1

OVERVIEW OF THE IMMUNE SYSTEM

INTRODUCTION

Anyone who has had the good fortune to hear a brilliant orchestra performance of a symphony composed by one of the great masters knows that each of the carefully tuned musical instruments contributes to the collective, harmonious sound produced by the musicians. In many ways, the normally tuned immune system continuously plays an orchestrated symphony to maintain homeostasis in the context of host defenses. However, as William Shakespeare noted, "untune that string, and, hark, what discord follows!" (Troilus and Cressida). Similarly, an untuned immune system can cause discord, which manifests as autoimmunity, cancer, or chronic inflammation. Fortunately, for most of us, our immune systems are steadfastly vigilant in monitoring themselves to ensure that each cellular component behaves and interacts symbiotically to generate protective immune responses that ensure good health.

In his penetrating essays discussing symbiosis and parasitism, scientist–author Lewis Thomas described the forces that would drive all living matter into one huge ball of protoplasm if regulatory and recognition mechanisms did not allow us to distinguish ***self*** from ***nonself***. The origins of these mechanisms go far back in evolutionary history; many originated as markers allowing cells to recognize and interact with one another to set up symbiotic households. For example, genetically related sponge colonies that are placed close together tend to grow toward one another and fuse into one large colony. However, unrelated colonies react differently, destroying cells that come in contact and leaving a zone of rejection between the colonies.

In the plant kingdom, similar types of recognition occur. In self-pollinating species, a pollen grain landing on the stigma of a genetically related flower will send a pollen tubule down the style to the ovary for fertilization. A pollen grain from a genetically distinct plant reacts in one of two ways: (1) it will fail to germinate or (2) the pollen tubule will disintegrate in the style. The opposite occurs in cross-pollinating species: self-marked pollen grains disintegrate, but nonself grains germinate and fertilize.

The nature of these primitive recognition mechanisms has not been completely worked out, but it almost certainly involves cell surface molecules that are able to specifically bind and adhere to other molecules on opposing cell surfaces. This simple method of molecular recognition has evolved over time into the very complex immune system that retains, as its essential feature, the ability of a protein molecule to recognize and bind specifically to a particular structure on another molecule. Such molecular recognition is the underlying principle involved in the discrimination between self and nonself during an immune response. It is the purpose of this book to describe how the fully mature immune system—which has evolved from this simple beginning—makes use of this principle of recognition in increasingly complex and sophisticated ways.

The study of immunology as a science has gone through several periods of quiescence and active development; the latter usually occurs following the introduction of a new technique or a changed paradigm for

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thinking about the subject. Perhaps the biggest catalyst for progress in this and many other biomedical areas has been the advent of molecular biologic techniques. It is important to acknowledge, however, that the reverse is also true: Certain technological advances in the field of molecular biology were made possible by earlier progress in the field of immunology. For example, the importance of immunologic methods (Chapter 5) used to purify proteins as well as identify specific complementary deoxyribonucleic acid (cDNA) clones cannot be understated. These advances were greatly facilitated by the pioneering studies of Kohler and Milstein (1975), who developed a method for producing monoclonal antibodies. Their achievement, which was rewarded with the Nobel Prize in Medicine, revolutionized research efforts in virtually all areas of biomedical science. Some monoclonal antibodies produced against so-called tumor-specific antigens have now been approved by the U.S. Food and Drug Administration for use to treat certain human malignancies. Monoclonal antibody technology is an excellent example of how the science of immunology has transformed not only medicine but also fields ranging from agriculture to the food science industry. Given the rapid advances occurring in immunology and many other biomedical sciences, including the sequencing of the human genome, every contemporary biomedical science textbook runs a considerable risk of being outdated before it appears in print. Nevertheless, we take solace from the observation that new formulations generally build on and expand existing information rather than replacing or negating it completely. We begin, therefore, with an overview of innate and acquired immunity, which continues to serve as a conceptual compass, orienting our fundamental understanding of host defense mechanisms.

INNATE AND ACQUIRED IMMUNITY

The English word ***immunity***, which refers to all the mechanisms used by the body as protection against environmental agents that are foreign to the body, arose from the Latin term *immunis*, meaning "exempt." The environmental agents may be microorganisms or their products, foods, chemicals, drugs, pollen, or animal hair, and dander. Immunity may be innate or acquired.

Innate Immunity

Innate immunity is conferred by a diverse array of cellular and subcellular components with which an individual is born. They are always present and available at very short notice to protect the individual from challenges by foreign invaders. Most of these elements are discussed in detail in Chapter 2. Table 1.1 summarizes and compares some of the major properties of the innate and adaptive immune systems. Elements of the innate immune system include body surfaces and internal components, such as the skin, the mucous membranes, and the cough reflex, all of which present effective barriers to environmental agents.

Chemical influences, such as pH and secreted fatty acids, also constitute effective barriers against invasion by many microorganisms. Another noncellular element of the innate immune system is the complement system. As in the previous editions of this book, we cover the subject of complement in a separate chapter (Chapter 13).

