1

OVERVIEW OF THE IMMUNE SYSTEM

INTRODUCTION

Anyone who has had the good fortune to hear an orchestra brilliantly perform 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 system is steadfastly vigilant in regard to tuning (regulating) itself to ensure that its cellular components behave and interact symbiotically to generate protective immune responses that ensure good health. In many ways the immune system can be described in anthropomorphic terms: its memory allows it to remember and recognize pathogens years or decades after initial exposure; it can distinguish between the body's own cells and those of another organism; and it makes decisions about how to respond to particular pathogens—including whether or not to respond at all, as will be discussed in later chapters.

In his penetrating essays, scientist–author Lewis Thomas, discussing symbiosis and parasitism, described the forces that would drive all living matter into one huge ball of protoplasm were it not for regulatory and recognition mechanisms that allow us to distinguish self from nonself. The origins of these mechanisms go far back in evolutionary history, and many, in fact, originated as markers for allowing cells to recognize and interact with each other to set up symbiotic households. Genetically related sponge colonies that are placed close to each other, for example, will tend to grow toward each other and fuse into one large colony. Unrelated colonies, however, will react in a different way, destroying cells that come in contact with each other 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 either will not germinate or the pollen tubule, once formed, will disintegrate in the style. The opposite occurs in cross-pollinating species: self-marked pollen grains disintegrate, whereas nonself grains germinate and fertilize.

The nature of these primitive recognition mechanisms has not been completely worked out, but almost certainly it 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 shaped 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

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this book to describe the mammalian immune system which has evolved from this simple beginning which makes use of this principle of recognition in increasingly complex and sophisticated ways.

Perhaps the greatest 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 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 (see Chapter 20) used to purify proteins as well as identify specific cDNA clones cannot be overstated. These advances were greatly facilitated by the pioneering studies of Köhler and Milstein (1975), who developed a method for producing monoclonal antibodies. Their achievement was rewarded with the Nobel Prize in Medicine. It 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 US Food and Drug Administration for use in patients to treat certain malignancies. Monoclonal antibody technology is, perhaps, one of the best examples of how the science of immunology has transformed not only the field of medicine but also fields ranging from agriculture to the food science industry.

Given the rapid advances occurring in immunology and the many other biomedical sciences and, perhaps most important, 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 the old rather than replacing or negating them completely. Let's begin, therefore, with an overview of innate and adaptive immunity (also called ***acquired immunity***) which continue to serve as a conceptual compass that orients our fundamental understanding of host defense mechanisms.

INNATE AND ADAPTIVE IMMUNITY

The Latin term ***immunis***, meaning "exempt," gave rise to 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. These agents may be microorganisms or their products, foods, chemicals, drugs, pollen, or animal hair and dander.

Our understanding of how the innate and adaptive immune systems interact to enable host immune responses to optimally protect the host from infectious pathogens is greatly enhanced by our knowledge of the cells and tissues of the immune system at large (see Chapter 3). Below is a brief overview of the innate and adaptive immune systems followed by an introduction to the development of the immune system.

Innate Immunity

Innate immunity is conferred by all those elements with which an individual is born and that are always present and available at very short notice to protect the individual from challenges by foreign invaders. The major properties of the innate immune system are discussed in Chapter 3. Table 1.1 summarizes and compares some of the features of the innate and adaptive immune systems. Elements of the innate system include body surfaces and internal components, such as the skin, the mucous membranes, and the cough reflex, which present effective barriers to environmental agents. Chemical influences, such as pH and secreted fatty acids, 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 Chapter 4.

Numerous other components are also features of innate immunity: fever, interferons, other substances released by leukocytes, and pattern recognition molecules ***(innate***

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

Property	Innate	Adaptive
Characteristics	Antigen nonspecific	Antigen specific
	Rapid response (minutes to 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 receptors)
	Soluble mediators (e.g., interferons, complement)	Secreted molecules (e.g., antibody)
	Pattern recognition molecules	
Major protective mechanisms	Inflammation and antiviral defenses	Antigen specificity and lifelong memory responses

receptors), which can bind to various microorganisms (e.g., Toll-like receptors or TLRs; see Chapter 3), as well as serum proteins such as β-lysin, the enzyme lysozyme, polyamines, and the kinins, among others. All of these elements either affect pathogenic invaders directly or enhance the effectiveness of host reactions to them. Other internal elements of innate immunity include 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 physical and chemical barriers.

