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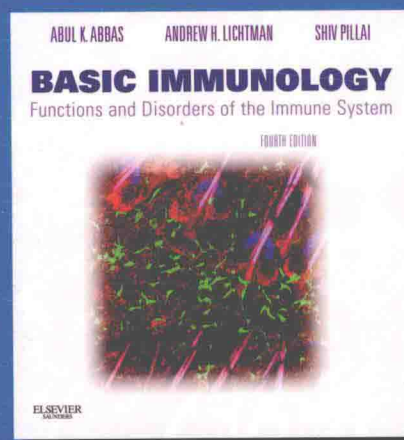
BASIC IMMUNOLOGY

Functions and Disorders of the Immune System

基础免疫学

(第4版)

ABUL K. ABBAS
ANDREW H. LICHTMAN
SHIV PILLAI



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基础免疫学

(第4版)

Basic Immunology Functions and Disorders of the Immune System (FOURTH EDITION)

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To Our Students

PREFACE

The fourth edition of *Basic Immunology* has been thoroughly revised to include recent important advances in our understanding of the immune system and to organize and present information in order to maximize its usefulness to students and teachers. The previous three editions of *Basic Immunology* have been enthusiastically received by students in the many courses that we and our colleagues teach, and we have not wavered from the guiding principles on which the book has been based through all the past editions. Our experience as immunology teachers and course directors has helped us to judge the right amount of detailed information that can be usefully included in introductory medical school and undergraduate courses, and the value of presenting the principles of immunology in a succinct and clear manner. We believe a concise and modern consideration of immunology is now a realistic goal, largely because immunology has matured as a discipline and has now reached the stage when the essential components of the immune system, and how they interact in immune responses, are understood quite well. As a result, we can now teach our students, with reasonable confidence, how the immune system works. In addition, we are better able to relate experimental results, using simple models, to the more complex, but physiologically relevant, issue of host defense against infectious pathogens. There has also been exciting progress in applying basic principles to understanding and treating human diseases.

This book has been written to address the perceived needs of both medical school and undergraduate curricula and to take advantage of the new understanding of immunology. We have tried to achieve several goals. First, we have presented the most important principles governing the function of the immune system by synthesizing key concepts from the vast amount of experimental data that emerge in the field of immunology. The choice of what is most important is based largely

on what is most clearly established by scientific investigation and what has the most relevance to human health and disease. We also have realized that in any concise discussion of complex phenomena it is inevitable that exceptions and caveats cannot be discussed in any detail. Second, we have focused on immune responses against infectious microbes, and most of our discussions of the immune system are in this context. Third, we have made liberal use of illustrations to highlight important principles, but have reduced factual details that may be found in more comprehensive textbooks. Fourth, we have also discussed immunologic diseases from the perspective of principles, emphasizing their relation to normal immune responses and avoiding details of clinical syndromes and treatments. We have added selected clinical cases in an appendix to illustrate how the principles of immunology may be applied to common human diseases. Finally, in order to make each chapter readable on its own, we have repeated key ideas in different places in the book. We feel such repetition will help students to grasp the most important concepts.

We hope that students will find this new edition of *Basic Immunology* clear, cogent, manageable, and enjoyable to read. We hope the book will convey our sense of wonder about the immune system and excitement about how the field has evolved and how it continues to grow in relevance to human health and disease. Finally, although we were spurred to tackle this project because of our associations with medical school courses, we hope the book will be valued by students of allied health and biology as well. We will have succeeded if the book can answer many of the questions these students have about the immune system and, at the same time, encourage them to delve even more deeply into immunology.

Several individuals played key roles in the writing of this book. Our new editor, James Merritt, has been an enthusiastic source of encouragement and advice. Our two talented illustrators, David

and Alexandra Baker of DNA Illustrations, have revamped all the artwork for this new edition, and have transformed our ideas into pictures that are informative and aesthetically pleasing. Sarah Wunderly has moved the book through the production process in an efficient and professional manner. Our development editor, Rebecca Gruliow, has kept the project organized and on track despite pressures of time and logistics. To all of them we owe our

many thanks. Finally, we owe an enormous debt of gratitude to our families, whose support and encouragement have been unwavering.

