Immune system

Immune Cells

The cells of the immune system are the various types of white blood cells collectively known as **leukocytes;** representative histological appearances of some of these can be seen in the human blood smear.

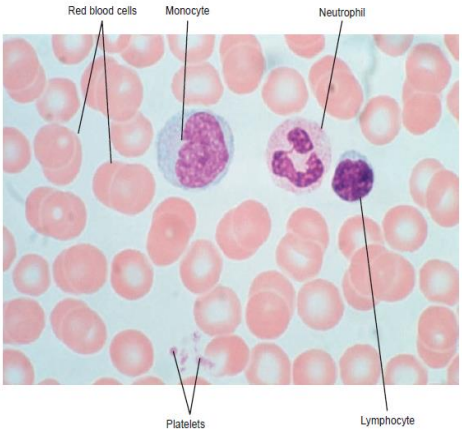


Figure 18.1 AP|R A light micrograph of a human blood smear showing the histological appearance of a few types of leukocytes along with numerous red blood cells and platelets.

Unlike erythrocytes, leukocytes can leave the circulatory system to enter the tissues where they function. Leukocytes can be classified into two groups:

1. The myeloid cells include the **neutrophils, basophils , eosinophils ,** and **monocytes**
2. Lymphoid cells include several types of **lymphocytes ,** including **B lymphocytes** (**B cells**) , **T lymphocytes** (**T cells**) , **natural killer** (**NK**) **cells ,** and **plasma cells .**

Plasma cells are not really a distinct cell type but differentiate from B lymphocytes during immune responses. The major functions of *plasma cells are to synthesize and secrete antibodies*. The functions of the other lymphocytes will be described shortly.

Macrophages; these are found in virtually all organs and tissues, their structures varying somewhat from location to location. They are ***derived***

from monocytes that pass through the walls of *blood vessels to enter the tissues* and transform into macrophages. In keeping with one of their major functions, *the engulfing of particles and pathogens by phagocytosis (the form of endocytosis whereby a cell engulfs and usually destroys particulate matter),*

Macrophages are *strategically placed* where they will encounter their targets.(why??) they are found in large numbers in the various epithelia in contact with the external environment, such as the skin and internal surfaces of respiratory and digestive system tubes. In several organs, they line the vessels through which blood or lymph flows.

- There are also cell populations that are not macrophages but exert certain macrophage-like functions such as phagocytosis.

Dendritic cells because of the characteristic extensions from their plasma membranes at certain stages of their life cycle (not to be confused with the dendrites found on neurons). They are highly motile and are found scattered in almost all tissues, but particularly at sites where the internal and external environments meet, such as the digestive tract. Upon activation, dendritic cells process phagocytized pathogens and migrate through the lymphatic vessels to secondary lymphoid organs where they activate T cells.

Mast cells are found throughout connective tissues, particularly beneath the epithelial surfaces of the body. They are derived from the differentiation of a unique set of bone marrow cells that have entered the blood and then left the blood vessels to enter connective tissue, where they differentiate and undergo cell division. Consequently, mature mast cells—unlike basophils, with which they share many characteristics—are not normally found in the blood. The most striking anatomical feature of mast cells is their very large number of

cytosolic vesicles, which *secrete locally acting chemical messengers such as histamine*.

TABLE 18.1 Cells Mediating Immune Responses

Name	Site Produced	Functions
Leukocytes (white blood cells)		
Neutrophils	Bone marrow	1. Phagocytosis 2. Release chemicals involved in inflammation (vasodilators, chemotaxins, etc.)
Basophils	Bone marrow	Carry out functions in blood similar to those of mast cells in tissues (see below)
Eosinophils	Bone marrow	1. Destroy multicellular parasites 2. Participate in immediate hypersensitivity reactions
Monocytes	Bone marrow	1. Carry out functions in blood similar to those of macrophages in tissues (see below) 2. Enter tissues and transform into macrophages
Lymphocytes	Mature in bone marrow (B cells and NK cells) and thymus (T cells); activated in peripheral lymphoid organs	Serve as recognition cells in specific immune responses and are essential for all aspects of these responses
B cells		1. Initiate antibody-mediated immune responses by binding specific antigens to the B cell's plasma membrane receptors, which are immunoglobulins 2. Upon activation, are transformed into plasma cells, which secrete antibodies 3. Present antigen to helper T cells
Cytotoxic T cells (CD8 cells)		Bind to antigens on plasma membrane of target cells (virus-infected cells, cancer cells, and tissue transplants) and directly destroy the cells
Helper T cells (CD4 cells)		Secrete cytokines that help to activate B cells, cytotoxic T cells, NK cells, and macrophages
NK cells		1. Bind directly and nonspecifically to virus-infected cells and cancer cells and kill them 2. Function as killer cells in antibody-dependent cellular cytotoxicity (ADCC)
Plasma cells	Peripheral lymphoid organs; differentiate from B cells during immune responses	Secrete antibodies
Macrophages	Bone marrow; reside in almost all tissues and organs; differentiate from monocytes	1. Phagocytosis 2. Extracellular killing via secretion of toxic chemicals 3. Process and present antigens to helper T cells 4. Secrete cytokines involved in inflammation, activation and differentiation of helper T cells, and systemic responses to infection or injury (the acute phase response)
Dendritic cells	Almost all tissues and organs; microglia in the central nervous system	Phagocytosis, antigen presentation
Mast cells	Bone marrow; reside in almost all tissues and organs; differentiate from bone marrow cells	Release histamine and other chemicals involved in inflammation

For now, we emphasize two points.

First, lymphocytes serve as recognition cells in adaptive immune responses and are essential for all aspects of these responses.

Second, neutrophils, monocytes, macrophages, and dendritic cells have a variety of activities, but particularly important is their *ability to secrete inflammatory mediators and to function as* ***phagocytes*****.** A phagocyte denotes any cell capable of phagocytosis.

Cytokines

The cells of the immune system secrete a multitude of protein messengers that regulate host cell division (mitosis) and function in both innate and adaptive immune responses. **Cytokines"** is the collective term for these messengers, each of which has its own unique name. Cytokines are produced not by distinct specialized glands but rather by a variety of individual cells.

The great majority of their actions occur at the site at which they are secreted, the cytokine acting as

1. autocrine or paracrine substance.
2. Cytokine circulates in the blood to exert hormonal effects on distant organs and tissues involved in host defenses.
3. Cytokines link the components of the immune system together. They are the chemical communication network that allows different immune system cells to "talk" to one another. This is called *cross talk*, and it is essential for the precise timing of the functions of the immune system.

Most cytokines are secreted by more than one type of immune system cell and by non-immune cells as well (for example, by endothelial cells and fibroblasts).

This often produces cascades of cytokine secretion, in which one cytokine stimulates the release of another, and so on.

Any given cytokine may exert actions on an extremely broad range of target cells. For example, the ***cytokine interleukin 2*** influences the function of most cells of the immune system. There is great redundancy in cytokine action; that is, different cytokines can have very similar effects. Cytokines are also involved in many non-immunologic processes, such as bone formation and uterine function.

TABLE 18.2 Features of Selected* Cytokines

Cytokine	Source	Target Cells	Major Functions
Interleukin 1, tumor necrosis factor-alpha, and interleukin 6	Antigen-presenting cells such as macrophages	Helper T cells; certain brain cells; numerous systemic cells	Stimulate IL-2 receptor expression; induce fever; stimulate systemic responses to inflammation, infection, and injury
Interleukin 2	Most immune cells	Helper T cells; cytotoxic T cells; NK cells; B cells	Stimulate proliferation Promote conversion to plasma cells
Interferons (type I)	Most cell types	Most cell types	Stimulate cells to produce antiviral proteins (innate response)
Interferons (type II)	NK cells and activated helper T cells	NK cells and macrophages	Stimulate proliferation and secretion of cytotoxic compounds
Chemokines	Damaged cells, including endothelial cells	Neutrophils and other leukocytes	Facilitate accumulation of leukocytes at sites of injury and inflammation
Colony-stimulating factors	Macrophages	Bone marrow	Stimulate proliferation of neutrophils and monocytes

*Note: This list is not meant to be exhaustive. There are . 100 known cytokines.

Innate Immune Responses

Innate immune responses defend against foreign cells or matter without having to recognize specific identities. These defenses recognize some ***general molecular property marking the invader as foreign such as***

1. Identity tags are often found in particular classes of carbohydrates or lipids that are in microbial cell walls
2. Plasma membrane receptors on certain immune cells
3. Variety of circulating proteins (particularly a family of proteins called complement), can bind to these carbohydrates and lipids at crucial steps in innate responses.

This use of a system based on carbohydrate and lipid for detecting the presence of foreign cells is a key feature that distinguishes innate responses from adaptive ones, which recognize foreign cells mainly by specific proteins the foreign cells produce.

Defenses at Body Surfaces

These including

1. The skin which is first lines of defense against pathogens are the barriers offered by surfaces exposed to the external environment, because very few pathogens can penetrate the intact skin.
2. The hairs at the entrance to the nose and the cough and sneeze reflexes.
3. A various skin glands, salivary glands, and lacrimal (tear) glands play a more active role in immunity by secreting antimicrobial chemicals.

These chemicals may include

1. Antibodies
2. enzymes such as lysozyme, which destroys bacterial cell walls;
3. Iron-binding protein called lactoferrin, which prevents bacteria from obtaining the iron they require to function properly.

4. The mucus secreted by the epithelial linings of the respiratory and upper gastrointestinal tracts also contains antimicrobial chemicals; more importantly, however, mucus is sticky. Particles that adhere to it are prevented from entering the blood. They are either swept by ciliary action up into the pharynx or then swallowed, as occurs in the upper respiratory tract, or are phagocytosed by macrophages in the various linings.
5. The acid secretion of the stomach can also kill pathogens, although some bacteria can survive to colonize the large intestine where they provide beneficial gastrointestinal functions.

