CHAPTER 10

The Immune System and Host Defense Against Infections

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INTRODUCTION

The human immune system comprises a diverse array of cells found throughout the human body (Box 10-1) that protect it against the pathogenic effects of infectious organisms that may enter and threaten the body. The goal of this chapter is to describe (at a level appropriate for a non-immunologist) how this protection is provided. Astonishing insights into immunity have been realized in the last few decades, more than can be covered in an introductory overview chapter. Additional information is provided in feature boxes scattered throughout this chapter, along with referrals to other sources for those who may want to learn more detail. The last 30 years have been an exciting and challenging time for both immunology and infectious disease epidemiology. In this chapter, you will encounter the best of both worlds.

Box 10-1  Cells of the Immune System

Cells of the immune system include lymphocytes, mononuclear phagocytes, and dendritic cells. These cells are derived from bone marrow precursors that circulate throughout the body in the bloodstream and populate the lymphoid organs, where they mature as described later in this chapter.

In the peripheral blood, approximately one-fourth of the white blood cells are lymphocytes and approximately one-twentieth are monocytes, the circulating form of mononuclear phagocytes. Less than 1% are dendritic cells. At any given time, only 2% of lymphocytes are found in the peripheral blood. The rest are present in the lymphoid tissues such as lymph nodes and collections of lymphoid aggregates that are found below mucosal surfaces in the body, such as gut-associated lymphoid tissue (GALT).

Research on immune functions uses many experimental methods, both in vivo and in vitro. In many cases, immunogenic cells perform the same functions in tissue culture, where they are relatively easy to measure, as they do in the body. Because these functions are generally similar across the immune systems of humans and of other animals, inferences from animal models of disease often have direct applicability to human host defense and immune function. Moreover, the advent of modern molecular microbiology and recombinant DNA methods has made it possible to isolate and characterize many of the molecules produced by immune cells that regulate and/or mediate the functions of the immune system, and also to gain insight into the functions of these molecules in animal models by inserting or deleting (“knocking out”) the genes that code for these molecules. These studies have revealed a complex and dynamic interaction between cells of the immune system and pathogens.

The immune system is traditionally considered to have three defining characteristics. First, it can discriminate between self and non-self—that is, what is normally present in the host and what is not. Second, it remembers what it has encountered (memory). Memory allows the immune system to react more quickly and effectively to a stimulus it has encountered previously. Third, it responds only to the pathogen that is at hand (specificity). In this chapter, we also explain how the immune system attains these characteristics.

Two distinct but interrelated arms of the immune system—one general and one highly specific—have evolved for the recognition of pathogens and foreign molecules. Both arms involve a complex of cell surface receptors and soluble molecules that work in concert to identify a pathogen through unique aspects of its molecular makeup, and tag it for elimination.
The first arm is designed to work within minutes after a pathogen establishes residency in the vertebrate host. It utilizes receptors that are constitutively expressed on mononuclear and polymorphonuclear phagocytic cells and on “killer” cells that recognize pathogen-associated molecular patterns (PAMPs). These receptors provide a general signal that certain types of microorganisms are present, and they initiate cellular mechanisms that can clear the foreign pathogen from the body. This ready-to-use capacity to rapidly recognize pathogens is referred to as the innate immune response. The term “innate” refers to the fact that these responses do not require time to develop but rather are ready to go at any time. The main cell types involved in innate immunity are macrophages, dendritic cells, and natural killer (NK) cells (Box 10-2 and Box 10-3). Epithelial cells also play a role in the innate immune response.

Most encounters with microorganisms and toxins are not obvious to the person who experiences them because the innate immune response is able to eliminate the threat of infection. However, in those situations where cells and molecules of the innate immune response fail to control and eliminate a pathogenic organism, the role of the innate response shifts to one of initiating, modulating, and mediating the second, highly specific arm of the vertebrate defense system—the adaptive immune response. The term “adaptive” refers to the fact that these responses take time to develop and are modified over this time to best respond to the specific infection. The cells that regulate and carry out most of the major effector functions of the adaptive immune response are lymphocytes called T cells and B cells. These lymphocytes express cell surface antigen-specific receptors that confer the inducibility and specificity that are the hallmarks of the adaptive immune response. In addition, after clearing the pathogen, the cells of the adaptive immune response develop a long-lived “memory” of the exposure that can be quickly mobilized upon re-exposure to the same antigens.

In the following review, we explore the cells and molecules that play key roles in the functions of both the innate and adaptive immune responses. The main cells involved in adaptive immunity are lymphocytes and macrophages (see Box 10-3).

Pathogens that reside inside cells pose a special challenge to the immune system, because they are not directly accessible to detection. However, cells containing pathogenids are themselves altered at the cell surface, and these changes can be recognized by both the innate and the adaptive immune systems. As mentioned earlier, the innate immune system can recognize molecular patterns present on the pathogen itself. It can also recognize patterns on the surface of infected cells, which may be genetically altered as a result of being infected. For example, infection of a cell may cause a normal surface molecule to be expressed at abnormally high or low levels. This is yet another example of how innate immunity does not depend on the identity of the infecting pathogen. (Innate immunity is also triggered by non-infectious processes that affect the integrity of cells, such as heat injury, radiation, toxic exposures, or, in some cases, neoplastic transformation.)
The first step in the immune response to a pathogen is the recognition of the pathogen. It has long been known that the immune system can distinguish self from non-self or foreign antigens. How this was accomplished remained a fascinating mystery for many years, but the essential mechanisms have now been clarified, in work that resulted in at least seven Nobel Prizes.

**RECOGNITION OF PATHOGENS**

What does the immune system actually recognize, or react to? Substances that can trigger an immune response are called antigens. More specifically, the receptors on cells of the immune response recognize small sub-regions on each antigen, termed epitopes or antigenic determinants. A single antigen molecule can have many epitopes that can be recognized by different receptors. Epitopes can be made up of amino acids, sugars, lipids, or nucleotides. In adaptive immunity, lymphocyte receptors recognize highly unique epitopes on pathogen-derived antigens. Those antigens that are recognized during this response are not normally present in the body, because they are derived from particular molecules present in bacteria, viruses, parasites, or other organisms. In contrast, the receptors used in the innate immune response recognize pathogen-derived antigens that are not species-specific, but rather are representative of a class of microorganism, such as virus, bacteria, fungi, or parasite.

In recent years, much work has been directed at defining the precise chemical nature of antigens, including which characteristics an antigen must have to elicit an effective immune response. This work has been motivated by very practical concerns, such as the need to develop vaccines and understand immune responses to dangerous organisms.