Abul K. Abbas
Andrew H. Lichtman
Shiv Pillai

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Introduction to the Immune System

Nomenclature, General Properties, and Components

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Immunity is defined as resistance to disease, specifically infectious disease. The collection of cells, tissues, and molecules that mediate resistance to infections is called the **immune system**, and the coordinated reaction of these cells and molecules to infectious microbes is the **immune response**. **Immunology** is the study of the immune system, including its responses to microbial pathogens and damaged tissues and its role in disease. **The most important physiologic function of the immune system is to prevent infections and to eradicate established infections**, and this is the principal context in which immune responses are discussed throughout this book.

The importance of the immune system for health is dramatically illustrated by the frequent observation that individuals with defective immune responses are susceptible to serious, often life-threatening infections (Fig. 1-1). Conversely, stimulating immune responses against microbes through vaccination is the most effective method for protecting individuals against infections; this approach has led to the worldwide eradication of smallpox, the only disease that has been eliminated from civilization by human intervention (Fig. 1-2). The emergence of acquired immunodeficiency syndrome (AIDS) in the 1980s tragically emphasized the importance of the immune system for defending individuals against infection. The impact of immunology, however, goes beyond infectious disease (see Fig. 1-1). The immune system

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 of cancer
The immune system recognizes and responds to tissue grafts and newly introduced molecules	Immune responses are barriers to transplantation and gene therapy
The immune system can injure cells and induce pathologic inflammation	Immune responses are the cause of allergic, autoimmune, and other inflammatory diseases

FIGURE 1-1 Importance of the immune system in health and disease. This table summarizes some of the physiologic functions of the immune system and its role in disease; AIDS, Acquired immunodeficiency syndrome.

prevents the growth of some tumors, and several methods to treat cancers by stimulating immune responses against tumor cells are in development. Immune responses also participate in the clearance of dead cells and in initiating tissue repair.

In contrast to these beneficial roles, abnormal immune responses are the causes of many inflammatory diseases with serious morbidity and mortality. The immune response is the major barrier to successful organ transplantation to treat organ failure. The products of immune

Disease	Maximum number of cases (year)	Number of cases in 2009	Percent 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
<i>Hemophilus influenzae</i> type B	~20,000 (1984)	25	-99.88
Hepatitis B	26,611 (1985)	3,020	-87.66

FIGURE 1-2 Effectiveness of vaccination for some common infectious diseases. This table illustrates the striking decrease in the incidence of selected infectious diseases for which effective vaccines have been developed. For some infections, such as hepatitis B, a vaccine has become available recently, and the incidence of the disease is continuing to decline. (Modified from Orenstein WA, Hinman AR, Bart KJ, Hadler SC: *Immunization*. In Mandell GL, Bennett JE, Dolin R, editors: *Principles and practices of infectious diseases*, ed 4, New York, 1995, Churchill Livingstone; and MMWR 58:1458-1469, 2010.)

cells are also of great practical use. For example, antibodies, which are proteins made by certain cells of the immune system, are used in clinical laboratory testing and in research as highly specific reagents for detecting a wide variety of molecules in the circulation and in cells and tissues. Antibodies designed to block or eliminate potentially harmful molecules and cells are in widespread use for the treatment of immunologic diseases, cancers, and other types of disorders. For all these reasons, the field of immunology has captured the attention of clinicians, scientists, and the lay public.

This chapter introduces the nomenclature of immunology, important general properties of all immune responses, and the cells and tissues that are the principal components of the immune system. In particular, the following questions are addressed:

- What types of immune responses protect individuals from infections?
- What are the important characteristics of immunity, and what mechanisms are responsible for these characteristics?

- How are the cells and tissues of the immune system organized to find and respond to microbes in ways that lead to their elimination?

We conclude the chapter with a brief overview of immune responses against microbes. The basic principles introduced here set the stage for more detailed discussions of immune responses in later chapters. A glossary of the important terms used in this book is provided in Appendix I.

INNATE AND ADAPTIVE IMMUNITY

Host defense mechanisms consist of innate immunity, which mediates the initial protection against infections, and adaptive immunity, which develops more slowly and provides more specialized and effective defense against infections (Fig. 1–3). Innate immunity, also called natural immunity or native immunity, is always present in healthy individuals (hence the term innate), prepared