Inflammation

Inflammation is the local response to infection or injury. The functions of inflammation are to destroy or inactivate foreign invaders and to set the stage for tissue repair. The key mediators are the cells that function as phagocytes. As noted earlier, the most important phagocytes are **neutrophils, macrophages, and dendritic cells**.

the responses for inflammations can be elicited by a variety of other injuries—***cold, heat, and trauma***, for example.

The sequence of local events in a typical innate inflammatory response to a bacterial infection(one caused, for example, by a cut with a bacteria-covered splinter)

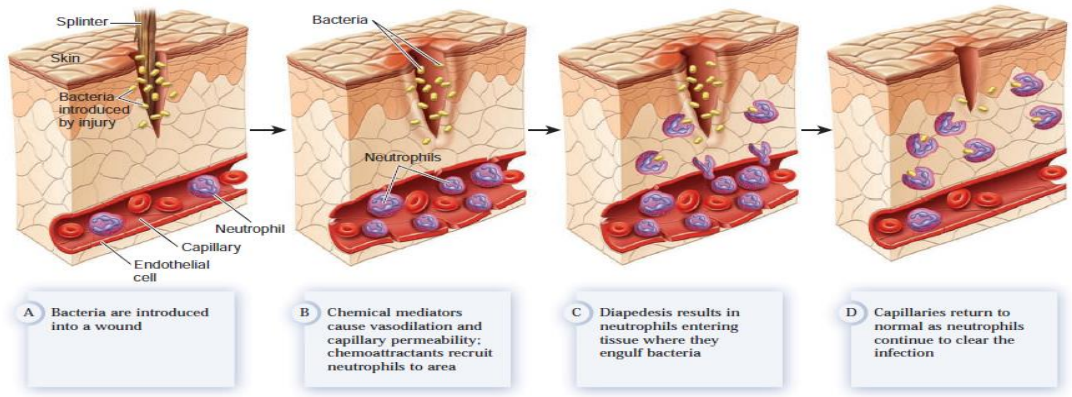


Figure 18.2 AP|R The local inflammatory events occurring in response to a wound.

The familiar signs of tissue injury and inflammation are local redness, swelling, heat, and pain. The events of inflammation that underlie these signs are induced and regulated by a large number of chemical mediators,

TABLE 18.3 Some Important Local Inflammatory Mediators

Mediator	Source
Kinins	Generated from enzymatic action on plasma proteins
Complement	Generated from enzymatic action on plasma proteins
Products of blood clotting	Generated from enzymatic action on plasma proteins
Histamine	Secreted by mast cells and injured cells
Eicosanoids	Secreted by many cell types including myeloid cells
Platelet-activating factor	Secreted by many cell types including myeloid cells, endothelial cells, platelets, damaged tissue cells
Cytokines, including chemokines	Secreted by activated immune cells, monocytes, macrophages, neutrophils, lymphocytes, and several nonimmune cell types, including endothelial cells and fibroblasts
Lysosomal enzymes, nitric oxide, and other oxygen-derived substances	Secreted by injured cells, neutrophils, and macrophages

The mediators fall into two general categories:

(1) Peptides (kinins, for example) generated in the infected area by enzymatic actions on proteins that circulate in the plasma

(2) Substances secreted into the extracellular fluid from cells that either already exist in the infected area (injured cells or mast cells, for example) or enter it during inflammation (neutrophils, for example).

If the invading bacteria enter the blood or lymph, then similar inflammatory responses would take place in any other tissue or organ the blood-borne or lymph-borne microorganisms reach.

Vasodilation and Increased Permeability to Protein

A variety of chemical mediators dilate most of the microcirculation vessels in an infected and/or damaged area. The mediators also cause the local capillaries and venules to become *permeable to proteins by inducing their endothelial cells to contract, opening spaces between them through which the proteins can move.*

The adaptive value of these vascular changes is twofold:

(1) The increased blood flow to the inflamed area (which accounts for the redness and warmth) increases the delivery of proteins and leukocytes; and (2) the increased permeability to protein ensures that the plasma proteins that participate in inflammation—many of which are normally restrained by the intact endothelium—can gain entry to the interstitial fluid.

the vasodilation and increased permeability to protein, however, cause net filtration of plasma into the interstitial fluid and the development of edema. This accounts for the swelling in an inflamed area, which is simply a consequence of the changes in the microcirculation and has no known adaptive value of its own.

Chemotaxis

With the onset of inflammation, circulating neutrophils begin to move out of the blood across the endothelium of capillaries and venules to enter the inflamed area.

This multistage process is known as **chemotaxis .** It involves a variety of protein and carbohydrate adhesion molecules on both the **endothelial cell and the neutrophil**. It is regulated by messenger molecules released by cells in the injured area, including the endothelial cells. These messengers are collectively called **chemoattractants** (also called **chemotaxins** or chemotactic factors).

In the first stage, the neutrophil is loosely tethered to the endothelial cells by certain adhesion molecules. This event, known as **margination ,** occurs as the neutrophil rolls along the vessel surface. In essence, this initial reversible event exposes the neutrophil to chemoattractants being released in the injured area.

These chemoattractants act on the neutrophil to induce the rapid appearance of another class of adhesion molecules in its plasma membrane—molecules that bind tightly to their matching molecules on the surface of endothelial cells. As a result, the neutrophils collect along the site of injury rather than being washed away with the flowing blood.

In the next stage, known as **diapedesis ,** a narrow projection of the neutrophil is inserted into the space between two endothelial cells, and the entire neutrophil squeezes through the endothelial wall and into the interstitial fluid. In this way, huge numbers of neutrophils migrate into the inflamed area.

Once in the interstitial fluid, neutrophils follow a chemotactic gradient and migrate toward the site of tissue damage (chemotaxis).

This occurs because pathogen-stimulated innate immune cells release chemoattractants. As a result, neutrophils tend to move toward the pathogens that entered into an injured area.

Movement of leukocytes from the blood into the damaged area is not limited to neutrophils. **Monocytes follow later**; once in the tissue, they undergo anatomical and functional changes that transform them to macrophages.

An important aspect of the multistep chemotaxis process is that it provides selectivity and flexibility for the migration of the various leukocyte types. Multiple adhesion molecules that are relatively distinct for the different leukocytes are controlled by different sets of chemo-attractants.

Killing by Phagocytes

Once neutrophils and other leukocytes arrive at the site of an infection, they begin the process of destroying invading pathogens by phagocytosis.

The initial step in phagocytosis is contact between the surfaces of the phagocyte and microbe. One of the major triggers for phagocytosis during this contact is the interaction of phagocyte receptors with certain carbohydrates or lipids in the microbial cell walls. Contact is not always sufficient to trigger engulfment, however, particularly with bacteria that are surrounded by a thick, gelatinous capsule. Instead, chemical factors produced by the body can bind the phagocyte tightly to the microbe and thereby enhance phagocytosis. Any substance that does this is known as an **opsonin ,** from the Greek word that means "to prepare for eating."

As the phagocyte engulfs the microbe (**Figure 18.4**), the internal, microbe-containing sac formed in this step is called a **phagosome .** A layer of plasma membrane separates the microbe from the cytosol of the phagocyte. The phagosome membrane then makes contact with one of the phagocyte's lysosomes, which is filled with a variety of hydrolytic enzymes. The membranes of the phagosome and lysosome fuse, and the combined vesicles are now called a **phagolysosome .**

Inside the phagolysosome, the lysosomal enzymes break down the microbe's macromolecules. In addition, other enzymes in the phagolysosome membrane produce **nitric oxide** as well as **hydrogen peroxide** and other oxygen derivatives, all of which are extremely destructive to the microbe's macromolecules.

Such intracellular destruction is not the only way phagocytes can kill pathogens. The phagocytes also release antimicrobial substances into the

extracellular fluid, where these chemicals can destroy the pathogens without prior phagocytosis. Some of these substances (for example, nitric oxide) secreted into the extracellular fluid (**Figure 18.5**) also function as inflammatory mediators. Thus, when phagocytes enter the area and encounter pathogens, positive feedback mechanisms cause inflammatory mediators, including chemokines, to be released that bring in more phagocytes.

Complement

The family of plasma proteins known as **complement** provides another means for extracellular killing of pathogens without prior phagocytosis. Certain complement proteins are always circulating in the blood in an inactive state. Upon activation of a complement protein in response to infection or damage, a cascade occurs so that this active protein activates a second complement protein, which activates a third, and so on. In this way, multiple active complement proteins are generated in the extracellular fluid of the infected area from inactive complement molecules that have entered from the blood. Because this system consists of at least 30 distinct proteins, it is extremely complex, and we will identify the roles of only a few of the individual complement proteins.

The central protein in the complement cascade is C3. Activation of C3 initiates a series of events. The first is the deposition of **C3b,** a component of C3, on the microbial surface. C3b acts as an opsonin that is recognized by phagocytes targeting the pathogen for destruction, as shown for a bacterium in **Figure 18.6** .

C3b is also part of a proteolytic enzyme that amplifies the complement cascade and leads to the downstream development of a multiunit protein called the **membrane attack complex** (**MAC**) .

The MAC embeds itself in the bacterial plasma membrane and forms pore like channels in the membrane, making it leaky. Water, ions, and small molecules enter the microbe, which disrupts the intracellular environment and kills the microbe. In addition to supplying a means for direct killing of pathogens, the complement system serves other important functions in inflammation (**Figure 18.7**).

Some of the activated complement molecules along the cascade cause, either directly or indirectly (by stimulating the release of other inflammatory mediators), vasodilation, increased micro-vessel permeability to protein, and chemotaxis.