Numerous other features of innate immunity include fever; interferons (Chapter 11); other substances released by leukocytes; pattern recognition molecules (***innate receptors***), which can bind to various microorganisms (e.g., Toll-like receptors; Chapter 2); and serum proteins such as β-lysin, the enzyme lysozyme, polyamines, and the kinins. All of these elements either affect pathogenic invaders directly or enhance the effectiveness of host reactions to them. Phagocytic cells such as granulocytes, macrophages, and microglial cells of the central nervous system, which participate in the destruction and elimination of foreign material that has penetrated the body's physical and chemical barriers, are also considered part of the innate immune system.

Acquired Immunity

Acquired immunity came into play relatively late in evolutionary terms and is present only in vertebrates.

TABLE 1.1. Major Properties of the Innate and Adaptive Immune Systems

Property	Innate	Adaptive
Characteristics	Antigen nonspecific	Antigen specific
	Rapid response (minutes-hours)	Slow response (days)
	No memory	Memory
Immune components	Natural barriers (e.g., skin, mucous membranes)	Lymphocytes
	Phagocytes and Natural Killer cells	Antigen recognition molecules (B- and T-cell recptors)
	Soluble mediators (e.g., complement)	Secreted molecules (e.g., antibody)
	Pattern recognition molecules	

Although an individual is born with the capacity to mount immune responses to a foreign substance, the number of B and T cells available for initiating such responses must be expanded before you are said to be immune to that substance. This is achieved following contact with an antigen by activation of lymphocytes bearing antigen-specific receptors. Antigenic stimulation of B cells, T cells, and antigen-presenting cells initiates a chain of events that leads to proliferation of activated cells, along with a genetic program of differentiation events that generate the B cells or T cells responsible for the humoral or cell-mediated responses, respectively. These events take days to weeks to unfold. Fortunately, the cellular and noncellular components of the innate immune system are mobilized more rapidly (within minutes to hours) to eliminate or neutralize the foreign substance. One way to think about this host defense strategy is to consider this as a one–two punch: (1) innate cells and noncellular elements of the immune system are always available to quickly remove or cordon off the invader; (2) cells of the acquired immune system (B and T cells) are programmed by virtue of their antigen-specific receptors to react with specific foreign substances. The clonal expansion of the cells of the acquired immune system gives rise to an arsenal of antigen-specific cells available for rapid responses to the same antigen in the future, a phenomenon referred to as ***memory responses***. By this process, the individual acquires the immunity to withstand and resist a subsequent attack by or exposure to the same offending agent.

The discovery of acquired immunity predates many of the concepts of modern medicine. It has been recognized for centuries that people who did not die from such life-threatening diseases as bubonic plague and smallpox were subsequently more resistant to the disease than were people who had never been exposed to it. The rediscovery of acquired immunity is credited to the English physician Edward Jenner, who, in the late-eighteenth century, experimentally induced immunity to smallpox. If Jenner performed his experiment today, his medical license would be revoked, and he would be the defendant in a sensational malpractice lawsuit: He inoculated a young boy with pus from a lesion of a dairy maid who had cowpox, a relatively benign disease that is related to smallpox. He then deliberately exposed the boy to smallpox. This exposure failed to cause disease! Because of the protective effect of inoculation with cowpox, the process of inducing acquired immunity has been termed ***vaccination*** (*vaccinia*, from the Latin word *vacca*, meaning "cow").

The concept of vaccination or immunization was expanded by Louis Pasteur and Paul Ehrlich almost 100 years after Jenner's experiment. By 1900, it had become apparent that immunity could be induced against not only microorganisms but also their products. We now know that immunity can be induced against innumerable natural and synthetic compounds, including metals, chemicals of relatively low molecular weight, carbohydrates, proteins, and nucleotides.

The compound that induces the acquired immune response is termed an ***antigen***, a term initially coined because these compounds were known to cause *anti*body responses to be *gen*erated. Of course, we now know that antigens can generate both antibody-mediated and T-cell-mediated responses.

Active, Passive, and Adoptive Immunization

Acquired immunity is induced by immunization, which can be achieved in several ways:

- ***Active immunization*** refers to immunization of an individual by administration of an antigen.
- ***Passive immunization*** refers to immunization through the transfer of specific antibody from an immunized individual to a nonimmunized individual.
- ***Adoptive immunization*** refers to the transfer of immunity by the transfer of immune cells.

Major Characteristics of the Acquired Immune Response. The acquired immune response has several general features that distinguish it from other physiologic systems, such as circulation, respiration, and reproduction:

- ***Specificity*** is the ability to discriminate among different molecular entities and to respond only to those uniquely required, rather than making a random, undifferentiated response.
- ***Adaptiveness*** is the ability to respond to previously unseen molecules that may in fact never have naturally existed before on earth.
- ***Discrimination between self and nonself*** is a cardinal feature of the specificity of the immune response; it is the ability to recognize and respond to molecules that are foreign (nonself) and to avoid making this response to those molecules that are self. This distinction, and the recognition of antigen, is conferred by specialized cells (lymphocytes) that bear antigen-specific receptors on their surface.
- ***Memory*** a property shared with the nervous system, is the ability to recall previous contact with a foreign molecule and respond to it in a learned manner—that is, with a more rapid and larger response. Another term often used to describe immunologic memory is ***anamnestic response***.

