CHAPTER

8

The Immune Response

The immune system is clearly essential for survival. It constantly defends the body against bacteria, viruses, and other foreign substances it encounters. It also detects and responds to abnormal cells and molecules that periodically develop in the body so that diseases such as cancers do not occur. An essential aspect of the immune response is the ability to recognize almost limitless numbers of foreign cells and nonself substances, distinguishing them from self molecules that are native to the body.

The major focus of this chapter is to present an overview of the immune cells, molecules, and tissues and to describe the normal mechanisms used to protect the body against foreign invaders.

THE IMMUNE SYSTEM

The *immune system* consists of the central and peripheral lymphoid tissues and the immune cells that protect the body against a myriad of microbes and foreign substances. The individual components of the substance that the immune system recognizes as foreign are called *antigens*. The interaction of the collective and coordinated components of the immune system and the antigens of a foreign agent is called the *immune response*.

Fundamental to the appropriate functioning of the immune system is the ability to regulate the recognition, amplification, and the response of the immune cells to a foreign agent. The immune system must recognize and differentiate one foreign pathogen from another, while simultaneously distinguishing these foreign molecules from normal cells and proteins in the body.

Properties of the Immune System

The body protects again bacteria, viruses, and other foreign substances by many different mechanisms. These include physical barriers, phagocytic cells in the blood and tissues, a class of lymphocytes called natural killer cells, and various blood-borne molecules that protect individuals from a potentially harmful environment. These mechanisms can be divided into two cooperative defense systems: the nonspecific or innate defense system and the specific or acquired immune system.

Nonspecific Immunity

As a first line of defense system, the nonspecific immune system distinguishes self from non-self but does not distinguish one type of pathogen from another. Nonspecific resistance to microbe invasion results from two general lines of defense. Microorganisms encounter the first line of resistance on exposure to the epithelial layers of our skin and mucous membranes that line our respiratory, gastrointestinal, and urogenital tracts. The second line of nonspecific defense involves chemical signals, antimicrobial substances, phagocytic and natural killer cells, and fever associated with the inflammatory response. These two lines of nonspecific defense mechanisms are important for excluding pathogens from our body and removing them if they enter. They also aid in proper signaling of the second defense system—specific immunity.

Specific Immunity

Specific or acquired immunity develops during an individual's lifetime, distinguishes self from nonself, and responds specifically to different pathogens and foreign molecules. White blood cells called *lymphocytes* are key players in the specific or acquired immune response. These cells include the T lymphocytes (also called T cells), which participate in cell-mediated immunity, and the B lymphocytes (also called B cells), which participate in humoral immunity. Cell-mediated immunity involves the production of cytotoxic T cells, which have the ability to destroy antigen-bearing cells. Humoral immunity is characterized by the transformation of B cells into plasma cells, which secrete immunoglobulins (antibodies) that have specific activity against the inciting antigen.

Specificity, Diversity, Memory, Self-limitation, and Self-nonself Recognition

A cardinal feature of the specific immunity provided by the T and B lymphocytes is that of specificity, diversity, memory, self-limitation, and self-nonself recognition. These cells can exactly recognize a particular microorganism or foreign molecule. Each lymphocyte targets a specific antigen and distinguishes subtle differences between distinct antigens. The approximately 10^{12} lymphocytes in the body have tremendous diversity. They can respond to the millions of different kinds of antigens encountered daily. This diversity occurs because an enormous variety of lymphocyte populations have been programmed during development, each to respond to a particular antigen.

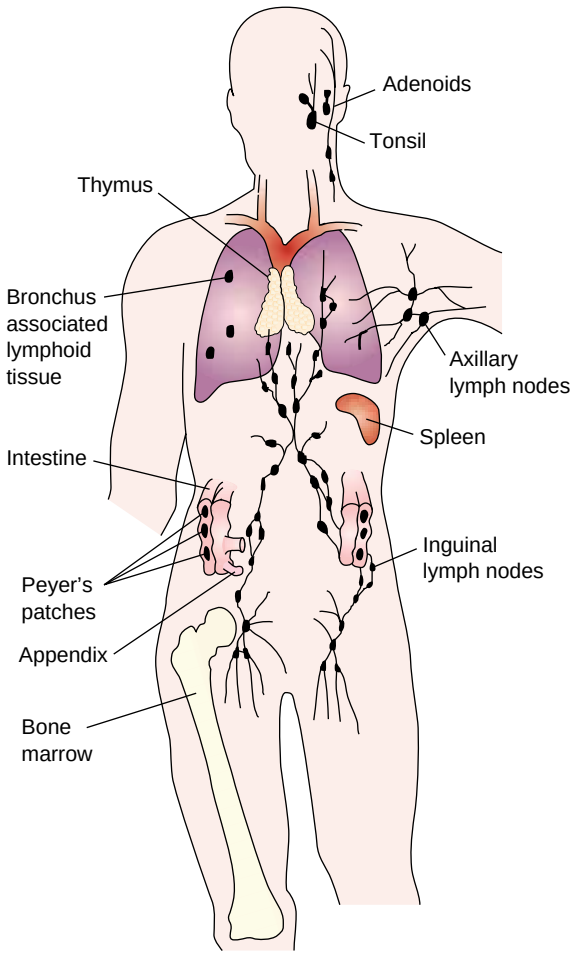
An evolutionary adaptation that is unique to the immune system is a memory response—the ability to recall and quickly produce a heightened immune response on subsequent exposure to the same foreign agent. After lymphocytes are stimulated by an antigen, they acquire a memory response. The memory T and B lymphocytes that are generated remain in the body for a long time and can respond more rapidly on repeat exposure than can naive cells. Because of this heightened state of immune reactivity, the immune system usually can respond to commonly encountered microorganisms so quickly and efficiently that one is unaware of the response.

Self-limitation refers to the ability of the stimulated lymphocytes to perform their functions for a brief period of time, sufficient to destroy the invading pathogen, and then die or differentiate into functionally quiescent memory cells. Self-limitation allows the immune system to return to a state of rest after it eliminates each antigen, thus enabling it to respond optimally to other antigens that an individual encounters.

Discrimination of self from nonself is one of the most important properties of the immune system. Immunologic unresponsiveness to self antigens, or self-tolerance, is essential for preventing reactions against one's own cells and tissues while maintaining a diverse repertoire of lymphocytes specific for foreign antigens.

Lymphoid Organs

The lymphoid organs are at the center of the immune response. These organs and tissues are widely distributed in the body and provide different, but often overlapping, functions (Fig. 8-1). The central lymphoid organs, the bone marrow and the thymus, provide the environment for immune cell production and maturation. The peripheral lymphoid organs function to trap and process antigen and promote its interaction with mature immune cells. Lymph nodes, spleen, tonsils, appendix, Peyer's patches in the intestine, and mucosa-associated lymphoid tissues in the respiratory, gastrointestinal, and reproductive systems comprise the peripheral lymphoid organs. Networks of lymph channels, blood vessels, and capillaries connect the lymphoid organs. The immune cells continuously circulate through



■ **FIGURE 8-1** ■ Central and peripheral lymphoid organs and tissues.

KEY CONCEPTS

COMPONENTS OF THE IMMUNE SYSTEM

- The immune system consists of immune cells; the central immune structures (the bone marrow and thymus), where immune cells are produced and mature; and the peripheral immune structures (lymph nodes, spleen, and other accessory structures), where the immune cells interact with antigen.
- The immune cells consist of the lymphocytes (T and B lymphocytes), which are the primary cells of the immune system, and the accessory cells such as the macrophages, which aid in processing and presentation of antigens to the lymphocytes.
- Cytokines are molecules that form a communication link between immune cells and other tissues and organs of the body.
- Recognition of self from nonself by the immune cells depends on a system of MHC membrane molecules that differentiate viral-infected and abnormal cells from normal cells (MHC I) and identify immune cells from other types of cells (MHC II).

the various tissues and organs to seek out and destroy foreign material.

Thymus

The thymus is an elongated, bilobed structure that is located in the neck region above the heart. The function of the thymus is central to the development of the immune system because it generates mature immunocompetent T lymphocytes. The thymus is a fully developed organ at birth, weighing approximately 15 to 20 g. At puberty, when the immune cells are well established in peripheral lymphoid tissues, the thymus begins regressing and is replaced by adipose tissue. Nevertheless, some thymus tissue persists into old age. Precursor T (pre-T) cells enter the thymus as functionally and phenotypically immature T cells. They progressively differentiate into mature T cells under the influence of the thymic hormones and cytokines. As the T cells multiple and mature, they acquire T cell receptors, surface markers that distinguish among the different types of T cells, and antigens that distinguish self from nonself. More than 95% of the thymocytes die in the thymus because they do not produce the appropriate type of self-antigens. Only those T cells able to recognize foreign antigen and not react to self-antigens are allowed to mature. This process is called *thymic selection.* Mature immunocompetent T cells leave the thymus in 2 to 3 days and enter the peripheral lymphoid tissues through the bloodstream.

Lymph Nodes

Lymph nodes are small aggregates of lymphoid tissue located along lymphatic vessels throughout the body. Each lymph node processes lymph from a discrete, adjacent anatomic site. Many lymph nodes are in the axillae, groin, and along the great vessels of the neck, thorax, and abdomen. These tissues are located along the lymph ducts, which lead from the tissues to the thoracic duct. Lymph nodes have two functions: removal of foreign material from lymph before it enters the bloodstream and serving as centers for proliferation of immune cells.

