



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Introduction to the Immune Response

Chapter 1

Books must follow sciences, and not sciences books.

Francis Bacon

A. Historical Orientation

What is immunology? Simply put, **immunology** is the study of the immune system. The **immune system** is a system of cells, tissues and their soluble products that recognizes, attacks and destroys entities that could endanger the health of an individual. The normal functioning of the immune system gives rise to **immunity**, a word derived from the Latin *immunitas*, meaning “to be exempt from.” This concept originated in the 1500s, before the causes of disease were understood. Survivors who resisted death during a first exposure to a devastating disease and who did not get sick in a subsequent exposure were said to have become “exempt from” the disease, or “immune.”

In 1796, the English physician Edward Jenner carried out experiments that solidified the birth of immunology as an independent science. At that time, smallpox was a disfiguring and often fatal disorder that decimated whole villages (**Plate 1-1**). Jenner observed that dairy-maids and farmers lacked the pock-marked complexions of their fellow citizens, and wondered whether those who worked with cattle might be resistant to smallpox because of their close contact with livestock. Cows of that era often suffered from cowpox disease, a disorder similar to smallpox but much less severe. In an experiment that would be prohibited on ethical grounds today, Jenner deliberately exposed an 8-year-old boy to fluid from a cowpox lesion (**Plate 1-2**). Two months later, he inoculated the same boy with infectious material from a smallpox patient. In this first example of successful vaccination, the boy did not develop smallpox. Jenner’s approach to smallpox prevention was quickly adopted in countries throughout Europe. The modern story of smallpox vaccination and the global eradication of this scourge is one of the most successful public health endeavors in history.

Jenner’s work was the first controlled demonstration of the **immune response**, but little was understood at that time about the cellular and molecular mechanisms underlying the observed immunity. In Jenner’s day, the cause of infectious disease was still a mystery, and theories of that time did not envision the transmission of disease-causing germs. In 1884, Robert Koch proposed the “germ theory of disease,” which

WHAT’S IN THIS CHAPTER?

A. Historical Orientation.....	3
B. The Nature of the Immune Response	4
C. Types of Immune Responses: Innate and Adaptive	6
I. General Features of Innate Immunity	8
II. General Features of Adaptive Immunity	10
D. Interplay between the Innate and Adaptive Responses.....	14
E. Clinical Immunology	17

In 1967, the World Health Organization (WHO) launched a vaccination campaign to eradicate smallpox from the planet, and in 1980 they announced their success. More details about the global eradication of smallpox can be found in Chapter 14.

Plate 1-1
Smallpox

Smallpox infection in a young Bangladeshi girl in 1973. Two hundred years earlier, in Edward Jenner's day, this disease was a widespread scourge. [Reproduced by permission of the Public Health Image Library, CDC]



Plate 1-2
The First Smallpox Immunization

A painting by E. Board depicts Edward Jenner vaccinating the young James Phipps against smallpox. [Reproduced by permission of Wellcome Library, London]



Selected landmark discoveries in immunology and immunologists who have won Nobel Prizes for their work are featured in Appendices A and B, respectively.

stated that microbes invisible to the naked eye were responsible for specific illnesses, and the first human disease-causing organisms or **pathogens** were identified in the late 1800s. At about the same time, Louis Pasteur applied Jenner's immunization technique for smallpox to the prevention of various animal diseases. Pasteur demonstrated that inoculation with a pathogen that had been weakened in the laboratory could protect against a subsequent exposure to the naturally occurring pathogen. It was Pasteur who coined the term **vaccination** (from the Latin *vaccinus*, meaning "derived from cows") for this procedure, in honor of Jenner's work. The research of Pasteur and other investigators spurred the evolution of immunology as a science distinct from (but related to) the established fields of microbiology, pathology, biochemistry and histology. Today, **immunology** can be defined as *the study of the cells and tissues that mediate immunity and the investigation of the genes and proteins underlying their function.*

B. The Nature of the Immune Response

A normal healthy person's body always strives to maintain **homeostasis**, a natural state of balance of all its organs and the nervous and circulatory systems. When this homeostasis is disturbed by either trauma, pathogens, or the deregulation of body cells (such as occurs in cancer), the immune system responds in an attempt to restore balance. At its simplest level, this response involves identifying and clearing damaged and dying cells from the body. More complex responses have evolved to counteract assault on

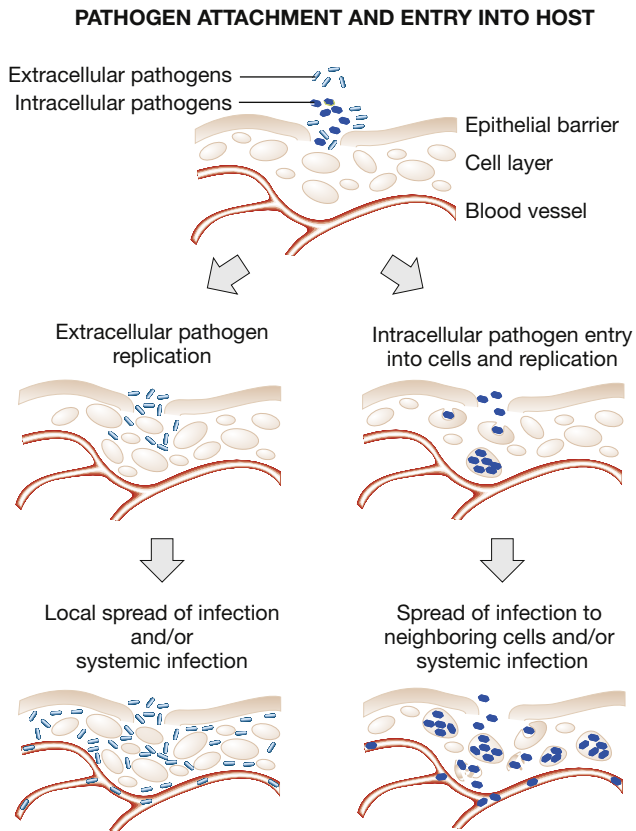


Fig. 1-1
Establishment of Infection by Extracellular and Intracellular Pathogens

Pathogens that are not blocked by epithelial barriers can gain access to underlying cell layers. Extracellular pathogens replicate outside host cells, whereas intracellular pathogens must enter host cells to replicate. In both cases, if infection is not controlled, the pathogen may spread locally in the tissues or enter the bloodstream and spread systemically.

the body by infectious agents, including bacteria, viruses, parasites and fungi. Because these foreign invaders are literally everywhere on Earth and constantly seeking vulnerable hosts, the immune system is constantly occupied with containing attacks from this quarter. Indeed, despite the successful eradication of smallpox and the development of antibiotics, infectious diseases remain among the biggest killers on the planet. Long-standing disorders such as malaria and tuberculosis, as well as “emerging” diseases caused by new pathogens such as West Nile virus, severe acute respiratory syndrome (SARS) virus, and H1N1 influenza virus, present ongoing challenges to the immune system.

Humans are surrounded by other organisms—in the air, in the soil, in the water, on the skin, and on the **mucosae**, the protective layers of epithelial cells that line the gastrointestinal, urogenital and respiratory tracts. While most of these organisms are harmless and some are even beneficial, some are pathogenic. Like all species, pathogens live to reproduce. In order to reproduce, however, many must penetrate a host’s body or one of its component cells. **Infection** is defined as the attachment and entry of a pathogen into the host. Once inside the body or cell, the pathogen replicates, generating progeny that spread into the body in a localized or systemic fashion. The manner of this replication determines whether the pathogen is considered extracellular or intracellular.

Extracellular pathogens, such as certain bacteria and parasites, do not need to enter cells to reproduce. After accessing the body, these organisms replicate first in the interstitial fluid bathing the tissues and may then disseminate via the blood (**Fig. 1-1**). **Intracellular pathogens**, such as viruses and other bacteria and parasites, enter a host cell, subvert its metabolic machinery, and cause it to churn out new virus particles, bacteria, or parasites. These pathogens may then also travel systemically by entering the blood. For both intracellular and extracellular pathogens, if the infectious agent overwhelms normal body systems or interferes with cellular functions, the body becomes “sick.” This sickness is manifested as a set of characteristic clinical symptoms that we call an “illness” or “disease.”