As we will see later, antibodies, a class of proteins secreted by certain lymphocytes, are required to activate the very first complement protein (C1) in the full sequence known as the **classical complement pathway.** However, lymphocytes are not involved in *nonspecific* inflammation, our present topic. How, then, is the complement sequence initiated during nonspecific inflammation? The answer is that there is an **alternative complement pathway,** one that is not antibody dependent and that bypasses C1. The alternative pathway is initiated as the result of interactions between carbohydrates on the surface of the microbes and inactive complement molecules beyond C1. These interactions lead to the formation of active C3b, the opsonin described in the previous paragraph, and the activation of the subsequent complement molecules in the pathway. However, not all microbes have a surface conducive to initiating the alternative pathway.

Other Opsonins in Innate Responses

In addition to complement C3b, other plasma proteins can bind nonspecifically to carbohydrates or lipids in the cell wall of microbes and facilitate opsonization. Many of these—for example, **C-reactive protein** —

are produced by the liver and are always found at some concentration in the plasma. Their production and plasma concentrations, however, are greatly increased during inflammation.

Tissue Repair

The final stage of inflammation is tissue repair. Depending upon the tissue involved, multiplication of organ-specific cells by cell division may or may not occur during this stage. For example, liver cells multiply but skeletal muscle cells do not. In any case, fibroblasts (a type of connective-tissue cell) that reside in the area divide rapidly and begin to secrete large quantities of collagen, and blood vessel cells proliferate in the process of angiogenesis. All of these events are brought about by chemical mediators, particularly a group of locally produced growth factors. Finally, remodeling occurs as the healing process winds down. The final repair may be imperfect, leaving a scar.

Interferons

Interferons are cytokines and are grouped into two families called type I and type II interferons. The **type I interferons** include several proteins that nonspecifically inhibit viral replication inside host cells. In response to infection by a virus, most cell types produce these interferons and secrete them into the extracellular fluid. The type I interferons then bind to plasma membrane receptors on the secreting cell and on other cells, whether they are infected or not (**Figure 18.8**).

This binding triggers the synthesis of dozens of different antiviral proteins by the cell. If the cell is already infected or eventually becomes infected, these proteins interfere with the ability of the viruses to replicate. Type I

interferons also play a role in the killing of tumor cells and in generating fever during an infection.

The actions of type I interferons just described are not specific. Many kinds of viruses induce interferon synthesis, and interferons in turn can inhibit the multiplication of many kinds of viruses. Recent research, however, has revealed that type I interferons also influence the nature of certain aspects of the adaptive immune response.

The one member of the **type II interferons** —called **interferongamma** —is produced by immune cells.

This interferon potentiates some of the actions of type I interferons, enhances the bacteria-killing activity of macrophages, and acts as a chemokine in the inflammatory process.

Toll-Like Receptors

At the beginning of this section, we mentioned that innate immunity often depends upon an immune cell recognizing some general molecular feature common to many types of pathogens. These features are called **pathogen-associated molecular patterns** (**PAMPs**) . We now ask, How is that recognition accomplished? In 1985, researchers interested in how embryonic animals differentiate into mature organisms discovered a protein they named Toll (now called Toll-1) that was required for the proper dorsoventral orientation of fruit flies. In 1996, however, it was discovered that Toll-1 also conferred upon *adult* fruit flies the ability to fight off fungal infections, a discovery that was recognized in 2011 with the awarding of the Nobel Prize in Physiology or Medicine. Since that time, a family of Toll proteins has been discovered in animals from nematodes to mammals, including humans, expressed in the plasma and endosomal membranes of macrophages and dendritic cells, among others. One function of these proteins is to recognize

and bind to highly conserved molecular features associated with pathogens (that is, PAMPs); these include lipopolysaccharide and other lipids and carbohydrates, viral and bacterial nucleic acids, and a protein found in the flagellum of many bacteria. When binding of one of these ligands occurs on the plasma membrane second messengers are generated within the immune cell, which leads to secretion of inflammatory mediators such as IL-1, IL-12, and TNF- a . These in turn stimulate the activity of immune cells involved in the innate immune response. Some of these signals also activate cells involved in the adaptive immune response. Because many of the Toll proteins are plasma-membrane- bound, bind to extracellular ligands, and induce second messenger formation, they are referred to as *receptors;* the family of proteins is known as **Toll-like receptors** (**TLRs**) .

Despite this, not all TLRs generate intracellular signals when bound to a ligand; some TLRs induce attachment of a microbe to a macrophage, for example, and thereby its phagocytosis and subsequent destruction. TLRs belong to a family of proteins called **pattern recognition receptors** (**PRRs**) , all of which recognize and bind to a variety of pathogen ligands. These ligands have conserved molecular features that are generally considered to be vital to the survival or function of that pathogen. It is estimated that as many as a thousand such molecular features are recognized by PRRs.

The importance of TLRs in mammals has been demonstrated in mice with a mutated form of one member of the family called Toll-4. These mice are hypersensitive to the effects of injections with lipopolysaccharide (to mimic a bacterial infection) and are less able to ward off bacterial infection. In humans, recent studies suggest that certain naturally occurring variants in a specific TLR are associated with increased risk of certain diseases.

TLRs are currently an active area of investigation among biologists because of their importance as developmental factors in invertebrates and their immune significance in some adult invertebrates and possibly all vertebrates. Certain domains of these receptors have even been identified in plants, where they seem also to be involved in disease resistance.

Therefore, TLRs may be among the first mechanisms to ever evolve in living organisms to protect against pathogen infection.

Adaptive Immune Responses

Overview

Lymphocytes are the essential cells in adaptive immune responses. Unlike innate response mechanisms, ***lymphocytes must recognize the specific foreign material to be attacked***. Any molecule that can trigger an adaptive immune response against itself or the cell bearing it is called an **antigen.**

Most antigens are either proteins or very large polysaccharides***. Antigen*** is any molecule that the host does not recognize as self. Antigens include the protein coats of viruses, specific proteins on foreign cells, some cancer cells, transplanted cells, and toxins.

The ability of lymphocytes to distinguish one antigen from another confers specificity upon the immune responses in which they participate.

A typical adaptive immune response can be divided into three stages:

1. ***The encounter and recognition of an antigen by lymphocytes.*** During its development, each lymphocyte synthesizes and inserts into its plasma membrane multiple copies of a single type of receptor that can bind to a specific antigen. If, at a later time, the lymphocyte ever encounters that antigen, the antigen becomes bound to the receptors. This binding is the physicochemical meaning of the word *recognize* in immunology. As a result, the ability of lymphocytes to distinguish one antigen from another is

determined by the nature of their plasma membrane receptors. *Each lymphocyte is specific for just one type of antigen.*

2. Lymphocyte activation. The binding of an antigen to a receptor must occur for **lymphocyte activation.** Upon binding to an antigen, the lymphocyte becomes activated and undergoes multiple rounds of cell division. As a result, many daughter lymphocytes develop from a single progenitor that are identical in their ability to recognize a specific antigen; this is called **clonal expansion .**

It is estimated that in a typical person the lymphocyte population expresses more than 100 million distinct antigen receptors. After activation, some lymphocytes will function as effector lymphocytes to carry out the attack response. Others will be set aside as **memory cells,** poised to recognize the antigen if it returns in the future.

3. The attack launched by the activated lymphocytes and their secretions.

The activated effector lymphocytes launch an attack against the antigens that are recognized by the antigen-specific receptor. Activated B cells, which comprise one group of lymphocytes, differentiate into plasma cells that secrete antibodies into the blood.

These antibodies opsonize pathogens or foreign substances and target them for attack by innate immune cells. Activated cytotoxic T cells, another type

of lymphocyte, directly attack and kill the cells bearing the antigens. Once the attack is successfully completed, the great majority of the B cells, plasma cells, and T cells that participated in it die by apoptosis. The timely death of these effector cells is a homeostatic response that prevents the immune response from becoming excessive and possibly destroying its own tissues. However, memory cells persist even after the immune response has been successfully completed.

Lymphoid Organs and Lymphocyte Origins

Lymphoid Organs

Like all leukocytes, lymphocytes circulate in the blood. At any moment, the great majority of lymphocytes are not actually in the blood, however, but in a group of organs and tissues collectively called the **lymphoid organs.** These are subdivided into primary and secondary lymphoid organs.

The **primary lymphoid organs** are the bone marrow and thymus. These organs are the initial sites of lymphocyte development. They supply the body with mature but naive lymphocytes—that is, lymphocytes that have not yet been activated by specific antigen. *The bone marrow and thymus are not normally sites in which naive lymphocytes undergo activation during an immune response*.

The **secondary lymphoid organs** include the lymph nodes, spleen, tonsils, and lymphocyte accumulations in the linings of the intestinal, respiratory, genital, and urinary tracts. It is in the secondary lymphoid organs that naive lymphocytes are activated to participate in adaptive immune responses.

Most of the lymphocytes in the secondary organs ***are not*** the same cells that originated in the primary lymphoid organs. The explanation of this seeming paradox is that, once in the secondary organ, a mature lymphocyte coming from the bone marrow or thymus can undergo cell division to produce additional identical lymphocytes, which in turn undergo cell division, and so on.

Lymphocytes from all the secondary lymphoid organs constantly enter the lymphatic vessels that drain them (all lymphoid organs, not just lymph nodes, are drained by lymphatic vessels) and are carried to the blood. Simultaneously, some blood lymphocytes are pushing through the endothelium of venules all over the body to enter the interstitial fluid. From there, they move into lymphatic capillaries and along the lymphatic vessels to lymph nodes. They may then leave the lymphatic vessels to take up residence in the node.

This recirculation is going on all the time, not just during an infection, although the migration of lymphocytes into an inflamed area is greatly increased by the chemotaxis process.

Lymphocyte trafficking greatly increases the likelihood that any given lymphocyte will encounter the antigen it is specifically programmed to recognize.