A lymph node is a bean-shaped tissue surrounded by a connective tissue capsule. Lymph enters the node through afferent channels that penetrate the capsule, and the lymph leaves through the efferent lymph vessels located in the deep indentation of the hilus (Fig. 8-2). Lymphocytes and macrophages flow slowly through the node, which allows trapping and interaction of antigen and immune cells. The reticular meshwork serves as a surface on which macrophages can more easily phagocytize antigens. Dendritic cells, which also permeate the lymph node, aid antigen presentation.

Spleen

The spleen is a large, ovoid organ located high in the left abdominal cavity. The spleen filters antigens from the blood and is important in response to systemic infections. The spleen is composed of red and white pulp. The red pulp is well supplied with arteries and is the area where senescent and injured red blood cells are destroyed. The white pulp contains concentrated areas of B and T lymphocytes permeated by macrophages and dendritic cells.

Other Secondary Lymphoid Tissues

Other secondary lymphoid tissues include the *mucosa-associated lymphoid tissues.* These nonencapsulated clusters of lymphoid tissues are located around membranes lining the respiratory, digestive, and urogenital tract. These gateways into the body contain the immune cells needed to respond to a large and diverse population of microorganisms. In some tissues, the lymphocytes are organized in loose clusters, but in other tissues such as the tonsils, Peyer's patches in the intestine, and the appendix, organized structures are evident. These tissues contain all the necessary cell components (*i.e.*, T cells, B cells, macrophages, and dendritic cells) for an immune response.

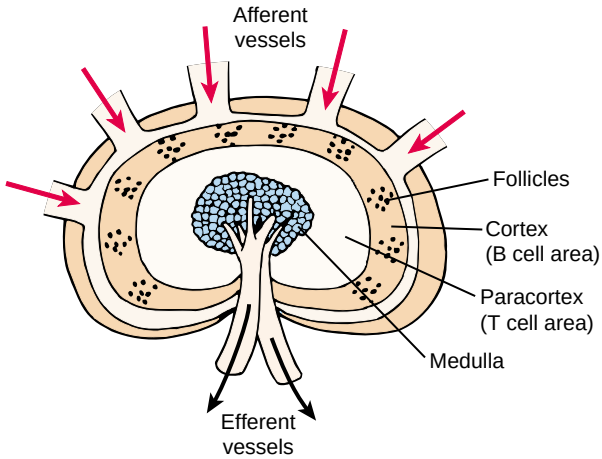


FIGURE 8-2 Structural features of a lymph node. Bacteria that gain entry to the body are filtered out of the lymph as it flows through the node.

Immunity at the mucosal layers helps to protect the vulnerable internal organs.

Antigens

Before discussing the cells and responses inherent to immunity, it is important to understand the substances that elicit a response from the host. *Antigens* or *immunogens* are substances foreign to the host that can stimulate an immune response. These foreign molecules are recognized by receptors on immune cells and by proteins, called *antibodies* or *immunoglobulins,* that are generated in response to the antigen. Antigens include bacteria, fungi, viruses, protozoans, and parasitic worms. Antigens also can include substances such as pollen, poison ivy plant resin, insect venom, and transplanted organs. Most antigens are macromolecules such as proteins and polysaccharides, although lipids and nucleic acids occasionally can serve as antigens. Chemically complex molecules tend to be good stimulators of immunity.

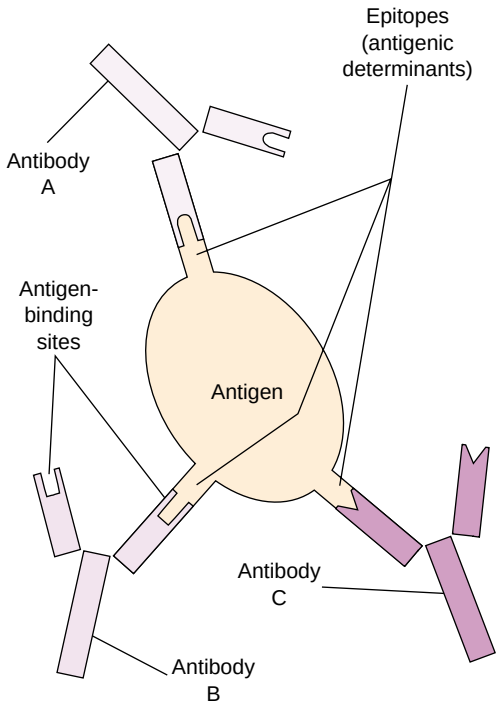
Antigens, which in general are large and complex, are biologically degraded into smaller chemical units or peptides. These discrete, immunologically active sites on antigens are called *antigenic determinants* or *epitopes* (Fig. 8-3). It is the unique molecular shape of an epitope that is recognized by a specific receptor found on the surface of the lymphocyte or by the antigen-binding site of an antibody. A single antigen may contain several antigenic determinants; each can stimulate a distinct clone of lymphocytes to respond. For example, different proteins that comprise a virus may function as unique antigens, each of which contains several antigenic determinants. Hundreds of antigenic determinants are found on complex structures such as the bacterial cell wall.

Smaller substances (molecular masses <10,000 daltons) usually are unable to stimulate an adequate immune response by themselves. When these low–molecular-weight compounds, known as haptens, combine with larger protein molecules, they function as antigens. The proteins act as carrier molecules for the haptens to form antigenic hapten-carrier complexes. An allergic response to the antibiotic penicillin is an example of a hapten-carrier complex that has medical importance. Penicillin (molecular mass of approximately 350 daltons) is incapable of causing an immune response by itself. However, penicillin can chemically combine with body proteins to form larger complexes that can then generate in some individuals an immune response to the penicillin epitope.

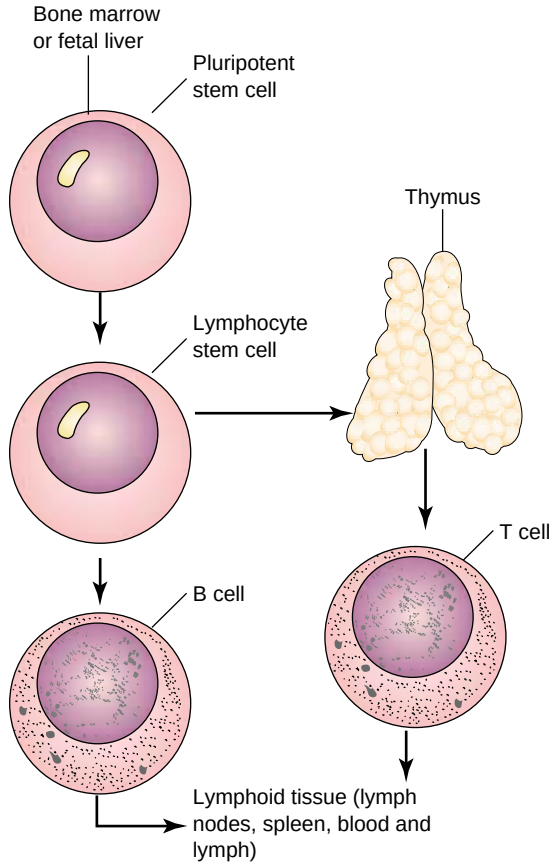
Immune Cells

The primary cells of the specific immune system are the lymphocytes. However, the recognition and activation of the specific immune responses depend on non-lymphoid cells, called *accessory cells,* which are not specific for different antigens. The accessory cells include the mononuclear phagocytes, dendritic cells, and other specialized antigen-presenting cells (APCs).

Lymphocytes represent 25% to 35% of blood leukocytes. Like other blood cells, lymphocytes are generated from stem cells in the bone marrow (Fig. 8-4). These undifferentiated cells congregate in the central lymphoid tissues, where they mature into distinct types of lymphocytes. One class of lymphocyte, the *B lymphocytes* (B cells), matures in the bone marrow and is essential for humoral or antibody-mediated immunity. The other class of lymphocytes, the *T lymphocytes*



■ **FIGURE 8-3** ■ Multiple epitopes on a complex antigen being recognized by their respective (A, B, C) antibodies.