Our bodies are under constant assault by harmful microbes, yet, most of the time, assaults by these organisms are successfully repelled and disease is prevented. This resistance is due to both basic and sophisticated immune responses that combat pathogens. Simply put, the job of the immune response is to “clean up” infections in the interstitial fluid, tissues and blood, and to destroy infected host cells so that neighboring host cells do not share their fate. Because pathogens are constantly evolving mechanisms to evade or block immune defenses, the immune system must constantly adapt to maintain its effectiveness. It is a continual horse race as to which will be the more successful mechanism: the body’s immune surveillance or the pathogen’s invasion and infection strategy. We note here that the immune response itself may cause limited collateral damage to tissues as part of its larger battle against pathogens, but such **immunopathic** effects are usually short-lived in an otherwise healthy individual.

At the turn of the twentieth century, there were two schools of thought on what mechanisms underlay immune responses. One group of scientists believed that immunity depended primarily on the actions of cells that destroyed or removed unwanted material from the body. This clearance process was referred to as **cell-mediated immunity**. However, another group of researchers was convinced that soluble molecules in the serum of the blood could directly eliminate foreign entities without the need for cellular involvement. In this case, the clearance process was referred to as **humoral immunity**, a term derived from the historical description of body fluids as “humors.” Today, we know that both cell-mediated and humoral responses occur simultaneously during an immune response and that both are often required for complete clearance of a threat.

The cells responsible for cell-mediated immunity are collectively called **leukocytes** (“leuko,” white; “cyte,” small body, i.e., a cell) or white blood cells. However, “blood cell” is a bit of a misnomer, because a majority of leukocytes reside in tissues and specialized organs, and move around the body through both the blood circulation and a system of interconnected vessels called the **lymphatic system**. The soluble molecules responsible for humoral immunity are proteins called **antibodies**, and antibodies are secreted by a particular type of leukocyte. The production of these antibodies and the mounting of cell-mediated immune responses depend on an elaborate signaling system by which leukocytes communicate with each other as well as with other cell types in the body. This signaling is mediated by small secreted proteins called **cytokines**, which are mainly produced by leukocytes.

C. Types of Immune Responses: Innate and Adaptive

The mammalian immune system can mount two types of responses: the **innate response** and the **adaptive response**. Recently, it has become increasingly clear that these two types of responses are less distinct and more interconnected than once thought. Indeed, researchers now believe that vertebrates are capable of a continuum of immune responses that bring more and more precise weapons to bear on a threat as required. More specifically, innate immunity is involved in all levels of immune response, whereas the adaptive response is mounted only when innate mechanisms signal that there is a relatively serious infection. In all cases, the objective is to clear the body of unwanted entities and re-establish homeostasis in the most efficient way possible.

Innate immune responses are triggered by disruptions to homeostasis caused by either non-infectious or infectious means. With respect to the former, innate responses help to repair tissues injured by trauma (such as that caused by a cut, a blow, or surgery) and remove dead cells and cells too damaged or old (senescent) to be of further use to the body. Products synthesized by leukocytes mediating innate responses (innate leukocytes) also help to prevent “bystander injury” of healthy tissues. With respect to invading pathogens, elements of the innate immune system are the first to confront the threat and work to eliminate it from the body. Such elements include pre-existing anatomical and physiological barriers that attempt to block pathogen entry, and other responses that are induced after the pathogen has gained entry. Only if innate responses are insufficient to control the situation and restore homeostasis, as is

often the case with infection by a rapidly replicating pathogen, is an adaptive response mounted. Together, the innate and adaptive immune responses allow a seamless escalation of countermeasures that maintain homeostasis in the face of cellular aging, tissue trauma and/or pathogen infection.

What exactly triggers the initial response by the innate system? In a word: recognition. Wherever cells are damaged or dying—either in the presence or absence of infection—particular host macromolecules are released into the extracellular milieu or become accessible on the surface of damaged cells or in cellular debris. These molecules are called **damage-associated molecular patterns (DAMPs)**. When a pathogen attacks, it furnishes common molecular structures on its own surface, or on the surface of cells it has infected, or as part of products it synthesizes. These structures are called **pathogen-associated molecular patterns (PAMPs)**. Cell damage or death in the absence of a pathogen gives rise to DAMPs only, but both DAMPs and PAMPs will be present when a pathogen invades (**Fig. 1-2**). It is the recognition of DAMPs and PAMPs by innate leukocytes that initiates innate responses.

DAMPs and PAMPs are recognized by host proteins called **pattern recognition molecules (PRMs)**, most of which are expressed by innate leukocytes. There is not a large array of different PRMs, meaning that there is a limited repertoire of molecular patterns that can be recognized. However, each PRM recognizes a DAMP or PAMP that is shared by many different damaged cells or pathogens. Thus, PRMs give the innate immune response the property of *broad recognition*. Furthermore, because innate leukocytes expressing PRMs are present in large numbers, these cells don't need to multiply to work effectively: the response is *immediate*. Finally, because innate leukocytes are activated but don't multiply in response to engagement of their PRMs, the speed and strength of their response is exactly the same upon a second exposure to the same pathogen or type of damage. The result is a response that is said to have *no memory*.

Recognition is also the key to initiating the adaptive immune response, but there are important differences. In contrast to the broad recognition of the PRMs mediating the innate response, the receptors expressed by the cells participating in the adaptive response (adaptive leukocytes) are equipped with receptors that recognize unique molecular structures on pathogens. These unique structures are called **antigens**, and the receptors that recognize them are **antigen receptors**. Together as a population, adaptive leukocytes express a vast array of antigen receptors capable of recognizing almost any structure, meaning that they represent a diverse **repertoire** of antigen specificities. However, the antigen receptor of any one adaptive leukocyte binds to an antigen exclusive to a single type of pathogen. Thus, antigen receptors have the property of *specific recognition*. Because adaptive leukocytes are very few in number, these cells must proliferate and expand their ranks after receptor engagement before they can be effective: the response is *delayed*. In addition, after adaptive leukocytes proliferate and act to eliminate the pathogen, some of these cells become long-lived so that the speed and strength of the adaptive response is increased upon a subsequent exposure to the same pathogen. The adaptive response is thus said to have *memory*. The distinguishing features of the innate and adaptive responses are summarized in **Table 1-1**.

Antigens got their names because they were first identified as pathogen components that could bind antibodies; i.e., they induced "antibody generation." "Antigen" now refers to structures targeted by humoral or cell-mediated responses.

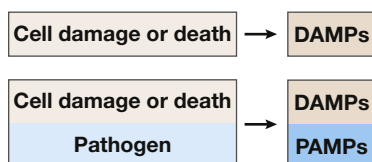


Fig. 1-2
DAMPs vs. PAMPs

A DAMP is a common molecular structure that is produced by host cells when they are damaged or dying (with or without pathogen infection). A PAMP is a common molecular structure shared by a wide variety of pathogens or their components or products. In the case of pathogen attack, both DAMPs and PAMPs will be present.