**Antigen Recognition in Adaptive Immunity: T and B Cells**

The cells that are responsible for specific recognition of foreign antigens (i.e., adaptive immunity) are B and T lymphocytes (see Box 10-3). These cells have surface proteins that bind to (recognize) antigens with high specificity and affinity: each particular surface protein can bind effectively to one and only one antigen. These surface recognition proteins are called antigen receptors, and it is the precision of these receptors (they will bind to only one epitope out of all possible epitopes) that is responsible for the amazing specificity of the immune system. (Box 10-4). For T cells, the epitope is usually a small peptide; for B cells, it is frequently more than a small peptide that is recognized. When the antigen receptor binds its antigen, the B or T cell becomes activated and the immune response is initiated.

Both B and T cells can recognize any antigen that might possibly be encountered, including synthetic antigens that do not exist in nature. How such a vast array of receptors could exist was a puzzle to immunologists during the many years when it was believed that each unique antibody molecule was encoded by its own gene, because there is not enough DNA in the entire body to code for one gene for each possible antibody. The key to this diversity was determined first for B cells (Figure 10-1), and subsequently shown to apply to T cells (Figure 10-2) as well. One section of the receptor protein consists of relatively constant amino acid sequences that are shared by many receptors and coded for by a small number of genes. The second section is a highly variable part of the receptor.

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**Box 10-4 Specificity of Antibodies**

For many years, the specificity of antibodies produced by immunizing experimental animals has been exploited to identify substances in experiments and in clinical medicine. This has been particularly true since the development of methods for making monoclonal antibodies to any desired antigen. Monoclonal antibodies are derived from a single B cell and, therefore, cannot be contaminated by antibodies with other specificities.
that recognizes the vast diversity of antigens which is created by allowing rearrangement of gene segments to generate a huge number of permutations (Box 10-5). The genes coding for the constant and variable segments are assembled within a given B or T cell into a single DNA sequence that codes for the final receptor molecule that will be expressed by that cell (see Box 10-7 for a more detailed description of this process).

Although generated by similar mechanisms, B- and T-cell antigen receptors work in different ways. The B-cell receptor recognizes antigens in their native form—that is, as they exist in nature. As a consequence, the antigen does not need to be manipulated in any way, and the B cell can recognize the antigen by itself. This is true whether the B-cell receptor, which is an antibody molecule, is attached to the surface membrane of the B cell, or has been secreted from the cell and is free of the B cell entirely.

The T-cell antigen receptor differs from the B cell antigen receptor in two ways. First, it cannot recognize native antigens. Instead, it recognizes only antigens that have been broken down into short, epitope-sized peptide fragments. This process, which is referred to as antigen processing, can occur within the cytoplasm of many types of cells, called antigen-presenting cells. The processed antigen is then carried to the surface of the antigen-presenting cell by major histocompatibility (MHC) proteins. (Box 10-6) This leads to the second major difference between B- and T-cell recognition of antigens: the T-cell receptor binds not only to the processed peptide, but also to the carrier (MHC) protein on the surface of the antigen-presenting cell. This process of re-expressing the processed antigen on the surface of the antigen-presenting cell is called antigen presentation. In other words, the T-cell antigen receptor, even though it is specific for one peptide, is also specific for one MHC protein, and T-cells recognize an antigen only if it is bound to the correct MHC protein. (Figure 10-3). For this reason, antigen recognition by T cells is said to be MHC-restricted, and antigen-presenting cells and T cells must be histocompatible for T-cell activation to occur. Because of MHC restriction, one person’s T cells will not recognize any

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<th>Box 10-5</th>
<th>Generation of Receptor Diversity</th>
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<td>The receptors for both T and B cells have a number of functional domains or regions. A large proportion of both of these receptors have common functions, such as anchoring the receptor to the cell membrane and binding to a number of accessory proteins both at the cell surface (to stabilize cell–cell interactions) and in the cytoplasm (where they act as a binding point for the proteins that participate in the transduction of signals from the cell membrane to the nucleus that result in cell activation and differentiation). These regions of the receptors are, therefore, termed constant regions. Both T- and B-cell receptors have a domain that is specifically responsible for binding to a small portion of an antigen (i.e., an epitope). Some aspects of these receptors are illustrated in Figures 10-1, 10-2, and 10-3. This antigen-binding site is unique for each different B-cell receptor (i.e., antibody) or T-cell receptor and is the source of antigen specificity for a B cell or a T cell, respectively. This part of the receptor is, therefore, called the variable region. The vast number of unique specificities used by the receptors of the adaptive immune response are generated by a random combinatorial mechanism that is independent of antigens. T-cell and B-cell receptors are composed of multiple protein chains. (See Figures 10-1, 10-2, and 10-3.) Each chain is encoded by a number of gene segments that are spliced together at the DNA level within a given T or B cell to form a complete gene for a specific receptor. A large number of germline gene segments encode the domains responsible for antigen recognition. These segments are assembled in a random fashion that, along with random insertions and deletions of nucleotides at splicing junctions, determines the final amino acid sequence of this variable region of the receptor protein, which in turn determines the antigen specificity of each receptor chain. Following molecular events that assemble the genes for the variable region of the receptor with those for the constant regions, the multiple protein chains are manufactured by the cell and joined to make the mature receptor. The interactions among the variable regions of these multichain molecules then determine the fine specificity of each receptor. Current estimates of the number of different T-cell and B-cell receptors that are generated by the random use of multiple germline variable genes, imprecise joining of gene segments, and random use of different chains generated approach $10^{15}$. This vast array of receptor molecules accounts for the astounding ability of the immune system to recognize any possible antigen.</td>
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RECOGNITION OF PATHOGENS

low concentrations, and they are important cells for presentation of antigens to T cells during mature immune responses. However, B cells specific for a given antigen are much less numerous than other antigen-presenting cells, which explains why the non-specific antigen-presenting cells are essential.

Because they vary so widely among individuals, the MHC proteins from different people will interact differently with the foreign proteins or peptides encountered by those individuals. Most of the antigens
associated with pathogens are complex molecules that can be degraded by antigen-processing cells into many different peptides. Among individuals with different MHC proteins (i.e., different HLA types), therefore, different peptides may bind most efficiently to a given individual’s repertoire of MHC proteins. For example, if a protein contains epitopes A and B, and individuals X and Y have different HLA types, then only epitope A may be presented by antigen-presenting cells in individual X and only epitope B may be presented by the corresponding cells in individual Y. Some individuals may have an MHC type that will not bind either of these epitopes; these individuals will not recognize this protein at all. This point means that immunizing a human population against a T-cell epitope (i.e., eliciting a cellular immune response at a population level) is much more difficult than eliciting a B-cell response, because B cells recognize native antigens, which is the same for everybody. Given the huge diversity of MHC proteins in the human population, development of vaccines that will induce general T-cell immunity represents an extremely formidable challenge. It is not a coincidence that almost all successful vaccines generated to date have depended largely on B-cell responses (i.e., antibodies) rather than T-cell responses.