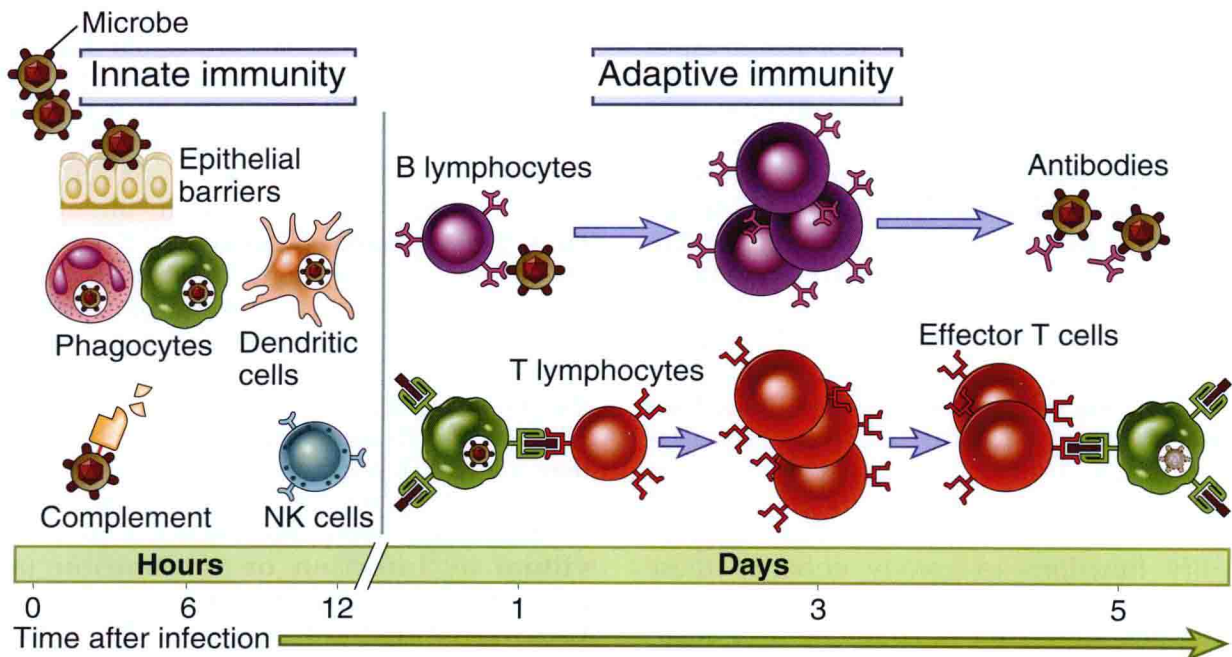


FIGURE 1–3 Principal mechanisms of innate and adaptive immunity. The mechanisms of innate immunity provide the initial defense against infections. Some mechanisms (e.g., epithelial barriers) prevent infections, and other mechanisms (e.g., phagocytes, natural killer [NK] cells, the complement system) eliminate microbes. Adaptive immune responses develop later and are mediated by lymphocytes and their products. Antibodies block infections and eliminate microbes, and T lymphocytes eradicate intracellular microbes. The kinetics of the innate and adaptive immune responses are approximations and may vary in different infections. 果：需安全本请在线购买：www.eitongbook.com

to block the entry of microbes and rapidly eliminate microbes that do succeed in entering host tissues. **Adaptive immunity**, also called specific immunity or acquired immunity, requires expansion and differentiation of lymphocytes in response to microbes before it can provide effective defense; that is, it adapts to the presence of microbial invaders. Innate immunity is phylogenetically older, and the more specialized and powerful adaptive immune system evolved later.

The first line of defense in innate immunity is provided by epithelial barriers and by cells and natural antibiotics present in epithelia, all of which function to block the entry of microbes. If microbes do breach epithelia and enter the tissues or circulation, they are attacked by phagocytes, specialized lymphocytes called natural killer cells, and several plasma proteins, including the proteins of the complement system. All these mechanisms of innate immunity specifically recognize and react against microbes. In addition to providing early defense against infections, innate immune responses enhance adaptive immune responses against the infectious agents. The components and mechanisms of innate immunity are discussed in detail in Chapter 2.

Defense against infectious microbes additionally requires adaptive immune responses, especially with microbes that are pathogenic for humans (i.e., capable of causing disease) and may have evolved to resist innate immunity. **The adaptive immune system consists of lymphocytes and their products, such as antibodies.** Whereas the mechanisms of innate immunity recognize structures shared by classes of microbes, the cells of adaptive immunity (lymphocytes) express receptors that specifically recognize a much wider variety of molecules produced by microbes as well as noninfectious substances. These substances are called **antigens**. Adaptive immune responses often use the cells and molecules of the innate immune system to eliminate microbes, and adaptive immunity functions to greatly enhance these antimicrobial mechanisms of innate immunity. For example, antibodies (a component of adaptive immunity) bind to microbes, and these coated microbes avidly bind to and activate phagocytes (a component of innate immunity), which ingest and destroy the microbes. Similar examples of the cooperation between innate

and adaptive immunity are discussed in later chapters.