TABLE 1-1 Comparison of Innate and Adaptive Immune Responses	
Innate	Adaptive
Pre-existing barriers and induced mechanisms	All mechanisms induced
Innate leukocytes express a small number of pattern recognition molecules (PRMs) of limited diversity that collectively recognize a wide range of threats	Adaptive leukocytes express an almost infinite number of extremely diverse antigen receptors, each of which is specific for a particular pathogen
Response is triggered by PRM binding to widely shared damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs)	Response is triggered by antigen receptor binding to a unique antigen derived from a specific pathogen
Number of leukocytes responding to a given threat is large, so no proliferation is required and response is fast	Number of leukocytes responding to a given threat is very small, so proliferation is required and response is slower
Responding cells do not proliferate and are short-lived, so level of defense is similar upon repeated exposure to the same pathogen	Responding cells proliferate and are long-lived, so level of defense is stronger and faster with repeated exposure to the same pathogen

From the point of view of the body’s leukocytes, a complex pathogen represents a collection of many different PAMPs, which evoke an innate response, and antigens, which may evoke an adaptive response if the innate response is not sufficient to eliminate the threat (**Fig. 1-3**). Anatomically, an innate response can be triggered at any point in the body because the majority of innate leukocytes are positioned where microbes most commonly attempt to gain access: just below the skin surface or at the mucosae protecting body tracts such as the gut and respiratory system. Most of the time, the innate response successfully eliminates an invader. Only those entities that succeed in overwhelming the innate defenses trigger adaptive responses that are initiated by adaptive leukocytes positioned in specialized anatomical regions called the **lymphoid tissues**, which include the spleen, tonsils and lymph nodes (see Ch. 2). The general characteristics of innate and adaptive immune responses primarily as they relate to pathogens are described in more detail in the next two sections.

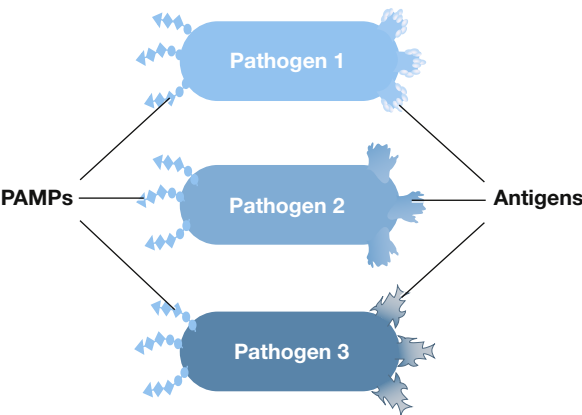
NOTE: Elements of an innate immune response can be found in all multicellular organisms, whereas the mechanisms of the more recently evolved adaptive immune response are present only in the higher vertebrates (fish and above). Appendix C contains a Table of Comparative Immunology that summarizes the immune system elements present in an evolutionarily diverse range of animals.

I. General Features of Innate Immunity

In this section, we present a general introduction to the central elements of innate immunity, namely *barrier defenses*, *complement activation*, *pattern recognition*, *inflammation*, *phagocytosis* and *target cell lysis*. More detailed information about the innate immune response can be found in Chapter 3 on innate immunity.

Fig. 1-3
PAMPs vs. Antigens

A given PAMP is expressed by a wide variety of pathogens and is recognized by PRMs whose engagement activates innate leukocytes. An antigen is a molecular structure that is generally unique to a specific pathogen and is recognized by a specific antigen receptor whose engagement activates a particular adaptive leukocyte.



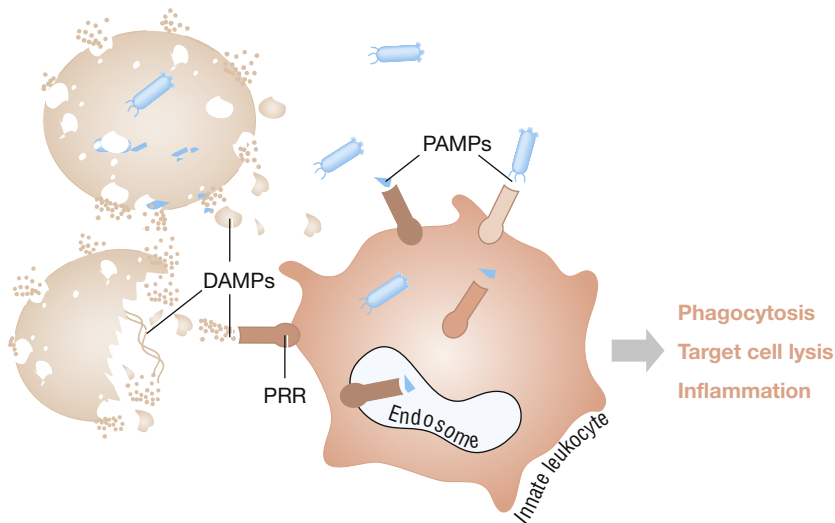


Fig. 1-4
PRR Engagement and Effector Functions of Innate Leukocytes

When PAMPs on a pathogen bind to the PRRs of an innate leukocyte, the cell becomes activated and attempts to clear the pathogen through phagocytosis, target cell lysis, and/or the induction of inflammation. The PRR may be expressed on the leukocyte surface, on its endosomal membranes or in its cytoplasm.

i) Barrier Defense

The first level of innate defense is mediated by a pre-existing collection of physical, chemical and molecular barriers that exclude foreign material in a way that is totally non-specific and requires no induction. These elements include **anatomical barriers** and **physiological barriers**. An example of an anatomical barrier is intact skin, while the low pH of stomach acid and the hydrolytic enzymes in body secretions are examples of physiological barriers.

ii) Complement Activation

Should barrier defense prove insufficient, other forms of innate defense are induced. A key player in the induced innate response is **complement**, a complex system of enzymes that circulates in the blood in an inactive state. Once activated, the complement system contributes directly and indirectly to innate and adaptive immune defenses, as described in detail in Chapter 3.

iii) Pattern Recognition

When invaders breach anatomical and physiological barriers, innate leukocytes start to take action as a result of pattern recognition mediated by the binding of PRMs to PAMPs furnished by pathogens and to DAMPs emanating from damaged host cells. As introduced previously, and as illustrated in **Figure 1-4**, PRMs come in several different forms, some of which are membrane-bound and others of which are soluble. PRMs that are expressed by innate leukocytes are called **pattern recognition receptors (PRRs)**. PRRs are located in the plasma membrane of an innate leukocyte, or are soluble molecules free in the leukocyte's cytoplasm, or are fixed in the membranes of intracellular vesicles called **endosomes**. Other PRMs are made by non-leukocytes and are present as soluble molecules free in the extracellular milieu. When these latter PRMs bind to a given PAMP or DAMP, they must then bind to another receptor fixed in a leukocyte membrane in order to trigger the appropriate clearance response. The clearance mechanisms typically induced following PRM or PRR engagement by a DAMP or PAMP are *inflammation*, *phagocytosis*, and/or *target cell lysis*. A brief description of each of these processes follows, with more detail provided in Chapter 3.

iv) Inflammation

When leukocyte PRRs are engaged by their ligands, intracellular signal transduction leads to the induction of new gene transcription and the synthesis of various “pro-inflammatory” cytokines. These cytokines in turn drive events responsible for the influx of first innate and later (if necessary) adaptive leukocytes into the site of injury

or infection. This influx is part of a process called **inflammation** or an **inflammatory response**, and the redness and swelling we commonly associate with inflammation are its outward physical signs. This inflammation is normal and helpful, and, when properly regulated, promotes a localized gathering of the cells and molecules necessary to repair tissue damage and clear pathogens. Once the threat is eliminated, the inflammation resolves naturally with time. However, if the inflammation fails to resolve and becomes chronic, it may become pathological. The powerful molecules secreted by the innate leukocytes participating in the inflammatory response can eventually cause tissue damage and impair immune system function if left to operate unchecked. Thus, properly controlled inflammation is part of a healthy innate response and essential for homeostasis, whereas excessive or prolonged inflammation is immunopathic and undermines homeostasis.

v) Phagocytosis

Innate leukocytes frequently use a sophisticated means of engulfing entities that is called **phagocytosis** (“eating of cells”). Phagocytosis is carried out primarily by three types of PRR-expressing cells: **neutrophils**, **macrophages** and **dendritic cells** (DCs); these cell types are consequently known as **phagocytes**. Neutrophils mainly engulf and destroy pathogens, while macrophages and DCs engulf not only pathogens but also dead host cells, cellular debris and host macromolecules. The phagocytosis of foreign entities by macrophages and DCs allows these cells to “present” unique antigens from this material on their cell surfaces in such a way that the antigens can be recognized by adaptive leukocytes that have been drawn to the site of inflammation. These cells are then activated and mediate antigen-specific protection.

vi) Target Cell Lysis

Cancer cells and cells infected with intracellular pathogens frequently express certain DAMPs and/or PAMPs on their cell surfaces that mark them as “target cells” for destruction by cells of the innate system. When these molecules are recognized and bound by PRRs of innate leukocytes, complex processes are initiated that result in the lysis of the cancer cell or infected cell, preventing it from causing further harm to the body. These types of innate responses are carried out primarily by neutrophils, macrophages and another type of innate leukocyte called a **natural killer cell** (NK cell).