**Antigen Recognition in Innate Immunity**

A third type of lymphocyte, termed natural killer (NK) cells, plays a key role in triggering innate immunity (Box 10-8).

The mechanism by which NK cells are triggered to kill has only recently been elucidated. Although they do not have antigen receptors, NK cells have surface receptors that inhibit their killing function. These inhibitory receptors, termed killer inhibitory receptors (KIRs), recognize abnormal levels of MHC Class I molecules on all other nucleated cells in the body. Thus, if the target cell expresses MHC Class I to a normal degree, the NK cell is not triggered and the target cell is not killed. Conversely, down-regulation of MHC Class I molecule expression (which is common in some virally-infected cells and some tumor cells) removes the inhibition of the NK cell, so that the target cell is killed.

This mechanism appears to be an important component of host defense against certain viral infections. Many viruses interfere with expression of MHC molecules by the host cell (possibly as a means of evading cytotoxic CD8+ T-cells, which require MHC Class I molecules to be expressed on the target cell, as discussed previously). Thus, NK cells help prevent the virus from getting away with this trick. This mechanism elegantly explains the function of NK cells.

After this understanding was reached, in somewhat of a surprise, stimulatory NK receptors were discovered by researchers. The function of NK cells is regulated by the balance of signals coming from the KIR and the stimulatory receptors. It has been hypothesized that stimulatory receptors on NK cells may be important in situations in which MHC proteins are over-expressed, which is uncommon in infectious diseases but may occur in neoplastic or pre-neoplastic conditions.

Macrophages and dendritic cells have been described in Box 10-2. How do they recognize antigens? In contrast to the specific recognition of particular antigens by T-cells, as described previously, macrophages and dendritic cells recognize molecules common to multiple pathogens, or structures derived from such antigens. For this reason, antigen receptors on these cells are referred to as pattern recognition receptors (Box 10-9).
Activation of Adaptive Immunity

Both T- and B-cell receptors are anchored in the cell membrane, and are associated with adjacent molecules that cross through the cell membrane into the cytoplasm of the cell. When the antigen receptor binds its antigen, these associated molecules are altered in such a way that intracellular enzymes are activated to cause the lymphocyte to begin to carry out its programmed functions.

The ability of an extracellular antigen to cause activation of intracellular processes requires a signal to cross the cell membrane, a process called signal transduction. (Latin scholars will understand the reason for this name.) Signal transduction is not as simple as just binding the antigen to the receptor; factors such as the affinity of the antigen for the receptor are important, and in most cases an additional signal besides the antigen receptor-induced signal is required for the cell to become fully activated (referred to as co-stimulation).

The second signal is not antigen-specific but can be mediated by binding of molecules on the antigen-presenting cell to other molecules on the surface of the lymphocyte (see the article by Ploegh for a review).

The sequence of biochemical events in lymphocyte signal transduction has been extensively researched, and reviews can be found in textbooks of immunology, such as those listed at the end of this chapter.

Activation of Innate Immunity

Activation of phagocytic cells through their pattern recognition receptors, or of NK cells through their activation and inhibitory receptors, occurs via a cascade of receptor-linked biochemical events similar to that which activates T cells through the T-cell receptor.

After Antigen Binding: Immune Activation

Lymphocytes in the blood are generally in a resting state, which means the cell is structurally and functionally quiescent or inactive. Both B and T lymphocytes have the morphology one would expect of such cells (Box 10-10). When a lymphocyte encounters the antigen it is programmed to recognize (through its antigen-receptor), however, the cell becomes transformed into an activated cell. Activated cells can make important immune regulatory and effector molecules and can also proliferate, or multiply, by mitosis. Thus the resting state in which most lymphocytes found in the peripheral blood is just a temporary phase, at least potentially. NK cells also circulate in a resting state, albeit with slightly more cytoplasm and pre-existing effector molecules than B or T cells.

The fact that immune cells generally exist in the resting state, along with the specificity of T- and B-cell receptors, allows the immune system to deploy its weapons only when and where they are needed. As discussed further in this section, the immune system includes powerful responses that can cause great damage to the host if not carefully controlled. Thus activation must be limited to those cells needed to neutralize a particular threat, and activation should be turned off as soon as possible after the threat has been removed or neutralized.

Dealing with the Pathogen: Immune Effector Mechanisms

Once a foreign antigen enters the body, innate immunity serves as the first line of defense and an important regulation step in the development of the humoral and cellular arms of the adaptive immune response. There is an important time element to these responses. Several days are required for the full development of
Cytokines are small proteins that function like hormones, except that as a general rule they do not circulate in the blood in meaningful quantities, but rather act over a distance of a few cell diameters. In other words, they act on cells adjacent, or in close proximity, to the secreting cell (this is called paracrine regulation, as distinguished from endocrine regulation, which implies circulation in the blood and action on distant cells). An example of paracrine function would be secretion by activated T-helper cells of cytokines that help nearby B cells differentiate into antibody-secreting cells, or cytokines that activate macrophages or killer T cells to become much more potent at killing microorganisms. In some cases, cytokines act on the secreting cell itself, which is called autocrine regulation. An example of autocrine regulation is the secretion by activated T-helper cells of cytokines that allow the activated T cells to proliferate and expand clonally.

The first cytokine was described in 1970, an event that was followed by the description of many immune functions (and other functions) that were mediated by possible cytokines. A major stumbling block to researchers in these early studies was the fact that cytokines are generally not present in the blood and, in fact, are extremely potent molecules with tiny physiological concentrations. Their relative rarity made biochemical purification and isolation of these molecules terribly difficult from a technical perspective, and greatly hampered the working out of cytokine networks. It was only with the advent of molecular biology, genetic cloning, and recombinant DNA methods that cytokines could be studied efficiently, because now genes for cytokines could be isolated and large quantities of pure proteins (i.e., uncontaminated by small amounts of other cytokines) could be generated. Such work ultimately allowed the identities, modes of action, and functional properties of unique cytokines to be defined.

The interleukin nomenclature is much more practical than naming proteins for their function. The latter is untenable because cytokines have many functions. For example, a cytokine that stimulated growth of B cells and one that stimulated metabolic activity of hepatocytes both turned out to have the same amino acid sequence as interleukin-6 (IL-6). In another case, a cytokine that killed certain tumor cells (tumor necrosis factor [TNF]) and a factor that caused wasting (cachectin) turned out to be identical proteins, and the name TNF won out.
Adaptive immune effector mechanisms

Almost all T-cells belong to one of two major subsets. The first is helper T-cells, which induce or permit functions of other immune cells. These cells express a protein called CD4 (Box 10-12) on their cell surface, and, therefore, are called CD4 (or CD4+) lymphocytes. CD4 lymphocytes produce cytokines that increase the ability of macrophages to kill ingested organisms, cause B cells to differentiate into antibody-producing cells, activate other helper T-cells to expand clonally as mentioned previously, and increase the ability of cytotoxic T cells and NK cells to kill target cells. The other major subset of T cells is suppressor/cytotoxic T-cells, which generally inhibit other cells or kill them; they express a surface protein called CD8. Adaptive immune mechanisms differ for extracellular versus intracellular pathogens.