Lymphocyte Origins

B lymphocytes (B *cells)* mature in the bone marrow and then are carried by the blood to the secondary lymphoid organs

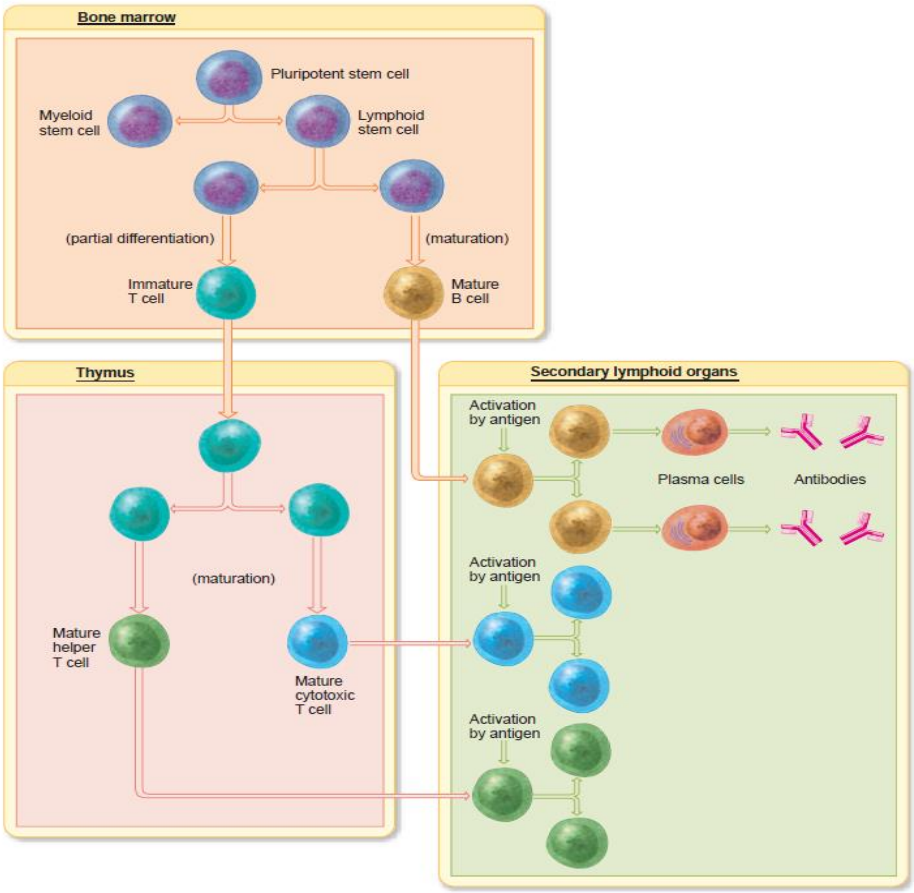


Figure 18.10 AP|R Derivation of B cells and T cells. NK cells are not shown because their transformations, if any, after leaving the bone marrow are still not clear.

This process of maturation and migration continues throughout a person's life. All generations of lymphocytes that subsequently arise from these cells by cell division in the secondary lymphoid organs will be identical to the parent cells; that is, they will be B-cell clones.

In contrast to the B cells, other lymphocytes leave the bone marrow in an immature state during fetal and early neonatal life. They are carried to the thymus and mature there before moving to the secondary lymphoid organs.

These cells are called *T lymphocytes* (or *T cells*). Like B cells, T cells also undergo cell division in secondary lymphoid organs, the progeny being identical to the original T cells and thereby part of that T-cell clone.

In addition to the B and T cells, there is another distinct population of lymphocytes called *natural killer* (*NK*) *cells.*

These cells arise in the bone marrow, but their precursors and life history are still unclear. As we will see, NK cells, unlike B and T cells, are not specific to a given antigen.

Functions of B Cells and T Cells

Upon activation, B cells differentiate into plasma cells, which secrete **antibodies,** proteins that travel all over the body to reach antigens identical to those that stimulated their production. In the body fluids outside of cells, the antibodies combine with these antigens and guide an attack that eliminates the antigens or the cells bearing them.

Antibody-mediated responses are also called ***humoral* responses**, the adjective *humoral* denoting communication "by way of soluble chemical messengers" (in this case, antibodies in the blood). Antibody-mediated responses have an extremely wide diversity of targets and are the major defense against bacteria, viruses, and other pathogens in the extracellular fluid and against toxic molecules (toxins).

In contrast to humoral responses, T-cell responses are **cell-mediated responses**. T cells constitute a family that has at least two major functional subsets, **cytotoxic T cells** and **helper T cells.** Recently, it has become clear that a third subset—called suppressor or **regulatory T cells** —inhibits the function of both B cells and cytotoxic T cells.

Another way to categorize T cells is not by function but rather by the presence of certain proteins, called **CD4 and CD8**, in their plasma membranes. Cytotoxic T cells have CD8 and so are also commonly called $CD8^+$ cells; helper T cells and regulatory T cells express CD4 and so are also commonly called $CD4^+$ cells.

Cytotoxic T cells are "attack" cells. Following activation, they travel to the location of their target, bind to them via antigen on these targets, and directly kill their targets via secreted chemicals. Responses mediated by cytotoxic T cells are directed against the body's own cells that have become cancerous or infected with viruses (or certain bacteria and parasites that, like viruses, take up residence inside host cells).

It is worth emphasizing the important geographic difference in antibody-mediated responses and responses mediated by cytotoxic T cells. The B cells (and plasma cells derived from them) remain in whatever location the recognition and activation steps occurred. The plasma cells send their

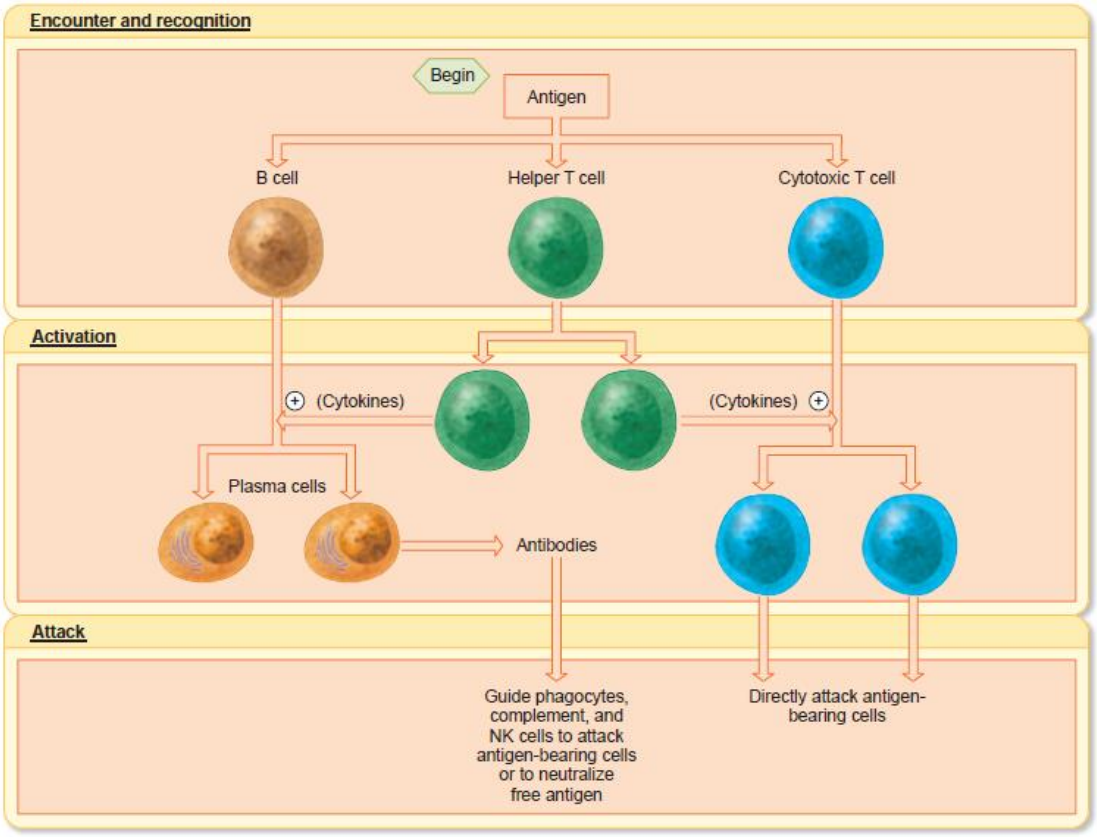
antibodies forth via the blood to seek out antigens identical to those that triggered the response. Cytotoxic T cells must enter the blood and seek out the targets.

Helper T cells go through the usual first two stages of the immune response. First, they combine with antigen and then undergo activation. Once activated, they migrate to the site of B-cell activation. B cells that have bound antigen present it to activated helper cells. Antigen-specific helper T cells make direct contact with the B cell, and the communication given by surface receptors—along with the secretion of cytokines— induces B-cell activation. The role of helper T cells in cytotoxic T-cell activation is more complex.

To activate cytotoxic T cells, activated helper T cells help other cells, most likely dendritic cells, to activate cytotoxic T cells. Unlike the B cell, which directly interacts with the helper T cell, the helper T cell assists cytotoxic T-cell activation indirectly through other cells. With only a few exceptions, B cells and cytotoxic T cells cannot function adequately unless they are stimulated by cytokines from helper T cells.

Helper T cells will be considered as though they were a homogeneous cell population, but in fact, there are different subtypes of helper T cells, distinguished by the different cytokines they secrete when activated. By

means of these different cytokines, they help different sets of lymphocytes, macrophages, and NK cells. Some of the cytokines secreted by helper T cells also act as inflammatory mediators.



gure 18.11 AP R Summary of the roles of B, cytotoxic T, and helper T cells in immune responses. Events of the attack phase are scribed in later sections. The ⊕ symbol denotes a stimulatory effect (activation) of cytokines.