TYPES OF ADAPTIVE IMMUNITY

The two types of adaptive immunity, humoral immunity and cell-mediated immunity, are mediated by different cells and molecules and provide defense against extracellular microbes and intracellular microbes, respectively (Fig. 1–4). **Humoral immunity** is mediated by proteins called **antibodies**, which are produced by cells called **B lymphocytes**. Antibodies are secreted into the circulation and mucosal fluids, and they neutralize and eliminate microbes and microbial toxins that are present outside of host cells, in the blood and in the lumens of mucosal organs, such as the gastrointestinal and respiratory tracts. One of the most important functions of antibodies is to stop microbes that are present at mucosal surfaces and in the blood from gaining access to and colonizing host cells and connective tissues. In this way, antibodies prevent infections from ever being established. Antibodies cannot gain access to microbes that live and divide inside infected cells. Defense against such intracellular microbes is called **cell-mediated immunity** because it is mediated by cells, which are called **T lymphocytes**. Some T lymphocytes activate phagocytes to destroy microbes that have been ingested by the phagocytes into intracellular vesicles. Other T lymphocytes kill any type of host cells that are harboring infectious microbes in the cytoplasm. Thus, the antibodies produced by B lymphocytes recognize extracellular microbial antigens, whereas T lymphocytes recognize antigens produced by intracellular microbes. Another important difference between B and T lymphocytes is that most T cells recognize only protein antigens, whereas B cells and antibodies are able to recognize many different types of molecules, including proteins, carbohydrates, nucleic acids, and lipids.

Immunity may be induced in an individual by infection or vaccination (active immunity) or conferred on an individual by transfer of antibodies or lymphocytes from an actively immunized individual (passive immunity). In **active immunity**, an individual exposed to the antigens of a microbe mounts an active response to eradicate the infection and develops resistance to later infection by that