By the time you reach the end of this book, you should understand the cellular and molecular bases of these features of the immune response.

Cells Involved in the Acquired Immune Response. For many years, immunology remained an empirical subject involving the study of the effects of injecting various substances into hosts. Most progress came in the form of more quantitative methods for detecting the products of the immune response. However, a major shift in focus occurred in the 1950s. The revelation that lymphocytes were the major cellular players in immune responses caused the birth of an entirely new field of study, cellular immunology.

A convenient way to define the cell types involved in acquired immunity is to divide the host defense mechanisms into two categories: B-cell responses and T-cell responses. While this is an oversimplified definition, it is, by and large, the functional outcome of acquired immune responses. B and T cells are derived from a common lymphoid precursor cell but differentiate along different developmental lines, as discussed in detail in Chapters 7 and 8, respectively. In short, B cells develop and mature in the bone marrow, and T cells develop in the bone marrow but undergo critical maturation steps in the thymus.

Antigen-presenting cells (APC), such as macrophages and dendritic cells, constitute the third cell type participating in the acquired immune response. Although these cells do not have antigen-specific receptors themselves, they process and present antigen to the antigen-specific receptors expressed by T cells. The APC express a variety of cell-surface molecules that facilitate their interaction with T cells. Among these are the ***major histocompatibility complex*** (***MHC***) molecules discussed in Chapter 8. MHC molecules are encoded by a set of polymorphic genes expressed within a population. In clinical settings, MHC molecules determine the success or failure of organ and tissue transplantation. In fact, this observation facilitated their discovery and the current terminology (major *histocompatibility* complex) used to define these molecules. (We now understand that their physiologic role is concerned with T cell–APC interactions.) Physiologically, APC process protein antigens intracellularly, resulting in the constellation of peptides that noncovalently bind to MHC molecules and ultimately get displayed on the cell surface.

Other cell types, such as neutrophils and mast cells, also participate in acquired immune responses. In fact, they participate in both innate and acquired immunity. While these cells have no specific antigen recognition properties and can be activated by a variety of substances, they are an integral part of the network of cells that participate in host defenses and often display potent immunoregulatory properties.

CLONAL SELECTION THEORY

A turning point in immunology came in the 1950s with the introduction of a Darwinian view of the cellular basis of specificity in the immune response. The now universally accepted ***clonal selection theory*** was proposed and developed by Jerne and Burnet (both Nobel Prize winners) and by Talmage. The clonal selection theory had a truly revolutionary effect on the field of immunology. It dramatically changed our approach to studying the immune system and affected all research carried out during the last half of the twentieth century. This work ultimately provided us with knowledge regarding the molecular machinery behind the activation and regulation of cellular elements of the immune system. The essential postulates of this theory are summarized below.

As discussed earlier, the specificity of immune responses is based on the ability of B and T lymphocytes to recognize particular foreign molecules (antigens) and respond to them in order to eliminate them. The process of clonal expansion of these cells is highly efficient, but there is always the rare chance that errors or mutations will occur. Such errors can result in the generation of B and T lymphocytes with receptors that bind to self-antigens and therefore display ***autoreactivity***. Under normal conditions, nonfunctioning cells may survive or be aborted with no deleterious consequences to the individual. In contrast, the rare self-reactive cells are clonally deleted or suppressed by other regulatory cells of the immune system charged with this role. If such a mechanism were absent, autoimmune responses might occur routinely. It is noteworthy that during the early stages of development, lymphocytes with receptors that bind to self-antigens are produced, but fortunately they are eliminated or functionally inactivated. This process gives rise to the initial repertoire of mature lymphocytes that are programmed to generate antigen-specific responses. As noted above, some errors can occur during this process, leading to the development of autoreactive cells (Fig. 1.1). The circumstances and predisposing genetic conditions that may lead to the latter phenomenon are discussed in Chapter 12.

As we have already stated, the immune system is capable of recognizing innumerable foreign antigens. How is a response to any one antigen accomplished? In addition to the now-proven postulate that self-reactive clones of lymphocytes are functionally inactivated or aborted, the clonal selection theory proposed the following:

- T and B lymphocytes of myriad specificities exist before there is any contact with the foreign antigen.
- Lymphocytes participating in an immune response express antigen-specific receptors on their surface membranes. As a consequence of antigen binding to the lymphocyte, the cell is activated and releases various products. In the case of B lymphocytes, these receptors, so-called ***B-cell receptors (BCRs)*** are the very molecules that subsequently get secreted as antibodies following B-cell activation.

