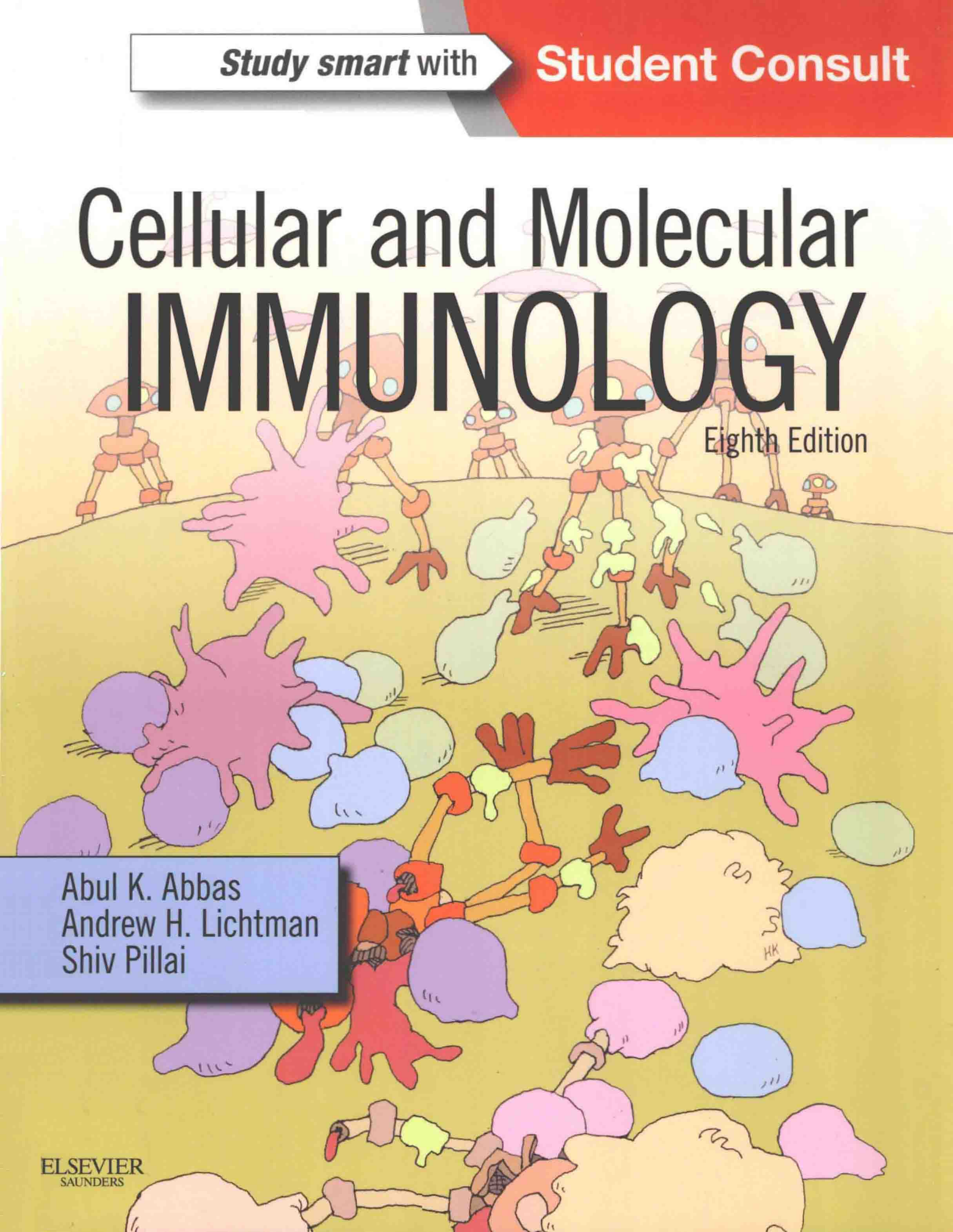
Study smart with Student Consult

Cellular and Molecular IMMUNOLOGY

Eighth Edition



Abul K. Abbas
Andrew H. Lichtman
Shiv Pillai

ELSEVIER
SAUNDERS

Cellular and Molecular Immunology

EIGHTH EDITION

Abul K. Abbas, MBBS
Distinguished Professor in Pathology
Chair, Department of Pathology
University of California San Francisco
San Francisco, California

Andrew H. Lichtman, MD, PhD
Professor of Pathology
Harvard Medical School
Brigham and Women's Hospital
Boston, Massachusetts

Shiv Pillai, MBBS, PhD
Professor of Medicine and Health Sciences and Technology
Harvard Medical School
Massachusetts General Hospital
Boston, Massachusetts

Illustrations by
David L. Baker, MA
Alexandra Baker, MS, CMI
DNA Illustrations, Inc.