II. General Features of Adaptive Immunity

In this section, we introduce the main features of adaptive immunity. The adaptive leukocytes referred to in previous sections are called *lymphocytes*. Lymphocytes are categorized as either **B lymphocytes** (B cells) or **T lymphocytes** (T cells). The fundamental functional and developmental characteristics of lymphocytes are responsible for the *specificity*, *division of labor*, *memory*, *diversity* and *tolerance* of the adaptive response. Each of these important concepts is introduced here as a prelude to more detailed discussions of these topics in later chapters.

i) Specificity

The specificity of an adaptive immune response for a particular antigen is determined by the nature of the antigen receptors expressed on the surfaces of T and B lymphocytes. Each lymphocyte expresses thousands of identical copies of a unique antigen receptor protein. Interaction of these antigen receptor molecules with antigen triggers activation of the lymphocyte. In contrast to the broad recognition mediated by PRRs, antigen binding to a lymphocyte antigen receptor usually hinges on the presence of a unique molecular shape unlikely to appear on more than one pathogen.

The antigen receptors on the surface of a B cell are called **B cell receptors** (BCRs), whereas those on the T cell surface are called **T cell receptors** (TCRs). In both cases, the antigen receptor is itself a complex of several proteins. Some of these proteins interact directly and specifically with antigen, while others convey the intracellular

TABLE 1-2 Division of Labor in Adaptive Immune Responses

Lymphocyte	Antigen Recognized	Pathogens Combatted	Mechanism Used by Effector Cells
B cell	Whole soluble antigen or whole antigen present on a pathogen surface	Extracellular pathogens	Antibody-mediated clearance of pathogen
Tc cell	Antigen peptide + MHC class I	Primarily intracellular pathogens	Lysis of infected host cells to prevent pathogen spread
Th cell	Antigen peptide + MHC class II	Many extracellular and intracellular pathogens	Secretion of cytokines required for activation of B cells and Tc cells, and stimulation of innate leukocytes

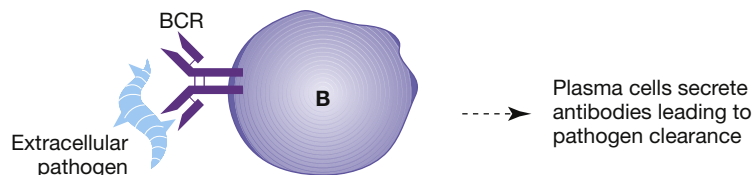
signals triggered by antigen binding into the cytoplasm and nucleus of the lymphocyte. These signals are critical for sustaining the activation of the lymphocyte and promoting its proliferation into an army of short-lived daughter **effector cells**. These effector cells then undertake the effector action appropriate for eliminating the pathogen furnishing the antigen.

ii) Division of Labor

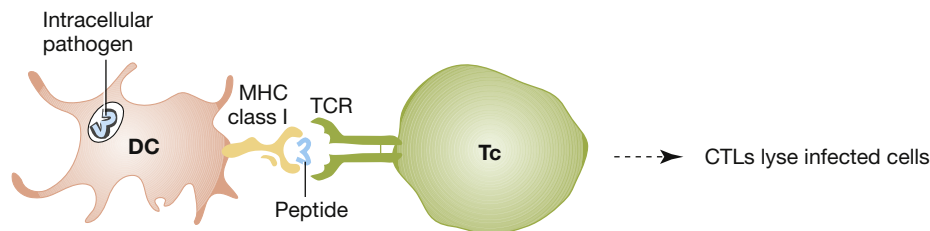
“Division of labor” in the adaptive response refers to the different but equally important contributions of B lymphocytes and two types of T lymphocytes. These two major T cell subsets are called **cytotoxic T cells** (Tc) and **helper T cells** (Th). The roles of B, Tc and Th cells in the adaptive response are defined by the distinct mechanisms by which they recognize and respond to antigen (**Table 1-2**).

B cells recognize antigen in a way that is fundamentally different from that used by Tc and Th lymphocytes. The BCR of a B cell binds directly to an intact antigen, which may be either a soluble molecule or a molecule present on the surface of a pathogen (**Fig. 1-5A**). Activation of a B cell in this way causes it to proliferate and produce

(A)



(B)



(C)

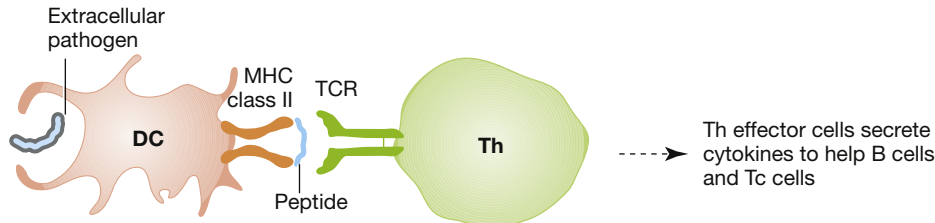


Fig. 1-5
Antigen Recognition and Effector Functions of B, Tc and Th Cells

(A) The BCR of a B cell binds directly to an antigen present on an extracellular pathogen, resulting in production of plasma cells (PCs). Antibody secreted by PCs leads to clearance of the pathogen. (B) The TCR on a Tc cell recognizes a pMHC complex composed of an antigenic peptide that is derived from an intracellular pathogen and presented on the MHC class I molecule of a DC. The Tc cell becomes activated and produces CTLs that can lyse cells infected with the same pathogen. (C) The TCR on a Th cell recognizes a pMHC complex composed of an antigenic peptide that is derived from an extracellular pathogen and presented on the MHC class II molecule of a DC. Th effector cells secrete cytokines to help B cells and Tc cells.

Antibody production by B cells is described in detail in Chapters 4 and 5.

“MHC” stands for “major histocompatibility complex,” a region on human chromosome 6 that contains genes encoding several types of molecules vital for the adaptive immune response. MHC genes and proteins are described in detail in Chapter 6.

identical daughter effector cells called **plasma cells** that secrete vast quantities of specific antibody. An **antibody** is a protein that is a modified, soluble form of the original B cell’s membrane-bound antigen receptor. Antibody molecules enter the host’s circulation and tissues, bind to the specific antigen, and mark it for clearance from the body, establishing a humoral response. Since antibodies are present in the extracellular milieu, such a response is effective against extracellular pathogens. However, antibodies are unable to penetrate cell membranes and so cannot attack an intracellular pathogen once it has entered a host cell.

Unlike BCRs, TCRs are unable to recognize whole, native antigens. Rather, a TCR recognizes a bipartite structure displayed on the surface of a host cell. This bipartite structure is made up of a host surface protein called an **MHC molecule** bound to a short peptide derived from a protein antigen. This complex is referred to as a **peptide–MHC complex (pMHC)**. Tc and Th cells are activated by the binding of their TCRs to specific pMHCs presented on the surface of a DC. DCs can acquire extracellular pathogen antigens by phagocytosis, and intracellular pathogen antigens either by infection or by phagocytosis of the debris of dead infected cells. Peptides from these antigens are bound to one of two types of MHC molecules, either **MHC class I** or **MHC class II**, and then displayed on the DC surface for inspection by T cells.

Tc cells recognize antigenic peptides that the DC has presented on MHC class I molecules (**Fig. 1-5B**). The activated Tc cell proliferates and differentiates into identical daughter effector cells called, for historical reasons, CTLs (cytotoxic T lymphocytes). CTLs can lyse any host cell displaying the same peptide–MHC class I complex recognized by the original Tc cell. MHC class I molecules are expressed on almost all body cells, making them all potential targets for CTL-mediated lysis. However, unlike DCs, most host cells cannot phagocytose extracellular entities. It is therefore only after infection with an intracellular pathogen that a host cell displays an antigenic pMHC complex that can be recognized by the TCR of first the Tc cell and then its daughter CTLs. The cell-mediated immunity directed against such infected host cells is critical to the clearance of intracellular pathogens.