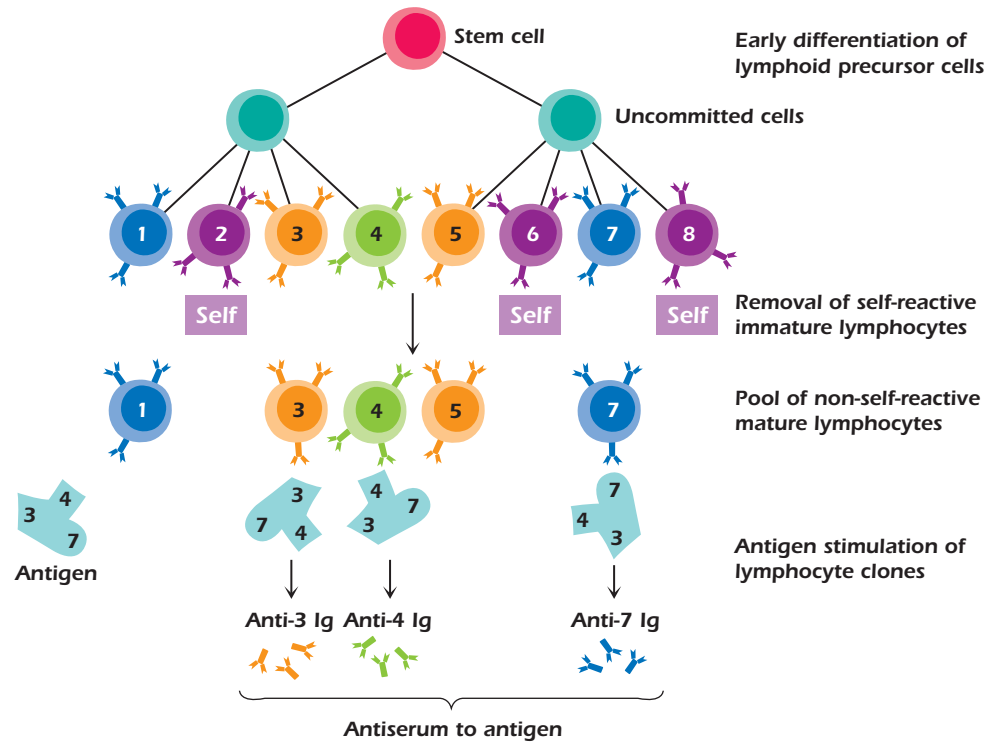

Figure 1.1. Clonal selection theory of B cells leading to antibody production.

- T cells have receptors denoted as ***T-cell receptors*** (***TCRs***). Unlike the B cell, the T-cell products are not the same as their surface receptors. Instead, other protein molecules, called cytokines, participate in elimination of the antigen by regulating the many cells needed to mount an effective immune response.
- Each lymphocyte carries on its surface receptor molecules of only a single specificity, as demonstrated in Figure 1.1. This is true for both B and T cells.

These three postulates describe the existence of a large repertoire of possible specificities formed by cellular multiplication and differentiation *before* there is any contact with the foreign substance requiring a response. Upon introduction of the foreign antigen, those cells with specificity for the antigen bind to it.

The remaining postulates of the clonal selection theory account for this process of selection by the antigen from among all the available cells in the repertoire:

- Surface receptors of the immunocompetent lymphocytes combine with the foreign antigen, or a portion of it, termed the ***epitope*** or ***antigenic determinant***. The cells expressing these epitope-specific receptors are then activated under appropriate conditions to proliferate and differentiate into clones of cells with the corresponding epitope-specific receptors.
- With B-cell clones, this process will lead to the synthesis of antibodies having specificity for the same antigen. In most cases, the antigen stimulating the response is complex and contains many different epitopes, each capable of activating a clone of epitope-specific B cells. Hence, the clonally secreted antibodies collectively constitute what is often referred to as polyclonal antiserum capable of interacting with the multiple epitopes expressed by the antigen. Several distinct regions (epitopes) of an antigen can be recognized; thus, several different clones of B cells will be stimulated to produce antibody. The collective response produces an antiserum that is made up of antigen-specific antibodies (Fig. 1.1);
- T cells are similarly selected by appropriate epitopes. Each selected T cell will be activated to divide and produce clones with specificity for the same antigen. Thus the clonal response to the antigen will be amplified, and subsequent exposure to the same antigen will now result in the activation of many cells or clones of that specificity. Instead of synthesizing and releasing antibodies like the B cells, the T cells synthesize and release cytokines. These cytokines, which are soluble mediators, exert their effect on other cells to grow or become activated, facilitating elimination of the antigen. All of the T-cell clones that recognize various epitopes on the same antigen will be activated to perform their function.

A final postulate was added to account for the ability to recognize self-antigens without making a response:

- Circulating self-antigens that reach the developing lymphoid system before some undesignated maturational step will serve to shut off those cells that recognize it specifically, and no subsequent immune response will be induced.