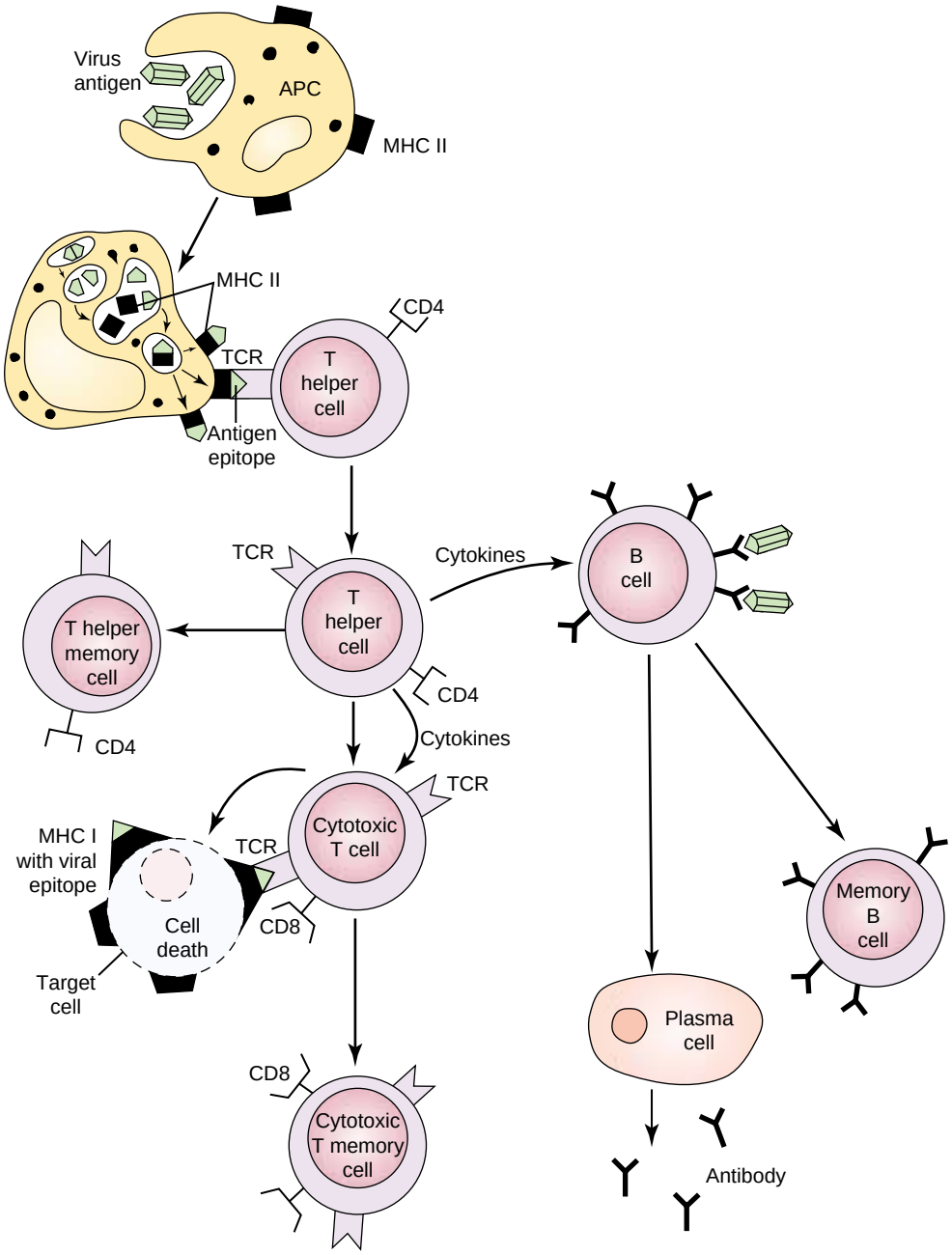
■ **FIGURE 8-4** ■ Pathway for T- and B-cell differentiation.

(T cells), complete their maturation in the thymus and are essential for cell-mediated immunity, as well as aiding with antibody production. Approximately 60% to 70% of blood lymphocytes are T cells, and 10% to 20% are B cells. The various types of lymphocytes are distinguished by their function and response to antigen, their cell membrane molecules and receptors, their types of secreted proteins, and their tissue location.

Activation of the lymphocytes is dependent upon the appropriate processing and presentation of antigen to the T lymphocytes by APCs such as macrophages (Fig. 8-5). On recognition of antigen and after additional stimulation by various secreted signaling molecules called *cytokines*, the T and B lymphocytes divide several times to form populations or clones of cells that continue to differentiate into effector cells that destroy the antigen and memory cells that retain the information needed for future encounters with the antigen.

Clusters of Differentiation

Mature T and B cells display surface molecules called *clusters of differentiation* (CD). These molecules serve to define functionally distinct T-cell subsets such as $CD4^+$ T helper cells and $CD8^+$ T cytotoxic cells. The many cell surface CD molecules detected on immune cells have allowed scientists to study the normal and abnormal processes displayed by these cells. In cell-mediated immunity, regulatory $CD4^+$ helper T cells enhance the response of other T and B cells, and effector cytotoxic T cells



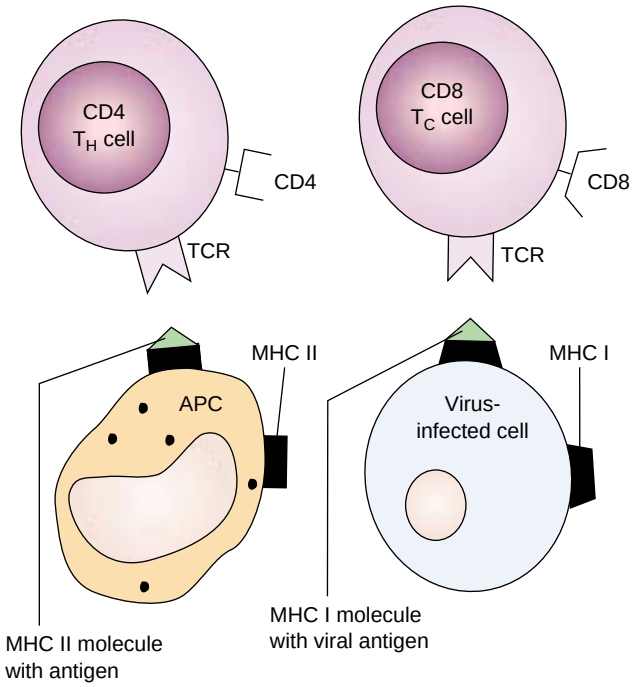
■ **FIGURE 8-5** ■ Pathway for immune cell participation in an immune response.

(CD8+) kill virus-infected cells and tumor cells. The human immunodeficiency virus (HIV) that causes acquired immunodeficiency syndrome (AIDS) infects and destroys the CD4+ helper T cell (see Chapter 10).

Major Histocompatibility Complex Molecules

An essential feature of specific immunity is the ability to discriminate between the body's own molecules and foreign antigens. Failure to distinguish self from nonself can lead to conditions such as autoimmune disease where the immune system destroys the body's own cells. Key recognition molecules essential for distinguishing self from nonself are the cell surface MHC antigens. These molecules, which in humans are coded by closely linked genes on chromosome 6, were first identified because of their role in organ and tissue transplantation. When cells are transplanted between individuals who are not identical for their MHC molecules, the immune system produces a vigorous immune response, leading to rejection of the transferred cells or organs. MHC molecules did not evolve to reject transplanted tissues, a situation not encountered in nature. Rather, these molecules are essential for correct cell-to-cell interactions among immune and body cells.

The MHC molecules involved in self-recognition and cell-to-cell communication fall into two classes, class I and class II (Fig. 8-6). *Class I MHC* molecules are cell surface glycoproteins that interact with antigen receptors and the CD8 molecule on T cytotoxic lymphocytes. They are found on nearly all nucleated cells in the body and thus are capable of alerting the immune system of any cell changes caused by viruses or products of mutated genes in cancer cells. In viral infected cells, viral protein antigens become associated with class I MHC molecules. As the virus multiplies, small peptides from degraded viral proteins



■ **FIGURE 8-6** ■ Interaction of a T-cell receptor (TCR) on a CD4 helper T (T_H) cell with class II MHC molecule on an antigen-presenting (APC) cell and CD8 cytotoxic (T_C) T cell with class I MHC molecule on a virus-infected cell.

complex with class I MHC molecules and are then transported to the infected cell membrane. This antigen-MHC I complex communicates to the T cytotoxic cell that the cell must be destroyed for the overall survival of the host. *Class II MHC* molecules, which are found primarily on APCs such as macrophages, dendritic cells, and B lymphocytes, communicate with an antigen receptor and a CD4 molecule on T helper lymphocytes. Class II MHC molecules bind to a fragment of antigen from pathogens that have been engulfed and digested during the process of phagocytosis. The engulfed pathogen is degraded in cytoplasmic vesicles and its peptide components complexed with class II MHC molecules. T helper cells recognize these complexes on the surface of APCs and become activated. These activated T cells multiply quickly and direct the immune response to the invading pathogen.

Each individual has a unique collection of several MHC proteins, and a variety of MHC molecules can exist in a population. Because of the number of MHC genes and the possibility of several alleles for each gene, it is almost impossible for any two individuals to be identical, unless they are identical twins. The uniqueness of these genes is essential for the immune system to distinguish self from nonself. In contrast to the receptors on T and B lymphocytes that bind a unique antigen molecule, each MHC protein can bind a broad spectrum of antigen peptides. Incorporation of the MHC molecules into the antigen presentation process allow for self/nonself recognition in establishing an appropriate immune response.

Human MHC proteins are called *human leukocyte antigens* (HLA) because they were first detected on white blood cells. Because these molecules play a role in transplant rejection and are detected by immunologic tests, they are commonly called antigens. The human class I MHC molecules are divided into types called HLA-A, HLA-B, and HLA-C, and the class II MHC molecules are identified as HLA-DR, HLA-DP, and HLA-DQ (Table 8-1). Additional, less well-defined class I and II MHC genes also have been described. Each of the gene loci that describes an HLA molecule can be occupied by multiple alleles or alternate genes. For example, there are more than 120 possible genes for the A locus and 250 genes for the B locus. Each of the gene products or antigens is designated by a number, such as HLA-B27.

Because the class I and II MHC genes are closely linked on one chromosome, the combination of HLA genes usually is inherited as a unit, called a *haplotype*. Each person inherits a chromosome from each parent and therefore has two HLA haplotypes. The identification or typing of HLA molecules is important in tissue or organ transplantation, forensics, and paternity evaluations. In organ or tissue transplantation, the closer the matching of HLA types, the greater is the probability of identical antigens and the lower the chance of rejection.

