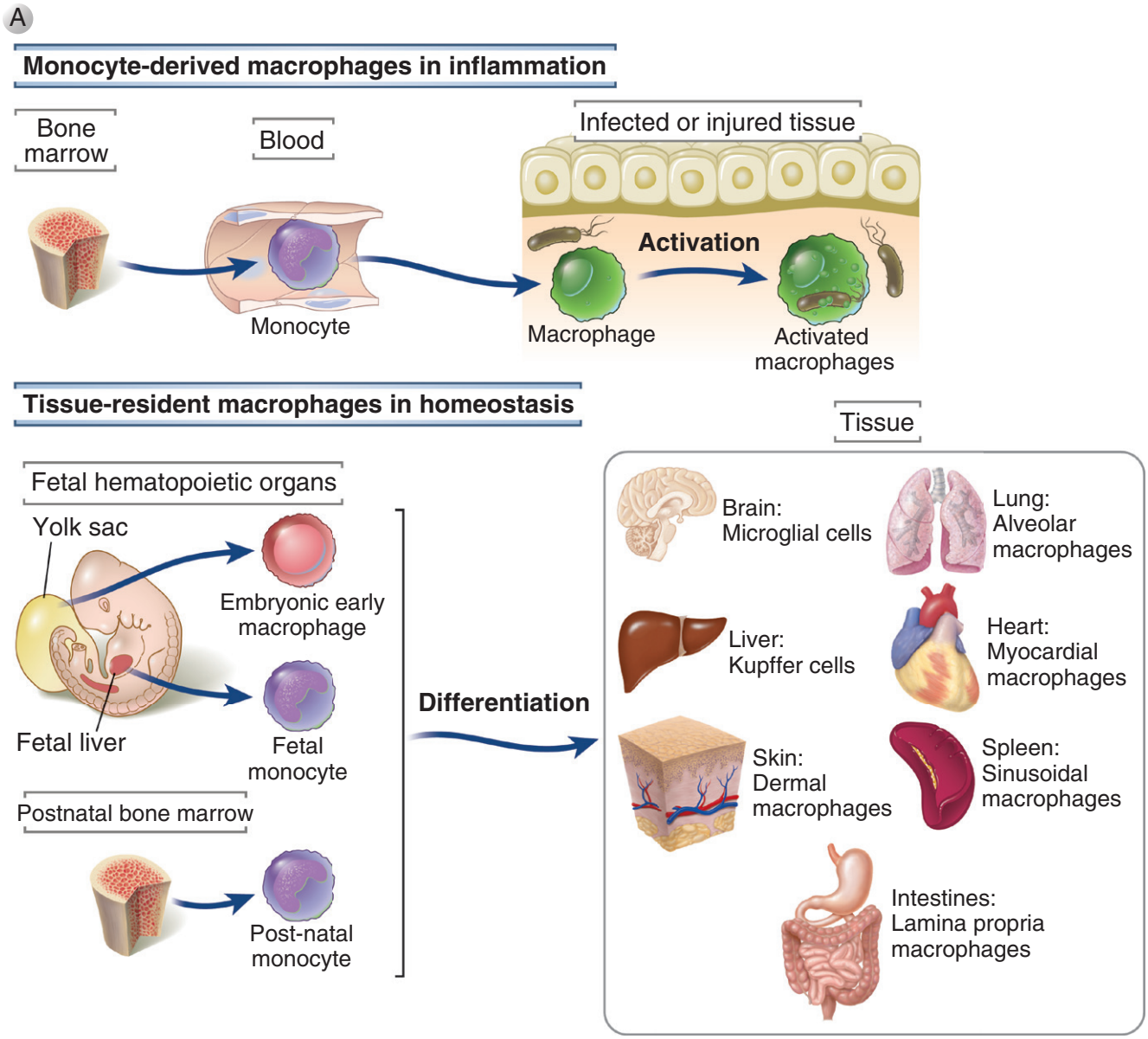

Fig. 2.2 Maturation of mononuclear phagocytes. (A) Pathways of macrophage development. During inflammatory reactions, precursors in the bone marrow give rise to circulating monocytes, which enter peripheral tissues and mature to form short-lived macrophages, which are activated locally. Many tissue-resident macrophages develop in fetal life from primitive hematopoietic precursors in the yolk sac and hematopoietic precursors in the fetal liver and bone marrow. Blood monocytes may contribute to the tissue-resident pool of macrophages in postnatal life to varying degrees between different tissues.

functions are mediated by cytokines secreted by the macrophages that act on various tissue cells.