HUMORAL AND CELLULAR IMMUNITY

Acquired immune responses have historically been divided into two separate arms of defense, namely, B-cell-mediated or ***humoral immunity*** and T-cell-mediated or ***cellular immunity***. Today, while we recognize that B and T cells have very distinct yet complementary molecular and functional roles within our immune system, we understand that the two arms are fundamentally interconnected at many levels. "Experiments of nature" was a term coined by Robert A. Good in the 1950s when describing the immune status of mice with a congenital mutation associated with an athymic phenotype (a similar phenomenon in humans is called DiGeorge syndrome). Good's experiments have provided significant insights into the interdependence of these two arms of the immune system. Athymic mice, those that fail to develop thymic tissue, develop a profound T-cell deficiency with accompanying abnormalities in B-cell function. Without T-cell help, B cells are unable to generate normal antibody responses and, in particular, to undergo immunoglobulin class switching (see Chapters 7 and 17). The help normally provided by T cells is delivered in several ways, including the synthesis and secretion of a variety of cytokines that regulate many events required for proliferation and differentiation of B cells (see Chapter 11).

B cells are initially activated to secrete antibodies after binding of antigens to antigen-specific ***immunoglobulin*** (***Ig***) molecules expressed by B cells. All serum globulins with antibody activity are referred to as immunoglobulins (see Chapter 4). It has been estimated that each B cell expresses 10^5 BCRs of identical specificity. Once ligated, the B cell receives signals to begin making the secreted form of this immunoglobulin, a process that initiates the full-blown antibody response with the purpose of eliminating the antigen from the host. Antibodies are a heterogeneous mixture of serum globulins, all of which share the ability to bind individually to specific antigens.

Immunoglobulins have common structural features which enable them to do two things: (1) recognize and bind specifically to a unique structural entity on an antigen (the epitope) and (2) perform a common biologic function after combining with the antigen. Immunoglobulin molecules consist of two identical light (L) chains and two identical heavy (H) chains linked by disulfide bridges. The resultant structure is shown in Figure 1.2. The portion of the molecule that binds antigen consists of an area composed of the amino-terminal regions of both H and L chains. Thus, each immunoglobulin molecule composed of 2H and 2L chains is symmetric and is capable of binding two identical eptitopes, either on the same antigen molecule or on two different molecules. There are other differences among immunoglobulin molecules in addition to variations in the antigen-binding portion, the most important of which occur in the H chains. There are five major classes of H chains (termed γ, μ, α, ε, and δ). On the basis of differences in their H chains, immunoglobulin molecules are divided into five major classes: IgG, IgM, IgA, IgE, and IgD. Each class has several unique biologic properties. For example, IgG is the only class of immunoglobulin that crosses the placenta, conferring the mother's immunity on the fetus, and IgA is the major antibody found in secretions such as tears and saliva. It is important to remember that antibodies in all five classes may possess precisely the same specificity against an antigen (antigen-combining regions), while at the same time having different functional (biologic effector) properties. The binding between antigen and antibody is not covalent but depends on many relatively weak forces, such as hydrogen bonds, van der Waals forces, and hydrophobic interactions. Since these forces are weak, successful binding between antigen and antibody depends on a very close fit over a sizable area, much like the contacts between a lock and a key.

Besides the help provided by T cells in the generation of antibody responses, noncellular components of the innate immune system, collectively termed the ***complement system***, play a key role in the functional activity of antibodies when they interact with antigen (Chapter 13). The reaction between antigen and antibody serves to activate this system, which consists of a series of serum enzymes. The end result is lysis of the target in the case of microbes such as bacteria or enhanced ***phagocytosis*** (ingestion of the antigen) by phagocytic cells. The activation of complement also results in the recruitment of highly ***phagocytic polymorphonuclear*** (**PMN**) cells or neutrophils, which are active in innate immunity.

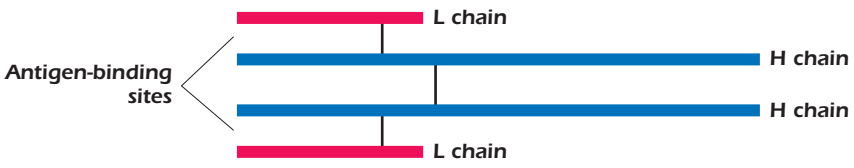

Figure 1.2. Typical antibody molecule composed of two heavy (H) and two light (L) chains. Antigen-binding sites are noted.

Cell-Mediated Immunity

In contrast to humoral immune responses that are mediated by antibodies, cell-mediated responses are T-cell mediated. However, this is an oversimplified definition. The effector cell responsible for the elimination of a foreign antigen such as a pathogenic microbe can be an activated T cell expressing a pathogen-specific TCR or a phagocytic cell that gets activated by innate receptors which they express and the cytokines produced by activated T cells (Fig. 1.3). Unlike B cells, which produce soluble antibody that circulates to bind specific antigens, each T cell, bearing approximately 10^5 identical antigen receptors (TCRs), circulates directly to the site of antigen expressed on APC and interacts with these cells in a *cognate* (cell-to-cell) fashion (Chapter 10).

There are several phenotypically distinct subpopulations of T cells, each of which may have the same specificity for an antigenic determinant (epitope). However, each subpopulation may perform different functions. This is somewhat analogous to the different classes of immunoglobulin molecules, which may have identical specificity but different biologic functions. Several major subsets of T cells exist, including helper T cells (T_H cells), which express molecules called CD4, and cytotoxic T cells (T_C cells), which express CD8 molecules on their surface. Another population of T cells possessing suppressor activity is the T-regulatory cell (T_{reg} cells).