ELSEVIER
SAUNDERS

ELSEVIER
SAUNDERS

1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

CELLULAR AND MOLECULAR IMMUNOLOGY
International Edition

ISBN: 978-0-323-22275-4
ISBN: 978-0-323-31614-9

Notices

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

With respect to any drug or pharmaceutical products identified, readers are advised to check the most current information provided (i) on procedures featured or (ii) by the manufacturer of each product to be administered, to verify the recommended dose or formula, the method and duration of administration, and contraindications. It is the responsibility of practitioners, relying on their own experience and knowledge of their patients, to make diagnoses, to determine dosages and the best treatment for each individual patient, and to take all appropriate safety precautions.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

Library of Congress Cataloging-in-Publication Data

Abbas, Abul K., author.
Cellular and molecular immunology / Abul K. Abbas, Andrew H. Lichtman, Shiv Pillai ; illustrations by David L. Baker, Alexandra Baker. -- Eighth edition.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-0-323-22275-4 (pbk. : alk. paper)
I. Lichtman, Andrew H., author. II. Pillai, Shiv., author. III. Title.
[DNLM: 1. Immunity, Cellular. 2. Antibody Formation--immunology. 3. Antigens--immunology. 4. Immune System Diseases--immunology. 5. Lymphocytes--immunology. QW 568]
QR185.5
616.07'97--dc23

2014014817

Senior Content Strategist: James Merritt
Senior Content Development Manager: Rebecca Gruliow
Publishing Services Manager: Jeff Patterson
Project Manager: Clay S. Broeker
Design Direction: Louis Forgione

Printed in Canada

Last digit is the print number: 9 8 7 6 5 4 3 2 1

Dedication

To Our Students, Our Colleagues, and Our Families

PREFACE

This eighth edition of *Cellular and Molecular Immunology* includes substantial additions and revisions, which we made to keep the textbook current with scientific advances and, at the same time, maintain the clear and readable style that has been typical of past editions. Whenever we have added new information, we have focused primarily on important concepts and have not increased the length of the book. We have also rewritten many sections for increased clarity, accuracy, and completeness.

Among the major changes is a reorganization of the chapters dealing with T lymphocyte responses in order to more clearly describe early T cell activation events, differentiation and functions of subsets of $CD4^+$ helper T cells, and functions of $CD8^+$ cytotoxic T cells. In addition, the entire book has been updated to include important recent advances in immunology. Some of the topics that have been significantly revised are innate lymphoid cells, the developmental pathways of macrophages and dendritic cells, and immune checkpoints in tumor immunity. It is remarkable and fascinating to us that new principles continue to emerge from analyses of the complex systems that underlie immune responses. Perhaps one of the most satisfying developments for students of human disease is that basic principles of immunology are now laying the foundation for rational development of new immunologic therapies. Throughout the book, we have tried to emphasize these new therapeutics and the fundamental concepts on which they are based.

We have also continued to improve our illustration program. New figures have been added, and previously used figures have been reviewed and often changed for accuracy and clarity. 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. The lists of suggested 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.

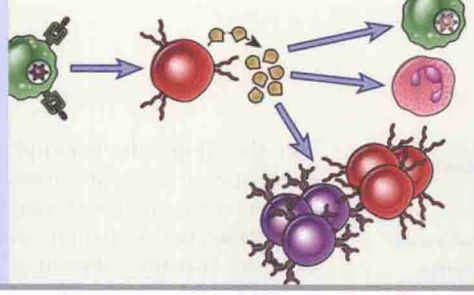
Individuals who have helped us with specific topics are (in alphabetical order) Drs. Jonathan Abbas, Mark Anderson, Homer Boushey, Andrew Gross, Stephen Hauser, Miriam Merad, Michael Rosenblum, Wayne Shreffler, and Catherine Wu; all were generous with advice and comments. We thank Dr. Hiroshi Kawamoto for the cover illustration. Our illustrators, David and Alexandra Baker of DNA Illustrations, remain full partners in the book and provide invaluable suggestions for clarity and accuracy. Several members of the Elsevier staff played critical roles. Our editor, James Merritt, has been a source of support and encouragement. Our managing editor, Rebecca Gruliow, shepherded the book through its preparation and into Production. Lou Forgione was responsible for managing the design, and Clay Broeker was in charge of 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.

Abul K. Abbas

Andrew H. Lichtman

Shiv Pillai

CONTENTS



CHAPTER

1

Properties and Overview of Immune Responses

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. Historically, immunity meant protection from disease and, more specifically, 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 physiologic function of the immune system is defense against infectious microbes. However, even noninfectious foreign substances can elicit immune responses. Furthermore, mechanisms that normally protect individuals from infection and eliminate foreign substances also are capable of causing tissue injury and disease in some situations. Therefore, a more inclusive definition of the immune response is a reaction to components of microbes as well as to macromolecules, such as proteins and polysaccharides, and small chemicals that are recognized as foreign, regardless of the physiologic or pathologic consequence of such a reaction. Under some situations, even self molecules can elicit immune responses (so-called autoimmune responses). Immunology is the study of immune responses in this broader sense and of the cellular and molecular events that occur after an organism encounters microbes and other foreign macromolecules.

Historians often credit Thucydides, in the fifth century BC in Athens, as having first mentioned immunity to an infection that he called plague (but that 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 an experimental science in which explanations of immunologic phenomena are based on experimental observations and the conclusions drawn from them. The evolution of immunology as an experimental discipline has depended on our ability to manipulate the function of the immune system under controlled conditions. Historically, the first clear example of this manipulation, and one that remains among the most dramatic ever recorded, was Edward Jenner's successful vaccination against smallpox. Jenner, an English physician, noticed that milkmaids who had recovered from cowpox never contracted 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. It led to the widespread acceptance of this method for inducing immunity to infectious diseases, and vaccination remains the most effective method for preventing infections (Table 1-1). 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.