- Tissue-resident macrophages also perform specialized organ-specific functions. For example, Kupffer cells in the liver support systemic metabolism, alveolar macrophages in the lung regulate surfactant levels by phagocytosis and catabolism, gut lamina propria macrophages support intestinal stem cell differentiation, and microglia in the brain are involved in synaptic pruning.

Monocyte-derived macrophages may respond to microbes nearly as rapidly as neutrophils do, but macrophages survive much longer at sites of inflammation. Unlike neutrophils, macrophages can undergo cell division at an inflammatory site. Therefore, macrophages are the dominant effector cells in the later stages of innate immune responses, several days after an infection begins.

Macrophage Receptors and Activation. ***Macrophages are activated to perform their functions by recognizing many different kinds of microbial molecules, as well as host molecules produced in response to infections and injury***. These various activating molecules bind to specific signaling receptors located on the surface of the macrophage (see Fig. 2.4). An example are Toll-like receptors (TLRs), which serve important roles in innate immunity; they will be discussed in detail in Chapter 4.

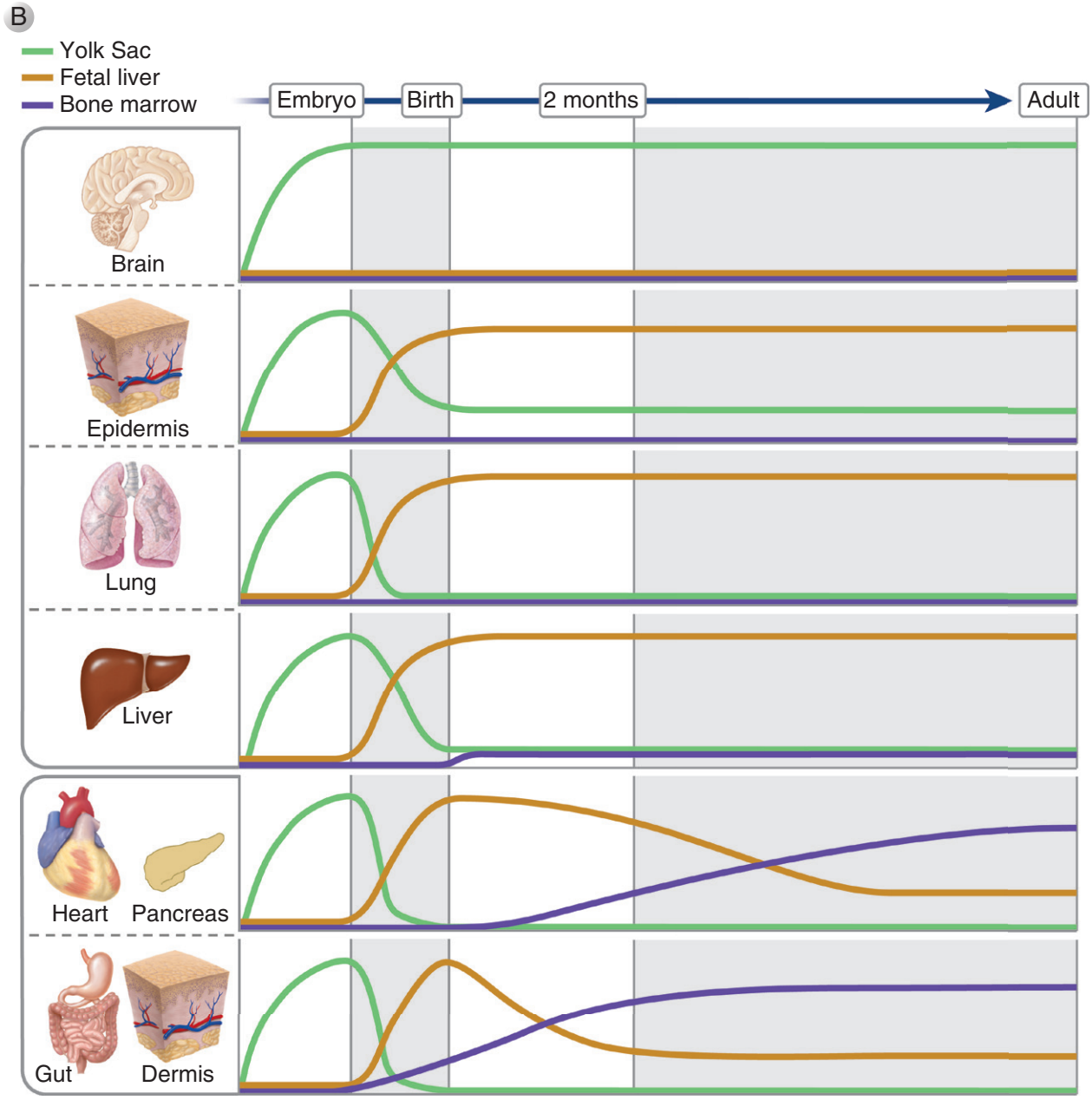

Fig. 2.2, cont'd (B) The relative contributions of precursors from the yolk sac, fetal liver, and postnatal bone marrow to macrophages resident in different tissues in the steady state, as determined by cell fate mapping studies in mice. B, Courtesy Florent Ginhoux and Svetoslav Chakarov. Modified from Ginhoux F, Guillams M. Tissue-resident macrophage ontogeny and homeostasis. *Immunity.* 2016;44:439–449.

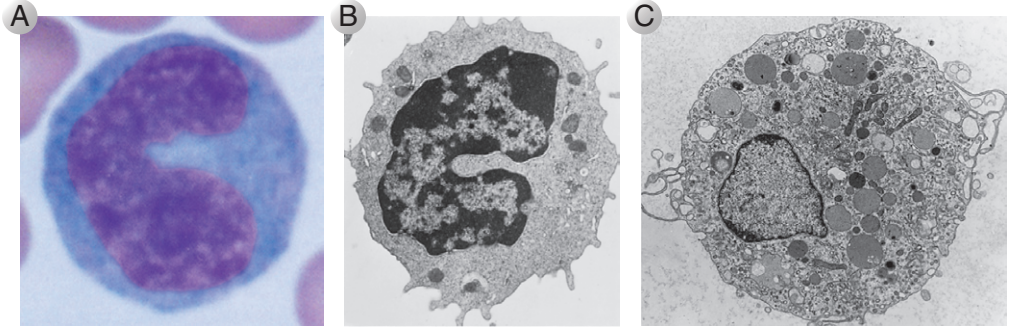

Fig. 2.3 Morphology of mononuclear phagocytes. (A) Light micrograph of a monocyte in a peripheral blood smear. (B) Electron micrograph of a peripheral blood monocyte. (C) Electron micrograph of an activated tissue macrophage showing numerous phagocytic vacuoles and cytoplasmic organelles. Courtesy Dr. Noel Weidner, Department of Pathology, University of California, San Diego.