The functions ascribed to the various subsets of T cells include the following:

- ***B-cell help***. T_H cells cooperate with B cells to enhance the production of antibodies. T_H cells function by releasing cytokines, which provide various activation signals for the B cells. As mentioned earlier, cytokines are soluble substances, or mediators that can regulate proliferation and differentiation of B cells. Additional information about cytokines is presented in Chapter 11.
- ***Inflammatory effects***. On activation, certain T_H cells releases cytokines that induce the migration and activation of monocytes and macrophages, leading to inflammatory reactions (Chapter 16).
- ***Cytotoxic effects***. Certain T cells, called T-cytotoxic (T_C) cells, are able to deliver a lethal hit on contact with their target cells, leading to their death. In contrast to T_H cells, T_C cells express molecules called CD8 on their membranes and are, therefore, $CD8^+$ cells.
- ***Regulatory effects***. Helper T cells can be further subdivided into different functional subsets that are commonly defined by the cytokines they release. As you will learn in subsequent chapters, these subsets (T_H1, T_H2) have distinct regulatory properties that are mediated by the cytokines they release (Chapter 11). T_H1 cells can negatively cross-regulate T_H2 cells and vice versa. Another population of regulatory or suppressor T cells coexpresses CD4 and a molecule called CD25 (CD25 is part of a cytokine receptor known as the interleukin 2 receptor α chain; Chapter 11). The regulatory activity of these $CD4^+/CD25^+$cells and their role in actively suppressing autoimmunity are discussed in Chapter 12.
- ***Cytokine effects***. Cytokines produced by each of the T-cell subsets (principally T_H cells) exert numerous effects on many cells, lymphoid and nonlymphoid. Thus, directly or indirectly, T cells communicate and collaborate with many cell types.

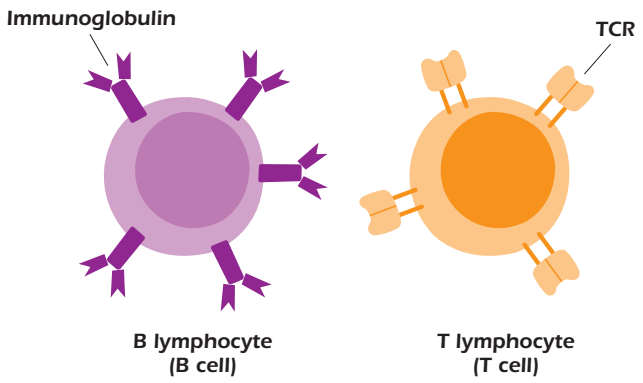

Figure 1.3. Antigen receptors expressed as transmembrane molecules on B and T lymphocytes.

For many years, immunologists have recognized that cells activated by antigen manifest a variety of effector phenomena. It is only in the last few decades that researchers began to appreciate the complexity of events that take place in activation by antigen and communication with other cells. We know today that just mere contact of the TCR with antigen is not sufficient to activate T cells. At least two signals must be delivered to the antigen-specific T cell for activation to occur: Signal 1 involves the binding of the TCR to antigen, which must be presented in the appropriate manner by APC. Signal 2 involves costimulators, including cytokines such as interleukin 1 (IL-1), IL-4, and IL-6 (Chapter 11) and cell surface molecules expressed on APC, such as CD40 and CD86 (Chapter 10). Recently, the term ***costimulator*** has been broadened to include stimuli such as microbial products (infectious nonself) and damaged tissue (Matzinger's "danger hypothesis") that will enhance signal 1 when that signal is relatively weak.

Once T cells are optimally signaled for activation, a series of events takes place and the activated cell undergoes proliferation and synthesizes and releases cytokines. In turn, these cytokines come in contact with appropriate cell surface receptors on different cells and exert their effect on these cells.

Although the humoral and cellular arms of acquired immune responses have been considered as separate and distinct components, it is important to understand that the response to any particular pathogen may involve a complex interaction between them along with components of innate immunity. All this ensures a maximal survival advantage for the host by eliminating the antigen and, as we shall see, by protecting the host from mounting an immune response against self.

GENERATION OF DIVERSITY IN THE IMMUNE RESPONSE

The most recent tidal surge in immunologic research represents a triumph of the marriage of molecular biology and immunology. Although cellular immunology had outlined the cellular basis and exquisite specificity of a large and diverse repertoire of responses, arguments abounded regarding the exact genetic mechanisms that enabled all these specificities to become part of the immune response in every individual of the species.

Briefly, the arguments were as follows:

- By various calculations, the number of antigenic specificities against which an immune response could possibly be mounted could range upward of 10^6–10^7.
- If every specific response, in the form of either antibodies or T-cell receptors, were encoded by a single gene, did this mean that $>10^7$ genes (one for each specific antibody or TCR) were required in every individual? How was this massive amount of DNA carried intact from individual to individual?