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), immunochemistry, recombinant DNA methodology, x-ray crystallography, and creation of genetically altered animals (especially transgenic and knockout mice) have changed immunology from a largely descriptive science into one in which diverse immune phenomena can be explained in structural and biochemical terms. 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.

TABLE 1-1 Effectiveness of Vaccines for Some Common Infectious Diseases

Disease	Maximum Number of Cases (Year)	Number of Cases in 2009	Percentage Change
Diphtheria	206,939 (1921)	0	−99.99
Measles	894,134 (1941)	61	−99.99
Mumps	152,209 (1968)	982	−99.35
Pertussis	265,269 (1934)	13,506	−94.72
Polio (paralytic)	21,269 (1952)	0	−100.0
Rubella	57,686 (1969)	4	−99.99
Tetanus	1,560 (1923)	14	−99.10
Haemophilus influenzae type B	~20,000 (1984)	25	−99.88
Hepatitis B	26,611 (1985)	3,020	−87.66

This table illustrates the striking decrease in the incidence of selected infectious diseases in the United States for which effective vaccines have been developed. 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. New York, 1995, Churchill Livingstone; and *Morbidity and Mortality Weekly Report* 58:1458–1469, 2010.

INNATE AND ADAPTIVE IMMUNITY

Defense against microbes is mediated by the early reactions of innate immunity and the later responses of adaptive immunity (Fig. 1-1 and Table 1-2). **Innate immunity** (also called **natural** or **native immunity**) provides the early line of defense against microbes. It consists of cellular and biochemical defense mechanisms that are in place even before infection and are poised to respond rapidly to infections. These mechanisms react to products of microbes and injured cells, and they respond in essentially the same way to repeated exposures. The mechanisms of innate immunity are specific for structures that are common to groups of related microbes and may not distinguish fine differences between 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, and natural killer (NK) cells and other innate lymphoid cells; and (3) blood proteins, including members of the complement system and other mediators of inflammation.

In contrast to innate immunity, there are other immune responses that are stimulated by exposure to infectious agents and increase in magnitude and defensive capabilities with each successive exposure to a particular microbe. Because this form of immunity develops as a response to infection and adapts to the infection, it is called **adaptive immunity** (also called **specific** or **acquired immunity**). The adaptive immune system recognizes and reacts to a large number of microbial and nonmicrobial substances. The defining characteristics of adaptive immunity are the ability to distinguish different substances, called **specificity**, and the ability to respond more vigorously to repeated exposures to the same microbe, known as **memory**. The unique components of adaptive immunity are cells called **lymphocytes** and their secreted products, such as **antibodies**. Foreign substances that induce specific immune responses or are recognized by lymphocytes or antibodies are called **antigens**.

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. The nomenclature for cytokines is inconsistent, with some named *Interleukin* followed by a number, and others named for a biological activity first attributed to them, such as tumor necrosis factor (TNF) or interferon. Among the many functions of cytokines we will discuss throughout this book are growth and differentiation of all immune cells, activation of effector functions of lymphocytes and phagocytes, and directed movement of immune cells from blood into tissues and within tissues. The large subset of structurally related cytokines that regulate cell migration and movement are called **chemokines**. Some of the most effective drugs developed recently to treat immunologic diseases target cytokines, which reflects the importance of these proteins in immune responses.

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. About 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 variable leucine-rich receptors that are capable of recognizing many antigens but are distinct from the antibodies and T cell receptors that appeared later in evolution. The more specialized defense mechanisms that constitute adaptive immunity are found in vertebrates only. Most of the components of the adaptive immune system, including lymphocytes with highly diverse antigen receptors, antibodies, and specialized lymphoid tissues, evolved coordinately within a short time in jawed vertebrates (e.g., sharks) about 360 million years ago.

Innate and adaptive immune responses are components of an integrated system of host defense in which numerous cells and molecules function cooperatively. The mechanisms of innate immunity provide effective initial defense against infections. However, many pathogenic microbes have evolved to resist innate immunity, and their elimination requires the more powerful mechanisms of adaptive immunity. There are numerous connections between the innate and adaptive immune systems. The innate immune response to microbes stimulates adaptive immune responses and influences the nature of the adaptive responses. Conversely, adaptive immune responses often work by enhancing the protective mechanisms of innate immunity, making them more capable of effectively combating pathogenic microbes.