Box 10-12  CD Nomenclature

| The letters “CD” stand for “cluster designation” and are used to denote proteins recognized by sets or clusters of monoclonal antibodies. CD numbers have been assigned through CD363 based on data presented at several international workshops. CD4 was the fourth protein to be assigned a CD number. |

Extracellular immune effector mechanisms

Protection against free-living extracellular organisms is provided mainly by antibodies and phagocytic cells. As mentioned earlier, the production of antibodies is mediated by B cells. When B cells become activated, they begin rearranging the genes that code for antibodies, and the cells begin to differentiate into cells that are actually tiny antibody factories, called plasma cells. Plasma cells are produced in the secondary lymphoid tissues (e.g., lymph nodes, spleen, Peyer’s patches) and eventually migrate to the bone marrow to secrete antibodies.

The antibodies produced by plasma cells are secreted proteins, although they are structurally similar to, and have the same antigen specificity as, the antibody molecules that are present in the membrane of the progenitor B cell. The function of antibodies is to bind to whole antigens, in their native forms, as mentioned previously. Antibodies are thus well designed to protect the host against extracellular antigens, such as bacteria that can grow outside cells. In many cases, these bacteria can grow quite rapidly, so it is important for the host defense to be able to mount a vigorous immune response as quickly as possible.

The main host defense against bacterial infection comprises ingestion of bacteria by white blood cells known as neutrophils. This process of ingestion (termed phagocytosis) is vastly more efficient if the bacteria have been coated with antibodies, because neutrophils have receptors on their cell surfaces that recognize the constant portion of the antibody molecule. The phenomenon of coating of bacteria by antibodies to facilitate phagocytosis is called opsonization. Other host proteins also facilitate phagocytosis and lysis of extracellular pathogens. For example, complement is a series of proteins that bind to microorganisms and to one another. The result is a cascade of reactions that generates membrane-bound proteins on the microorganism that can be recognized by phagocytic cells through complement receptors. (Complement proteins are not as efficient as antibodies in facilitating phagocytosis.) Antibodies can also directly interfere with replication of pathogens, binding of obligate intracellular pathogens to their target cells, and binding of toxins to their target molecules.

Antibodies are categorized into one of five classes: immunoglobulins M, D, G, A, and E. Antibodies in the various classes have different chemical structures, localization in the body, and functions. As might be expected given these distinctions, antibodies serve different roles in the host defense against infections, as described later in the sections on mucosal immunity and B-cell immune deficiency.

Intracellular immune effector mechanisms

MHC Class I proteins, which are produced inside the cell and then move to the cell surface, carry with them peptides that are being produced inside the cell. If the cell has been infected by a virus and viral proteins are being produced, peptides derived from these viral proteins will be carried to the cell surface in this way. There, the MHC I–viral peptide complex can be recognized (“seen,” in immunological parlance) by virus-specific CD8+ T cells that come in contact with the infected cell. These cells, in turn, will be activated by the interaction between the MHC Class I–viral peptide complex and the specific T-cell receptors, and the T-cells will kill the infected cell (Box 10-13). Because antigen processing and presentation outpace viral production after the virus enters a cell, the infected cell can be recognized and killed even before a new virus is produced or expressed on the cell surface. This factor is key to controlling the viral infection. The same pathway also explains why MHC Class I molecules are expressed on all (nucleated) cells in the body: it allows the immune system to “see” the internal state of all cells, a process termed immune surveillance.

In contrast to this “intracellular” pathway of antigen processing, Class II MHC molecules become
The cytotoxic mechanism of NK cells is similar to that by which cytotoxic T cells kill—namely, perforin/granzyme- and Fas/Fas ligand-mediated induction of programmed cell death (apoptosis) of the target cells.\textsuperscript{15,20} NK cells also play an immunoregulatory role through the production of cytokines—especially interferon, which enhances the immune response against viruses and other intracellular pathogens by activating macrophages.

Other effector mechanisms also contribute to innate immunity. Neutrophils and macrophages can ingest microorganisms, especially those that have been coated with antibody. (Because antibody is produced by the adaptive immune system, this is an example of co-operation of innate and adaptive immunity.) Antibody molecules can also bind to antibody receptors on the surface of killer cells (such as NK cells); this binding involves the constant end of the antibody molecule, so that the antigen receptor is free and can bind to antigen. The resulting antibody–effector cell unit can then recognize and kill a target cell, a process known as antibody-dependent cellular cytotoxicity (ADCC). Finally, a series of serum proteins called complement proteins can bind to microorganisms and other target cells, either killing the cells outright (by forming large pores in their outer membranes) or rendering them susceptible to phagocytosis.

**Box 10-13 T-Cell Killing Mechanisms**

Two mechanisms by which T cells kill cells are known:

- In the first, a T-cell product, perforin, binds to the target cell membrane and causes pores to form in it. A second T-cell product, granzyme, facilitates this process and also induces programmed cell death in the target cell. (Programmed cell death is a mechanism by which cells can self-destruct.)
- In the second mechanism, T cell molecules termed Fas-ligand bind to Fas proteins on the target cell, again inducing programmed cell death.

Which mechanism kills the target cell is influenced by many factors, including the nature of the infection in the cell.\textsuperscript{13}

Cytokines of the Innate and Adaptive Immune Systems

Up to this point we have described innate and adaptive immunity separately. This separation is convenient conceptually, but substantial overlap in these systems is actually observed in the body, and this is certainly true for the cytokines involved in these aspects of immunity. In this section, we describe the most important cytokines in each system, but also point out how these cytokines overlap in function between innate and adaptive immunity.

Cytokines have several important characteristics. They are produced in tiny amounts, are short-lived, and generally act locally rather than systemically. They are synthesized only briefly after cell stimulation, due to transient gene expression and unstable RNA. Cytokines exert many activities, and many cytokines share the same activities (i.e., the cytokine network is redundant). Cytokines typically act via binding to very-high-affinity receptors, although some cytokines have intermediate- or low-affinity receptors that become activated only when very high concentrations of cytokine are present. Cytokine receptors sometimes can bind more than one cytokine, and also sometimes share component structures.
Among the many actions of cytokines on target cells are activation; stimulation of proliferation; production of other proteins, including other cytokines, cytokine receptors, or antibodies; production of one class of antibody rather than another; differentiation; and death. These processes may be either stimulated or inhibited depending on the combination and concentration of cytokines produced. Approximately 60 major (and many minor) cytokines have primary influence on the innate and adaptive immune response. Some of these cytokines, and some of their actions, are mentioned here.