The pioneering studies of Tonegawa (a Nobel laureate) and Leder, using molecular biologic techniques, finally addressed these issues by describing a unique genetic mechanism by which immunologic receptors expressed on B cells (BCRs) of enormous diversity could be produced with a modest amount of DNA.

The technique evolved by nature was one of genetic recombination, in which a protein could be encoded by a DNA molecule composed of a set of recombined minigenes that made up a complete gene. Given small sets of these minigenes, which could be randomly combined to make the complete gene, it was possible to produce an enormous repertoire of specificities from a limited number of gene fragments. This idea is discussed in detail in Chapter 6.

Although this mechanism was first elucidated to explain the enormous diversity of antibodies that not only are released by B cells but also, in fact, constitute the antigen- or epitope-specific BCRs, it was subsequently established that the same mechanisms operate in generating diversity of the antigen-specific TCR. The mechanisms involved in generating diversity of TCRs are discussed in Chapter 8. For now, all you need to know is that various techniques of molecular biology, which permit genes to be both analyzed and moved from one cell to another, have continued the onrushing tide of progress in the field of immunology.

BENEFITS OF IMMUNOLOGY

So far we have discussed the theoretical aspects of immunology. However, its practical applications are of paramount importance for survival.

The field of immunology has been in the limelight since the successful use of polio vaccines in the mid-twentieth century. More recently, the transplantation of the human heart and other major organs, such as the liver, has been the focus of a great deal of publicity. Public interest in immunology has intensified in light of the potential application of immune responses to the detection and management of cancer. In the 1980s, awareness of immunology among the general public was also heightened because of the alarming spread of acquired immunodeficiency syndrome (AIDS).

The innate and acquired immune systems play an integral role in the prevention of and recovery from infectious diseases and are, without question, essential to the survival of the individual. In the 1800s, Metchnikoff was the first to propose that phagocytic cells formed the first line of defense against infection and that the inflammatory response could actually serve a protective function for the host. Indeed, innate immune responses are responsible for the detection and rapid destruction of most infectious agents that we encounter in daily life. We now know that innate immune responses operate in concert with adaptive immune responses to generate antigen-specific effector mechanisms that lead to the death and elimination of the invading pathogen. Chapter 20 presents information about the response of our immune systems to microorganisms and exploitation of these mechanisms through immunoprophylaxis. Vaccination against infectious diseases has been and continues to be an effective form of prophylaxis. Immunoprophylaxis against the virus that causes poliomyelitis has significantly reduced the incidence of this devastating disease. Indeed, one of the most widespread diseases, smallpox, has been virtually eliminated from the face of the earth. The last documented case of natural transmission of smallpox virus was in 1972. Unfortunately, the threat of biologic weapons has prompted new concerns regarding the reemergence of smallpox and certain other infectious diseases. Fortunately, public health vaccination initiatives can prevent or significantly curtail the threat of weaponized microbiological agents.

Recent developments in immunology also hold the promise of immunoprophylaxis against malaria and several other parasitic diseases that plague many parts of the world

and affect billions of people. Vaccination against diseases of livestock promises to increase the production of meat in developing countries, while inoculations targeting various substances that play roles in the reproductive processes in mammals offer the possibility of long-term contraception in humans and companion animals such as cats and dogs.

DAMAGING EFFECTS OF THE IMMUNE RESPONSE

The enormous survival value of immune responses is self-evident. Acquired immunity directed against a foreign material has as its ultimate goal the elimination of the invading substance. In the process, some tissue damage may occur as the result of the accumulation of components with nonspecific effects. This damage is generally temporary. As soon as the invader is eliminated, the situation at the site of the immune response reverts to normal.

There are instances in which the power of the immune response, although directed against innocuous foreign substances—such as some medications, inhaled pollen particles, or substances deposited by insect bites—produces a response that may result in severe pathologic consequences and even death. These responses are known collectively as hypersensitivity reactions or allergic reactions. An understanding of the basic mechanisms underlying these disease processes has been fundamental in their treatment and control. In addition, studying these processes has contributed much to our knowledge of normal immune responses. Normal and hyperreactive immune responses both utilize essentially identical mechanisms; however, in hypersensitivity, these mechanisms are misdirected or out of control (see Chapters 14–16).

Given the complexity of immune responses and their potential for inducing damage, they must operate under carefully regulated conditions, like any other physiologic system. These multiple controls include feedback inhibition by soluble products and cell–cell interactions of many types, which may either heighten or reduce the response. The net result is to maintain a state of homeostasis so that, when the system is disrupted by a foreign invader, just enough response is generated to control the invader, and then the system returns to equilibrium—in other words, the immune response is shut down. However, memory of that particular invader is retained so that a more rapid and heightened response will occur should the invader return. A disturbance in these regulatory mechanisms may be caused by a condition such as a congenital defect, hormonal imbalance, or certain infections, any of which can have disastrous consequences. AIDS is a timely example; AIDS is associated with an infection of T lymphocytes that participate in regulating immune responses. As a result of infection with the human immunodeficiency virus (HIV), which causes AIDS, there is a decrease in occurrence and function of a vital subpopulation of T cells, which leads to immunologic deficiency and renders the patient powerless to resist infections by microorganisms that are normally benign.