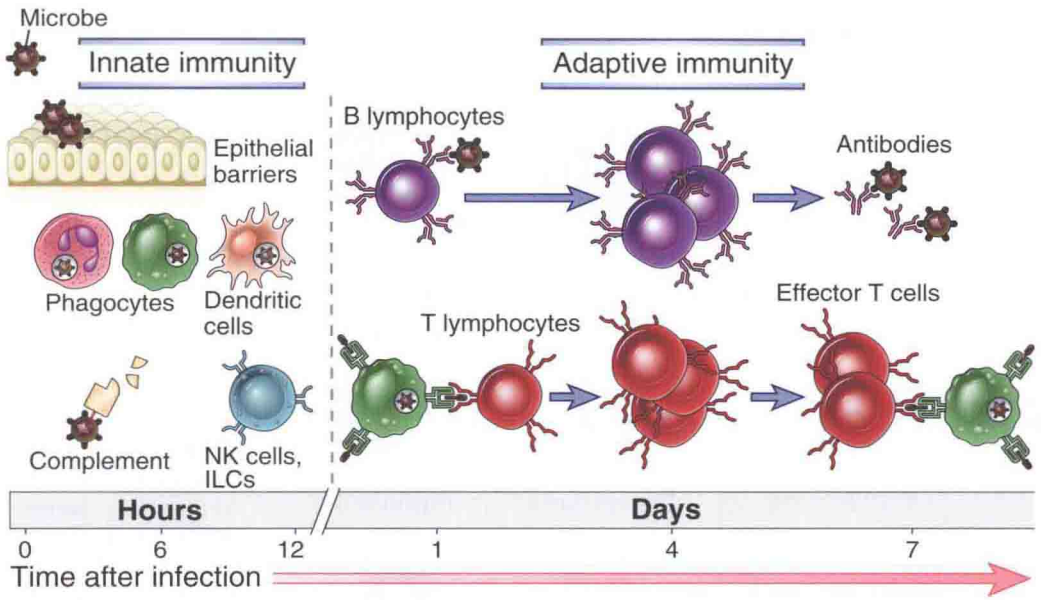


FIGURE 1-1 Innate and adaptive immunity. The mechanisms of innate immunity provide the initial defense against infections. Adaptive immune responses develop later and require the activation of lymphocytes. The kinetics of the innate and adaptive immune responses are approximations and may vary in different infections. *ILC*, innate lymphoid cell; *NK*, natural killer.

TYPES OF ADAPTIVE IMMUNE RESPONSES

There are two types of adaptive immune responses, called humoral immunity and cell-mediated immunity, that are mediated by different components of the immune system and function to eliminate different types of microbes (Fig. 1-2). **Humoral immunity** is mediated by molecules in the blood and mucosal secretions, called **antibodies**, which are produced by cells called **B lymphocytes** (also called **B cells**). Antibodies recognize microbial antigens, neutralize the infectivity of the microbes, and target microbes for elimination by various effector mechanisms. Humoral immunity is the principal defense mechanism against extracellular microbes and their toxins because secreted antibodies can bind to these microbes and toxins and assist in their elimination. Antibodies themselves are specialized and may activate different mechanisms to combat microbes (**effector mechanisms**). For example, different types of antibodies promote the ingestion of microbes by host cells (phagocytosis), bind to and trigger the release of inflammatory mediators from cells, and are actively transported into the lumens of mucosal organs and through the placenta to provide defense against ingested and inhaled microbes and against infections of the newborn, respectively.

Cell-mediated immunity, also called **cellular immunity**, is mediated by **T lymphocytes** (also called **T cells**). Intracellular microbes, such as viruses and some bacteria, survive and proliferate inside phagocytes and other host cells, where they are inaccessible to circulating antibodies. Defense against such infections is a function of cell-mediated immunity, which promotes the destruction of microbes residing in phagocytes or the killing of infected cells to eliminate reservoirs of infection. Some T lymphocytes also contribute to eradication of extracellular microbes by recruiting leukocytes that destroy these pathogens and by helping B cells make effective antibodies.

TABLE 1-2 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 microbial and nonmicrobial antigens
Diversity	Limited; germline encoded	Very large; receptors are produced by somatic recombination of gene segments
Memory	None	Yes
Nonreactivity to self	Yes	Yes
Components		
Cellular and chemical barriers	Skin, mucosal epithelia; antimicrobial molecules	Lymphocytes in epithelia; antibodies secreted at epithelial surfaces
Blood proteins	Complement, others	Antibodies
Cells	Phagocytes (macrophages, neutrophils), natural killer cells, innate lymphoid cells	Lymphocytes

Protective immunity against a microbe is usually induced by the host's response to the microbe (Fig. 1-3). The form of immunity that is induced by exposure to a foreign antigen is called **active immunity** because the immunized individual plays an active role in responding