Th cells recognize antigenic peptides that a DC has presented on MHC class II molecules (**Fig. 1-5C**). The activated Th cell proliferates and differentiates into identical Th effector cells that can recognize the same pMHC structure that activated the original Th cell. However, MHC class II molecules are expressed only by certain cell types that can act as specialized **antigen-presenting cells (APCs)**, including DCs, macrophages and activated B cells. In the course of a pathogen attack, APCs can capture the pathogen and/or its products or components, and then display peptides derived from its antigens on MHC class II. When the TCR of a Th effector cell recognizes this pMHC structure, the cell is stimulated to produce cytokines that assist B cells and Tc cells to become fully activated. In this way, Th cells contribute to both humoral and cell-mediated adaptive responses, and are thus crucial for protection against many extracellular and intracellular pathogens. In addition, cytokines secreted by Th cells stimulate innate leukocytes, thereby reinforcing this arm of immunity. The combined efforts of Tc, Th and B lymphocytes and many types of innate leukocytes may be necessary to eliminate a particularly wily invader.

iii) Immunological Memory

The innate response deals with a given threat in a very similar way each time it enters the body. In contrast, the adaptive system can “remember” that it has seen a particular antigen before. This **immunological memory** means that an enhanced adaptive response is mounted upon a second and subsequent exposures to a given pathogen, so that signs of clinical illness are mitigated or prevented. In other words, immunity is achieved because the body has effectively “adapted” its defenses and acquired the ability to exclude a particular pathogen.

Immunological memory arises in the following way. A constant supply of resting B and T cells is maintained throughout the body, with each lymphocyte expressing its complement of unique antigen receptor proteins. When a pathogen antigen enters the

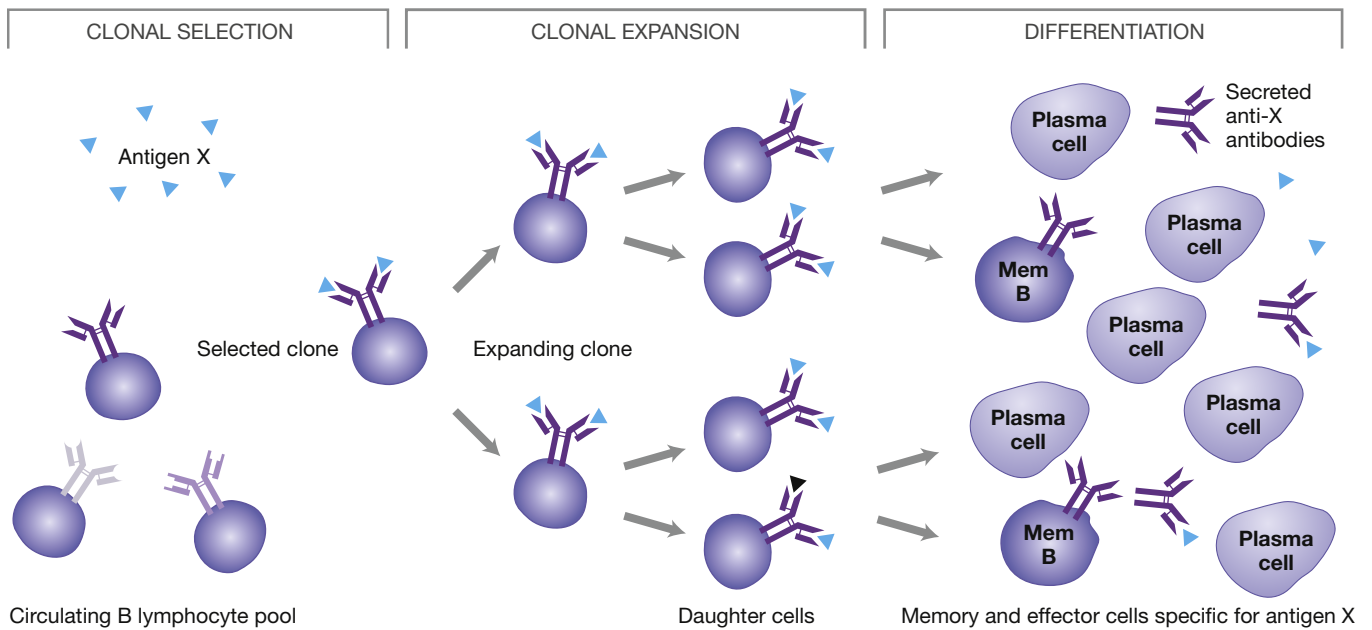


Fig. 1-6
Clonal Selection and Generation of Memory and Effector Lymphocytes

When antigen X enters the body, only those lymphocytes with receptors that specifically recognize X will be selected to proliferate and generate daughter cells that differentiate into effector cells and memory cells. This figure illustrates this principle for B cells, where antigen X triggers the generation of plasma cell effectors and memory B cells (Mem B) specific for antigen X.

body for the first time, a process of **clonal selection** takes place in which only those lymphocytes bearing receptors specific for that antigen are triggered to respond. The selected cells leave the resting state and multiply to generate daughter cells all expressing the same antigen-specific BCR or TCR. The differentiation of these daughter cells gives rise to the short-lived effector cells required to eliminate the pathogen, as well as long-lived **memory cells** that persist in the tissues essentially in a resting state until a subsequent exposure to the same pathogen (**Fig. 1-6**). The attack on the pathogen by this first round of effector cells is called the **primary immune response**. The second (or subsequent) time that the particular pathogen enters the body, it is met by an expanded army of clonally selected, antigen-specific memory cells that undergo much more rapid differentiation into effector cells than occurred during the first antigen encounter. The result is a stronger and faster **secondary immune response** that eliminates the pathogen before it can cause illness. New populations of memory cells are also produced during the secondary response, ensuring that the host maintains long-term or even lifelong immunity to that pathogen.

NOTE: The generation of protective memory lymphocytes is the basis of vaccination. A healthy person is immunized with a vaccine containing pathogen antigens in order to provoke the production of memory cells that will prevent disease from developing if the individual is ever naturally infected by that pathogen. Vaccination is described in detail in Chapter 14.

Clonal selection is explained in detail in Chapter 5 for B cells and in Chapter 9 for T cells.

iv) Diversity

The degree of diversity of antigens recognized also distinguishes the adaptive response from the innate response. Whereas the innate immune system exhibits a genetically fixed and finite capacity for antigen recognition, the recognition capacity of the adaptive immune system is nearly limitless. In fact, our bodies are capable of recognizing totally synthetic antigens that do not occur in nature. This huge diversity arises from the combined actions of several genetic mechanisms that affect the genes encoding the

Somatic recombination, the process that shuffles the DNA of the genes encoding BCRs in B cells and TCRs in T cells, is achieved by specialized genetic mechanisms that are described in Chapter 4 for B cells and Chapter 8 for T cells.

The establishment of central tolerance during lymphocyte development is described in Chapter 5 for B cells and in Chapter 9 for T cells. Processes regulating mature lymphocytes, including mechanisms of peripheral tolerance, are described in Chapter 10.

antigen receptors. Some of these mechanisms operate before a lymphocyte encounters antigen, and some after.