Another important form of regulation is the prevention of immune responses against self-antigens. During the developmental stages leading to the generation of mature B and T lymphocytes, there are checkpoints that eliminate or functionally silence these self-reactive cells (discussed in Chapter 12). Sometimes, however, rare autoreactive cells may develop, causing the body to mount an immune response against its own tissues. This type of immune response is termed autoimmunity and is the cause of diseases such as some forms of arthritis, thyroiditis, and type I diabetes, which are very difficult to treat.

THE FUTURE OF IMMUNOLOGY

A peek into the world of the future of immunology suggests many exciting areas of research. The application of molecular and computational techniques promises significant dividends. To cite just a few examples, we focus on vaccine development and control of immune responses. Rather than the laborious, empirical search for an attenuated virus or bacterium for use in immunization, it is now possible to use pathogen-specific protein sequence data and sophisticated computational methods (*bioinformatics*) to identify candidates to be tested. Alternatively, DNA vaccines involving the injection of DNA vectors that encode immunizing proteins may revolutionize vaccination protocols in the not-too-distant future. The identification of various genes and the proteins or peptides that they are encoding makes it possible to design vaccines against a wide spectrum of biologically important compounds.

Another area of great promise is control of immune responses. Techniques of gene isolation, clonal reproduction, the polymerase chain reaction, and biosynthesis have contributed to rapid progress in the characterization and synthesis of various cytokines that enhance and control the activation of various cells associated with immune responses. Powerful and important modulators have been synthesized using recombinant DNA technology and are being tested for their therapeutic efficacy in a variety of diseases, including many different cancers. In some cases, cytokine research efforts have already moved from the bench to the bedside with the development of therapeutic agents used to treat patients.

Finally, probably one of the most exciting areas of research is the genetic engineering of cells and even whole animals, such as mice, that lack one or more specific traits (gene knockout) or that carry a specific trait (transgenic). These and other immune-based experimental systems are the subject of Chapter 5. They allow the immunologist to

study the effects of such traits on the immune system and on the body as a whole with the goals of understanding the intricate regulation, expression, and function of immune responses and controlling the trait to benefit the individual. Our growing understanding of the functioning of the immune system, combined with the recently acquired ability to alter and manipulate its components, carries enormous implications for the future of humankind.

THE SHORT COURSE BEGINS HERE

This brief overview of the immune system is intended to introduce you to the complex yet fascinating subject of immunology. In the remaining chapters we provide a more detailed account of the workings of the immune system. We begin with its cellular components (Chapter 2), followed by a description of the structure of the reactants (Chapters 3 and 4) and the general methodology for measuring their reactions (Chapter 5). This is followed by chapters describing the formation and activation of the cellular and molecular components of the immune apparatus required to generate a response (Chapters 6–9). A discussion of the control mechanisms that regulate the scope and intensity of immune responses completes the description of the basic nature of immunity (Chapter 10). Next is a chapter on cytokines (Chapter 11), the soluble mediators that regulate immune responses and play a significant role in hematopoiesis, followed by chapters that deal with the great variety of immune-mediated diseases. These vary from responses to self-antigens (autoimmunity; Chapter 12) to those produced by aberrant immune responses (hypersensitivity; Chapters 14–16) to ineffective or absent immune responses (immunodeficiency; Chapter 17). Also included in this group is a chapter on the complement system (Chapter 13). Following the chapters that describe the role of the immune response in transplantation (Chapter 18) and antitumor reactions (Chapter 19), a final chapter focuses on the spectrum of microorganisms that challenge the immune system and how immune responses are mounted in a vigilant, orchestrated fashion to protect the host from infectious diseases. Included in Chapter 20 is a discussion of immunoprophylaxis using vaccines that protect us from a variety of pathogenic organisms. Without question, the successful use of vaccines helped revolutionize the field of medicine in the twentieth century. What lies ahead in the twenty-first century are research efforts related to the development of crucial new vaccines to protect humankind from naturally occurring pathogenic viruses and microorganisms that have just begun to plague us (such as bird flu), have been engineered as potential biologic weapons, or have yet to be identified.

As you read the chapters that follow, we urge you to take note of cross-references to clinical correlations associated with basic immunologic concepts that appear as clinical cases in the companion book by W. Strober and S.R.S. Gottesman (*Immunology: Clinical Case Studies and Pathophysiology*). These will appear in the form of icons and clinical case titles such as the example below:

X-linked Agammaglobulinemia

With the enormous scope of the subject and the extraordinary richness of detail available, we have made every effort to adhere to fundamental elements and basic concepts required to achieve an integrated, if not extensive, understanding of the immune response. If your interest has been piqued, many current books, articles, and reviews and growing numbers of educational Internet sites, including the one that supports this textbook (see the Preface), are available to help you further explore the exciting field of immunology.

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