**Cytokines of the Innate Response**

Cells of the innate immune system that produce cytokines include macrophages, NK cells, epithelial cells, endothelial cells (cells that form the blood vessel wall), dendritic cells, platelets, mast cells, and fibroblasts.

**Tumor Necrosis Factor**

Tumor necrosis factor (TNF) is produced primarily by macrophages in response to lipopolysaccharides of gram-negative bacteria, but also by T cells and NK cells. TNF receptors are expressed on most cell types, and binding of TNF to these receptors can lead to either cell activation or cell death (death occurs by activating cellular enzymes that cause the cell to degrade itself, a process known as apoptosis or programmed cell death). TNF recruits monocytes and neutrophils to sites of infection, where it then activates them to kill pathogens and to secrete other molecules that attract anti-inflammatory cells. Release of TNF causes fever; this cytokine is one of the most important mediators of septic shock, an often-fatal condition characterized by hypotension and intravascular coagulation. TNF also activates lipoprotein lipase in adipocytes, and for this reason chronic production of TNF can result in wasting (cachexia). Drugs that inhibit TNF have been reported to reduce tissue damage in inflammatory diseases such as rheumatoid arthritis but can increase susceptibility to tuberculosis, thus demonstrating the importance of TNF in host defense against this infection.

**Interleukin-1**

Like TNF, IL-1 is produced by macrophages in response to microbial products, activates innate immune responses, induces fever, and causes cachexia. Unlike TNF, IL-1 is also produced by epithelial and endothelial cells, and does not induce programmed cell death. This interleukin helps to activate T cells. IL-1 release is stimulated by TNF. IL-1 exists in two forms, α and β, that stimulate the IL-1 receptor; a third form of IL-1 inhibits this receptor. The IL-1 receptor is present on T cells, fibroblasts, and epithelial and endothelial cells.

**Interleukin-6**

IL-6 is also produced by macrophages, but also by fibroblasts and endothelial cells. Production is enhanced by IL-1 and TNF. Receptors for IL-6 are present on activated B cells and hepatocytes, and IL-6 serves as a growth and differentiation factor for B cells and as a potent stimulator of production of acute-phase reactants by the liver.

**Interleukin-12**

IL-12 is produced by macrophages and dendritic cells stimulated by lipopolysaccharide, viral infections, and intracellular pathogens. This cytokine’s production is also stimulated by interferon-α from NK cells and T cells. IL-12 is a major stimulator of the cell-mediated adaptive immune response and, therefore, is critical for the control of intracellular pathogens. This effect appears to be mediated through stimulation of production of interferon-gamma (IFN-γ) by NK cells and T cells, which in turn activates the cytotoxic function of macrophages. IL-12 is considered one of the main cytokines that directs the adaptive cellular immune response as opposed to the humoral response. The IL-12 receptor is present on NK and T cells exposed to IFN-γ and dendritic cells exposed to IL-15. Deficiency of this receptor has been associated with exacerbation of mycobacterial infections.

**Type I Interferons: Interferon-alpha and Interferon-beta**

Early on in the study of immune responses to virus infection, researchers came to appreciate that certain secreted factors interfered with viral replication in previously uninfected cells. These factors were termed “interferons.” Two classes of anti-viral, or type I, interferons exist: IFN-α, which is actually a family of approximately 20 closely related proteins all encoded on separate genes, and IFN-β, which is encoded by a single gene. IFN-β is the main secreted type I interferon.

While type I interferons are produced by a broad spectrum of cell types in response to nearly all virus species, some cells are specialized for their synthesis. For example, plasmacytoid dendritic cells can produce as much as 1000 times more type I interferon than other cells.

Type I interferons are an essential component of the innate immune response to virus challenge because they hold viral replication in check long enough that a specific and robust T-cell–mediated adaptive immune response can be generated to eliminate the
virus from the body. Type I interferons use three main mechanisms to control virus replication and dissemination. First, they induce resistance in uninfected cells by activating mechanisms that result in the destruction of viral RNA and blocking of the production of viral proteins. Second, they activate NK cells, which are effective in detecting and killing virally-infected cells. Third, they induce the expression of Class I MHC molecules on the surface of infected cells, thereby rendering the infected cells more susceptible to killing by virus-specific cytotoxic CD8 T cells.

**Interleukin-10**

We have taken the dramatic step of listing this cytokine out of numerical order because, unlike the preceding cytokines, it was first described as an inhibitor, rather than a stimulator, of immune reactions. Specifically, IL-10 inhibits the functions of activated antigen-presenting cells, such as the production of IL-12 and IFN-γ and the expression of Class II MHC molecules and costimulatory molecules. Thus, it has a major effect on antigen presentation and T-cell activation. Interestingly, no fewer than seven viruses, including Epstein-Barr virus and cytomegalovirus, produce proteins that mimic the effects of IL-10 by binding to IL-10 receptors. Presumably the inhibition induced favors viral replication. In mice that lack IL-10 (IL-10 “knockouts”), immune regulation is abnormal, and a condition resembling inflammatory bowel disease develops.

**Chemokines**

Chemokines are small proteins secreted by a variety of cells—not just immune cells—to attract or recruit immune cells to the site of an infection or inflammatory response. Lymphocytes and other immune cells respond to chemokines through the expression of chemokine receptors on their cell surface. Chemokines can be secreted into the extravascular tissues. They then diffuse into the bloodstream, where they activate endothelial cells so that intravascular cells such as lymphocytes, monocytes, and neutrophils are given a signal telling them to exit the blood where the endothelial cells are activated.

**Interleukin-2**

IL-2 is produced primarily by antigen-activated CD4+ T cells, with peak secretion occurring 8–12 hours after activation. Antigen-induced activation also results in the expression of high-affinity IL-2 receptors, so that antigen-activated T cells can preferentially respond to IL-2 production by proliferating. Thus IL-2 is an autocrine T-cell growth factor (and can be used to expand the numbers of T cells for several weeks in vitro). Lower-affinity IL-2 receptors are expressed by naive T cells, NK cells, and B cells.

**Interleukin-4**

IL-4 is produced by antigen-activated CD4+ T cells, but can also be made by mast cells, eosinophils, and basophils. This cytokine mediates expansion of CD4+ cells with a type 2 cytokine secretion pattern (also known as Th2; functional T-cell subsets are discussed later in this chapter). To this end, IL-4 also inhibits type 1 (Th1) responses such as IFN-γ production. It stimulates B cells to produce IgE and, along with IL-10, one subclass of IgG (IgG4). IL-4 is associated with responses to parasites, wound repair, and adaptive responses to environmental antigens that lead to allergic reactions.