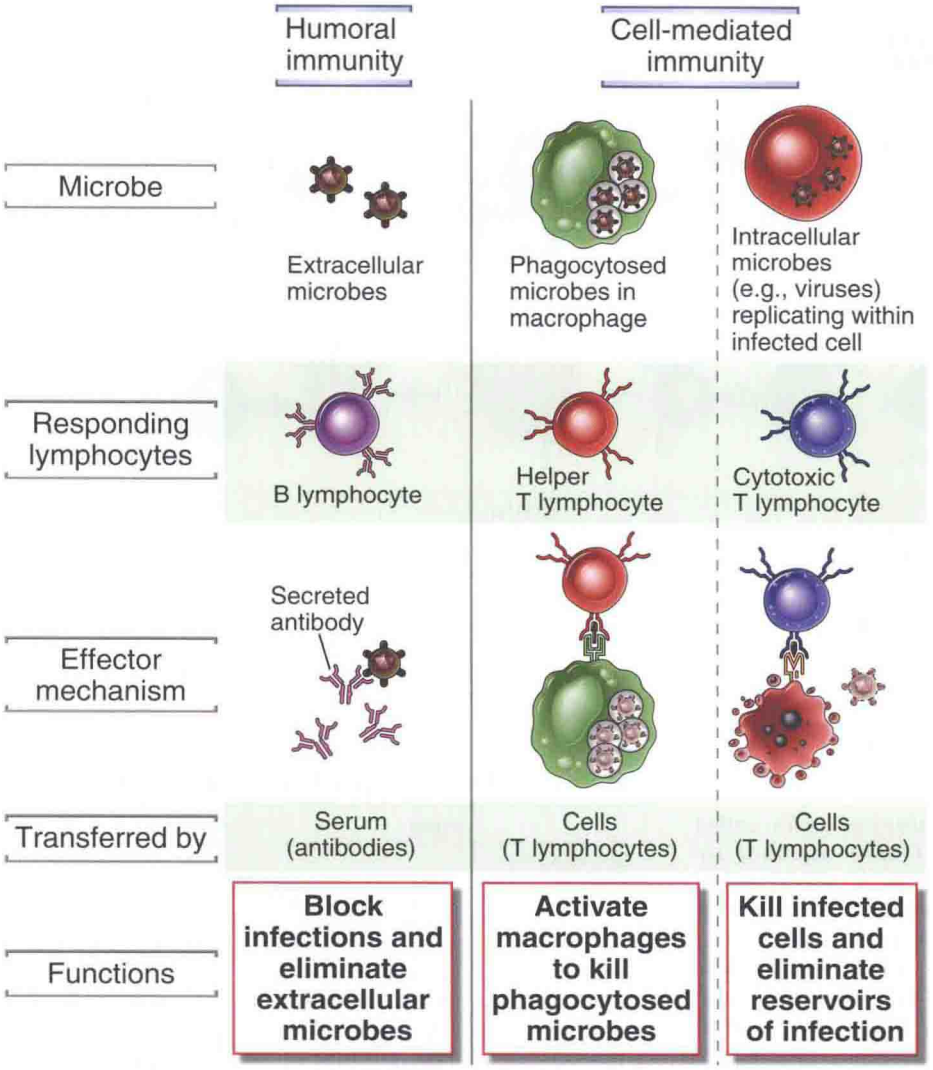


FIGURE 1-2 Types of adaptive immunity. In humoral immunity, B lymphocytes secrete antibodies that prevent infections and eliminate extracellular microbes. In cell-mediated immunity, helper T lymphocytes activate macrophages to kill phagocytosed microbes, or cytotoxic T lymphocytes directly destroy infected cells.

to the antigen. 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 can also be conferred on an individual by transferring serum or lymphocytes from a specifically immunized individual in experimental situations, a process known as adoptive transfer (see Fig. 1-3). The recipient of such a transfer becomes immune to the particular antigen without ever having been exposed to or having responded to that antigen. Therefore, this form of immunity is called **passive immunity**. Passive immunization is a useful method for conferring resistance rapidly, without having to wait for an active immune response to develop. 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 before they develop the ability to produce antibodies themselves. Passive immunization against toxins by the administration of antibodies from immunized animals is a lifesaving treatment for potentially lethal infections, such as rabies, and snake bites. The technique of adoptive transfer has also made it possible to define the various cells and molecules that are responsible for mediating specific immunity. In fact, humoral immunity was originally defined as the type of immunity that could be transferred to unimmunized, or naive, individuals with antibody-containing cell-free portions of the blood (i.e., plasma or serum) obtained from previously immunized individuals. Similarly, cell-mediated immunity was defined as the type of immunity that could be transferred to naive animals with cells (T lymphocytes) from immunized animals, but not with plasma or serum.