Monocytes, Macrophages, and Dendritic Cells

Monocytes and tissue macrophages are a part of the mononuclear phagocyte system, which in turn is part of the reticuloendothelial system. All of the cells of the mononuclear phagocytic system arise from common precursors in the bone marrow that produce the blood monocytes (see Chapter 11). The monocytes migrate to various tissues where they mature into macrophages. Macrophages are characterized as large cells with extensive cytoplasm and numerous vacuoles. The tissue macrophages are scattered in connective tissue or clustered in

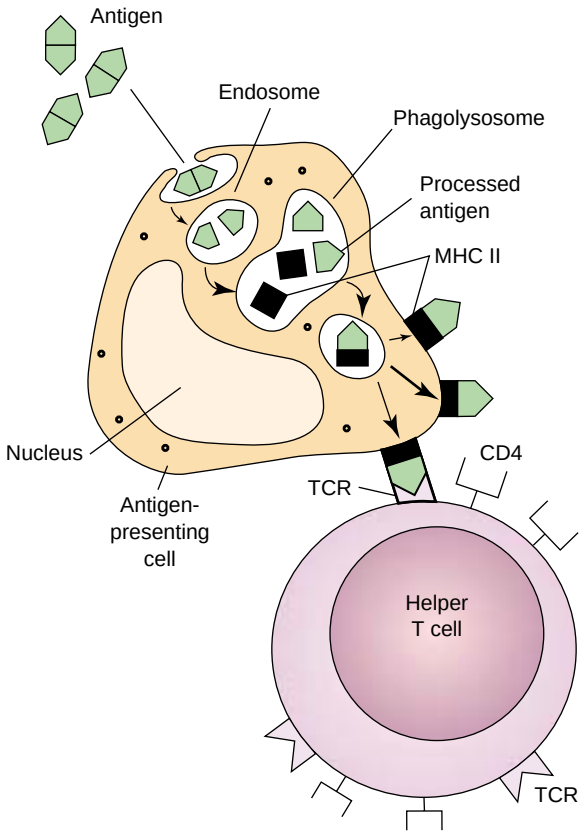
TABLE 8-1 Properties of MHC Class I and MHC Class II Molecules

Properties	MHC Class I	MHC Class II
HLA antigens	HLA-A, HLA-B, HLA-C	HLA-DR, HLA-DP, HLA-DQ
Distribution	Virtually all nucleated cells	Restricted to immune cells, antigen-presenting cells, B cells, and macrophages
Functions	Present processed antigen to cytotoxic $CD8^+$ T cells; restrict cytolysis to virus-infected cells, tumor cells, transplanted cells	Present processed antigenic fragments to $CD4^+$ T cells; necessary for effective interaction among immune cells

HLA, human leukocyte antigen; MHC, major histocompatibility complex.

organs such as the lung (*i.e.*, alveolar macrophages), liver (*i.e.*, Kupffer's cells), spleen, lymph nodes, peritoneum, central nervous system (*i.e.*, microglial cells), and other areas.

Macrophages have important functions in both innate and antigen-specific immune responses. As phagocytic cells with antigen nonspecific activity, they help to contain infectious agents until specific immunity can be marshaled. In addition, early in the host response, the macrophage functions as an accessory cell to ensure amplification of the inflammatory response and initiation of specific immunity. Macrophages are activated by the presence of antigen to engulf and digest foreign particles (Fig. 8-7). Activated macrophages act as APCs that break down complex antigens into peptide fragments that can associate with class II MHC molecules. Macrophages can then present these complexes to the helper T cell so that nonself-self recognition and activation of the immune response can occur. Macrophages also secrete cytokines that produce fever and prime T and B lymphocytes that have recognized antigen.



■ **FIGURE 8-7** ■ Presentation of antigen to helper T cell by an antigen-presenting cell (APC).

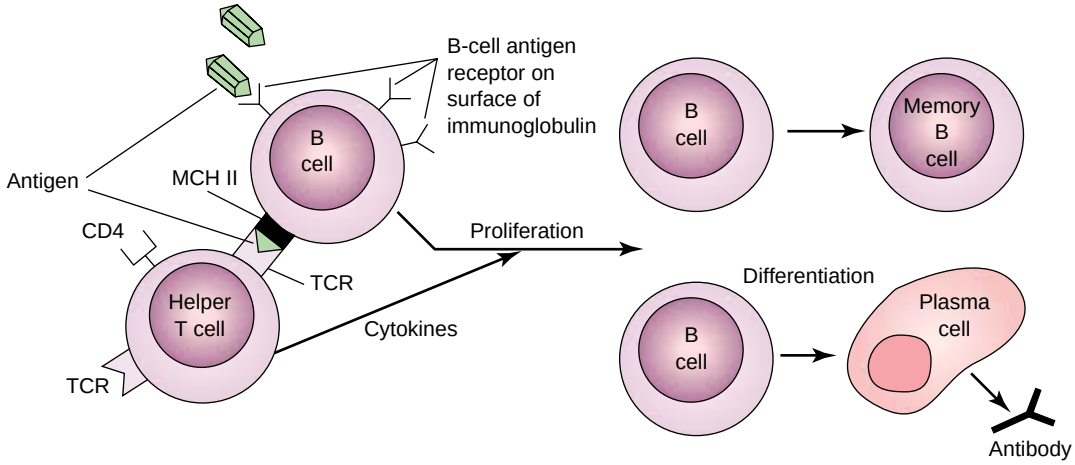
As the general scavenger cell of the body, the macrophage can be fixed in a tissue or can be free to migrate from an organ to lymphoid tissues. Macrophages also can serve as phagocytic effector cells in humoral and cell-mediated immune responses. They can remove antigen–antibody aggregates or, under the influence of T-cell cytokines, they can destroy virus-infected cells or tumor cells.

Dendritic cells share with the macrophage the important task of presenting antigen to T lymphocytes. These distinctive, star-shaped cells with long extensions of their cytoplasmic membrane provide an extensive surface rich in class II MHC molecules, which is essential for initiation of an acquired immune response. Dendritic cells are found in lymphoid tissues and other body areas where antigen enters the body. In these different environments, dendritic cells can acquire specialized functions and appearances, as do macrophages. Langerhans' cells are specialized dendritic cells in the skin, whereas follicular dendritic cells are found in the lymph nodes. Langerhans' cells are constantly surveying the skin for antigen and can transport foreign material to a nearby lymph node. Skin dendritic cells and macrophages also are involved in cell-mediated immune reactions of the skin, such as delayed allergic contact hypersensitivity.

B Lymphocytes

B lymphocytes can be identified by the presence of surface immunoglobulin that functions as the antigen receptor, class II MHC proteins, complement receptors, and specific CD molecules. During the maturation of B cells, which occurs in the bone marrow, stem cells change into immature precursor (pre-B) cells (Fig. 8-8). This B cell then acquires a unique surface receptor and a specific type of effector antibody (*e.g.*, immunoglobulin M [IgM] or IgD). This stage of maturation is programmed into the B cells and does not require antigen for its stimulation. CD molecules also change as the B cell matures. The CD surface markers are useful for defining immature and undifferentiated cells in B-cell malignancies. The mature B cell leaves the bone marrow, enters the circulation, and migrates to the various peripheral lymphoid tissues, where it is stimulated to respond to a specific antigen.

The commitment of a B-cell line to a specific antigen is evident by the expression of the surface immunoglobulin receptors. B cells that encounter antigen complementary to their sur-

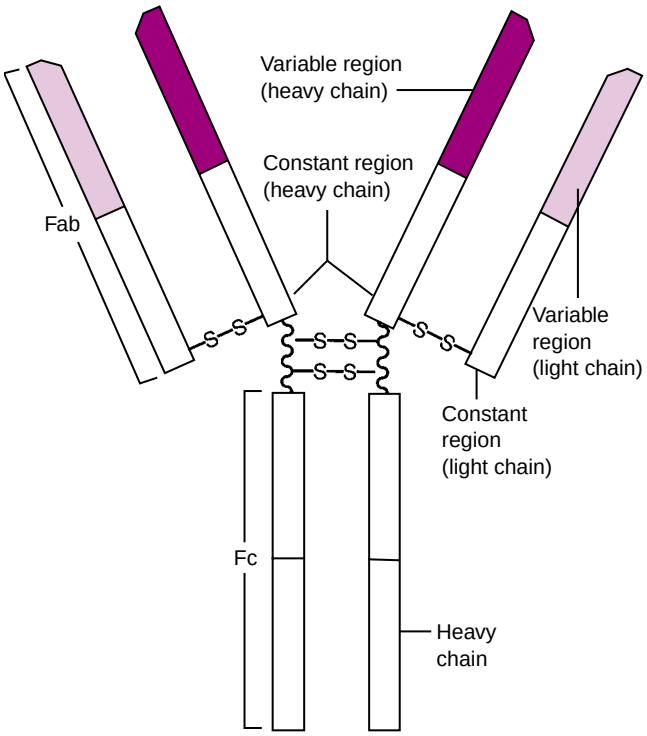


■ **FIGURE 8-8** ■ Pathway for B-cell differentiation.

face immunoglobulin receptor and receive T-cell help undergo a series of changes that transform them into antibody-secreting plasma cells or into memory B cells (Fig. 8-8). The activated B cell that divides and maturates into a plasma cell can produce thousands of antibody molecules per second. The antibodies are released into the blood and lymph, where they bind and remove their unique antigen with the help of other immune cells and molecules. Longer-lived memory B cells are generated and distributed into the peripheral tissues in preparation for subsequent antigen exposure.