**Type II Interferon: Interferon-gamma**

IFN-γ is produced by T cells and NK cells. It is a defining cytokine for type 1 T-helper cells (Th1 cells, discussed later in this chapter), which produce it in response to antigen; in contrast, NK cells produce IFN-γ after exposure to pathogens. In both cases, IFN-γ production is amplified by IL-12, which for T cells is typically derived from the antigen-presenting cell. The functions of IFN-γ favor inflammation:

- Activation of cells that kill pathogens (e.g., macrophages, NK cells, neutrophils)
- Activation of antigen presentation including increased expression of MHC molecules (both Class I and Class II) by antigen-presenting cells
- Stimulation of production of IL-12, which in turn further amplifies inflammatory responses
- Stimulation (along with TNF) of endothelial cells to attract immune cells
- Stimulation of production of IgG1 and inhibition of IgG4 and IgE
- Inhibition of Th2 and Th17 responses

Deficiency of IFN-γ, or its receptor, as has been reported in a few cases of mutations in the gene encoding IFN-γ or the receptor, increases susceptibility to intracellular pathogens, pathogens that are killed
by macrophages, and pathogens that are otherwise controlled by being walled off in granulomas.\(^{2,23}\) Mycobacterial infections including tuberculosis are particularly affected.

**Interleukin-17**

This cytokine, officially designated IL-17A, is a member of an extended family of similar molecules (IL-17A through F). It is produced mainly by CD4 T cells (designated T\(_{H17}\) cells), but can also be produced by CD8 T cells, NK cells, and neutrophils. Engaging the receptor for this cytokine on epithelial cells, endothelial cells, and fibroblasts results in the expression of cytokines and chemokines that recruit neutrophils and other cells that are important for the control of extracellular bacterial and fungal infections. In addition, members of the IL-17 family help to regulate the body’s responses to commensal microorganisms and to mediate the pathology attendant to several autoimmune diseases.

**THE ROLE OF CYTOKINE EXPRESSION IN DEFINING FUNCTIONALLY DIFFERENT EFFECTOR CD4 T-CELL LINEAGES**

The cytokine response to pathogen challenge is complex and varies depending on a number of factors, including the genetics and immunological history of the host. However, within this variable response, patterns can be observed. These patterns have been used to help structure our understanding of the dynamics of the immune response, especially in relation to CD4 T cell responses.

Based on the cytokines they secrete, CD4 T cells have been classified into five subsets that carry out distinctive functions: T\(_{H1}\), T\(_{H2}\), T\(_{H17}\), T\(_{FH}\) (T follicular helper cells), and T\(_{reg}\) (regulatory T cells).

T\(_{H1}\) and T\(_{H2}\) cells were the first of the CD4 subsets to be recognized. Th1 cells are characterized by the production of IFN-\(\gamma\). They stimulate immune mechanisms that control intracellular pathogens such as viruses, certain bacteria (e.g., *Mycobacterium* and *Listeria*), and certain protozoan parasites (e.g., *Toxoplasma* and *Leishmania*). IFN-\(\gamma\) is a key cytokine for activating both cytotoxic CD8 T cells, which kill virus-infected cells, and macrophages, which are an essential cell type for killing intracellular eukaryotic pathogens. T\(_{H2}\) cells are defined by IL-4, IL-13, IL-10, and IL-5, which stimulate B-cell maturation and the production of antibodies. Thus T\(_{H2}\) cells are important for the control of extracellular helminth parasites—multicellular pathogens such as nematodes (round worms) and flukes (flat worms)—through the activation of eosinophils, mast cells, and basophils. Importantly, T\(_{H2}\) cytokines are required for production of IgE antibodies, which are responsible for the human response known as allergy and also play an important role in immunity against parasites. Recently, it has been appreciated that T\(_{H2}\)-derived cytokines promote macrophage and fibroblast differentiation into cells that produce matrix proteins at the site of tissue injury, thereby promoting tissue repair.

The third major subset is T\(_{H17}\) cells, which produce mainly the IL-17 family of cytokines (i.e., IL-17A and IL-17F). This subset is induced early in the response against extracellular bacteria and fungi, and its release results in a rapid influx of neutrophils into the site of infection. T\(_{H17}\) cells have also been shown to promote inflammation in a number of autoimmune diseases and have been implicated as playing a role in anti-tumor immunity.

The fourth major subset is T follicular helper cells (T\(_{FH}\) cells), which were identified very recently. These cells carry out what has long been appreciated as one of the essential functions of CD4 T cells: to provide help to B cells for the production of antibody. T\(_{FH}\) cells are found in the secondary lymphoid tissues. They secrete the cytokine IL-21 and provide the cognate interactions required by B cells to proliferate and to switch from producing IgM to IgG, IgA, or IgE.

The final subclass of CD4 T cells is regulatory T cells. T\(_{reg}\) cells differ from the other CD4 cell subclasses, which activate and expand immune responses, in that they inhibit the magnitude and scope of immune responses. Specifically, T\(_{reg}\) cells limit immune responses against foreign antigens and prevent the induction of autoimmune responses that can lead to disease. T\(_{reg}\) cells produce regulatory cytokines such as IL-10, and can work either directly on the other CD4 T-cell subsets or indirectly by curtailing the function of antigen presenting cells. T\(_{reg}\) cells are also characterized by expression of the high-affinity IL-2 receptor and certain nuclear transcription factors.

**MUCOSAL IMMUNITY**

Most interactions between the human host and the microbial world occur either at the skin or at mucosal surfaces, such as the gastrointestinal tract and the respiratory tract. Immunity at these sites is referred to as mucosal immunity. Despite its importance, our understanding of mucosal immunity is quite limited, due to the difficulty of obtaining tissue or secretions from
mucosal surfaces (in contrast to the ease of obtaining blood for study of systemic immune responses). The gastrointestinal tract provides an ideal environment for bacterial growth and contains trillions of bacteria. The host must be protected from invasion by these bacteria, but this must be accomplished without the vigorous inflammatory response that maintains the sterility of the host’s internal environment, because such a strong response would destroy the mucosal protective barrier. Thus, mucosal immunity differs in fundamental ways from systemic immunity, and mechanisms that operate in systemic immunity cannot be assumed to operate in the mucosal setting.