Adaptive Immunity

Adaptive immunity came into play relatively late in evolutionary terms, and is present only in vertebrates. Although an individual is born with the capacity to mount immune responses to foreign substances, the number of B and T cells available for mounting such responses must be expanded before one is said to be immune to that substance. This is achieved by activation of lymphocytes bearing antigen-specific receptors following their contact with the antigen. Antigenic stimulation of B cells and T cells together with antigen-presenting cells (APCs) initiates a chain of events that leads to proliferation of activated cells together with a program of differentiation events that generate the B- or T-effector cells responsible for the humoral or cell-mediated responses, respectively. These events take time to unfold (days to weeks). Fortunately, the cellular and noncellular components of the innate system are rapidly mobilized (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 launched initially by innate cells and noncellular elements of the immune system that are always available to quickly remove or cordon off the invader, followed by a round of defense that calls into play cells of the adaptive immune system (B and T cells) that are programmed to react with the foreign substance by virtue of their antigen-specific receptors. Moreover, the clonal expansion of these cells—a process first explained by the clonal selection theory discussed in the section below—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 adaptive 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 adaptive 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 (vaccinia, from the Latin word *vacca*, meaning "cow"), the process of inducing adaptive immunity has been termed ***vaccination***.

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 to which the adaptive immune response is induced is called an ***antigen***, a term initially coined due to the ability of these compounds to cause antibody responses to be generated. Of course, we now know that antigens can generate antibody-mediated (B cell-derived) and T cell-mediated responses.

Below we introduce the subject of the origins of B and T cells and other cells of the immune system in a process known as ***hematopoiesis***.

HEMATOPOIESIS AND THE DEVELOPMENT OF THE IMMUNE SYSTEM

The bone marrow is the anatomical site where all hematopoietic cells originate from the self-renewing ***hematopoietic stem cell*** (HSC) (Figure 1.1). During fetal development, the process of hematopoiesis occurs in the yolk sac and paraaortic mesenchyme. Hematopoiesis then shifts to the liver between the third and fourth months of gestation, and finally shifts to the bone marrow. During times of exceptional demand for blood cells (e.g., hemorrhage) or when the bone marrow is injured, the liver and spleen become sites of extramedullary hematopoiesis.

As shown in Figure 1.1, the HSC gives rise to common lymphoid progenitor cells and myeloid progenitors. The former then differentiates into lymphocyte populations (B and T cells) in a process known as ***lymphopoiesis***. Lymphoid progenitor cells also give rise to a subpopulation of dendritic cells as well as natural killer (NK) cells and innate immune cells (ILC). Myeloid progenitor cells ultimately differentiate into neutrophils, eosinophils, basophils, erythrocytes (red blood cells), and monocytes which further differentiate into macrophages and dendritic cells. Myeloid progenitors also give rise to megakaryocytes which undergo an intricate series of remodeling that results in the release of thousands of platelets from a single