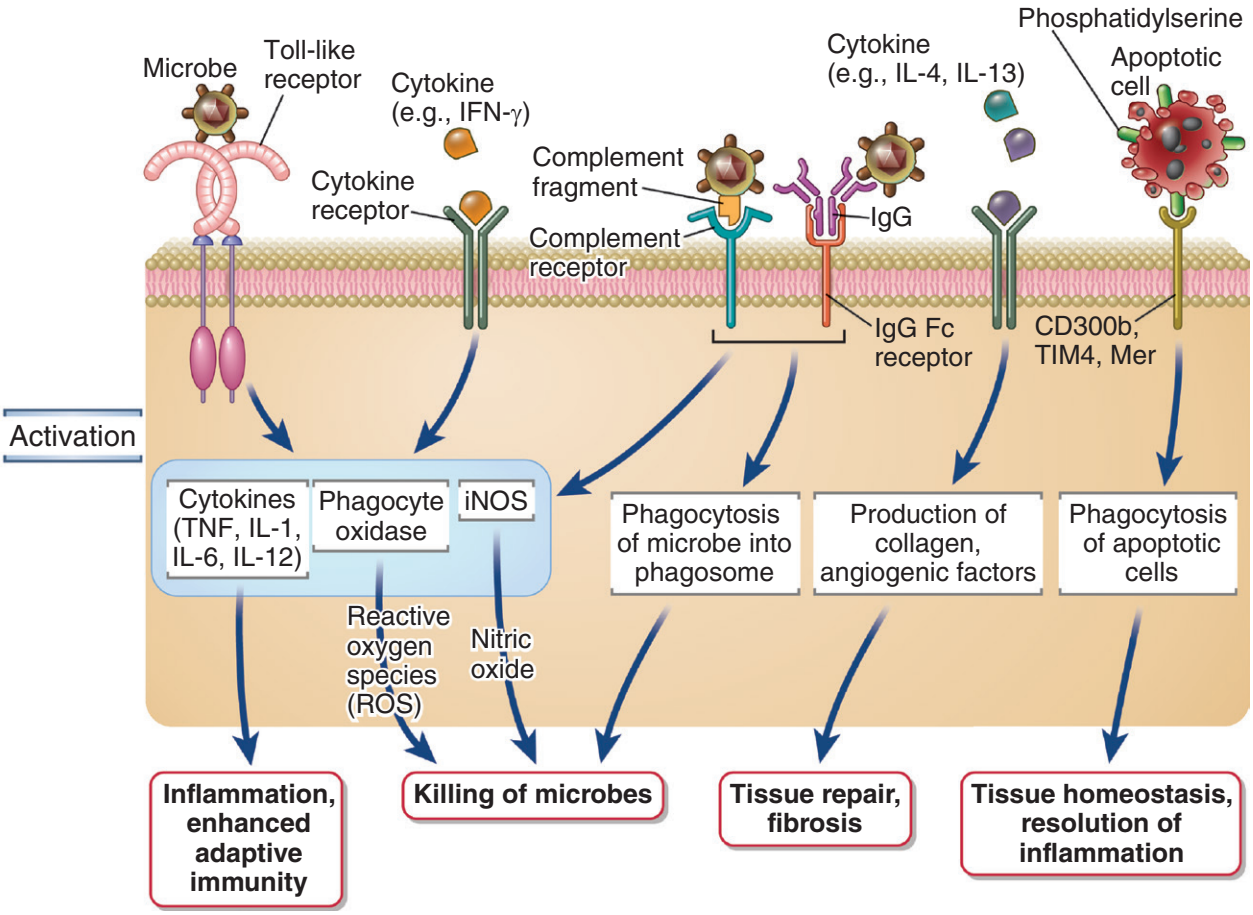

Fig. 2.4 Functions of macrophages. Macrophages are activated by microbial products such as lipopolysaccharides and by natural killer cell–derived interferon-γ (*IFN-γ*). The process of macrophage activation leads to the activation of transcription factors, the transcription of various genes, and the synthesis of proteins that mediate the functions of these cells. In adaptive cell-mediated immunity, macrophages are activated by stimuli from T lymphocytes (CD40 ligand and IFN-γ) and respond in essentially the same way (see Fig. 10.7). Macrophages also may be activated by other signals to promote tissue repair and fibrosis (not shown). *IgG*, Immunoglobulin G; *IL*, interleukin; *iNOS*, inducible nitric oxide synthase; *TIM4*, T-cell immunoglobulin 4.