Epithelial cells are a key component of mucosal immunity. While not traditionally regarded as immune cells, these cells are linked by tight junctions that provide a physical barrier excluding bacteria from the systemic environment, and they secrete proteins that inhibit the growth of bacteria and reduce bacterial attachment to the epithelial surface, thereby promoting bacterial excretion from the gastrointestinal tract. Epithelial cells also bear toll-like receptors (TLRs), described earlier in this chapter, that recognize pathogen-associated molecular patterns (PAMPs) that are unique to bacteria or viruses. Engagement of TLRs causes epithelial cells to secrete products with antimicrobial and pro-inflammatory activity, such as alpha- and beta- defensins, which can disrupt bacterial cell walls. Although TLRs can be triggered by both pathogenic and non-pathogenic bacteria, several mechanisms exist that reduce activation of mucosal immune responses by these receptors. First, the receptors tend to be located within or on the basolateral surface, of the epithelial cell, rather than its apical surface, so they become engaged only when bacteria have invaded the epithelial barrier. Second, TLRs that engage common bacterial components are present at reduced levels in epithelial cells compared with other cells with antibacterial activity, such as macrophages. Third, continuous exposure to bacterial products may downregulate the expression of TLRs on the luminal epithelial surface. In addition to these mechanisms, intestinal epithelial cells secrete proteins that directly inhibit their own production of pro-inflammatory factors following exposure to bacteria.

The transition from the innate immune response to the adaptive response depends on the ability of dendritic cells to present antigens to T cells involved in the induction of both cell-mediated and humoral immunity. The gastrointestinal tract contains a diverse array of dendritic cell populations with distinct functional capabilities. Some of these dendritic cells are clearly programmed, such as the epithelial cells at this site, to downregulate inflammatory responses. An important property of these cells is their ability to direct the humoral response to the production of immunoglobulin A (IgA), as opposed to immunoglobulin G (IgG), which has a greater propensity to induce inflammatory responses. Unlike IgG, for example, IgA does not activate the pro-inflammatory complement pathway. The attenuation of inflammatory responses by gastrointestinal dendritic cells has been attributed to their continuous exposure to microbial and dietary products.

Thus IgA remains the mainstay of resistance to bacterial invasion from the mucosa of the gastrointestinal tract. Uniquely among immunoglobulins, IgA secreted into the gastrointestinal tract is linked to a protein termed secretory component, which protects the immunoglobulin from digestion and anchors it, through its Fc receptor, to the mucus covering the epithelial cells. Here, IgA can inhibit binding of pathogens to the epithelial surface, preventing colonization or invasion, and can also block bacterial toxins from interacting with host cells. Further, through engagement of its Fc receptor on phagocytic cells, IgA can promote uptake of pathogens without eliciting an inflammatory response. Because exposure to viruses at mucosal surfaces tends to be episodic, rather than sustained as with bacteria, the need to attenuate the pro-inflammatory component of the T-cell-mediated responses following viral infection at mucosal surfaces is less critical. In turn, these responses more closely resemble those observed systemically. Antiviral IgA responses also contribute to the elimination of ongoing viral infection and provide protective immunity against subsequent infection.

Other mucosal sites share with the gastrointestinal tract a predilection toward mitigation of immune responses, but the patterns are not always the same as those of the GI tract. For example, because potent acquired immune responses might lead to rejection of a fetus or paternal sperm, the female genital tract has evolved as a site at which elicitation of humoral or cell-mediated immune responses is tightly regulated. In distinction to the GI tract, protection from microbial challenge depends more prominently on innate immune mechanisms. This difficulty in eliciting protective immunity may account, at least in part, for the widespread distribution of sexually transmitted infections (STIs) and the poor outcomes of efforts to develop STI-targeted vaccines.
RESPIRATORY IMMUNE ENVIRONMENT

Another important site of mucosal immunity is the respiratory system. Unlike the gastrointestinal tract, the respiratory tract, while not sterile, does not carry a massive microbial burden. Indeed, one of the main tasks of the respiratory mucosal immune system is to capture and prevent commensal and pathogenic microorganisms (as well as airborne environmental antigens) from reaching the delicate air spaces in the lungs, where inflammation can impair gas exchange with potentially dire consequences. (The hairs of the nose and the sweeping cilia on epithelial cells help by providing physical barriers to pathogen entry.) The respiratory immune defenses are sometimes termed the nasopharynx-associated lymphoid tissues (NALT; tonsils and nasal submucosal glands) and the bronchi-associated lymphoid tissues (BALT; bronchial submucosal glands and diffuse lymphoid follicles of the lower airways). The mucus coating the nasopharyngeal epithelium is another important physical barrier that traps microorganisms; it is rich in antimicrobial molecules (e.g., IgA, lactoferrin, and lysozyme).

As in the intestinal tract, the epithelial layers of the respiratory tract play a key role in local immune surveillance and regulation. When perturbed, the nasopharyngeal epithelia cells secrete pro-inflammatory cytokines (e.g., TNF, IL-1, IL-6) and chemokines that summon cells of the innate response. Bronchial epithelial cells generate cytokines such as IL-5, IL-6, IL-10, and transforming growth factor-beta (TGF-β) that both direct B-cell differentiation to IgA production and promote T-cell-mediated adaptive immunity in the respiratory tract.

COMMON MUCOSAL IMMUNE SYSTEM

An important attribute of mucosal immunity is the characteristic that a response generated at one mucosal site is transferred to other mucosal surfaces. Thus a pathogen-specific secretory IgA response generated initially in the small intestine will be propagated not only along the entire length of the small and large intestines, but also to the respiratory tract, salivary glands, mammary glands, ocular tissues, and other mucosal sites. This phenomenon has given rise to the concept of a common mucosal immune system. It is mediated by the ability of lymphocytes generated at one site to circulate via the blood and lymph to other mucosal sites that express common mucosal homing receptors. Lymphocytes that are activated in a mucosal environment are induced to express distinct receptors on their surface that allow them to move to any mucosal site. One of the advantages of a common mucosal immune system is that mothers can transfer protection against gastrointestinal pathogens to their newborns, via pathogen-specific IgA that is secreted into breast milk.

TOLERANCE AND THE REGULATION OF THE IMMUNE RESPONSE

One of the most remarkable qualities of the immune system is that it recognizes and responds to a seemingly infinite array of foreign and pathogen-associated molecules, but it does not respond to self molecules. This immunological unresponsiveness to self is referred to as tolerance or self-tolerance. Tolerance is maintained by several mechanisms. First, lymphocytes with receptors for self-antigens are eliminated in the thymus or bone marrow before they fully mature (producing central tolerance). Second, self-reacting lymphocytes are rendered functionally non-responsive (anergy) or induced to self-destruct (by apoptosis, a form of programmed cell death) when their receptors engage self-antigens without proper co-stimulation (producing peripheral tolerance). Imbalances in the regulation of tolerance can lead to autoimmune disorders.

Another important aspect of immune regulation is the down-regulation of the scope and duration of inflammatory responses. Again, multiple mechanisms come into play. Although immune-mediated elimination of antigens is important in limiting inflammatory responses, it has recently become clear that active mechanisms play a role in limiting these responses. In particular, T-regulatory cells (T_{reg}) suppress self-reactivity, thereby playing a key role in balancing reactivity and tolerance. Perturbation of T_{reg} function can lead to prolonged exuberant immune responses, tissue damage, and immune-mediated pathology.