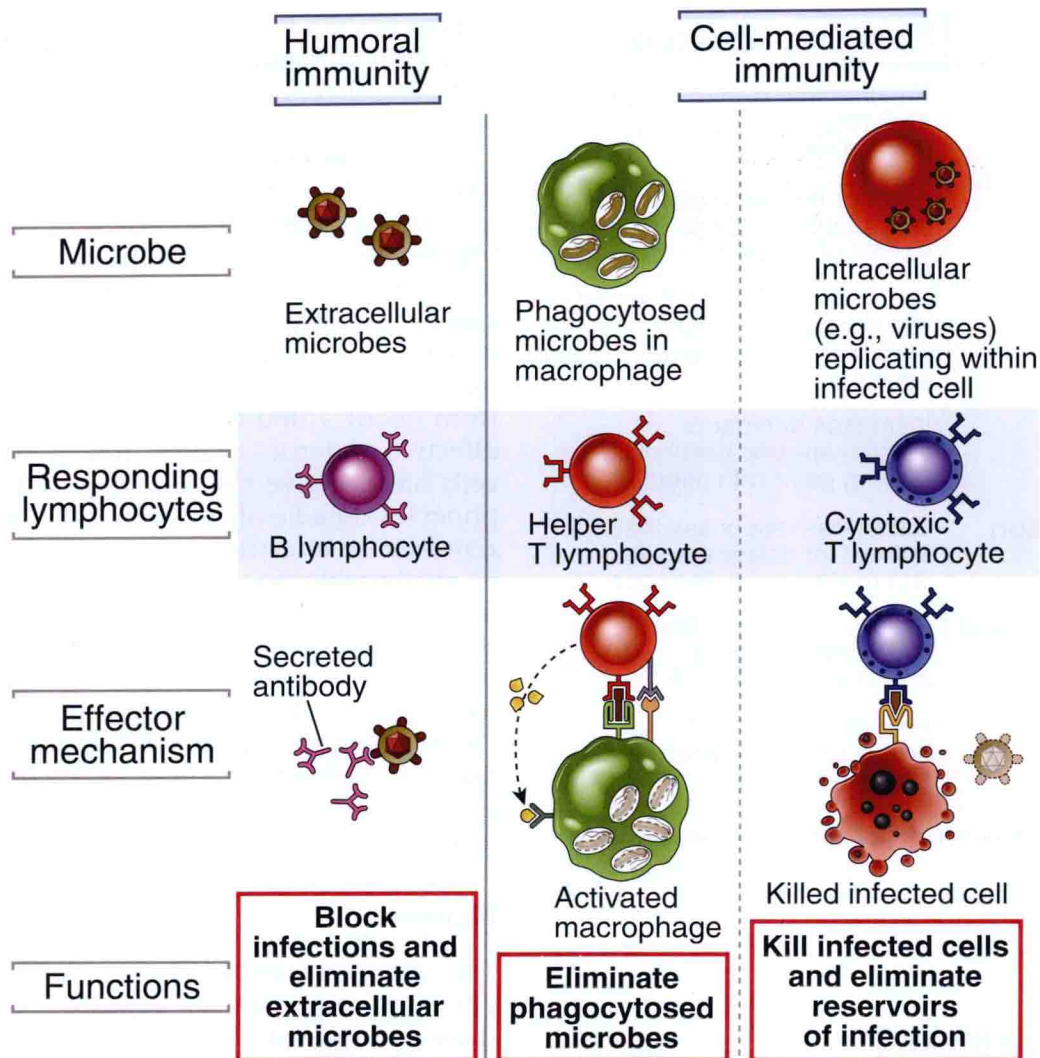


FIGURE 1–4 Types of adaptive immunity. In humoral immunity, B lymphocytes secrete antibodies that eliminate extracellular microbes. In cell-mediated immunity, different types of T lymphocytes recruit and activate phagocytes to destroy ingested microbes and kill infected cells.

microbe. Such an individual is said to be immune to that microbe, in contrast with a naive individual, not previously exposed to that microbe's antigens. We are concerned mainly with the mechanisms of active immunity. In **passive immunity**, a naive individual receives antibodies or cells (e.g., lymphocytes, feasible only in genetically identical [inbred] animals) from another individual already immune to an infection; for the lifetime of the transferred antibodies or cells, the recipient is able to combat the infection. Passive immunity is therefore useful for rapidly conferring immunity even before the individual is able to mount an active response, but it does not induce long-lived resistance to

the infection. The only physiologic example of passive immunity is seen in newborns, whose immune systems are not mature enough to respond to many pathogens but who are protected against infections by acquiring antibodies from their mothers through the placenta and breast milk.

PROPERTIES OF ADAPTIVE IMMUNE RESPONSES

Several properties of adaptive immune responses are crucial for the effectiveness of these responses in combating infections (Fig. 1–5).

Feature	Functional significance
Specificity	Ensures that distinct antigens elicit responses that target those antigens
Diversity	Enables immune system to respond to a large variety of antigens
Memory	Leads to rapid and enhanced responses to repeated exposures to the same antigens
Clonal expansion	Increases 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 immune system to respond to newly encountered antigens
Nonreactivity to self	Prevents injury to the host during responses to foreign antigens

FIGURE 1-5 Properties of adaptive immune responses. This table summarizes the important properties of adaptive immune responses and how each feature contributes to host defense against microbes.

Specificity and Diversity

The adaptive immune system is capable of distinguishing among millions of different antigens or portions of antigens. **Specificity** is the ability to distinguish between many different antigens. It implies that the total collection of lymphocyte specificities, sometimes called the **lymphocyte repertoire**, is extremely **diverse**. The basis for this remarkable specificity and diversity is that lymphocytes express clonally distributed receptors for antigens, meaning that the total population of lymphocytes consists of many different clones (each made up of one cell and its progeny), and each clone expresses an antigen receptor that is different from the receptors of all other clones. The **clonal selection hypothesis**, formulated in the 1950s, correctly predicted that clones of lymphocytes specific for different antigens develop before an encounter with these antigens, and each antigen elicits an immune response by selecting and activating the

lymphocytes of a specific clone (Fig. 1–6). We now know the molecular basis for how the specificity and diversity of lymphocytes are generated (see Chapter 4).

The **diversity** of the lymphocyte repertoire, which enables the immune system to respond to a vast number and variety of antigens, also means that very few cells, perhaps as few as one in 100,000 or one in 1 million lymphocytes, are specific for any one antigen. The total number of naive (unactivated) lymphocytes that can recognize and react against any one antigen ranges from about 1,000 to 10,000 cells. To mount an effective defense against microbes, these few cells have to give rise to a large number of lymphocytes capable of destroying the microbes. The remarkable effectiveness of immune responses is attributable to several features of adaptive immunity, including (1) marked expansion of the pool of lymphocytes specific for any antigen on exposure to that antigen, (2) positive feedback loops that amplify immune responses, and (3) selection mechanisms that preserve the most useful lymphocytes. These characteristics of the adaptive immune system are described in later chapters.