The primary source of antigen receptor diversity is a gene rearrangement process that occurs during the development of B cells and T cells *prior* to encounter with antigen. The genes encoding antigen receptors are not individual continuous entities. Rather, the BCR and TCR genes are assembled from a large collection of pre-existing gene segments by a mechanism called **somatic recombination**. A single, random combination of gene segments is thus created in each developing lymphocyte. As a result, a lymphocyte population is generated in which the antigen receptor proteins are vastly diverse in specificity because they are encoded by hundreds of thousands of different DNA sequences. In the case of B cells, additional mutational mechanisms operate that result in further structural diversification of antibody proteins. The sheer numbers of B and T lymphocyte clones generated in a healthy individual guarantee that there will be at least one clone expressing a unique receptor sequence for every antigen encountered during the host's life span. As alluded to previously, these clones, with their array of antigen receptor specificities, are collectively called the individual's *lymphocyte repertoire*.

v) Tolerance

The generation of lymphocyte clones that can theoretically recognize any antigen in the universe raises the question of how the body avoids lymphocyte attacks on molecules present in its tissues. This avoidance is called **tolerance**, the fifth aspect in which the adaptive response exhibits more refinement than the innate response. As stated previously, the specificity of each antigen receptor is randomly determined by somatic recombination during early lymphocyte development. By chance, some of the genetic sequences produced will encode receptors that recognize self molecules (*self antigens*). These lymphocytes must be identified as recognizing self and then either removed from the body entirely, or at least inactivated, to ensure that an individual has an effective lymphocyte repertoire that does not attack healthy tissue. Tolerance is established in two broad stages, each of which involves multiple mechanisms. The first stage, called **central tolerance**, occurs during early lymphocyte development. The mechanisms of central tolerance are designed to eliminate clones that recognize self antigens, thus establishing a lymphocyte repertoire that targets "non-self." In the second stage, called **peripheral tolerance**, any B and T lymphocytes that recognize self but somehow escaped the screening of central tolerance and completed their development are functionally silenced by another set of inactivating mechanisms.

D. Interplay between the Innate and Adaptive Responses

Although we described the innate and adaptive responses separately in the preceding sections, in reality, they occur in a continuum that brings stronger and stronger weaponry to bear when (and only when) it is needed. Our bodies normally deal with a pathogen attack in three broad and overlapping phases, two of which involve innate responses and the last of which requires adaptive immunity (**Fig. 1-7**). An individual pathogen, such as a single influenza virus particle, is dealt with by these phases sequentially, but because the actual assault on the host involves billions of such particles, not every particle is in the same phase at the same time. As a result, in the host as a whole, and for an infecting pathogen population as a whole, all three phases may be happening concurrently.

The first phase is mediated by the innate physical barriers, which offer immediate protection. The components making up these barriers (skin, mucosae, gut enzymes) are non-inducible in that they pre-exist and do not develop or change in response to the presence of a foreign entity. Should these barriers be penetrated, the second, inducible phase of innate defense becomes effective 4–96 hours after the threat enters

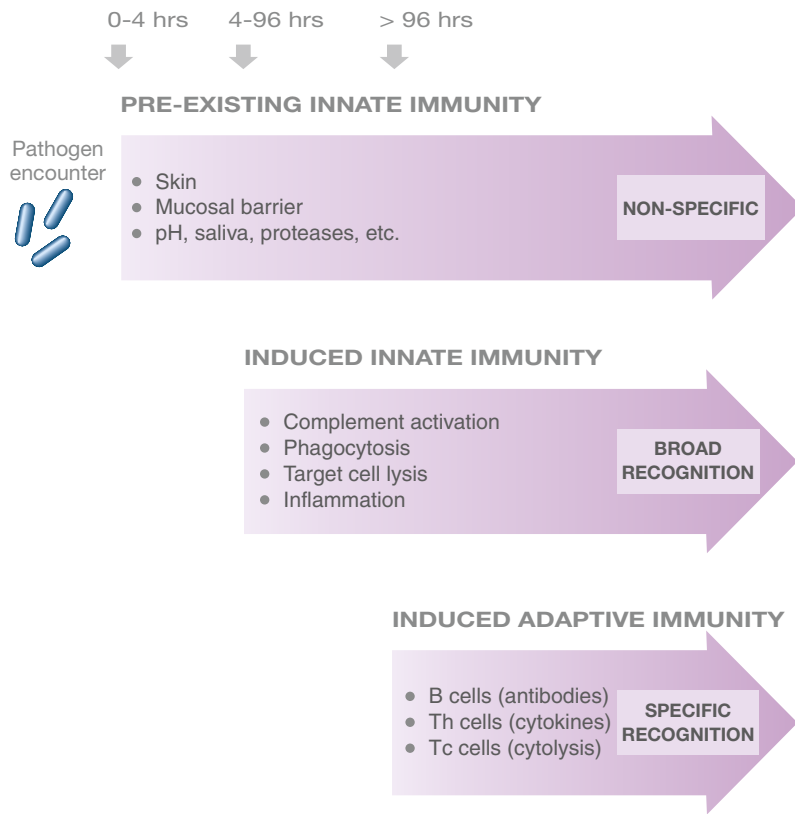


Fig. 1-7
The Three Phases of Host Immune Defense

A pathogen attempting to enter the body first encounters pre-existing barriers and enzymes that block access non-specifically. If the pathogen manages to enter the underlying cell layer, mechanisms mediated by complement and innate leukocytes are induced due to relatively broad recognition of PAMPs. If a more targeted, pathogen-specific response becomes necessary, elements of innate immunity then facilitate induction of highly specific adaptive responses initiated by engagement of the antigen receptors of B, Th or Tc lymphocytes.

the body. Innate leukocytes activated by the binding of PRRs to PAMPs provided by the attacking pathogen, or to DAMPs present due to host cell injury or death, work quickly to eliminate the invader using the mechanisms of inflammation, phagocytosis and target cell lysis. Complement activation also contributes to clearance at this stage. In many cases, the incursion is completely controlled by the two phases of innate defense before adaptive immunity is even triggered. However, the cells of the innate response are ultimately limited both in numbers and in recognition capacity. Fortunately, even if the pathogen ultimately manages to thwart complete elimination by innate immunity, some of the invaders and/or their components or products will have been taken up by innate leukocytes and presented as foreign antigens to T lymphocytes. The third and final phase of host defense mediated by adaptive immunity is thus initiated. Th, Tc and B cells are clonally selected and activated, and then proliferate and differentiate into memory cells and large numbers of daughter effector cells that eliminate the pathogen via humoral and/or cell-mediated mechanisms. Because it takes time for the clonally selected lymphocytes to produce effector cells, adaptive responses are not usually observed until at least 96 hours after the start of infection.

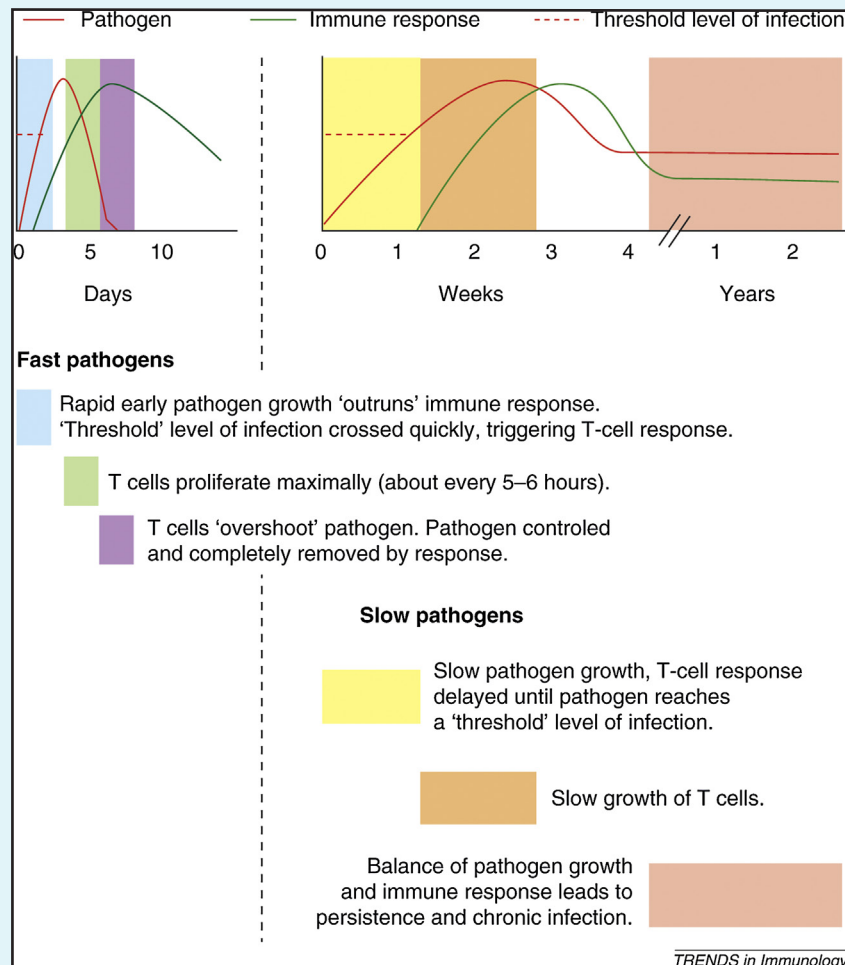
The second and third phases of immune defense are more tightly interwoven than it may first appear. Innate and adaptive immunity do not operate in isolation, and each depends on or is enhanced by elements of the other (**Fig. 1-8**). The lymphocytes of the adaptive response require the involvement of cells and cytokines of the innate system to become activated and undergo differentiation into effector and memory lymphocytes. Conversely, activated lymphocytes secrete products that stimulate and improve the effectiveness of innate leukocytes. The interplay between innate and adaptive immunity is sustained by cytokine signaling and through direct intercellular contacts between innate and adaptive leukocytes. By cooperating in this way, innate and adaptive immunity combine to mount an optimal defense against pathogens.