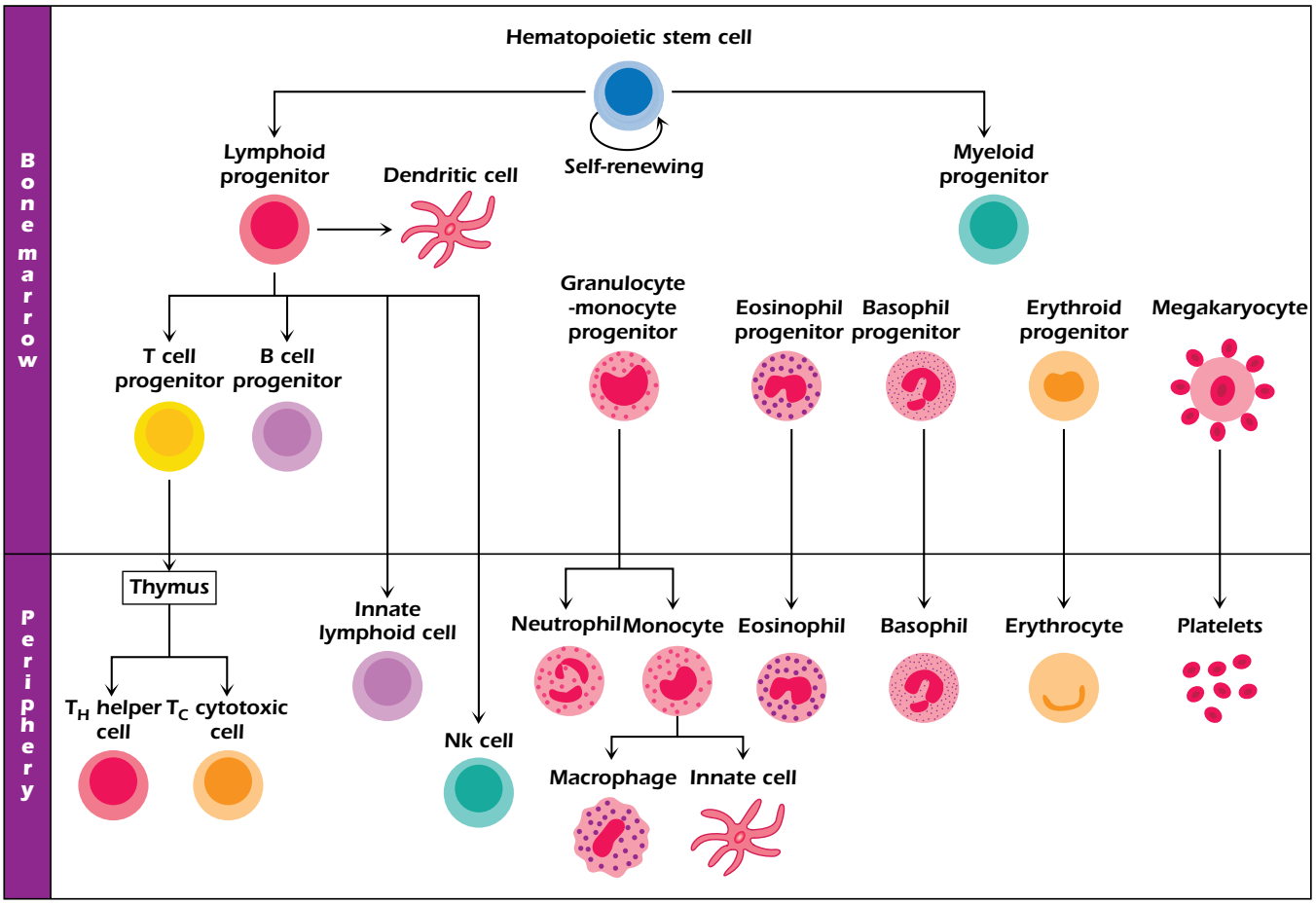

Figure 1.1. Self-renewing hematopoietic stem cells differentiate into lymphoid and myeloid progenitors. These cells differentiate along lineage-specific lines in the bone marrow. Most of these cells mature there and then travel to peripheral organs via the blood. Mast cells and macrophages undergo further maturation outside the bone marrow. T cells develop into mature T-cell subsets in the thymus before entering the periphery.

megakaryocyte. In later chapters, we will discuss in more detail the major characteristics of each of the hematopoietic cells as well as the major steps of lymphocyte development.