Regulatory T cells are believed to suppress the ability of certain B and cytotoxic T cells to attack a person's own proteins, which can occur in diseases known as autoimmune diseases. As such, investigators are actively pursuing the possibility that regulatory T cells could someday prove effective in the treatment or prevention of certain autoimmune diseases.

Also, the *suppression* of regulatory T cells has been proposed as a possible means of increasing cytotoxic T-cell activity in, for example, someone with cancer.

Lymphocyte Receptors

As described earlier, the ability of lymphocytes to distinguish one antigen from another is determined by the lymphocytes' receptors. Both B cells and T cells express receptors on their plasma membrane.

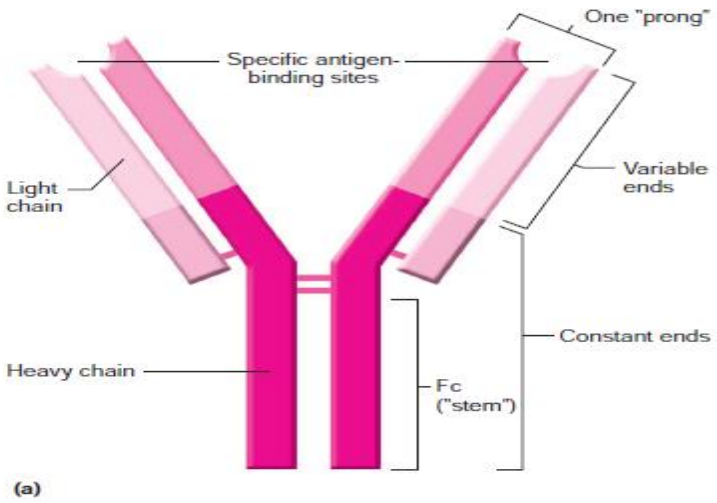
B-Cell Receptors

Recall that once B cells are activated by antigen and helper T-cell cytokines, they proliferate and differentiate into plasma cells, which secrete antibodies. The plasma cells derived from a particular B cell can secrete only one particular antibody. Each B cell always displays on its plasma membrane copies of the particular antibody its plasma cell progeny can produce.

This surface protein (glycoprotein, to be more accurate) acts as the receptor for the antigen specific to it.

B-cell receptors and plasma cell antibodies constitute the family of proteins known as **immunoglobulins.** The receptors themselves, even though they are identical to the antibodies to be secreted by the plasma cell derived from the activated B cell, are technically not antibodies because only *secreted*

immunoglobulins are called antibodies. Each immunoglobulin molecule is composed of four interlinked polypeptide chains.



The two long chains are called heavy chains, and the two short ones, light chains. There are five major classes of immunoglobulins, determined by the amino acid sequences in the heavy chains and a portion of the light chains. The classes are designated by the letters A, D, E, G, and M following the symbol Ig for immunoglobulin; thus, we have IgA, IgD, and so on.

Immunoglobulins have a "stem" called the **Fc** portion and comprising the lower half of the two heavy chains. The upper part of each heavy chain and its associated light chain form an **antigen- binding site** —the amino acid sequences that bind antigen. The amino acid sequences of the Fc portion plus an additional portion of the heavy chains and part of the light chains are identical for all immunoglobulins of a single class (IgA, IgD, and so on). In

contrast to the identical (or "constant") regions of the heavy and light chains, the amino acid sequences of the antigen-binding sites vary from immunoglobulin to immunoglobulin in a given class and are therefore known as variable ends. Each of the five classes of antibodies, therefore, could contain up to millions of unique immunoglobulins, each capable of combining with only one specific antigen (or, in some cases, several antigens whose structures are very similar). The interaction between an antigen-binding sites of an immunoglobulin and an antigen is analogous to the lock and-key interactions that apply generally to the binding of ligands by proteins.

One more point should be mentioned: B-cell receptors can bind antigen whether the antigen is a molecule dissolved in the extracellular fluid or is present on the surface of a foreign cell, such as a microbe, floating free in the fluids. In the latter case, the B cell becomes linked to the foreign cell via the bonds between the B-cell receptor and the surface antigen.

Any given B cell or clone of identical B cells possesses unique immunoglobulin receptors— that is, receptors with unique antigen-binding sites.

Consequently, the body arms itself with millions of clones of different B cells to ensure that specific receptors exist for the vast number of different

antigens the organism *might* encounter during its lifetime. The particular immunoglobulin that any given B cell displays as a receptor on its plasma membrane (and that its plasma cell progeny will secrete as antibodies) is determined during the cell's maturation in the bone marrow.

T-Cell Receptors

T-cell receptors for antigens are two-chained proteins that, like immunoglobulins, have specific regions that differ from one T-cell clone to another. However, T-cell receptors remain embedded in the T-cell membrane and are not secreted like antibodies. As in B-cell development, multiple DNA rearrangements occur during T-cell maturation, leading to millions of distinct T-cell clones—distinct in that the cells of any given clone possess receptors of a single specificity. For T cells, this maturation occurs during their residence in the thymus.

In addition to their general structural differences, the B-cell and T-cell receptors differ in a much more important way: *The T-cell receptor cannot combine with antigen unless the antigen is first complexed with certain of the body's own plasma membrane proteins.* The T-cell receptor then combines with the entire complex of antigen and body (self) protein.

The self-plasma membrane proteins that must be complexes with the antigen in order for T-cell recognition to occur constitute a group of proteins coded

for by genes found on a single chromosome and known collectively as the **major histocompatibility complex** (**MHC)**. The proteins are therefore called **MHC proteins** (in humans, also known as the human leukocyte antigens, or HLAs). Because no two persons other than identical twins have the same sets of MHC genes, no two individuals have the same MHC proteins on the plasma membranes of their cells. MHC proteins are, in essence, cellular "identity tags"—that is, genetic markers of biological self.

The MHC proteins are often called "restriction elements" because the ability of a T cell's receptor to recognize an antigen is restricted to situations in which the antigen is first complexes with an MHC protein. There are two classes of MHC proteins: I and II.

Class I MHC proteins are found on the surface of virtually all cells of the body except erythrocytes.

Class II MHC proteins are found mainly on the surface of macrophages, B cells, and dendritic cells. Under certain conditions, other cell types are induced to express class II MHC.

Another important point is that the different subsets of T cells do not all have the same MHC requirements.

TABLE 18.4	MHC Restriction of the Lymphocyte Receptors
Cell Type	**MHC Restriction**
B	Do not interact with MHC proteins
Helper T	Class II, found only on macrophages, dendritic cells, and B cells
Cytotoxic T	Class I, found on all nucleated cells of the body
NK	Interaction with MHC proteins not required for activation

Cytotoxic T cells require antigen to be associated with class I MHC proteins, whereas helper T cells require class II MHC proteins. One reason for this difference in requirements stems from the presence, as described earlier, of CD4 proteins on the helper T cells and CD8 proteins on the cytotoxic T cells; CD4 binds to class II MHC proteins, whereas CD8 binds to class I MHC proteins.

Antigen Presentation to T Cells

T cells can bind antigen only when the antigen appears on the plasma membrane of a host cell complexes with the cell's MHC proteins. Cells bearing these complexes, therefore, function as **antigen-presenting cells** (**APCs)**.

Presentation to Helper T Cells

Helper T cells require class II MHC proteins to function. *Only macrophages, B cells, and dendritic cells express class II MHC* proteins and therefore can function as APCs for helper T cells.

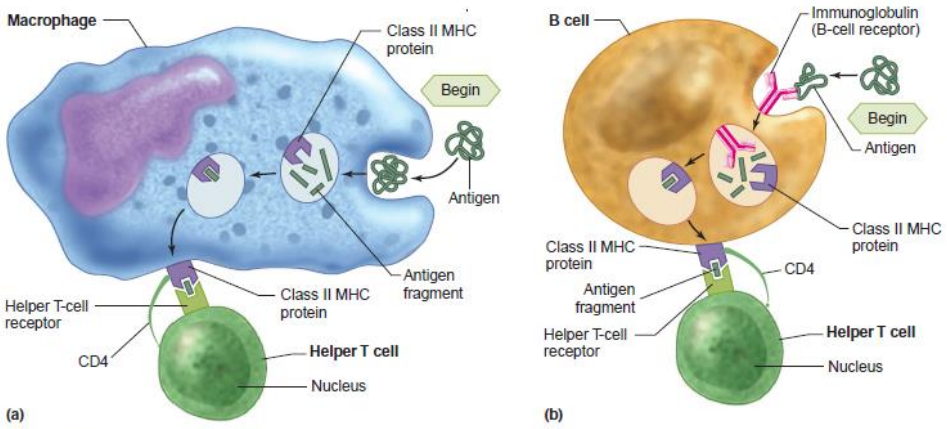


Figure 18.13 AP R Sequence of events by which antigen is processed and presented to a helper T cell by (a) a macrophage or (b) a B cell. In both cases, begin the figure with the antigen in the extracellular fluid.

After a microbe or non-cellular antigen has been phagocytized by a macrophage or dendritic cell in a *nonspecific* response, it is partially broken down into smaller peptide fragments by the cell's proteolytic enzymes. The resulting digested fragments then bind (within endosomes) to class II MHC

proteins synthesized by the cell. This entire complex is then transported to the cell surface, where it is displayed in the plasma membrane. It is to this complex on the cell surface of the macrophage or dendritic cell that a specific helper T cell binds. Note that it is not the intact antigen but rather the peptide fragments, called antigenic determinants or **epitopes ,** of the antigen that are complexes to the MHC proteins and presented to the T cell. Despite this, it is customary to refer to "antigen" presentation rather than "epitope" presentation.