Focus on Relevant Research

"The Race between Infection and Immunity: How do Pathogens Set the Pace?" by Davenport, M.P., Belz, G. T. and Ribeiro, R.M., (2009) *Trends in Immunology* 30, 61–66.

Normal host homeostasis is re-established when the host wins (at least for that moment) the ongoing horse race between the host's immune system and a pathogen attempting to establish infection. Pathogens replicate at widely divergent rates, with some bacteria and viruses able to double their population size within a couple of hours. Fast-replicating pathogens therefore initially get ahead of the host's immune defenses, but then are caught and destroyed as the specialized cells of the immune system become activated. The mystery highlighted by the authors of this article is why slow-replicating pathogens are able to establish infections at all, and why so many of the most damaging chronic infections we experience, like those of the hepatitis B and C viruses and the bacteria causing tuberculosis, are caused by some of the slowest-replicating pathogens. The answer may lie in achieving certain threshold levels of infection that supply adequate amounts of the molecular triggers needed to spark first the innate response and then the adaptive response. If a pathogen

replicates rapidly, large amounts of DAMPs and PAMPs are present that immediately activate innate leukocytes, including the APCs needed to initiate T cell responses. These T cells proliferate quickly enough to overwhelm the pathogen and eliminate it. In contrast, a slow-replicating pathogen may generate only low levels of DAMPs and PAMPs that do not activate large numbers of APCs, delaying the T cell response. Even once the T cell response is initiated, without sufficient cytokines produced by activated APCs, T cell proliferation may be slow and insufficient to completely eliminate the pathogen. The pathogen then survives to establish a low level of infection that doesn't kill the host but makes him/her miserable. The memory T cell response is of little help, as it only controls rather than eliminates the slow-replicating pathogen. An uneasy balance is set up between the pathogen and the host immune system that results in chronic infection. The contrast in immune response kinetics between what the authors call "fast" and "slow" pathogens is illustrated in Figure 1 from their article.



The pace of pathogen replication may have implications for vaccination strategies. Currently, vaccination often uses a harmless pathogen antigen to induce the host to respond and generate large populations of memory lymphocytes, which stand guard ready to mount a faster and stronger response should the real pathogen attack. For a fast-replicating pathogen, this tactic is successful because these types of pathogens readily generate enough PAMPs, DAMPs and antigen to surpass the thresholds of APC and T cell activation. With the “head start” provided by memory lymphocytes, the pathogen may not get to replicate at all. However, a slow-replicating pathogen

Focus on Relevant Research–Cont'd

may not provide sufficient antigen to reach even the lower threshold required by memory T cells, meaning that the vaccine will not have offered an advantage to the host. Worse, if the large numbers of memory T cells present after vaccination compete for the miserly quantities of antigen present, and so proliferate only slowly, the pathogen may in fact get a better foothold than if the host had NOT been vaccinated. These considerations should encourage us to experimentally test the threshold hypothesis and to refine our approach to vaccination accordingly.

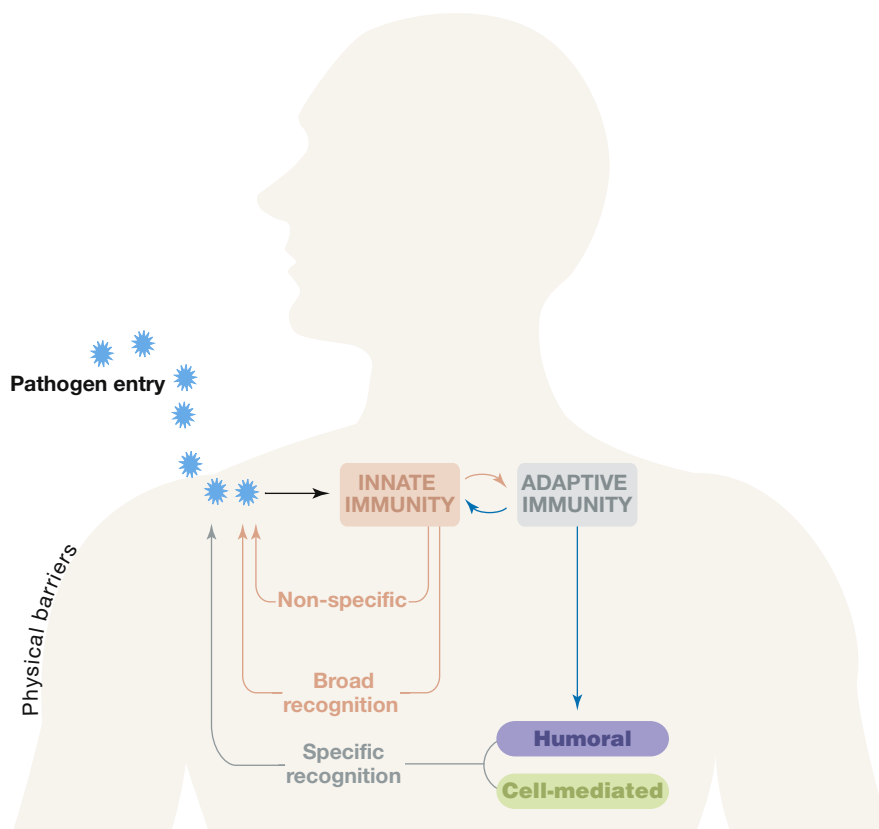


Fig. 1-8
Interplay between Innate and Adaptive Responses in Host Defense

Innate and adaptive immune mechanisms work together to allow a full range of responses of appropriate strength and specificity. In addition to their direct and broadly protective role, innate immune responses recruit adaptive leukocytes and contribute to their activation. Once activated, lymphocytes mount humoral and cell-mediated anti-pathogen responses that are highly specific. Cytokines are produced that further stimulate both the innate and adaptive responses. Innate and adaptive immunity thus work synergistically to protect the host from all threats.

E. Clinical Immunology

When the immune system is functioning normally, harmful entities are recognized, and the host is protected from external attack by pathogens and internal attack by cancers. Some localized tissue damage may result from the normal inflammatory response that develops as innate leukocytes work to eliminate the threat, but these immunopathic effects are limited and controlled. As well, the tolerance of the healthy immune system prevents cells of the adaptive response from attacking normal self tissues.

Sometimes a person's immune system is incomplete, either because of **primary immunodeficiency** or **acquired immunodeficiency**. In primary immunodeficiencies, the failure of the immune system is congenital; that is, an affected individual is born with a genetic defect that impairs his/her ability to mount innate and/or adaptive immune responses. In an acquired immunodeficiency, an external factor such as a nutritional

A healthy immune response is crucial for providing an individual with immunity to infectious diseases (Ch. 13) and may be made more robust through vaccination (Ch. 14).