Memory

The immune system mounts larger and more effective responses to repeated exposures to the same antigen. The response to the first exposure to antigen, called the **primary immune response**, is mediated by lymphocytes called naive lymphocytes that are seeing antigen for the first time (Fig. 1–7). The term naive refers to these cells being immunologically inexperienced, not having previously responded to antigens. Subsequent encounters with the same antigen lead to responses called **secondary immune responses** that usually are more rapid, larger, and better able to eliminate the antigen than primary responses. Secondary responses are the result of the activation of memory lymphocytes, which are long-lived cells that were induced during the primary immune response. **Immunologic memory** optimizes the ability of the immune system to combat persistent and recurrent infections, because each encounter with a microbe generates more memory cells and activates previously generated memory cells. Memory also is one of the reasons why vaccines confer long-lasting protection against infections.

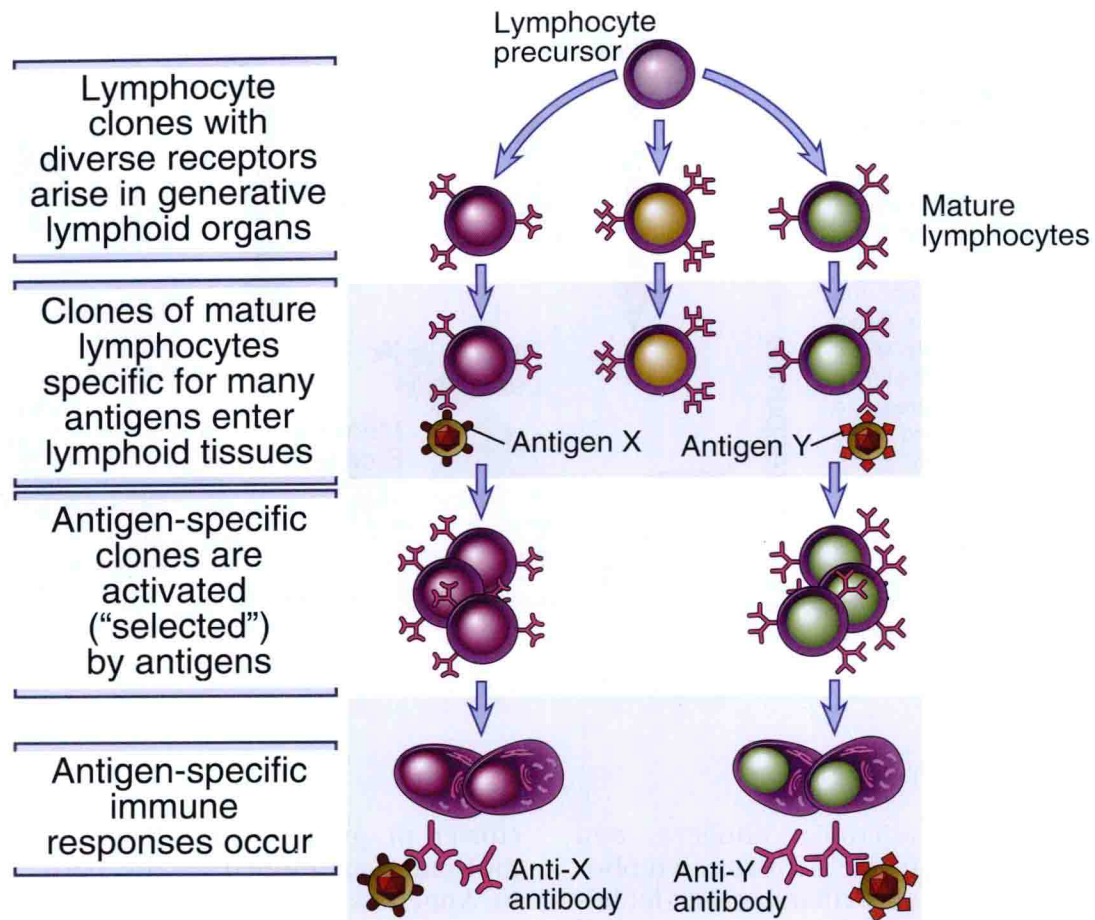


FIGURE 1–6 Clonal selection. Mature lymphocytes with receptors for many antigens develop before encountering these antigens. A clone refers to a population of lymphocytes with identical antigen receptors and therefore specificities; all these cells are presumably derived from one precursor cell. Each antigen (e.g., X and 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 cells, but the same principle applies to T lymphocytes. The antigens shown are surface molecules of microbes, but clonal selection also is true for extracellular soluble and intracellular antigens.