B cells process antigen and present it to helper T cells is essentially the same as just described for dendritic cells and macrophages. The ability of B cells to present antigen to helper T cells is a **second function** of B cells in response to antigenic stimulation, the other being the differentiation of the B cells into antibody-secreting plasma cells.

The binding between a helper T-cell receptor and an antigen bound to class II MHC proteins on an APC is the essential ***antigen-specific*** event in helper T-cell activation. However, this binding by itself will not result in T-cell activation.

In addition, interactions occur between other (non-antigenic) pairs of proteins on the surfaces of the attached helper T cell and APC, and these provide a necessary **co-stimulus** for T-cell activation .

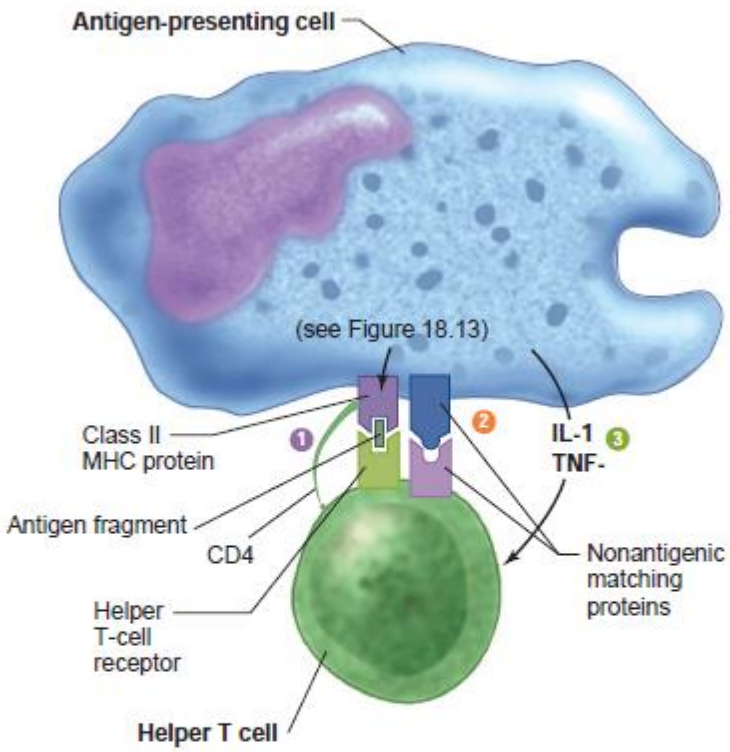


Figure 18.14 AP|R Three events are required for the activation of helper T cells: (1) presentation of the antigen bound to a class II MHC protein on an antigen-presenting cell (APC); (2) the binding of matching nonantigenic proteins in the plasma membranes of the APC and the helper T cell (costimulus); and (3) secretion by the APC of the cytokines interleukin 1 (IL-1), tumor necrosis factor-alpha (TNF-a), and other cytokines, which act on the helper T cell.

Finally, the antigenic binding of the APC to the T cell, along with the co-stimulus , causes the APC to secrete large amounts of the cytokines **interleukin 1** (**IL-1**) and **tumor necrosis factor-alpha** (**TNF-** a) , which act as paracrine substances on the attached helper T cell to provide yet another important stimulus for activation.

Thus, the APC participates in the activation of a helper T cell in three ways:

(مهمة جدا جدا)

(1) Antigen presentation.

(2) Provision of a co-stimulus in the form of a matching non-antigenic plasma membrane protein

(3) Secretion of IL-1, TNF- a , and other cytokines

The activated helper T cell itself now secretes various cytokines that have both **autocrine** effects on the helper T cell and **paracrine** effects on adjacent B cells and any nearby cytotoxic T cells, NK cells, and still other cell types. Recent evidence suggests that helper T cells may program dendritic cells to activate CD81 T cells.

Presentation to Cytotoxic T Cells

Because class I MHC proteins are synthesized by virtually all nucleated cells, any such cell can act as an APC for a cytotoxic T cell. This distinction helps explain the major function of cytotoxic T cells—destruction of *any* of the body's own cells that have become cancerous or infected with viruses.

The key point is that the antigens that complex with class I MHC proteins arise *within* body cells. They are endogenous antigens, synthesized by a body cell.

In the case of viruses, once a virus has taken up residence inside a host cell, the viral nucleic acid causes the host cell to manufacture viral proteins that are foreign to the cell. A cancerous cell has had one or more of its genes altered by chemicals, radiation, or other factors. The altered genes, called ***oncogenes,*** code for proteins that are not normally found in the body. Such proteins act as antigens.

In both virus-infected cells and cancerous cells, some of the endogenously produced antigenic proteins are hydrolyzed by cytosolic enzymes (in proteasomes) into peptide fragments, which are transported into the endoplasmic reticulum. There, they are complexes with the host cell's class I MHC proteins and then shuttled by exocytosis to the plasma membrane surface, where a cytotoxic T cell specific for the complex can bind to it

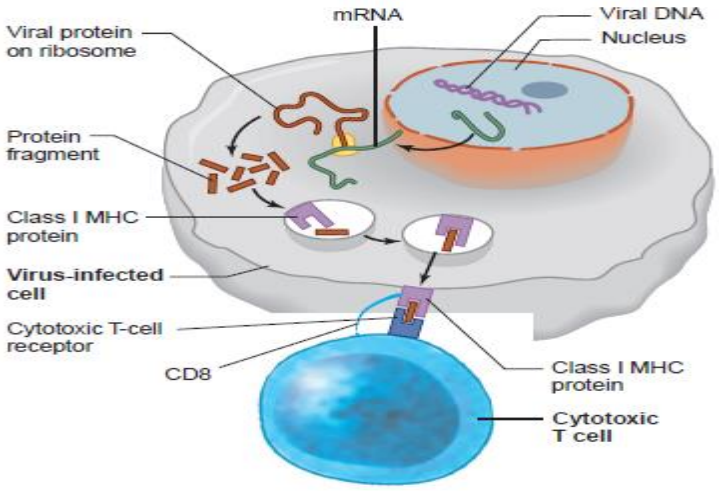


Figure 18.15 AP|R Processing and presentation of viral antigen to a cytotoxic T cell by an infected cell. Begin this figure with the viral DNA in the cell's nucleus. The viral DNA induces the infected cell to produce viral protein, which is then hydrolyzed (by proteasomes). The fragments are complexed to the cell's class I MHC proteins in the endoplasmic reticulum, and these complexes are then shuttled to the plasma membrane.

NK Cells

As noted earlier, NK (natural killer) cells constitute a distinct class of lymphocytes. They have several functional similarities to those of cytotoxic T cells. For example, their major targets are virus-infected cells and cancer cells, and they attack and kill these target cells directly after binding to them. However, *unlike cytotoxic T cells, NK cells are not antigen-specific; that is, each NK cell can attack virus-infected cells or cancer cells without recognizing a specific antigen*. They have neither T-cell receptors nor the immunoglobulin receptors of B cells, and the exact nature of the NK-cell surface receptors that permits the cells to identify their targets is unknown . MHC proteins are not involved in the activation of NK cells.

Why, then, do we deal with them in the context of *specific* (adaptive) immune responses? The reason is that, as will be described subsequently, their participation in an immune response is greatly enhanced either by certain antibodies or by cytokines secreted by helper T cells activated during adaptive immune responses.

Development of Immune Tolerance

Our basic framework for understanding adaptive immune responses requires consideration of one more crucial question. How does the body develop what is called **immune tolerance** —lack of immune responsiveness to self? This may seem a strange question given the definition of an antigen as a foreign molecule that can generate an immune response.

Recall that the huge diversity of lymphocyte receptors is ultimately the result of multiple, random DNA cutting and recombination processes. It is virtually certain, therefore, that in each person, clones of lymphocytes would have emerged with receptors that could bind to that person's own proteins.

The existence and functioning of such lymphocytes would be disastrous because such binding would launch an immune attack against the cells expressing these proteins.

There are at least two mechanisms— ***clonal deletion*** and ***clonal inactivation*** — that explain why normally there are no active lymphocytes that respond to self-components.

First, during fetal and early postnatal life, T cells are exposed to a wide mix of self-proteins in the thymus. Those T cells with receptors capable of binding self-proteins are destroyed by apoptosis (programmed cell death). This process is called **clonal deletion.**

The second process, **clonal inactivation,** occurs not in the thymus but in the periphery and causes potentially self-reacting T cells to become nonresponsive.

What are the mechanisms of clonal deletion and inactivation during fetal and early postnatal life?

Recall that full activation of a helper T cell requires not only an antigen specific stimulus but a nonspecific co- stimulus (interaction between complementary non-antigenic proteins on the APC and the T cell). *If this co-stimulus is not provided, the helper T cell not only fails to become activated by antigen but dies or becomes inactivated forever.* This is the case during early life. The induction of co-stimulatory molecules requires activated, antigen-presenting cells. Signaling through Toll-like receptors (TLRs) and secretion of inflammatory cytokines are two mechanisms of activating

antigen-presenting cells to express co-stimulatory molecules that provide co-stimulus for T-cell activation.

This completes the framework for understanding adaptive immune responses. The next two sections utilize this framework in presenting typical responses from beginning to end, highlighting the interactions between lymphocytes and describing the attack mechanisms used by the various pathways

Antibody-Mediated Immune Responses:

Defenses against Bacteria, Extracellular Viruses, and Toxins

A classical antibody-mediated response is one that results in the destruction of bacteria. The sequence of events, which is quite similar to the response to a virus in the extracellular fluid,

TABLE 18.5 Summary of Events in Antibody-Mediated Immunity Against Bacteria

I. In secondary lymphoid organs, bacterial antigen binds to specific receptors on the plasma membranes of B cells.

II. Antigen-presenting cells (APCs)—most likely the dendritic cells but macrophages and B cells—
   A. Present to helper T cells' processed antigen complexed to class II MHC proteins on the APCs;
   B. Provide a costimulus in the form of another membrane protein; and
   C. Secrete IL-1, TNF-a, and other cytokines, which act on the helper T cells.