Macrophages are also activated when other plasma membrane receptors bind opsonins on the surface of microbes. Opsonins are substances that coat microbial cells or other particles and thereby target them for phagocytosis. Examples of opsonin receptors are complement receptors, which bind fragments of complement proteins attached to microbial surfaces, and immunoglobulin G (IgG) Fc receptors, which bind to one end of IgG antibody molecules that already have microbes bound at the other end, as discussed in Chapter 13. Macrophage phagocytosis of healthy host cells is prevented in part by an inhibitory receptor on the macrophage called SIRPα, which recognizes CD47, a membrane protein on healthy cells that functions as a "don't eat me" signal. When CD47 binds to SIRPα, inhibitory signals are generated in the macrophage that prevent phagocytosis. In adaptive immunity, macrophage antimicrobial functions are activated by some T-lymphocyte cytokines and membrane proteins that bind to signaling receptors on the macrophage membrane (see Chapter 10).

Subsets of Macrophages. ***Macrophages can acquire distinct functional capabilities in response to different types of activating stimuli.*** The clearest example of this is the activation of macrophages by different cytokines made by subsets of T cells. Some of these cytokines activate macrophages to become efficient at killing microbes, called **classical activation**, and these cells are often called M1 macrophages. Other cytokines activate macrophages to promote tissue remodeling and repair, called **alternative activation**, and these cells are called M2 macrophages. These different pathways of activation and the cytokines involved are discussed in Chapter 10. Analyses of phenotypes and transcriptional profiles indicate that multiple macrophage subsets exist that do not neatly fall into M1 or M2 categories. The relationship between blood monocyte subsets, discussed earlier, and M1-like and M2-like macrophage subsets is not well understood. Macrophages may also assume different morphologic forms after activation by external stimuli, such as microbes. Some develop abundant cytoplasm and are called epithelioid cells because of their resemblance to epithelial cells of the skin. Activated macrophages can fuse to form multinucleated giant cells, which occurs frequently in certain types of microbial infections, such as with mycobacteria, and in response to indigestible foreign bodies.

Mast Cells, Basophils, and Eosinophils

Mast cells, basophils, and eosinophils are three additional types of myeloid cells that play roles in innate and adaptive immune responses. All three share the common property of having cytoplasmic granules filled with various inflammatory and antimicrobial mediators, which are released from the cells on activation. Another common feature of these cells is their involvement in immune responses that protect against helminths and reactions that cause allergic diseases. We will introduce the features of these cells in this section and discuss their functions in more detail in Chapter 20.

Mast Cells

Mast cells are bone marrow–derived cells that are most abundant in the skin and mucosal epithelia; on activation, they release many potent inflammatory mediators that defend against infections by helminthic parasites or cause symptoms of allergic diseases. A cytokine called stem cell factor (or c-KIT ligand) is essential for mast cell development. Normally, mature mast cells are not found in the circulation but are present in tissues, usually adjacent to small blood vessels and nerves (Fig. 2.1B). Their cytoplasm contains numerous membrane-bound granules, which are filled with preformed inflammatory mediators, such as histamine, and acidic proteoglycans that serve to store some mediators and bind basic dyes, imparting a dark blue color to the granules when special stains are used. Various stimuli can activate mast cells to release their cytoplasmic granule contents into the extracellular space, as well as to synthesize and release cytokines and inflammatory lipid mediators. The released histamine and other mediators promote changes in the blood vessels that cause inflammation. Mast cells express high-affinity plasma membrane receptors for a type of antibody called IgE and are usually coated with these antibodies. When the IgE antibodies on the mast cell surface bind to antigen, signaling events are induced that lead to the activation of the cell. Mast cells are also activated when they recognize microbial products, independent of IgE, and in this way they function as tissue sentinels of the innate immune system.

Basophils

Basophils are blood granulocytes with many structural and functional similarities to mast cells. Like other granulocytes, basophils are derived from hematopoietic precursors, mature in the bone marrow (from progenitors distinct from those of mast cells), and circulate in the blood. Basophils constitute less than 1% of blood leukocytes (see Table 2.1). Although they are normally not present in tissues, basophils may be recruited to some inflammatory sites. These cells also contain granules that bind basic dyes (Fig. 2.1C), and they are capable of synthesizing many of the same mediators as mast cells. Like mast cells, basophils express IgE receptors, bind IgE, and can be triggered by antigen binding to IgE. Because basophil numbers are low in tissues, their importance in host defense and allergic reactions is uncertain.