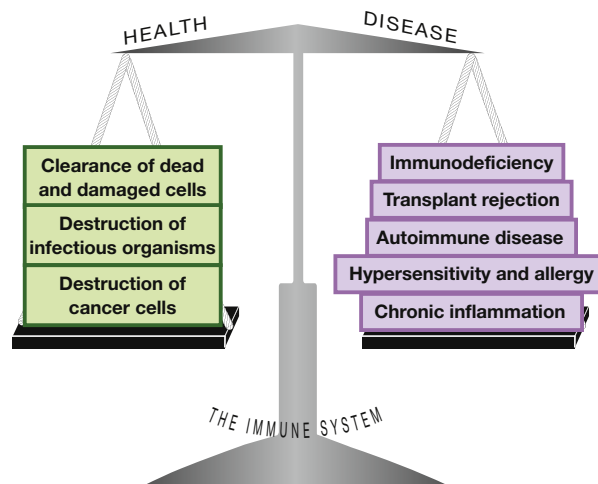


Fig. 1-9
Role of the Immune System in Health and Disease

The way in which the immune system responds can maintain a healthy body or lead to disease. In a healthy individual, the immune system mounts an appropriate response that clears damaged cells and kills infectious organisms or cancerous cells. However, the immune system is a powerful and multi-faceted weapon that requires strict controls to remain in balance. When the immune system fails to respond adequately, or mounts an overzealous or inappropriate attack, or ignores normal control mechanisms, a wide variety of disease states can result.

imbalance or a pathogen may cause the loss of an immune system component. For example, in acquired immunodeficiency syndrome (AIDS), the human immunodeficiency virus (HIV) destroys the T lymphocytes needed to fight infection. In both primary and acquired immunodeficiencies, patients show a heightened susceptibility to recurrent infections and sometimes develop tumors. The prognosis for most of these diseases is very poor and treatment options are limited.

What happens when the immune system is complete but malfunctions, or when its normal functioning has undesirable effects? There are several instances in which inappropriate actions of the immune system can result in pathologic consequences that tip the balance from health to disease (**Fig. 1-9**). Firstly, the normal attack of a healthy immune system on a foreign tissue transplant meant to preserve life results in **transplant rejection** and deleterious consequences for the transplant patient. Secondly, when the tolerance of an individual's adaptive immune response fails, self tissues are attacked in a way that can lead to **autoimmune disease**. Thirdly, an immune response that is too strong or long can result in **hypersensitivity** to an entity. In this situation, the normal inflammation that accompanies the response gets out of control and causes significant collateral tissue damage. When an individual's normal adaptive immune system responds inappropriately to an antigen that is generally harmless, the immune response is manifested clinically as a form of hypersensitivity called **allergy**. Lastly, if normal regulation of the inflammatory response is lost for an extended period for any reason, chronic inflammation ensues that can set up conditions allowing the development of tumors, heart disease or autoimmune disorders.

The remainder of this book will take the reader on a logical tour of the immune response. Chapter 2 continues our Basic Immunology section, providing detailed descriptions of the various cells, tissues and cytokines involved in mediating immune responses. Chapters 3–12 cover all aspects of the innate and adaptive immune responses in depth. The chapters in our Clinical Immunology section, Chapters 13–20, address immunological principles not only of practical value to the more medically oriented reader but also of interest to all who seek to understand the pivotal role of the immune system in health and disease. It is our hope that the reader will come away with a solid understanding of the cellular and molecular mechanisms underlying immunity and how these mechanisms can go awry to cause illness. We also provide a glimpse of how researchers seek to manipulate these mechanisms with the goal of ensuring good health for all.

The pathological consequences of immune system irregularities include immunodeficiency (Ch. 15), cancer (Ch. 16 and 20), transplant rejection (Ch. 17), hypersensitivity (Ch. 18) and autoimmune disease (Ch. 19).

Chapter 1 Take-Home Message

- The immune system is a central player in the maintenance of human health.
- Immune responses depend on the coordinated action of leukocytes that travel throughout the body to recognize and eliminate threats posed by trauma as well as by extracellular and intracellular pathogens, toxins and cancerous cells.
- Cytokines are secreted intercellular messenger proteins that mediate complex interactions among leukocytes.
- Complete protection from and clearance of unwanted entities often involve both innate and adaptive responses.
- Some innate mechanisms require no induction and are completely non-specific, whereas others are inducible and involve broad recognition of a limited number of molecular patterns (PAMPS and DAMPs) by PRMs.
- Adaptive responses are mounted after innate responses have failed to remove an unwanted entity, and are dependent on cytokines produced during the innate response.
- Adaptive immunity involves the selective activation of lymphocytes by the engagement of their antigen receptors by antigens derived from the particular inciting entity.
- The three subsets of lymphocytes are Th, Tc and B cells, which use distinct mechanisms to recognize antigen and carry out effector functions to eliminate specific entities.
- Elements of innate immunity influence adaptive immunity and vice versa.
- Malfunctions of the immune system are related to autoimmune disorders, allergy and other hypersensitivities, transplantation rejection, primary and acquired immunodeficiencies, chronic inflammation, and cancer development.

Did You Get it? A Self-Test Quiz

Section A

- 1) Can you define these terms? immunology, immune system, immunity, pathogen
- 2) What was Koch's theory and why was it important?
- 3) Who coined the term "vaccination" and on what basis?

Section B

- 1) Can you define these terms? homeostasis, mucosae, leukocyte, cytokine, immunopathic
- 2) What is the difference between infection and disease?
- 3) What is the major difference between extracellular and intracellular pathogens?
- 4) Distinguish between cell-mediated and humoral immunity.

Section C

- 1) Can you define these terms? senescent, phagocytosis, inflammation, PRM, PRR, MHC, lymphocyte, TCR, BCR, antibody, clonal selection, tolerance, self antigen, immunological memory
- 2) What are three major differences between innate and adaptive immune responses?
- 3) Distinguish between DAMPs and PAMPs.

- 4) Distinguish between PRMs and antigen receptors.
- 5) Can you give two examples of innate barrier defenses?
- 6) Describe three types of PRMs.
- 7) Is inflammation good or bad, and why?
- 8) How does target cell lysis help protect the body?
- 9) Describe five important characteristics of the adaptive response.
- 10) How do Th, Tc and B cells differ in antigen recognition?
- 11) How does each lymphocyte subset contribute to immunity against extracellular and/or intracellular pathogens?
- 12) Why is the secondary immune response stronger and faster than the primary response?
- 13) What are the two stages of tolerance?

Section D

- 1) Can you describe the three phases of immune defense and the components that mediate them?
- 2) How do the innate and adaptive responses influence each other and why is this important?

Section E

- 1) Can you describe four examples of diseases arising from immune system failure?

Can You Extrapolate? Some Conceptual Questions

- 1) Two patients have experienced the piercing of their skin by a metal object. Patient #1 is having surgery in the course of an elective hip replacement in a modern hospital. Patient #2 is not so lucky and has stepped on a rusty nail in her garden. What sort of DAMPs and/or PAMPs might be present in each case, and what sorts of immune responses might you expect to find in these patients?
- 2) If a person's immune system was unable to produce memory lymphocytes, how would this affect his/her innate and adaptive responses upon repeated exposure to a given pathogen?
- 3) Why are B lymphocyte responses usually associated with defense against extracellular rather than intracellular pathogens? How might they also help protect a host against intracellular pathogens?

Would You Like To Read More?

Chaplin, D. D. (2010). Overview of the immune response. *Journal of Allergy & Clinical Immunology*, 125(Issue 2, Suppl 2), S3–23.

Iwasaki, A., & Medzhitov, R. (2010). Regulation of adaptive immunity by the innate immune system. *Science*, 327(5963), 291–295.

Matzinger, P. (2007). Friendly and dangerous signals: Is the tissue in control? *Nature Immunology*, 8(1), 11–13.

Moser, M., & Leo, O. (2010). Key concepts in immunology. *Vaccine*, 28(Suppl 3), 2–13.