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

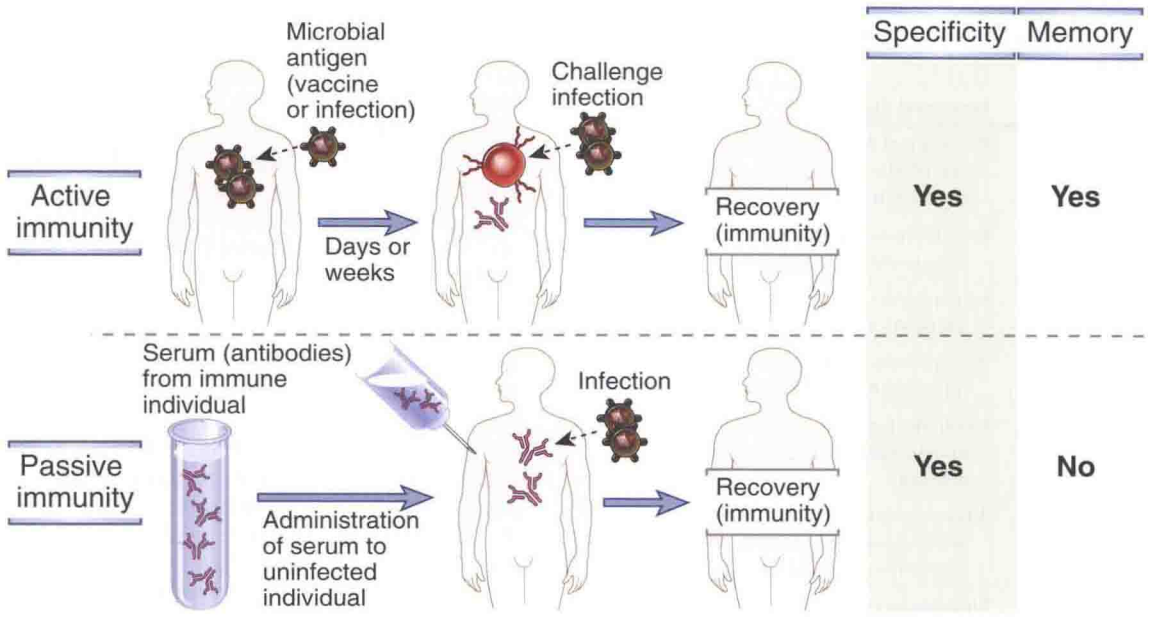


FIGURE 1-3 Active and passive immunity. Active immunity is conferred by a host response to a microbe or microbial antigen, whereas passive immunity is conferred by adoptive transfer of antibodies or T lymphocytes specific for the microbe. Both forms of immunity provide resistance to infection and are specific for microbial antigens, but only active immune responses generate immunologic memory. Therapeutic passive transfer of antibodies, but not lymphocytes, is done routinely and also occurs during pregnancy (from mother to fetus).

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 also coined the term *antibodies* (*antikörper* in German) for the serum proteins that bound toxins, and substances that generated antibodies were called *antigens*. The modern definition of antigens includes substances 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 the term antigen is often used interchangeably with immunogen. The properties of antibodies and antigens are described in Chapter 5. Ehrlich's concepts are a remarkably prescient model for the function of B cells in humoral immunity. This early emphasis on 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).

Elie 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 cellular theory of immunity 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 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; 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.

CARDINAL FEATURES OF ADAPTIVE IMMUNE RESPONSES

All humoral and cell-mediated immune responses to foreign antigens have a number of fundamental properties that reflect the properties of the lymphocytes that mediate these responses (Table 1-3).

- ***Specificity and diversity.*** Immune responses are specific for distinct antigens and, in fact, for different portions of a single complex protein, polysaccharide,

TABLE 1-3 Cardinal Features of Adaptive Immune Responses

Feature	Functional Significance
Specificity	Ensures that the immune response to a microbe (or nonmicrobial antigen) is targeted to that microbe (or antigen)
Diversity	Enables the immune system to respond to a large variety of antigens
Memory	Increases the ability to combat repeat infections by the same microbe
Clonal expansion	Increases the number of antigen-specific lymphocytes to keep pace with microbes
Specialization	Generates responses that are optimal for defense against different types of microbes
Contraction and homeostasis	Allows the immune system to recover from one response so that it can effectively respond to newly encountered antigens
Nonreactivity to self	Prevents injury to the host during responses to foreign antigens

or other macromolecule (Fig. 1-4). The parts of such antigens that are specifically recognized by individual lymphocytes are called **determinants** or **epitopes.** This fine specificity exists because individual lymphocytes express membrane receptors that can distinguish subtle differences in structure between distinct epitopes. Clones of lymphocytes with different specificities are present in unimmunized individuals and are able to recognize and respond to foreign antigens. This concept is the basic tenet of the clonal selection hypothesis, which is discussed in more detail later in this chapter.

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 discriminate 10^7 to 10^9 distinct antigenic determinants. This ability of the lymphocyte repertoire to recognize a very large number of antigens is the result of variability in the structures of the antigen-binding sites of lymphocyte receptors for antigens, called **diversity**. In other words, there are many different clones of lymphocytes that differ in the structures of their antigen receptors and therefore in their specificity for antigens, 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 that these receptors are said to be clonally distributed. The molecular mechanisms that generate such diverse antigen receptors are discussed in Chapter 8.

- ***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, larger, and often qualitatively different from the first, or primary, immune response to that antigen (see Fig. 1-4). Immunologic memory occurs because each exposure to an antigen generates long-lived memory cells specific for the antigen, which are more numerous than the naive lymphocytes specific for the antigen that exist before antigen exposure. In addition, memory cells have special characteristics that make them more efficient at responding to and eliminating the antigen than are naive lymphocytes that have not previously been exposed to the antigen. For instance, memory B lymphocytes produce antibodies that bind antigens with higher affinities than do antibodies produced in primary immune responses, and memory T cells react much more rapidly and vigorously to antigen challenge than do naive T cells.
- ***Clonal expansion.*** Lymphocytes specific for an antigen undergo considerable proliferation after exposure to that antigen. The term *clonal expansion* refers to an