III. In response, the helper T cells secrete IL-2, which stimulates the helper T cells themselves to proliferate and secrete IL-2 and other cytokines. These activate antigen-bound B cells to proliferate and differentiate into plasma cells. Some of the B cells differentiate into memory cells rather than plasma cells.

IV. The plasma cells secrete antibodies specific for the antigen that initiated the response, and the antibodies circulate all over the body via the blood.

V. These antibodies combine with antigen on the surface of the bacteria anywhere in the body.

VI. Presence of antibody bound to antigen facilitates phagocytosis of the bacteria by neutrophils and macrophages. It also activates the complement system, which further enhances phagocytosis and can directly kill the bacteria by the membrane attack complex. It may also induce antibody-dependent cellular cytotoxicity mediated by NK cells that bind to the antibody's Fc portion.

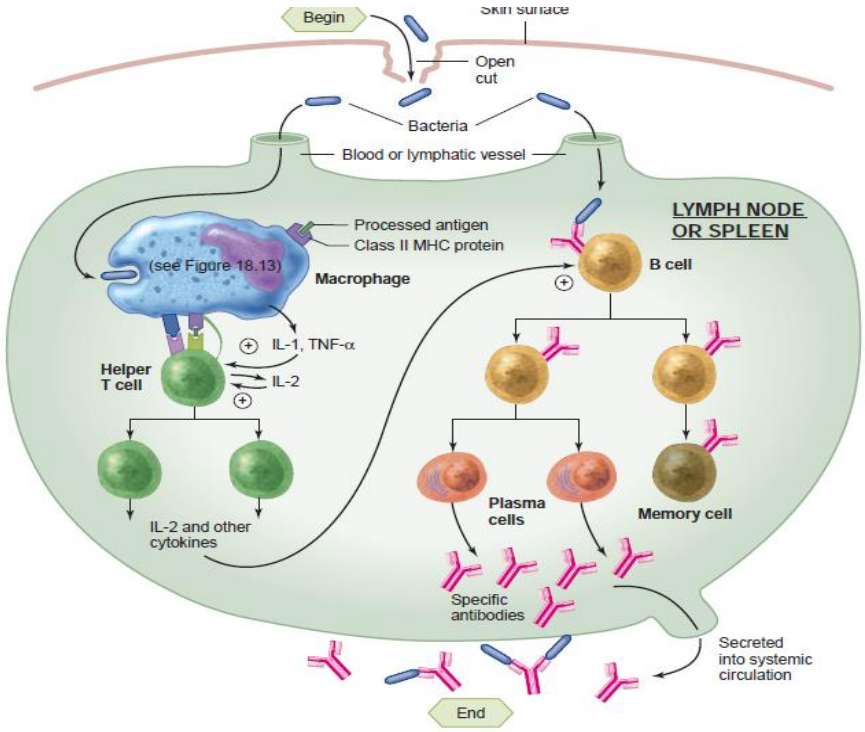


Figure 18.16 AP|R Summary of events by which a bacterial infection leads to antibody synthesis in secondary lymphoid organs. Refer back to Figure 18.13 for additional details about intracellular processing of antigen. The secreted antibodies travel by the blood to the site of infection, where they bind to bacteria of the type that induced the response. The attack triggered by antibodies' binding to bacteria is described in the text.

Antigen Recognition and B-Cell Activation

This process starts the same way as for nonspecific responses, with the bacteria penetrating one of the body's linings and entering the interstitial fluid. The bacteria then enter the lymphatic system and/or the bloodstream and are taken up by the lymph nodes and/or the spleen, respectively. There, a B cell, using its immunoglobulin receptor, recognizes the bacterial surface antigen and binds the bacterium.

In a few cases (notably, bacteria with cell-wall polysaccharide capsules), this binding is all that is needed to trigger B-cell activation.

For the great majority of antigens, however, antigen binding is not enough, and signals in the form of cytokines released into the interstitial fluid by helper T cells near the antigen-bound B cells are also required.

For helper T cells to react against bacteria by secreting cytokines, they must bind to a complex of antigen and class II MHC protein on an APC. Let us assume that in this case the APC is a macrophage that has phagocytized one of the bacteria, hydrolyzed its proteins into peptide fragments, complexes them with class II MHC proteins, and displayed the complexes on its surface. A helper T cell specific for the complex then binds to it, beginning the activation of the helper T cell. Moreover, the macrophage helps this activation Process in two other ways:

(1) It provides a co-stimulus via non-antigenic plasma membrane proteins,

(2) It secretes IL-1 and TNF- a.

The co-stimulus activates the helper T cell to secrete another cytokine named **Interleukin-2** (**IL-2)**. Among other functions, IL-1 and TNF- a stimulate the helper T cell to express more receptors for IL-2.

IL-2, acting in an autocrine manner, then provides a proliferative stimulus to the activated helper T cell. The cell divides, beginning the mitotic cycles that lead to the formation of a clone of activated helper T cells; these cells then release not only IL-2 but other cytokines as well.

Once activated, helper T cells migrate to **lymph nodes** where they interact with antigen-presenting B cells. The helper T cell stimulates B-cell activation by **direct contact and cytokine release**.

Other cytokines—notably, IL-4 possibly produced by basophils—are also important in this step. Once activated, the B cell differentiates into a plasma cell that secretes antibodies that recognize the specific antigen. Thus, a series of protein messengers interconnects the various cell types, the helper T cells serving as the central coordinators.

As stated earlier, however, some of the B-cell progeny differentiate not into plasma cells but instead into memory cells, whose characteristics permit them to respond more rapidly and vigorously should the antigen reappear at a future time.

The example we have been using employed a macrophage as the APC to helper T cells, but B cells can also serve in this role. The binding of the helper T cell to the antigen-bound B cell ensures maximal stimulation of the B cell by the cytokines secreted by that helper T cell and any of its progeny that remain nearby.

Antibody Secretion

After their differentiation from B cells, plasma cells produce thousands of antibody molecules per second before they die in a day or so. We mentioned

earlier that there are five major classes of antibodies. The most abundant are the **IgG** antibodies, commonly called **gamma globulin ,** and **IgM** antibodies. These two groups together provide the bulk of specific immunity against bacteria and viruses in the extracellular fluid. **IgE** antibodies participate in defenses against multicellular parasites and also mediate allergic responses.

IgA antibodies are secreted by plasma cells in the linings of the gastrointestinal, respiratory, and genitourinary tracts; these antibodies generally act locally in the linings or on their surfaces. They are also secreted by the mammary glands and, therefore, are the major antibodies in milk. The functions of **IgD** are still unclear.

The antibodies (mostly IgG and IgM) circulate through the lymph and blood to return to the infected site. At sites of infection, the antibodies leave the blood (recall that nonspecific inflammation has already made capillaries and venules leaky at these sites) and combine with the type of bacterial surface antigen that initiated the immune response.

These antibodies then direct the attack against the bacteria to which they are now bound. Consequently, immunoglobulins play two distinct roles in immune responses during the initial recognition step:

(1) Those on the surface of B cells bind to antigen brought to them

(2) Those secreted by the plasma cells (antibodies) bind to bacteria bearing the same antigens, "marking" them as the targets to be attacked.

The Attack: Effects of Antibodies

The antibodies bound to antigen on the microbial surface do not directly kill the microbe but instead *link up the microbe physically to the actual killing mechanisms—phagocytes* (neutrophils and macrophages), complement, or NK cells. This linkage not only triggers the attack mechanism but ensures that the killing effects are restricted to the microbe. Linkage to specific antibodies helps protect adjacent normal structures from the toxic effects of the chemicals employed by the killing mechanisms.

Direct Enhancement of Phagocytosis

Antibodies can act directly as opsonins. The mechanism is analogous to that for complement C3b in that the antibody links the phagocyte to the antigen.

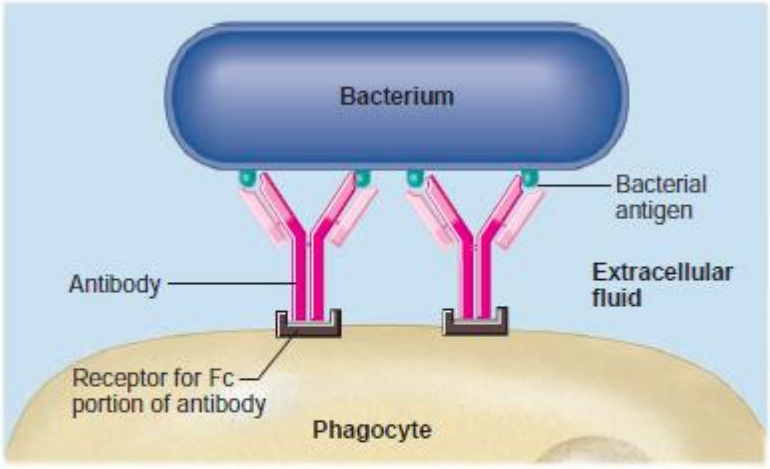


Figure 18.17 AP|R Direct enhancement of phagocytosis by antibody. The antibody links the phagocyte to the bacterium. Compare this mechanism of opsonization to that mediated by complement C3b (see Figure 18.6).