Eosinophils

Eosinophils are granulocytes that express cytoplasmic granules containing enzymes that are harmful to the cell walls of helminthic parasites but can also damage host tissues. Eosinophil granules contain mainly basic proteins that bind acidic dyes, such as eosin, and thus appear red in stained blood smears and tissue sections (Fig. 2.1D). Eosinophils are bone marrow–derived and circulate in the blood, from where they may be recruited into tissues. The cytokines GM-CSF, interleukin-3 (IL-3), and IL-5 promote eosinophil maturation from myeloid precursors. Various membrane receptors on eosinophils, including Fc receptors for IgA and IgG, TLRs, and IL-5 receptors, can generate signals that activate the cells to release their granule contents. Some eosinophils are normally present in peripheral tissues, especially in mucosal linings of the respiratory, gastrointestinal, and genitourinary tracts, and their numbers can increase by recruitment from the blood in the setting of inflammation.

Dendritic Cells

Dendritic cells (DCs) are tissue-resident and circulating cells that detect the presence of microbes and initiate innate immune defense reactions, and they capture microbial proteins for display to T cells to initiate adaptive immune responses. These cells are named because of their long membranous projections, reminiscent of the dendrites of neurons. Most DCs, other than plasmacytoid DCs, are widely distributed in lymphoid tissues, mucosal epithelium, and organ parenchyma (Fig. 2.5). The location of DCs in epithelia and tissues where microbes enter, their ability to capture antigens and take them to lymph nodes where naive T cells circulate, and their rapid responses to microbes all impart to these cells a unique set of roles in the immune system, serving as sentinels of infection that begin the rapid innate response but also link innate responses with the development of adaptive immune responses. We will discuss the role of DCs as mediators of innate immunity and as APCs in Chapters 4 and 6, respectively. Here we will introduce the general properties of DCs.

Development and Features of Dendritic Cell Subsets. Subsets of DCs can be defined on the basis of different cell surface markers, transcription factors, development from different precursor cells, tissue localization, and functions. We will describe the major subsets that are important in immune responses and are distinguished from one another by their functions and development, and by the expression of different surface molecules and transcription factors (Fig. 2.6 and Table 2.3). The common properties of these DC subsets include dependence on the cytokine FLT3L for their development, expression of the CD11c protein, and the ability to present antigens to and activate naive T cells or induce T-cell tolerance.

- **Conventional DCs** (cDCs, also called classical DCs) are the major type of DC involved in capturing protein antigens of microbes that enter through epithelial barriers and presenting the antigens to T cells. Conventional DCs were first identified by their morphology and ability to stimulate strong T-cell responses and are the most numerous DC subset in epithelia and lymphoid organs. They arise from