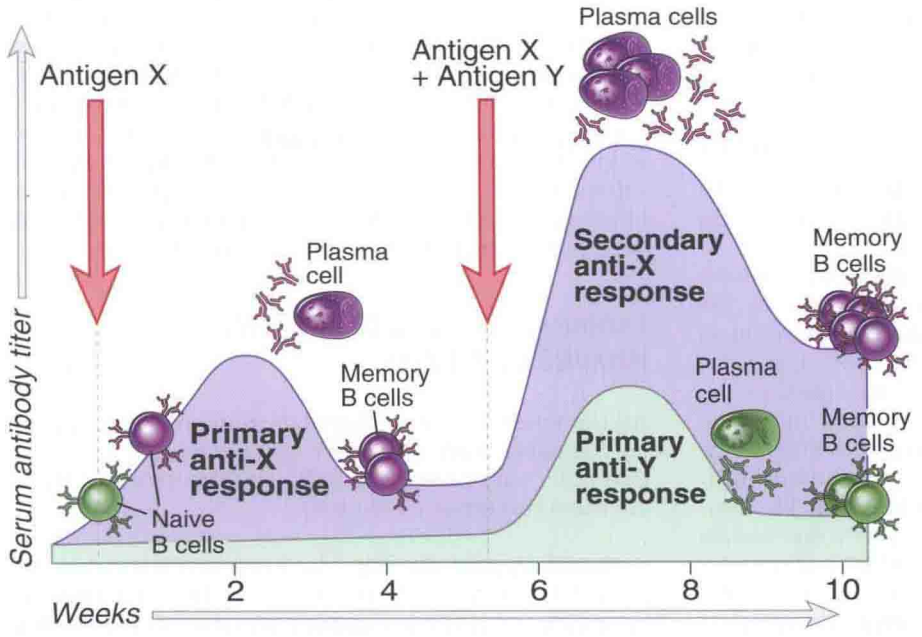


FIGURE 1-4 Specificity, memory, and contraction of adaptive immune responses. Antigens X and Y induce the production of different antibodies (specificity). The secondary response to antigen X is more rapid and larger than the primary response (memory). Antibody levels decline with time after each immunization (contraction, the process that maintains homeostasis). The same features are seen in cell-mediated immune responses.

increase in the number of cells that express identical receptors for the antigen and thus belong to a clone. This increase in antigen-specific cells enables the adaptive immune response to keep pace with rapidly dividing infectious pathogens.

- ***Specialization.*** As we have already noted, the immune system responds in distinct and special ways to different microbes, maximizing the effectiveness of antimicrobial defense mechanisms. Thus, humoral immunity and cell-mediated immunity are elicited by different classes of microbes or by the same microbe at different stages of infection (extracellular and intracellular), and each type of immune response protects the host against that class of microbe. Even within humoral or cell-mediated immune responses, the nature of the antibodies or T lymphocytes that are generated may vary from one class of microbe to another. We will return to the mechanisms and functional significance of such specialization in later chapters.
- ***Contraction and homeostasis.*** All normal immune responses wane with time after antigen stimulation, thus returning the immune system to its resting basal state, a state called **homeostasis** (see Fig. 1-4). This contraction of immune responses occurs largely because responses that are triggered by antigens function to eliminate the antigens, thus eliminating an essential stimulus for lymphocyte survival and activation. Lymphocytes (other than memory cells) that are deprived of these stimuli die by apoptosis.
- ***Nonreactivity to self.*** One of the most remarkable properties of every normal individual's immune system is its ability to recognize, respond to, and eliminate many foreign (non-self) antigens while not reacting harmfully to that individual's own (self) antigenic substances. 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.

These features of adaptive immunity are necessary if the immune system is to perform its normal function of host defense (see Table 1-3). Specificity and memory enable the immune system to mount heightened responses to persistent or recurring exposure to the same antigen and thus to combat infections that are prolonged or occur repeatedly. Diversity is essential if the immune system is to defend individuals against the many potential pathogens in the environment. Specialization enables the host to "custom design" responses to best combat different types of microbes. Contraction of the response allows the system to return to a state of rest after it eliminates each foreign antigen and to be prepared to respond to other antigens. Self-tolerance is vital for preventing harmful reactions against one's own cells and tissues while maintaining a diverse repertoire of lymphocytes specific for foreign antigens.

Immune responses are regulated by a system of positive feedback loops that amplify the reaction and by control mechanisms that prevent inappropriate 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 response needed to eradicate that infection. Many control mechanisms become active in immune responses to prevent excessive activation of lymphocytes, which may cause collateral damage to normal tissues, and to avoid responses against self antigens. In fact, a balance between activating and inhibitory signals is characteristic of all immune responses. We will mention specific examples of these fundamental features of the immune system throughout this book.

CELLULAR COMPONENTS OF THE ADAPTIVE IMMUNE SYSTEM

The principal cells of the adaptive immune system are lymphocytes, antigen-presenting cells, and effector cells. Lymphocytes are the cells that specifically recognize and respond to foreign antigens and are therefore the mediators of humoral and cellular immunity. There are distinct subpopulations of lymphocytes that differ in how they recognize antigens and in their functions (Fig. 1-5). **B lymphocytes** are the only cells capable of producing antibodies. They recognize extracellular soluble and cell surface antigens, and they differentiate into antibody-secreting plasma cells, thus functioning as the mediators of humoral immunity. **T lymphocytes**, the cells of cell-mediated immunity, recognize the antigens of intracellular microbes and the T cells either help phagocytes to destroy these microbes or they 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). T lymphocytes have a restricted specificity for antigens; they recognize peptides derived from foreign proteins that are bound to host proteins called **major histocompatibility complex** (MHC) molecules, which are expressed on the surfaces of other cells. As a result, these T cells recognize and respond to cell surface–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). In response to antigenic stimulation, helper T cells secrete cytokines, which are responsible for many of the cellular responses of innate and adaptive immunity and thus function as the "messenger molecules" of the immune system. The cytokines secreted by helper T lymphocytes stimulate the proliferation and differentiation of the T cells themselves and activate other cells, including B cells, macrophages, and other leukocytes. CTLs kill cells that produce foreign antigens, such as cells infected by viruses and other intracellular microbes. Some T lymphocytes, which are called **regulatory T cells**, function mainly to inhibit immune responses. A small population of T lymphocytes that express some cell surface proteins found on NK cells are called **NKT cells;** their specificities and role