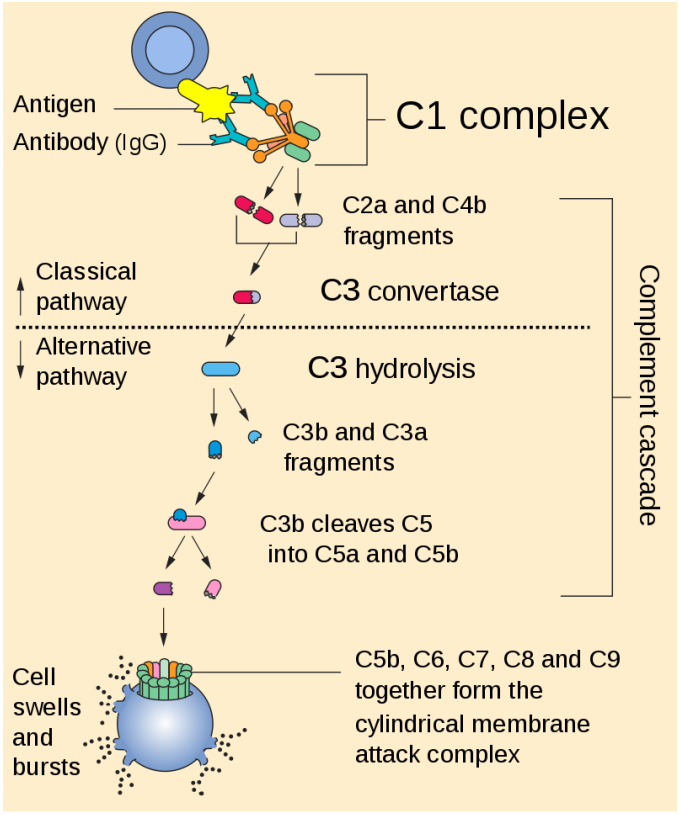
The phagocyte has membrane receptors that bind to the **Fc portion** of an antibody. This linkage promotes attachment of the antigen to the phagocyte and the triggering of phagocytosis of the bacterium.

Activation of the Complement System

The plasma complement system is activated in ***nonspecific*** **(innate)** inflammatory responses via the **alternative complement pathway**.

In contrast, in **adaptive immune responses**, the presence of antibody of the IgG or IgM class bound to antigen activates the **classical complement**

pathway. The first molecule in this pathway, C1, binds to the Fc portion of an antibody that has combined with antigen.



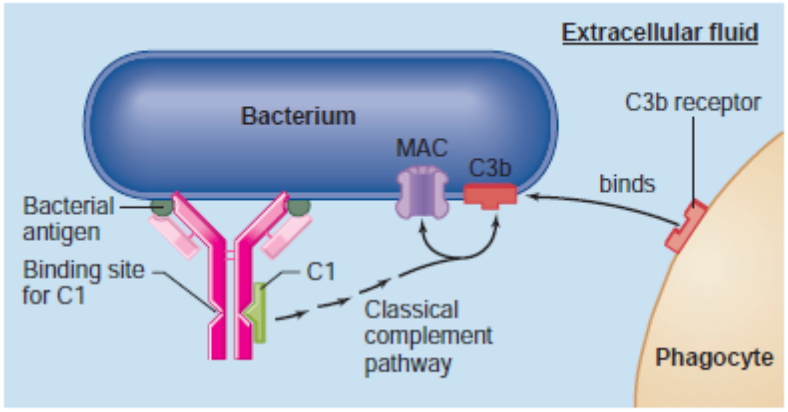


Figure 18.18 Activation of classical complement pathway by binding of antibody to bacterial antigen. C1 is activated by its binding to the Fc portion of the antibody. The membrane attack complex (MAC) is then generated, along with C3b, which acts as an opsonin by binding the bacteria to a phagocyte. C3b also plays a role in initiating the MAC (not shown here).

This results in activation of the enzymatic portions of C1, thereby initiating the entire classical pathway. The end product of this cascade, the **membrane attack complex (MAC)**, can kill the cells the antibody is bound to by making their membranes leaky. In addition, another activated complement molecule **(C3b)** functions as an opsonic to **enhance phagocytosis** of the microbe by neutrophils and macrophages. As a result, antibodies enhance phagocytosis both directly and via activation of complement C3b.

It is important to note that C1 binds not to the unique antigen-binding sites in the antibody's prongs but rather to ***complement-binding sites in the Fc portion***. Because the latter are the same in virtually all antibodies of the IgG and IgM classes, the complement molecule will bind to *any* antigen bound antibodies belonging to these classes. In other words, there is only one set of complement molecules and, once activated, they do essentially the same thing regardless of the specific identity of the invader.

Antibody-Dependent Cellular Cytotoxicity

Both a particular complement molecule (C1) and a phagocyte can bind nonspecifically to the Fc portion of an antibody bound to antigen. NK cells can also do this. Antibodies can link target cells to NK cells, which then kill the targets directly by secreting toxic chemicals. This is called **antibody dependent cellular cytotoxicity** (**ADCC**), because killing (cytotoxicity) is

carried out by cells (NK cells) but the process depends upon the presence of antibody. Note that the antibodies confer specificity upon ADCC, just as they do on antibody-dependent phagocytosis and complement activation.

This mechanism for bringing NK cells into play is the one exception, mentioned earlier, to the generalization that the mechanism by which NK cells identify their targets is unclear.

Direct Neutralization of Bacterial Toxins and Viruses

Toxins secreted by bacteria into the extracellular fluid can act as antigens to induce antibody production. The antibodies then combine with the free toxins, thereby preventing interaction of the toxins with susceptible cells. Because each antibody has two binding sites for antigen, clumplike chains of antibody–antigen complexes form, and these clumps are then phagocytized. A similar binding process occurs as part of the major antibody-mediated mechanism for eliminating viruses in the extracellular fluid. Certain of the viral surface proteins serve as antigens, and the antibodies produced against them combine with them, preventing attachment of the virus to plasma membranes of potential host cells. This prevents the virus from entering a cell. As with bacterial toxins, chains of antibody– virus complexes are formed and can be phagocytized.

Active and Passive Humoral Immunity

The response of the antibody-producing machinery to invasion by a foreign antigen varies enormously, depending upon whether the machinery has previously been exposed to that antigen. Antibody production occurs slowly over several weeks following the first contact with an antigen, but any subsequent infection by the same invader elicits an immediate and considerable outpouring of additional specific antibodies. This response, which is mediated by the memory B cells described earlier, is one of the key features that distinguishes innate and adaptive immunity. It confers a greatly enhanced resistance toward subsequent infection with that particular microorganism. Resistance built up as a result of the body's contact with microorganisms and their toxins or other antigenic components is known as **active immunity.**

Until the twentieth century, the only way to develop active immunity was to suffer an infection, but now the injection of microbial derivatives in vaccines is used. A ***vaccine*** may consist of small quantities of living or dead pathogens, small quantities of toxins, or harmless antigenic molecules derived from the Micro-organism or its toxin. The general principle is always the same: **Exposure of the body to the antigenic substance results in an active immune response along with the induction of the memory**

cells required for rapid, effective response to possible future infection by that particular organism.

A second kind of immunity, known as **passive immunity,** is simply the direct transfer of antibodies from one person to another, the recipient thereby receiving preformed antibodies.

Such transfers occur between mother and fetus because **IgG** can move across the placenta. Also, a breast-fed child receives **IgA** antibodies in the mother's milk; the intestinal mucosa is permeable to **IgA** antibodies during early life. These are important sources of protection for the infant during the first months of life, when the antibody-synthesizing capacity is relatively poor.

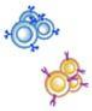
The same principle is used clinically when specific antibodies (produced by genetic engineering) or pooled gamma globulin injections are given to patients exposed to or suffering from certain infections such as hepatitis. Because antibodies are proteins with a limited life span, the protection afforded by this transfer of antibodies is relatively short-lived, usually lasting only a few weeks or months.

Summary

It is now possible to summarize the interplay between innate and adaptive immune responses in resisting a bacterial infection.

When a particular bacterium is encountered for the first time, *innate* defense mechanisms resist its entry and, if entry is gained, attempt to eliminate it by phagocytosis and non-phagocytic killing in the inflammatory process. Simultaneously, bacterial antigens induce the relevant specific B-cell clones to differentiate into plasma cells capable of antibody production. If the innate defenses are rapidly successful, these slowly developing *specific* immune responses may never play an important role. If the innate responses are only partly successful, the infection may persist long enough for significant amounts of antibody to be produced. The presence of antibody leads to both enhanced phagocytosis and direct destruction of the foreign cells, as well as to neutralization of any toxins the bacteria secrete. All subsequent encounters with that type of bacterium will activate the specific responses much sooner and with greater intensity. That is, the person may have active immunity against those bacteria.

Innate Vs. Adaptive Immunity

	Innate immunity	Adaptive Immunity
Components	 1. Physical and chemical barriers 2. Phagocytic leukocytes 3. Dendritic cells 4. Natural Killer cells 5. Plasma proteins (complement)	 1. Humoral immunity (B cells, which mature into antibody secreting plasma cells) 2. Cell-mediated immunity (T cells, which mature into effector helper and cytotoxic T cells)
Activity	Always present	Normally silent
Response and potency	Immediate response, but has a limited and lower potency	Slower response (over 1-2 weeks, but is much more potent
Specificity	General: can recognize general classes of pathogens (i.e. bacteria, viruses, fungi, parasites) but cannot make fine distinctions	Recognizes highly specific antigens
Course	Attempts to immediately destroy the pathogen, and if it can't, it contains the infection until the more powerful adaptive immune system acts.	Slower to respond; effector cells are generally produced in 1 week and the entire response occurs over 1-2 weeks. However, this course can vary somewhat during different responses in an individual.
Memory?	No--reacts with equal potency upon repeated exposure to the same pathogen.	 Yes--memory cells "remember" specific pathogens; upon re-exposure to a pathogen, these cells mount a much faster and more potent second response

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