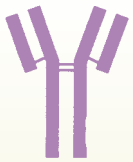
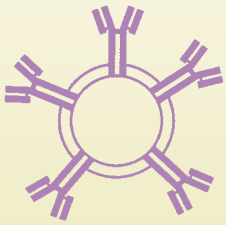
Immunoglobulins. Antibodies comprise a class of proteins called *immunoglobulins*. The immunoglobulins have been divided into five classes: IgG, IgA, IgM, IgD, and IgE (Table 8-2), each with a different role in the immune defense strategy. Immunoglobulins have a characteristic four-polypeptide structure consisting of at least two identical antigen-binding sites (Fig. 8-9). Each immunoglobulin is composed of two identical light (L) chains and two identical heavy (H) chains to form a Y-shaped molecule. The two forked ends of the immunoglobulin molecule bind antigen and are called *Fab* (*i.e.*, antigen-binding) fragments, and the tail of the molecule, which is called the *Fc* fragment, determines the biologic properties that are characteristic of a particular class of immunoglobulins. The amino acid sequence of the heavy and light chains shows constant (C) regions and variable (V) regions. The *constant regions* have sequences of amino acids that vary little among the antibodies of a particular class of immunoglobulin. The constant region allows for separation of immunoglobulins into classes (*e.g.*, IgM, IgG) and it allows each class of antibody to interact with certain effector cells and molecules. For example, IgG can tag an antigen for recognition and destruction by phagocytes. The *variable regions* contain the antigen-binding sites of the molecule. The wide variation in the amino acid sequence of the variable regions seen from antibody to antibody allows this region to serve as the antigen-binding site. A unique amino acid sequence in this region determines a distinctive three-dimensional pocket that is complementary to the antigen, allowing recognition and binding of the antigen. Each B-cell clone produces antibody with one specific antigen-binding variable region or domain. During the course of the immune response, class switching (*e.g.*, from IgM to IgG) can occur, causing the B-cell clone to produce any of the following antibody types.

IgG (gamma globulin) is the most abundant of the circulating immunoglobulins. It is present in body fluids and readily enters the tissues. IgG is the only immunoglobulin that crosses the placenta and can transfer immunity from the mother to the fetus. This class of immunoglobulin protects against bacteria, toxins, and viruses in body fluids and activates the complement system. There are four subsets of IgG (*i.e.*, IgG1, IgG2, IgG3, and IgG4) that have some restrictions in their response to certain types of antigens. For example, IgG2 appears to be responsive to bacteria that are encapsulated with a polysaccharide



■ **FIGURE 8-9** ■ Schematic model of an IgG molecule showing the constant and variable regions of the light and dark chains.

TABLE 8-2 Classes and Characteristics of Immunoglobulins

Figure	Class	Percentage of Total	Characteristics
	IgG	75.0	Displays antiviral, antitoxin, and antibacterial properties; only Ig that crosses the placenta; responsible for protection of newborn; activates complement and binds to macrophages
	IgA	15.0	Predominant Ig in body secretions, such as saliva, nasal and respiratory secretions, and breast milk; protects mucous membranes
	IgM	10.0	Forms the natural antibodies such as those for ABO blood antigens; prominent in early immune responses; activates complement
	IgD	0.2	Found on B lymphocytes; needed for maturation of B cells
	IgE	0.004	Binds to mast cells and basophils; involved in parasitic infections, allergic and hypersensitivity reactions

covering, such as *Streptococcus pneumoniae, Haemophilus influenzae,* and *Neisseria meningitidis.*

IgA is the second most abundant of the immunoglobulins. It is a secretory immunoglobulin found in saliva, tears, colostrum (*i.e.,* first milk of a nursing mother), and in bronchial, gastrointestinal, prostatic, and vaginal secretions. IgA prevents the attachment of viruses and bacteria to epithelial cells and is considered a primary defense against local infections in mucosal tissues.

IgM is a macromolecule that forms a polymer of five basic immunoglobulin units. It cannot cross the placenta and does not transfer maternal immunity. It is the first circulating immunoglobulin to appear in response to an antigen and is the first antibody type made by a newborn. This is diagnostically useful because the presence of IgM suggests a current infection by a specific pathogen. The identification of newborn IgM, rather than maternally transferred IgG, to a specific pathogen is indicative of an in utero or newborn infection.

IgD is found primarily on the cell membranes of B lymphocytes. It serves as an antigen receptor for initiating the differentiation of B cells.

IgE is involved in inflammation, allergic responses, and combating parasitic infections. It binds to mast cells and basophils. The binding of antigen to mast cell- or basophil-bound IgE triggers these cells to release histamine and other mediators important in inflammation and allergies.

T Lymphocytes

T lymphocytes function in the activation of other T cells and B cells, in the control of viral infections, in the rejection of foreign tissue grafts, and in delayed hypersensitivity reactions (see Chapter 10). Collectively, these immune responses are called *cell-mediated* or *cellular immunity.* Besides the ability to respond to cell-associated antigens, the T cell is integral to immunity because it regulates self-recognition and amplifies the response of B and T lymphocytes.

T lymphocytes arise from bone marrow stem cells, but unlike B cells, pre-T cells migrate to the thymus for their maturation. There, the immature T lymphocyte acquires a T-cell receptor (TCR). The TCR for antigen is composed of membrane proteins expressed only on the T lymphocytes and binds specifically to antigen-peptide-MHC complexes on the surface of APCs or target cells. As with the variable proteins on the immunoglobulin molecule, the TCR proteins differ among T cells with different antigen specificity.

Maturation of subpopulations of T cells (*i.e.*, $CD4^+$ and $CD8^+$) also occurs in the thymus. Mature T cells migrate to the peripheral lymphoid tissues and, on encountering antigen, multiply and differentiate into memory T cells and various effector T cells.

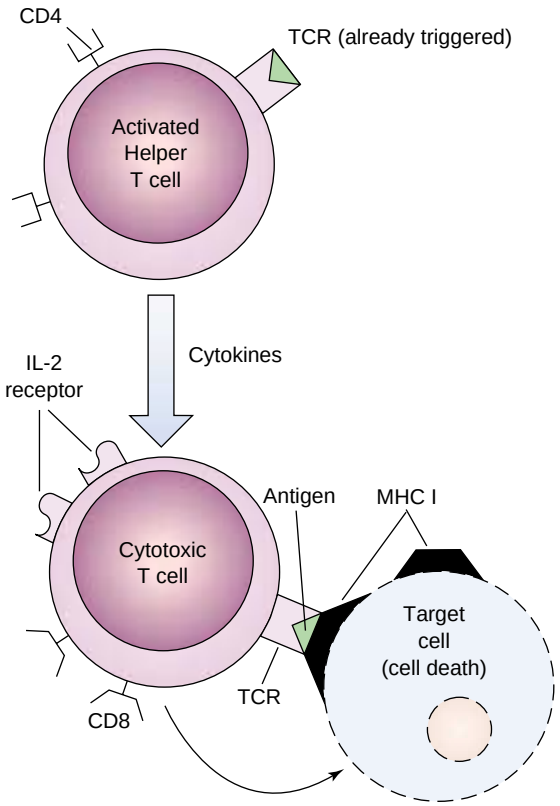
The $CD4^+$ helper T cell (T_H) serves as a master switch for the immune system. Activation of helper T cells depends on the recognition of antigen in association with class II MHC molecules. Activated helper T cells secrete cytokines that influence the function of nearly all other cells of the immune system. These cytokines activate and regulate B cells, cytotoxic T cells, natural killer (NK) cells, macrophages, and other immune cells. Distinct subpopulations of helper T cells (*i.e.*, T_H1 and T_H2) have been identified and shown to secrete different patterns of cytokines. The pattern of cytokine production determines whether an antibody- or cell-mediated immune response develops. This differential expression of cytokines can influence expressions of some diseases (*i.e.*, lepromatous and tuberculoid leprosy).

The cytotoxic $CD8^+$ T cells become activated after recognition of class I MHC–antigen complexes on target cell surfaces such as body cells infected by viruses or transformed by cancer (Fig. 8-10). The recognition of class I MHC–antigen complexes on infected target cells ensures that neighboring uninfected host cells, which express class I MHC molecules alone or with self-peptide, are not indiscriminately destroyed. The $CD8^+$ T cells destroy target cells by releasing cytolytic enzymes, toxic cytokines, and pore-forming molecules (*i.e.*, perforins) or by triggering programmed cell death (apoptosis) in the target cell. The perforin proteins produce pores in the target cell membrane, allowing entry of toxic molecules and loss of cell constituents. The $CD8^+$ T cells are especially important in controlling replicating viruses and intracellular bacteria because antibody cannot penetrate living cells.

Natural Killer Cells

Natural killer cells are lymphocytes that are functionally, genotypically, and phenotypically distinct from T cells, B cells, and monocyte-macrophages. The NK cell is a nonspecific effector cell that can kill tumor cells and virus-infected cells. They are called *natural killer cells* because, unlike T cytotoxic cells, they do not need to recognize a specific antigen before being activated. Both NK cells and T cytotoxic cells kill after contact with a target cell. The NK cell is programmed automatically to kill foreign cells, in contrast with the $CD8^+$ T cells, which need to be activated to become cytotoxic. However, programmed killing is inhibited if the NK cell membrane molecules contact MHC self-molecules on normal host cells.