The immune system has evolved to exploit each of the hematopoietic cell populations. As we have already pointed out, it is convenient to discuss the major arms of the immune system beginning with elements of the innate immune system followed by the adaptive immune system. But it is important to underscore the interrelationship of these two arms of our immune system. Clearly, they are interrelated developmentally due to their common hematopoietic precursor, the hematopoietic stem cell. A classic example of their functional interrelationship is illustrated by the roles played by innate immune cells involved in ***antigen presentation***. These so-called ***antigen-presenting cells*** (APCs) do just what their name implies: they present antigens (e.g., pieces of phagocytized bacteria) to T cells within the adaptive immune system. As will be discussed in great detail in subsequent chapters, T cells must interact with APCs that display antigens for which they are specific in order for the T cells to be activated to generate antigen-specific responses.

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. This was the now universally accepted clonal selection theory 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 stimulated research carried out during the last half of the twentieth century. This work ultimately provided us with knowledge regarding the molecular machinery associated with activation and regulation of cellular elements of the immune system. The essential postulates of this theory are summarized below.

As we have discussed earlier, the specificity of the immune response 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, resulting in the generation of cells bearing receptors that bind poorly or not at all to the antigen, or, in a worse-case scenario, cells that have autoreactivity. Under normal conditions, nonfunctional 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, among others. 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 also produced, but fortunately they are also eliminated or functionally inactivated. This process gives rise to the initial repertoire of mature lymphocytes that are programmed to generate antigen-specific responses with a relatively minute population functionally benign, albeit potentially autoreactive cells (Figure 1.2). 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 substance serving as 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.
- T cells have receptors denoted as T-cell receptors (TCRs). Unlike the B-cell products, the T-cell products are not the same as their surface receptors but are other protein molecules, called cytokines, that 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 1.2 for B cells, and which also holds true for T cells.

These postulates describe the existence of a large repertoire of possible specificities formed by cellular multiplication and differentiation before there is any contact with the

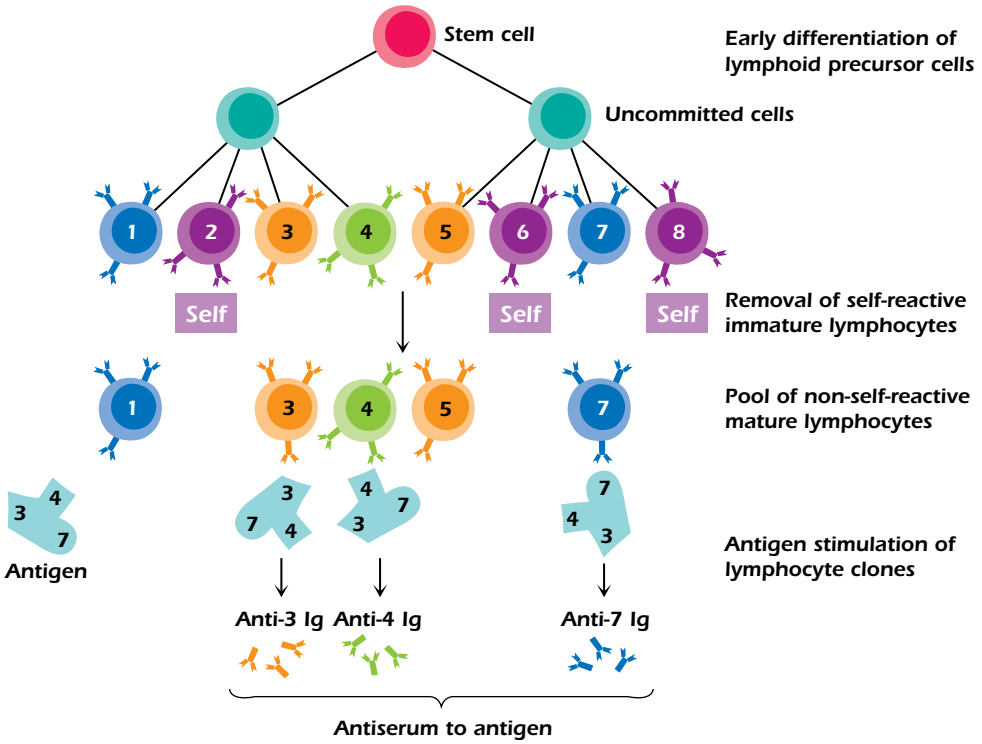

Figure 1.2. Clonal selection theory of B cells leading to antibody formation.

foreign substance to which the response is to be made. The introduction of the foreign antigen then selects from among all the available specificities those with specificity for the antigen, enabling binding to occur. The scheme shown in Figure 1.2 for B cells also applies to T cells; however, T cells have receptors that are not antibodies and secrete molecules other than antibodies.