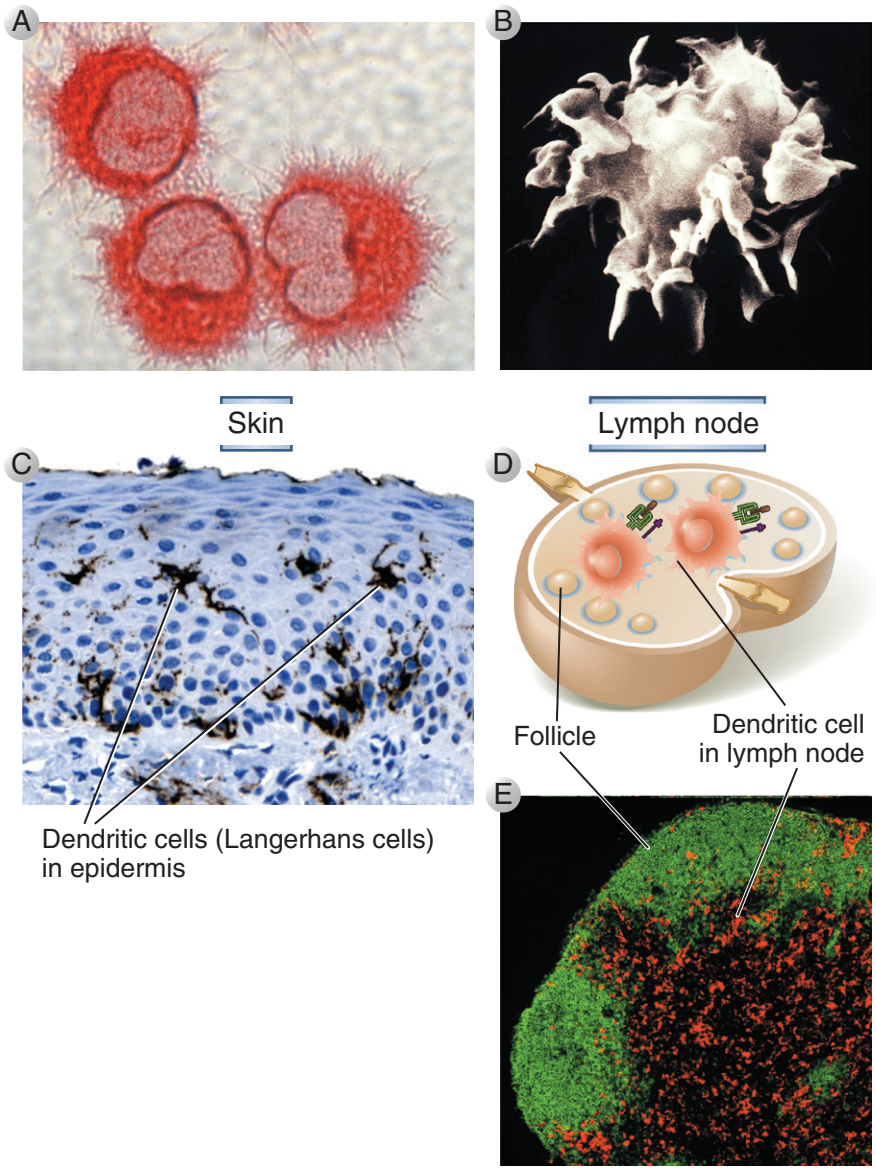

Fig. 2.5 Dendritic cells. (A) Light micrograph of cultured dendritic cells (DCs) derived from bone marrow precursors. (B) A scanning electron micrograph of a DC showing extensive membrane projections. (C) A section of the skin stained with antibodies specific for Langerhans cells, a special type of skin DC found in the epithelial layer (which appear *dark brown* in this immunoenzyme stain). (D and E) DCs in a lymph node, illustrated schematically (D) and in a section of a mouse lymph node (E) stained with fluorescently labeled antibodies against B cells in follicles (*green*) and DCs in the T-cell zone (*red*). A and B, Courtesy of Dr. Y-J Liu, MD, Anderson Cancer Center, Houston, Texas. C, Courtesy of Dr. Jarish Cohen, University of California San Francisco School of Medicine, San Francisco, CA. E, Courtesy of Drs. Kathryn Pape and Jennifer Walter, University of Minnesota School of Medicine, Minneapolis, Minnesota.

bone marrow HSCs through a developmental pathway that includes a common precursor of both monocytes and conventional DCs, some of which develop into committed precursors for cDCs (called pre-cDCs). All these steps take place in the bone marrow. The pre-cDCs migrate to peripheral tissues, where they mature into cDCs. Similar to tissue macrophages, these DCs constantly sample the environment in which they reside.

- Conventional DCs may be further divided into two main subsets called major, or cDC2, and cross-presenting, or cDC1 (see Fig. 2.6 and Table 2.3). cDC2 cells are the most numerous DCs and are potent at capturing exogenous antigens and inducing $CD4^+$ T-cell responses. The cDC1 subset is specialized to present antigens to naive $CD8^+$ T cells by a process called cross-presentation, discussed in Chapter 6; this subset can also present antigens to $CD4^+$ cells.
- **Plasmacytoid dendritic cells** (pDCs) produce the antiviral cytokines type I interferons (IFNs) in response to viruses and may capture blood-borne microbes and carry their antigens to the spleen for presentation to T cells. These DCs are called plasmacytoid because after activation, they begin to resemble plasma cells morphologically. They develop in the bone marrow from a precursor distinct from that for conventional DCs and are found in the blood and in small numbers

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