The mechanism of NK cytotoxicity is similar to T-cell cytotoxicity in that it depends on production of pore-forming proteins (*i.e.*, NK perforins), enzymes, and toxic cytokines. NK cell activity can be enhanced in vitro on exposure to interleukin-2 (IL-2), a phenomenon called *lymphokine-activated killer* activity. These activated NK cells are used in the treatment of cancer. NK cells also participate in *antibody-dependent cellular cytotoxicity*, a mechanism by which a cytotoxic effector cell can kill an antibody-coated target cell. The role of NK cells probably is one of immune surveillance for cancerous or virally infected cells.



■ **FIGURE 8-10** ■ Destruction of target cell by cytotoxic T cell. Cytokines released from the activated helper T cell enhance final destruction of the target cell by the cytotoxic T cell.

Cytokines and the Immune Response

Cytokines are low–molecular-weight regulatory proteins that are produced during all phases of an immune response. Cytokines are made primarily by and act predominantly on immune cells. These intercellular signal molecules are very potent, act at very low concentrations, and usually regulate neighboring cells. Cytokines modulate reactions of the host to foreign antigens or injurious agents by regulating the movement, proliferation, and differentiation of leukocytes and other cells (Table 8-3). Cytokines are synthesized by many cell types but are made primarily by activated T helper cells and macrophages.

These regulator molecules can be named for the general cell type that produces them (*e.g.*, lymphokines, monokines). More specifically, they are named by an international nomenclature (*i.e.*, interleukins 1 through 18) for the biologic property that was first ascribed to them. For example, *interferons* (IFNs) were named because they interfered with virus multiplication. Cytokines commonly affect more than one cell type

TABLE 8-3 Characteristic Biologic Properties of Human Cytokines

Cytokine	Biologic Activity
Interleukin-1 (alpha and beta)	Activates resting T cells; is cofactor for hematopoietic growth factor; induces fever, sleep, adrenocorticotropic hormone release, neutropenia, and other systemic acute-phase responses; stimulates synthesis of cytokines, collagen, and collegenases; activates endothelial and macrophagic cells; mediates inflammation, catabolic processes, and nonspecific resistance to infection
Interleukin-2	Growth factor for activated T cells; induces synthesis of other cytokines, activates cytotoxic lymphocytes
Interleukin-3	Support growth of pluripotent (multilineage) bone marrow stem cells; is growth factor for mast cells
Interleukin-4	Growth factor for activated B cells, resting T cells, and mast cells; induces MHC class I antigen expression on B cells; enhances cytotoxic T cells; activates macrophages
Interleukin-5	B-cell differentiating and growth factor; promotes differentiation of eosinophils; promotes antibody production (IgA)
Interleukin-6	Acts as cofactor for immunoglobulin production by B cells; stimulates hepatocytes to produce acute-phase proteins
Interleukin-7	Stimulates pre-B cells and thymocytes; stimulates myeloid precursors and megakaryocytes
Interleukin-8	Chemoattracts neutrophils and T lymphocytes; regulates lymphocyte homing and neutrophil infiltration
Interleukin-10	Suppresses cytokine production by T helper cells; inhibits antigen presentation
Interleukin-12	Enhances activation of cytotoxic T, NK, and macrophages; acts opposite to IL-10
Interferon-gamma (γ)	Induces MHC class I, class II, and other surface antigens on a variety of cells; activates macrophages and endothelial cells; augments or inhibits other cytokine activities; augments NK cell activity; exerts antiviral activity
Interferon (alpha and beta) (α and β)	Exerts antiviral activity; induces class I antigen expression; augments NK cell activity; has fever-inducing and antiproliferative properties
Tumor necrosis factor (alpha) (α)	Direct cytotoxin for some tumor cells; induces fever, sleep, and other acute-phase responses; stimulates the synthesis of other cytokines, collagen, and collagenases; activates endothelial and macrophagic cells; mediates inflammation, catabolic processes, and septic shock
Colony-stimulating factor (CSF)	Promotes neutrophilic, eosinophilic, and macrophagic bone marrow colonies; activates mature granulocytes
Granulocyte–macrophage CSF	
Granulocyte CSF	Promotes neutrophilic colonies
Macrophage CSF	Promotes macrophagic colonies

MHC, major histocompatibility complex; NK, natural killer.

and have more than one biologic effect. For example, IFN-γ inhibits virus replication and is a potent activator of macrophages and NK cells. Specific cytokines can have biologic activities that overlap. Maximization of the immune response and protection against detrimental mutations in a single cytokine are possible benefits of redundancy.

The production of cytokines often occurs in a cascade, in which one cytokine affects the production of subsequent cytokines or cytokine receptors. Some cytokines function as antagonists to inhibit the biologic effects of earlier cytokines. This pattern of expression and feedback ensures appropriate control of cytokine synthesis and subsequently of the immune response. Excessive cytokine production can have serious adverse effects, including those associated with septic shock, food poisoning, and types of cancer.

Cytokines generate their responses by binding to specific receptors on their target cells. Many cytokine receptors share a common structural shape and a cytoplasmic tail that interacts with a family of cytoplasmic signaling proteins responsible for the induction of the genes for cell responses. Most cytokines are released at cell-to-cell interfaces, where they bind to receptors on nearby cells. The short half-life of cytokines ensures that excessive immune responses and systemic activation do not occur.

The biologic properties of cytokines fall into several major groups. One group of cytokines (*e.g.*, IL-1, IL-6, TNF) mediates inflammation by producing fever and the acute-phase response and by attracting and activating phagocytes (*e.g.*, IL-8, IFN-γ). Other cytokines are maturation factors for the hematopoiesis of white or red blood cells (*e.g.*, IL-3, granulocyte-macrophage colony-stimulating factor [GM-CSF]). Recombinant CSF molecules are being used to increase the success rates of bone marrow transplantations. Most of the interleukin cytokines function as cell communication molecules among T cells, B cells, macrophages, and other immune cells. The availability of recombinant cytokines offers the possibility of several clinical therapies for which stimulation or inhibition of the immune response is desirable.

Interleukin 1 and 2

The major function of IL-1 is as a mediator of the inflammatory response. In concert with IL-6 and TNF-α, IL-1 can stimulate the production of an acute-phase response, mobilize neutrophils, produce a fever, and activate the vascular epithelium. IL-1 also can serve as a priming signal in the activation of $CD4^+$ T cells and the growth and differentiation of B cells. The major source of IL-1 is the macrophage, although it also is produced by keratinocytes, Langerhans' cells, normal B cells, cultured T cells, fibroblasts, neutrophils, and smooth muscle cells.

The presence of IL-2, formerly known as *T-cell growth factor*, is necessary for the proliferation and function of helper T, cyto-

toxic T, B, and NK cells. IL-2 interacts with T lymphocytes by binding to specific membrane receptors that are present on activated T cells but not on resting T cells. The expression of high-affinity IL-2 receptors can be triggered by specific antigen and other stimulatory signals. Sustained T-cell proliferation relies on the presence of IL-2 and IL-2 receptors; if either is missing, cell proliferation ceases, and the cell dies. This cytokine ensures maximum amplification of immune responses if antigen is present. The drugs cyclosporine and tacrolimus, which are used to prevent rejection of heart, kidney, and liver transplants, function primarily by inhibiting the synthesis of IL-2.

Interferons

The IFNs are a family of cytokines that protect neighboring cells from invasion by intracellular parasites, including viruses, rickettsiae, malarial parasites, and other organisms. Bacterial toxins, complex polysaccharides, and several other chemical substances can induce IFN production. Not all the substances that induce IFN are antigenic.

There are three types of IFN: IFN-α, produced by leukocytes; IFN-β, produced by fibroblasts; and IFN-γ, produced by T and NK cells. IFN-α and IFN-β are grouped as type I IFNs to distinguish them from IFN-γ (type II). Type I-secreted IFNs interact with receptors on neighboring cells to stimulate the translation of an antiviral protein that affects viral synthesis and its spread to uninfected cells. The actions of IFNs are not pathogen specific; they are effective against different types of viruses and intracellular parasites. However, they are species specific. Animal IFNs do not provide protection in humans. The IFN produced during immune reactions is primarily IFN-γ. IFN-γ functions to activate macrophages, generate cytotoxic lymphocytes, and enhance NK cell activity.

Tumor Necrosis Factor

Like IL-1, TNF-α is a cytokine with multiple immunologic and inflammatory effects. It was first described as an activity in serum that induced hemorrhagic necrosis in certain tumors, and can function as a circulating mediator of wasting disease. TNF is produced by activated macrophages and other activated cells, such as T cells. Besides functioning as a major chemical mediator in the inflammatory response and indirectly affecting the fever response, TNF may function as a costimulator of T cells. This cytokine is an especially potent stimulator of IL-1, IL-6, and IL-8. In bacterial sepsis, high serum levels of TNF may mediate endotoxic shock. TNF is primarily responsible for the tissue wasting seen in cases of chronic inflammation.

Hematopoietic Colony-Stimulating Factors

Colony-stimulating factors are cytokines that stimulate bone marrow pluripotent stem and progenitor or precursor cells to produce large numbers of platelets, erythrocytes, neutrophils, monocytes, eosinophils, and basophils (see Chapter 11). The CSFs were named according to the type of target cell on which they act (see Table 8-3). GM-CSF acts on the granulocyte–monocyte progenitor cells to produce monocytes, neutrophils, and dendritic cells; G-CSF more specifically induces neutrophil proliferation; and M-CSF specifically directs the mononuclear phagocyte progenitor. Other cytokines, including IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, and IL-11, also may influence hematopoiesis.