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.

- Immunocompetent lymphocytes combine with the foreign antigen, or a portion of it termed the epitope or antigenic determinant, by virtue of their surface receptors. They are stimulated under appropriate conditions to proliferate and differentiate into clones of cells with the corresponding epitope-specific receptors.
- With B-cell clones, this will lead to the synthesis of antibodies having the same specificity. 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, collectively, the clonally secreted antibodies constitute what is often referred to as polyclonal antiserum, which is capable of interacting with the multiple epitopes expressed by the antigen.
- T cells are similarly selected by appropriate epitopes or portions thereof. Each selected T cell will be activated to divide and produce clones of the same specificity. Thus the clonal response to the antigen will be amplified, the cells will release various cytokines, 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. Several distinct regions of an antigen (epitopes) can be recognized: several different clones of B cells will be stimulated to produce antibody, whose sum total is an antigen-specific antiserum that is made up of antibodies of differing specificity (see Figure 1.1); all 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.

ACTIVE, PASSIVE, AND ADOPTIVE IMMUNIZATION

Adaptive 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 Adaptive Immune Response

The adaptive immune response has several generalized features that characterize it and distinguish it from other physiological systems, such as circulation, respiration, and reproduction. These features are as follows.

- ***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 a response to those molecules that are self. This distinction, and the recognition of antigen, is conferred by specialized cells (lymphocytes) that bear on their surface antigen-specific receptors.
- ***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 immunological memory is ***anamnestic response***.

When 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 Adaptive Immune Responses

For many years, immunology remained an empirical subject in which the effects of injecting various substances into hosts were studied primarily in terms of the products elicited. Most progress came in the form of more quantitative methods for detecting these products of the immune response. A major change in emphasis came in the 1950s

with the recognition that lymphocytes were the major cellular players in the immune response, and the field of cellular immunology came to life.

A convenient way to define the cell types involved in adaptive immunity is to divide the host defense mechanisms into two categories, namely B-cell and T-cell responses. While this is an oversimplified definition, it is, by and large, the functional outcome of adaptive immune responses. Thus, defining the cells involved begins with a short list, namely B and T cells. These cells are derived from a common lymphoid precursor cell but differentiate along different developmental lines, as discussed in detail in Chapters 8–10. In short, B cells develop and mature in the bone marrow whereas T-cell precursors emerge from the bone marrow and undergo critical maturation steps in the thymus.

Antigen-presenting cells, such as macrophages and dendritic cells, constitute the third cell type that participates in the adaptive immune response. Although these cells do not have antigen-specific receptors as do the lymphocytes, they process and present antigen to the antigen-specific receptors expressed by T cells. The APCs express a variety of cell-surface molecules that facilitate their ability to interact with T cells. Among these are the major histocompatibility complex (MHC) molecules as discussed in Chapter 8. MHC molecules are encoded by a set of polymorphic genes expressed within a population. While we now understand that their physiological role is concerned with T cell–APC interactions, 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. Physiologically, APCs 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 adaptive immune responses. In fact, they participate in both innate and adaptive 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.

HUMORAL AND CELLULAR IMMUNITY

Adaptive immune responses have historically been divided into two separate arms of defense: B-cell-mediated or humoral immune responses, and T-cell-mediated or cellular responses. 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," a term coined by Robert A. Good in the 1950s when describing the immune status of humans with a congenital mutation associated with an athymic phenotype, have provided significant insights related to the interdependence of these two arms of the immune system. Athymic mice that fail to develop thymic tissue (a similar phenomenon in humans is called ***DiGeorge syndrome***) results in a profound T-cell deficiency with accompanying abnormalities in B-cell function. The molecular explanation for the latter is now well understood. Without T-cell help, B cells are unable to generate normal antibody responses and, in particular, to undergo immunoglobulin class switching (see Chapter 9). The help normally provided by T cells is delivered in several ways, including their synthesis and secretion of a variety of cytokines that regulate many events in B cells required for proliferation and differentiation (see Chapter 11).