Other Features of Adaptive Immunity

Adaptive immune responses have other characteristics that are important for their functions (see Fig. 1–5). When lymphocytes are activated by antigens, they undergo proliferation, generating many thousands of clonal progeny cells, all with the same antigen specificity. This process, called **clonal expansion**, rapidly increases the number of cells specific for the antigen encountered, enabling few antigen-specific lymphocytes to serve their defensive role, and ensures that adaptive immunity keeps pace with rapidly proliferating microbes. Immune responses are specialized, and different responses are designed to defend best against different classes of microbes. All immune responses are self-limited and decline as the infection is eliminated, allowing the system

to return to a resting state, prepared to respond to another infection.

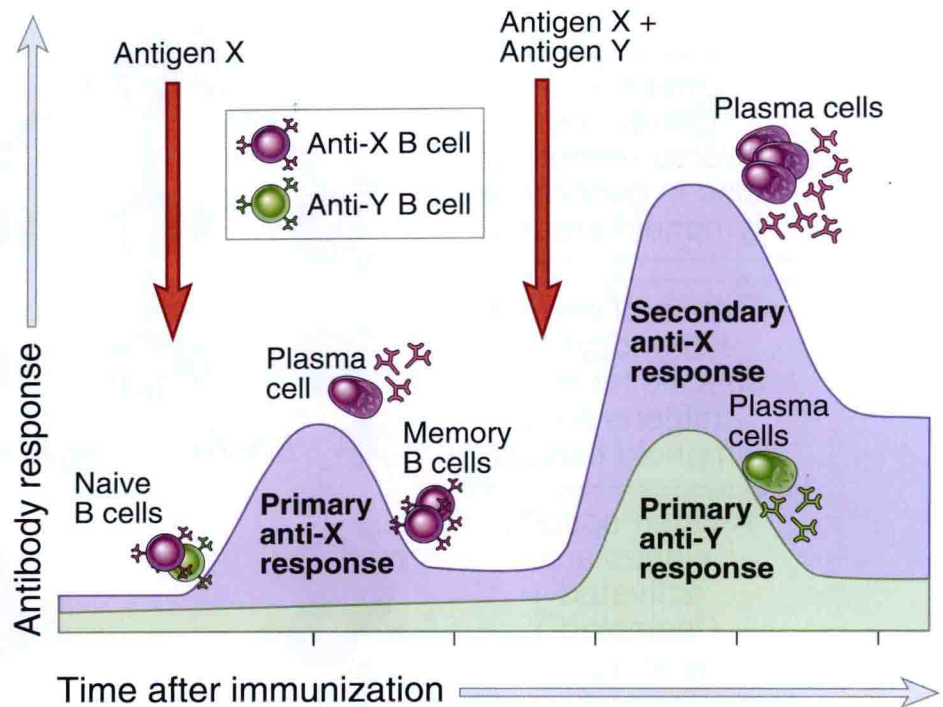
The immune system is able to react against an enormous number and variety of microbes and other foreign antigens, but it normally does not react against the host's own potentially antigenic substances—so-called **self antigens**. This unresponsiveness to self is called **immunological tolerance**, referring to the ability of the immune system to coexist with (tolerate) potentially antigenic self molecules, cells, and tissues.

CELLS OF THE IMMUNE SYSTEM

The cells of the adaptive immune system consist of lymphocytes, antigen-presenting cells that

FIGURE 1-7 Primary and secondary immune responses.

Antigens X and Y induce the production of different antibodies (a reflection of specificity). The secondary response to antigen X is more rapid and larger than the primary response (illustrating memory) and is different from the primary response to antigen Y (again reflecting specificity). Antibody levels decline with time after each immunization. The level of antibody produced is shown as arbitrary values and varies with the type of antigen exposure. Only B cells are shown, but the same features are seen with T cell responses to antigens. The time after immunization may be 1-3 weeks for a primary response and 2-7 days for a secondary response, but the kinetics vary depending on the antigen and nature of immunization.



capture and display microbial antigens, and effector cells (which include activated lymphocytes and other cells, particularly other leukocytes) that eliminate microbes (Fig. 1-8). This section describes the important functional properties of the major cell populations; a discussion of cellular morphology may be found in histology textbooks. The cells of innate immunity are described in Chapter 2.