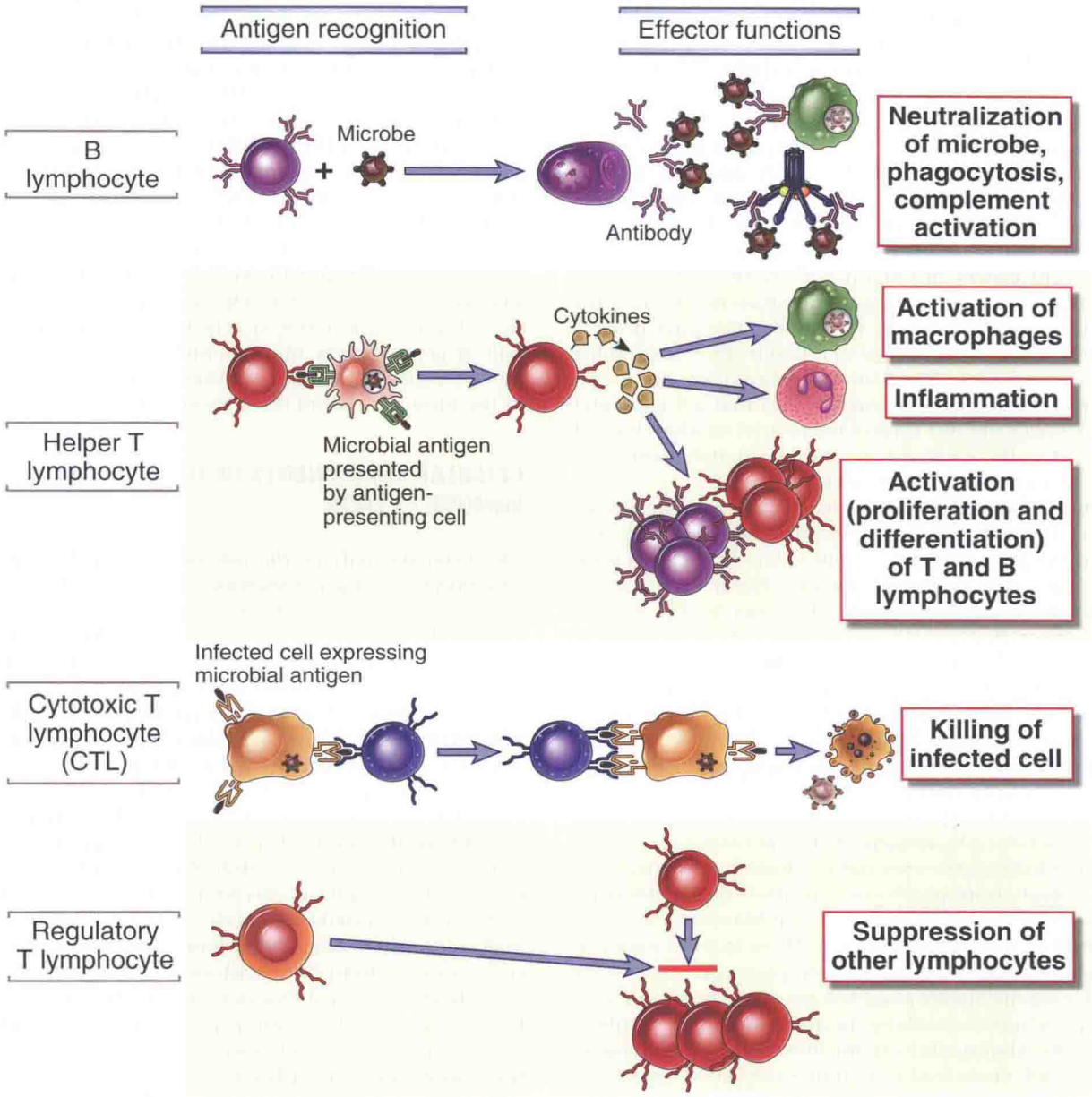


FIGURE 1-5 Classes of lymphocytes. B lymphocytes recognize soluble antigens and develop into antibody-secreting cells. Helper T lymphocytes recognize antigens on the surfaces of antigen-presenting cells and secrete cytokines, which stimulate different mechanisms of immunity and inflammation. Cytotoxic T lymphocytes recognize antigens on infected cells and kill these cells. Regulatory T cells suppress and prevent immune responses (e.g., to self antigens).

in host defense are not well understood. We will return to a more detailed discussion of the properties of lymphocytes in Chapter 2 and in later chapters. Different classes of lymphocytes can be distinguished by the expression of surface proteins that are named CD molecules and numbered (see Chapter 2).

The initiation and development of adaptive immune responses require 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**, which capture microbial antigens that enter from the external environment, transport these antigens to lymphoid organs, and present the antigens to naive T lymphocytes to initiate immune responses. Other cell types function as APCs at different stages of cell-mediated and humoral immune responses. We will describe the functions of APCs in Chapter 6.

The activation of lymphocytes by antigen leads to the generation of numerous mechanisms that function to eliminate the antigen. Antigen elimination often requires the participation of cells that are called **effector cells** because they mediate the final effect of the immune response, which is to get rid of the microbes. Activated T lymphocytes, mononuclear phagocytes, and other leukocytes function as effector cells in different immune responses.

Lymphocytes and APCs are concentrated in anatomically discrete lymphoid organs, where they interact with one another to initiate immune responses. Lymphocytes