Mechanisms of the Immune Response

The immune response is a complex series of interactions among the components of the immune system and the antigens of infectious agents and other pathogens. It consists of active or passive immunity and involves humoral and cell-mediated immune mechanisms. The complement system links the humoral immune response with the inflammatory response and the lysis and phagocytosis of pathogens.

Active Versus Passive Immunity

Active or acquired immunity can be achieved through exposure to a specific antigen or through transfer of protective antibodies to an antigen. It is acquired through immunization or actually having a disease. Active immunity, although long lasting once established, requires a few days to weeks after a first exposure to become sufficiently developed to contribute to the destruction of the pathogen. However, on subsequent exposure to the same agent, the immune system usually is able to react within hours because of the presence of memory B and T lymphocytes.

Passive immunity is immunity transferred from one source to another source. An infant receives passive immunity naturally from the transfer of antibodies from its mother in utero and through a mother's breast milk. Normally, an infant has few infectious diseases during the first 3 to 6 months because of the protection provided by the mother's antibodies. Passive immunity also can be artificially provided by the transfer of antibodies produced by other people or animals. Some protection against infectious disease can be provided by the injection of hyperimmune serum, which contains high concentrations of antibodies for a specific disease, or immune serum or gamma globulin, which contains a pool of antibodies for many infectious agents. Passive immunity produces only short-term protection that lasts weeks to months.

KEY CONCEPTS

THE IMMUNE RESPONSE

- The immune response involves a complex series of interactions between components of the immune system and the antigens of a foreign pathogen.
- *Passive immunity* represents a temporary type of immunity that is transferred from another source (in utero transfer of antibodies from mother to infant).
- Active immunity depends on a response by the person's immune system and is acquired through immunization or actually having a disease.
- Humoral immunity consists of protection provided by the B lymphocyte-derived plasma cells, which produce antibodies that travel in the blood and interact with circulating and cell surface antigens.
- Cell-mediated immunity consists of protection provided by cytotoxic T lymphocytes, which protect against virus-infected or cancer cells.

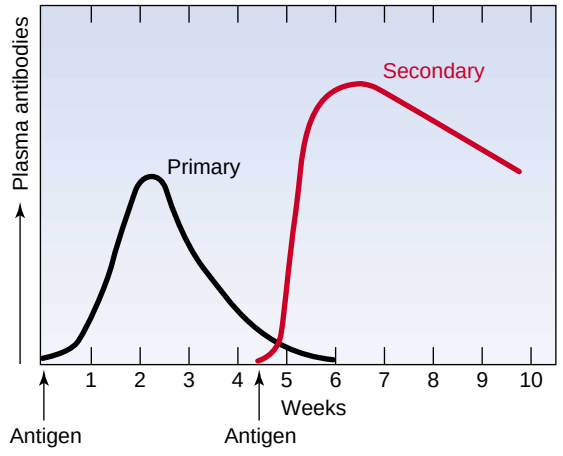
Humoral Immunity

Humoral, or antibody-mediated immunity, relies on the presence of antibodies in the blood or body fluids. The combination of antigen with antibody can result in several effector responses, such as precipitation of antigen–antibody complexes, agglutination or clumping of cells, neutralization of bacterial toxins and viruses, lysis and destruction of pathogens or cells, adherence of antigen to immune cells, complement activation, and facilitation of phagocytosis. Phagocytic cells can more effectively bind, engulf, and digest antigen–antibody aggregates or immune complexes than they can antigen alone. Antibody can also neutralize a virus by blocking the sites on the virus that it uses to bind to the host cell, thereby negating its ability to infect the cell.

Two types of responses occur in the development of humoral immunity: a primary and a secondary response (Fig. 8-11). A *primary immune response* occurs when the antigen is first introduced into the body. During this primary response, there is a latent period or lag before the antibody can be detected in the serum. During this latent period, B cells are activated to proliferate and differentiate into antibody-secreting plasma cells. Recovery from many infectious diseases occurs at the time during the primary response when the antibody concentration is reaching its peak. The *secondary* or *memory response* occurs on second or subsequent exposures to the antigen. During the secondary response, the rise in antibody occurs sooner and reaches a higher level because of the available memory cells. The booster immunization given for some infectious diseases, such as tetanus, makes use of the secondary or memory response. For a person who has been previously immunized, administration of a booster shot causes an almost immediate rise in antibody to a level sufficient to prevent development of the disease.

Cell-mediated Immunity

Cell-mediated immunity provides protection against viruses, intracellular bacteria, and cancer cells. In cell-mediated immunity, the actions of T lymphocytes and macrophages predominate. The most aggressive phagocyte, the macrophage, becomes activated after exposure to T-cell cytokines, especially IFN-γ. As in humoral immunity, the initial stages of cell-mediated immunity are directed by an APC displaying the antigen peptide–class II MHC complex to the helper T cell. Helper T cells become activated after recognition by the TCR of the antigen–MHC complex and by priming with IL-1. The activated helper T cell then synthesizes IL-2 and the IL-2 receptor. These molecules drive the multiplication of clones of helper T cells, which amplify the response. Further differentiation of the helper T cells leads to production of additional cytokines (*e.g.*, IFN-γ, TNF, IL-12), which enhance the activity of cytotoxic T cells and effector macrophages. A cell-mediated immune response usually occurs through the cytotoxic activity of cytotoxic T cells and the enhanced engulfment and killing by macrophages.



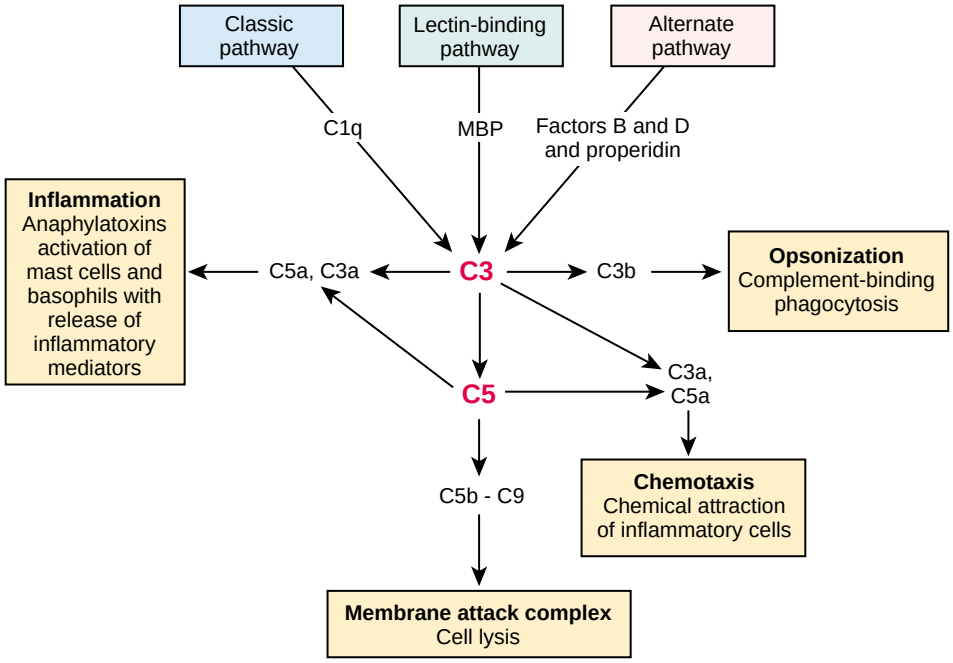
■ **FIGURE 8-11** ■ Primary and secondary phases of the humoral immune response to the same antigen.

The Complement System

The complement system is a primary mediator of the humoral immune response that enables the body to produce an inflammatory response, lyse foreign cells, and increase phagocytosis. The complement system, like the blood coagulation system, consists of a group of proteins that normally are present in the circulation as functionally inactive precursors. These proteins make up 10% to 15% of the plasma protein fraction. For a complement reaction to occur, the complement components must be activated in the proper sequence. Uncontrolled activation of the complement system is prevented by inhibitor proteins and the instability of the activated complement proteins at each step of the process. There are three parallel but independent mechanisms for recognizing microorganisms that result in the activation of the complement system: the classic, the alternate, and the lectin-mediated pathways. All three pathways of activation generate a series of enzymatic reactions that proteolytically cleave successive complement proteins in the pathway. The consequence is the deposition of some complement protein fragments on the pathogen surface, thereby producing tags for better recognition by the phagocytic cells. Other complement fragments that are released into the tissue fluids further stimulate the inflammatory response.

The classic pathway of complement activation is initiated by antibody bound to antigens on the surface of microbes or through soluble immune complexes (Fig. 8-12). The alternate and the lectin pathways do not use antibodies and are part of the innate immune defenses. The alternate pathway of complement activation is initiated by the interaction with certain polysaccharide molecules characteristic of bacterial surfaces. The lectin-mediated pathway is initiated following the binding of a mannose-binding protein to mannose-containing molecules commonly present on the surface of bacteria and yeast.

The activation of the three pathways produces similar effects on C3 and subsequent complement proteins. The classic pathway of complement activation was the first discovered and is the best studied. The major proteins of the classic system are designated by a numbering system from C1 to C9. The classic pathway is triggered when complement-fixing antibodies, such as IgG or IgM, bind to antigens. The immune complexes trigger a series of enzyme reactions that act in a cascade fashion. Modified or split complement proteins (*e.g.*, C3b, C3a, C5a) released during activation function in the next step of the pathway or are released into the tissue fluid to produce biologic effects important in inflammation. C3 has a central role in the



■ **FIGURE 8-12** ■ Classic, lectin, and alternative complement pathways.

complement pathway because it is integral to all three pathways. The triggering of C3 initiates several mechanisms for microbial destruction. One result of activation of C3 is the formation of the membrane attack complex formed by C5 to C9. Several structurally modulated complement proteins bind to form pores in the membrane of foreign cells that lead to eventual cell lysis.