Lymphocytes

Lymphocytes are the only cells that produce receptors specific for diverse antigens and are the key mediators of adaptive immunity. Although all lymphocytes are morphologically similar and rather unremarkable in appearance, they are heterogeneous in lineage, function, and phenotype and are capable of complex biologic responses and activities (Fig. 1-9). These cells often are distinguishable by surface proteins that may be identified using panels of monoclonal antibodies. The standard nomenclature for these proteins is the **CD** (cluster of differentiation) numerical designation, which is used to delineate surface proteins that define a particular cell type or stage of cell differentiation and that are recognized by a

cluster or group of antibodies. (A list of CD molecules mentioned in the book is provided in Appendix II.)

As alluded to earlier, B lymphocytes are the only cells capable of producing antibodies; therefore they are the cells that mediate humoral immunity. B cells express membrane forms of antibodies that serve as the receptors that recognize antigens and initiate the process of activation of the cells. Soluble antigens and antigens on the surface of microbes and other cells may bind to these B lymphocyte antigen receptors, initiating the process of B cell activation. This leads to the secretion of soluble forms of antibodies with the same antigen specificity as the membrane receptors.

T lymphocytes are responsible for cell-mediated immunity. The antigen receptors of most T lymphocytes recognize only peptide fragments of protein antigens that are bound to specialized peptide display molecules called major histocompatibility complex (MHC) molecules on the surface of specialized cells called antigen-presenting cells (see Chapter 3). Among T lymphocytes, $CD4^+$ T cells are called **helper T cells** because they help B lymphocytes to produce antibodies and help phagocytes to destroy ingested microbes. $CD8^+$ T lymphocytes


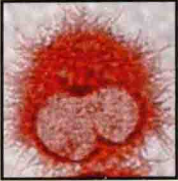


Cell type	Principal function(s)
<p>Lymphocytes: B lymphocytes; T lymphocytes; natural killer cells</p>  <p><i>Blood lymphocyte</i></p>	<p>Specific recognition of antigens:</p> <p>B lymphocytes: mediators of humoral immunity</p> <p>T lymphocytes: mediators of cell-mediated immunity</p> <p>Natural killer cells: cells of innate immunity</p>
<p>Antigen-presenting cells: dendritic cells; macrophages; follicular dendritic cells</p>   <p><i>Dendritic cell</i> <i>Blood monocyte</i></p>	<p>Capture of antigens for display to lymphocytes:</p> <p>Dendritic cells: initiation of T cell responses</p> <p>Macrophages: effector phase of cell-mediated immunity</p> <p>Follicular dendritic cells: display of antigens to B lymphocytes in humoral immune responses</p>
<p>Effector cells: T lymphocytes; macrophages; granulocytes</p>  <p><i>Neutrophil</i></p>	<p>Elimination of antigens:</p> <p>T lymphocytes: helper T cells and cytotoxic T lymphocytes</p> <p>Macrophages and monocytes: cells of the mononuclear phagocyte system</p> <p>Granulocytes: neutrophils, eosinophils</p>

FIGURE 1-8 Principal cells of the immune system. This table shows the major cell types involved in immune responses, and the key functions of these cells. Micrographs in the left panels illustrate the morphology of some cells of each type. Note that tissue macrophages are derived from blood monocytes.

are called **cytotoxic T lymphocytes** (CTLs) because they kill cells harboring intracellular microbes. Some CD4⁺ T cells belong to a special subset that functions to prevent or limit immune responses; these are called **regulatory T lymphocytes**. Another class of lymphocytes is called **natural killer (NK) cells**, which also kill infected host cells, but unlike B and T cells, they do not express clonally distributed antigen receptors. NK cells are components of innate immunity, capable of rapidly attacking infected cells.

All lymphocytes arise from stem cells in the bone marrow (Fig. 1-10). **B lymphocytes mature in the bone marrow, and T lymphocytes mature in an organ called the thymus.** These sites in which mature lymphocytes are produced (generated) are called the **generative lymphoid organs**. Mature lymphocytes leave the generative lymphoid organs and enter the circulation and the **peripheral lymphoid organs**, where they may encounter antigen for which they express specific receptors.