SELECTIVE IMMUNE DEFICIENCIES: WINDOWS INTO THE NORMAL ROLES AND FUNCTIONS OF THE IMMUNE SYSTEM

As in other areas of medicine, much of what we know about the normal function and importance for human health of specific types of cells and specific proteins is derived from clinical syndromes in which these cells or proteins are absent or not functional (or experimental conditions designed to mimic these syndromes).
B-Cell Immune Deficiency

Syndromes exist in humans in which B cells fail to develop and the patient cannot produce antibodies. These syndromes are generally due to a mutation in one of the genes involved in the genetic rearrangements required for antibody generation. In birds, removal of the eponymous bursa of Fabricius leads to a virtually identical syndrome. Humans may develop a disease called common variable immune deficiency, in which the ability to produce some or all antibodies is lost. The mechanism of this disease is complex, but it is not due to congenital mutations because the patient makes antibodies for many years before the onset of the disease. In at least some cases, the deficiency is due to overactive suppression of antibody production.

The primary symptom of antibody deficiency is recurrent bacterial infections with common extracellular bacteria such as *Staphylococcus* or *Streptococcus*. Pneumonia and sinusitis are especially common. The reason why a lack of antibodies predisposes individuals to this type of infection is that opsonization of these bacteria by antibodies is so important in allowing host phagocytic cells to ingest and kill the bacteria. Without antibodies, the phagocytic cells are outpaced by the rapidly growing bacteria and cannot do their job of clearing the infection. The types of infection may depend on the type of antibody that is missing. For example, if the deficiency is confined to IgA, the infections tend to be mucosal (e.g., sinusitis). (Recurrent infections are also seen when neutrophils are defective or absent.) However, if the missing antibodies are replaced by periodic injections of pooled antibodies, normal protection is restored and the clinical consequences of the underlying antibody deficiency can be prevented.

T-Cell Immune Deficiency

The clinical picture of selective T-cell deficiency was recognized based on animal experiments in which the thymus was removed, and on the clinical manifestations in human syndromes when the thymus fails to develop. It consists of recurrent infections with parasites, viruses, and intracellular bacteria. A similar picture has been recognized in transplant recipients whose cellular immunity is pharmacologically suppressed to prevent rejection of the graft (although this presentation can also be complicated by recurrent extracellular bacterial infections if neutrophils are depleted by the therapy). Congenital T-cell deficiencies can be due to mutations in the genes required for T-cell receptor rearrangement, T-cell signal transduction, or T-cell maturation. Clinical manifestations can vary according to the specific defect.

The clinical manifestations of cellular immune deficiency were sufficiently established that when the first clusters of cases of AIDS in the United States occurred in the late 1970s and early 1980s, researchers recognized almost immediately that it was a new disease characterized by acquired cellular immune deficiency.25–27 Notably, only a few cases of *Pneumocystis carinii* pneumonia and other opportunistic illnesses were required for this recognition, because these illnesses were (and are) exceedingly rare in people with no known reason to be immunocompromised. In fact, the manifestations of AIDS are a perfect illustration of the consequences of cellular immune deficiency. No further description will be given here, because a very thorough description of AIDS appears elsewhere in this book.

Deficiencies in specific cytokines have also been reported, due to mutations in the gene for the cytokine or the receptor for the cytokine. These conditions usually manifest as difficulty controlling certain infections, as with tuberculosis in deficiency of IFN-γ.

Treatment of cellular immune deficiency is still in its infancy. In theory, these diseases can be treated by replacing missing cytokines or cells. In reality, replacement of cytokines has proved challenging because of the local nature of most cytokines’ action, along with the toxicity of cytokines when administered systemically or in high concentrations. Bone marrow transplantation has been used successfully, and in one disease (adenosine deaminase deficiency) gene therapy has been tried with some success.

NK-Cell Immune Deficiency

For a long time after NK cells were discovered, researchers continued to debate whether they had any clinical importance. As so often happens, this question was answered by a clinical case.28 The patient was a girl who presented at the age of 13 with a life-threatening infection with varicella-zoster virus. Before this event, she had experienced recurrent ear infections and low white blood cell counts. At age 17 she had disseminated cytomegalovirus infection, and at age 19 she developed an infection with herpes simplex virus with fever and generalized rash. Between infections, the patient’s antibody levels, T-cell subset ratios, and T-cell responses in vitro (including the response to varicella-zoster virus) were normal, and live vaccines had caused no clinical problems for her. She was found to have a complete absence of NK cells, with no detectable NK cells in the blood and no detectable NK cell function in vitro. This case implicated NK cells in host defense against herpesviruses, as all of the patient’s viral infections involved...
this class of virus. The patient remains the only case of NK cell deficiency that has been reported, but her presentation is important because it clearly demonstrates the in vivo function of NK cells.

Other functions of NK cells in host defense have been described, and were discussed earlier in this chapter, but their clinical importance is less clear. NK-cell function is reduced in HIV infection, and NK cells can directly lyse some intracellular pathogens such as *Toxoplasma gondii* and *Trypanosoma cruzi*. NK cells also have antitumor activity in vitro.

**Other Immune-Mediated Diseases Related to Infectious Organisms**

Why do most lymphocytes circulate in a resting state? As discussed earlier, immune reactivity is a double-edged sword: the same mechanisms that kill microorganisms or infected cells can severely damage normal cells and body constituents.

A good example of this dual nature is seen in toxic shock syndrome, which is characterized by circulatory collapse, hypotension, shock, and, in some cases, death. Bacterial proteins can cause this syndrome by a variety of mechanisms. The common denominator of these mechanisms is the activation of very high numbers of T cells, resulting in excessive production of cytokines, which in turn leads to vasodilation and shock (Box 10-14).

Another demonstration of the risks of having an overactive immune system involves autoimmune disease. Autoimmunity in the thyroid gland and the pancreas, for example, can cause tissue damage leading to hypothyroidism and diabetes (due to lack of insulin), respectively. Infections have been postulated to cause some autoimmune diseases (Box 10-15). Inflammation due to infections has also been hypothesized to contribute to the etiology of—if not cause—other diseases not traditionally considered infectious, such as atherosclerosis and certain cancers.

**CONCLUSION**

This chapter offered an introduction to the immune system and its role in host defense against infections. By necessity, many of the details of how immune reactions are regulated have been omitted. Keep in mind that most, if not all, of the principles and generalizations described here have exceptions, sometimes important ones. Curious readers can pursue their interests, which we hope have been stimulated (in a non-MHC restricted way, of course!).

**RECOMMENDED TEXTBOOKS OF IMMUNOLOGY**


REFERENCES