The alternate and lectin pathways are activated by microbial surface molecules and substitute other molecules for the proteins in the first two steps of the classic complement pathway. The *alternate pathway* uses protein factors B, D, and properdin for activation, whereas the *lectin pathway* uses mannose-binding protein (MBP) and accessory proteins. Both pathways require the presence of C3b and subsequent complement proteins to generate biologic effects similar to those of the classic complement pathway. Whatever the mechanism of activation of the complement system, the effects produced range from lysis of a variety of different cells to direct mediation of the inflammatory process.

The activation of complement can result in formation of products that produce opsonization, chemotaxis, anaphylaxis, and cell membrane attack (Fig. 8-12). A major biologic function of complement activation is opsonization—the coating of antigen–antibody complexes such that antigens are engulfed and cleared more efficiently by macrophages. Chemotactic complement products (C3a and C5a) can trigger an influx of leukocytes. These white blood cells remain fixed in the area of complement activation through attachment to specific sites on C3b and C4b molecules. Anaphylatoxins (C3a and C5a) lead to activation of basophils and mast cells and release of inflammatory mediators that produce smooth muscle contract and increased vascular permeability. The late phase of the complement cascade involves the mediation of the membrane attack complex (MAC) that leads to the lytic destruction of many kinds of cells, including red blood cells, platelets, bacteria, and lymphocytes.

Regulation of the Immune Response

Self-regulation is an essential property of the immune system. An inadequate immune response may lead to immunodeficiency, but an inappropriate or excessive response may lead to conditions varying from allergic reactions to autoimmune diseases. This regulation is not well understood and involves all aspects of the immune response—antigen, antibody, cytokines, regulatory T cells, and the neuroendocrine system.

With each exposure to antigen, the immune system must determine the branch of the immune system to be activated and the extent and duration of the immune response. After exposure to an antigen, the immune response to that antigen develops after a brief lag, reaches a peak, and then recedes. Normal immune responses are self-limited because the response eliminates the antigen, and the products of the response, such as cytokines and antibodies, have a short or limited life span and are secreted only for brief periods after antigen recognition. Evidence suggests that cytokine feedback from the helper T cell controls several aspects of the immune response.

Another facet of immune self-regulation is inhibition of immune responses by tolerance. The term *tolerance* is used to define the ability of the immune system to be nonreactive to self-antigens while producing immunity to foreign agents. Tolerance to self-antigens protects an individual from harmful autoimmune reactions. Exposure of an individual to foreign antigens may lead to tolerance and the inability to respond to potential pathogens that cause infection. Tolerance exists not only to self-tissues, but to maternal-fetal tissues. Special regulation of the immune system also is evident in defined privileged sites, such as the brain, testes, ovaries, and eyes. Immune

damage in these areas could result in serious consequences to the individual and the species.

In summary, immunity is the resistance to a disease that is provided by the immune system. It can be acquired actively through immunization or by having a disease, or passively by receiving antibodies or immune cells from another source. Antigens have antigenic determinant sites or epitopes, which the immune system recognizes with specific receptors that distinguish the antigens as nonself and as unique foreign molecules. Immune mechanisms can be classified into two types: specific or acquired and nonspecific or innate immunity. Specific or acquired immunity involves humoral and cellular mechanisms whereby the immune cells differentiate self from nonself and recognize and respond to a unique antigen. The humoral immune response involves antibodies produced by activated B lymphocytes. Cell-mediated immunity depends on T-cell responses to cellular antigens. Nonspecific immune mechanisms can distinguish between self and nonself but cannot differentiate among antigens. They include the complement system, cytokines, and the phagocytic activities of neutrophils and macrophages. The cytokines, produced largely by T cells, function as intercellular signals that regulate immune and inflammatory responses.

DEVELOPMENTAL ASPECTS OF THE IMMUNE SYSTEM

Embryologically, the immune system develops in several stages, beginning at 5 to 6 weeks as the fetal liver becomes active in hematopoiesis. Development of the primary lymphoid organs (*i.e.*, thymus and bone marrow) begins during the middle of the first trimester and proceeds rapidly. Secondary lymphoid organs (*i.e.*, spleen, lymph nodes, and tonsils) develop soon after. These secondary lymphoid organs are rather small but well developed at birth and mature rapidly during the postnatal period. The thymus at birth is the largest lymphoid tissue relative to body size and normally is approximately two thirds its mature weight, which it achieves during the first year of life.

Transfer of Immunity From Mother to Infant

Protection of a newborn against antigens occurs through transfer of maternal antibodies. Maternal IgG antibodies cross the placenta during fetal development and remain functional in the newborn for the first months of life (Fig. 8-13). IgG is the only class of immunoglobulins to cross the placenta. Levels of maternal IgG decrease significantly during the first 3 to 6 months of life while infant synthesis of immunoglobulins increases. Maternally transmitted IgG is effective against most microorganisms and viruses. The largest amount of IgG crosses the placenta during the last weeks of pregnancy and is stored in fetal tissues, and infants born prematurely have deficient amounts. Because of the transfer of IgG antibodies to the fetus, an infant born to a mother infected with HIV has a positive HIV antibody test result, although he or she may not be infected with the virus.

Cord blood does not normally contain IgM or IgA. If present, these antibodies are of fetal origin and represent exposure to intrauterine infection. The infant begins producing IgM antibodies within a few months after birth in response to the immense antigenic stimulation of his or her new environment. Premature infants appear to be able to produce IgM as well as do term infants. At approximately 6 days of age, the neonate's IgM rises sharply, and this rise continues until approximately 1 year of age, when the adult level is achieved.

Serum IgA normally is first detected at approximately 13 days after birth. The level increases during early childhood until adult levels are reached between the sixth and seventh year. Maternal IgA also is transferred to the infant in colostrum or milk by breast-feeding. These antibodies provide local immunity for the intestinal system and have been shown to decrease diarrheal infections in underdeveloped countries. These evolutionary adaptations of the immune system have increased the survival of our species and optimized the development of other important organs in the early months of life.

Immune Response in the Elderly

Aging is characterized by a declining ability to adapt to environmental stresses. One of the factors thought to contribute to this problem is a decline in immune responsiveness. This includes changes in cell-mediated and antibody-mediated immune responses. Elderly persons tend to be more susceptible to infections, have more evidence of autoimmune and immune complex disorders than do younger persons, and have a higher incidence of cancer. Experimental evidence suggests that vaccination is less successful in inducing immunization in older persons than in younger adults. However, the effect of altered immune function on the health of elderly persons is clouded by the fact that age-related changes or disease may affect the immune response.

The alterations in immune function that occur with advanced age are not fully understood. There is a decrease in the size of the thymus gland, which is thought to affect T-cell function. The size of the gland begins to decline shortly after sexual maturity, and by 50 years of age, it usually has diminished to

15% or less of its maximum size. A common finding is a slight decrease in the proportion of T cells to other lymphocytes and a decrease in $CD4^+$ and $CD8^+$ cells.

More evident are altered responses of the immune cells to antigen stimulation, increasing the proportion of lymphocytes that become unresponsive, while the remainder continue to function relatively normally. T and B cells show deficiencies in activation. In the T-cell types, the $CD4^+$ subset is most severely affected. Evidence indicates that aged T cells have a decreased rate of synthesis of the cytokines that drive the proliferation of lymphocytes and a diminished expression of the receptors that interact with those cytokines. For example, it has been shown that IL-2 synthesis decreases markedly with aging. Although B-cell function is compromised with age, the range of antigens that can be recognized is not diminished. If anything, the repertoire is increased to the extent that B cells begin to recognize some self-antigens as foreign antigens. This may be the basis for the increased incidence of autoimmune disease in the elderly.

In summary, a newborn is protected against antigens in early life by passive transfer of maternal antibodies through the placenta (IgG) and in colostrum (IgA) through breast-feeding. Some changes are seen with aging, including an increase in autoimmune diseases. The impact of alterations in immune function that occur with aging is not fully understood.

REVIEW QUESTIONS

- Compare the properties of innate or nonspecific and specific or acquired immunity.
- Differentiate between the central and peripheral lymphoid structures in terms of generation of immune cells and interaction with antigens.
- Characterize the significance and function of major histocompatibility complex molecules in terms of recognizing self from nonself and distinguishing between body cells and immune cells.
- Describe the phagocytic and antigen presenting functions of the macrophage as they relate to the immune response.
- Explain why destruction of the $CD4^+$ helper T cells by the human immunodeficiency virus has such a devastating effect on the immune system.
- Explain the body's rationale for using natural killer (NK) cells, rather than B lymphocytes, to destroy mutant cells with the potential for development into cancer cells.
- State the function of the five classes of immunoglobulins.
- Describe the properties of cytokines and their functions in terms of the immune response and production of symptoms such as fever and malaise that accompany an acute infectious process.
- Characterize the role of the complement system in mediation of the immune response.
- Explain the transfer of passive immunity from mother to fetus and explain why infants who have high circulating levels of IgM at birth are thought to have contracted the infection in utero.

connection

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