Humoral Immunity

B cells are initially activated to secrete antibodies after the binding of antigens to antigen-specific membrane immunoglobulin (Ig) molecules (BCRs), which are expressed by these cells. It has been estimated that each B cell expresses approximately 100,000 BCRs of exactly the same 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 whose purpose is to eliminate 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. All serum globulins with antibody activity are referred to as immunoglobulins (see Chapter 6). These molecules have common structural features, which enable them to do two things: (1) recognize and bind specifically to a unique structural entity on an antigen (namely, the epitope), and (2) perform a common biological 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 1.3. The portion of the molecule that binds antigen consists of an area composed of the amino-terminal regions of both H and L

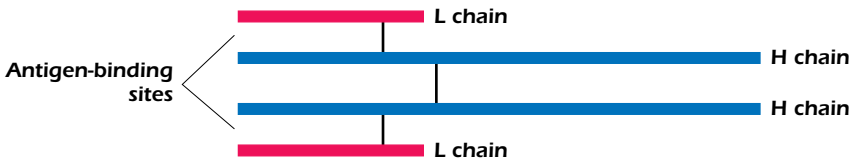

Figure 1.3. Typical antibody molecule composed of two heavy (H) and two light (L) chains. Antigen-binding sites are noted.

chains. Thus each immunoglobulin molecule is symmetrical and is capable of binding two identical epitopes present on the same antigen molecule or on different molecules.

In addition to differences in the antigen-binding portion of different immunoglobulin molecules, there are other differences, the most important of which are those 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 of which has several unique biological 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 (biological 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 sizeable 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 (see Chapter 4). The reaction between antigen and antibody serves to activate this system, which consists of a series of serum enzymes, the end-result of which 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.

Cell-Mediated Immunity

In contrast to humoral immune responses that are mediated by antibody, cell-mediated responses are T cell mediated. However, this is an oversimplified definition since 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 that they express and the cytokines produced by activated T cells (Figure 1.4). Unlike B cells, which produce soluble antibody that circulates to bind its specific antigens, each T cell, bearing approximately 100,000 identical antigen receptors (TCRs), circulates directly to the site of antigen expressed on APCs and interacts with these cells in a cognate (cell-to-cell) fashion (see Chapters 8 and 10). Activated T cells do release soluble mediators such as cytokines but these are not antigen specific.

There are several phenotypically distinct subpopulations of T cells, each of which may have the same specificity for an antigenic determinant (epitope), although each subpopulation may perform different functions. This is somewhat analogous to the different classes of immunoglobulin molecules, which may have identical specificity but different biological functions. Several major subsets of T cells exist: 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 that possesses suppressor activity is the T regulatory (Treg) cells.

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

- ***B-cell help.*** T_H helper cells cooperate with B cells to enhance the production of antibodies. Such T 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, among other functions. Additional information about cytokines is presented in Chapter 11.
- ***Inflammatory effects***. On activation, certain T_H cells release cytokines that induce the migration and activation of monocytes and macrophages, leading to inflammatory reactions (Chapter 15).
- ***Cytotoxic effects.*** As illustrated in Figure 1.1, T cells differentiate into subpopulations commonly defined as T_H helper cells (*a.k.a.* T_H cells), discussed below, and T_C cytotoxic cells (T_C cells). As the name implies, the latter cells have cytotoxic effects on other cells, a phenomenon that will be discussed further in later chapters. Upon contact with a specific target cell, T_C cells are able to deliver a lethal hit, leading to the death of the latter. T_C cells all express membrane molecules called CD8 and are, therefore, $CD8^+$ cells.

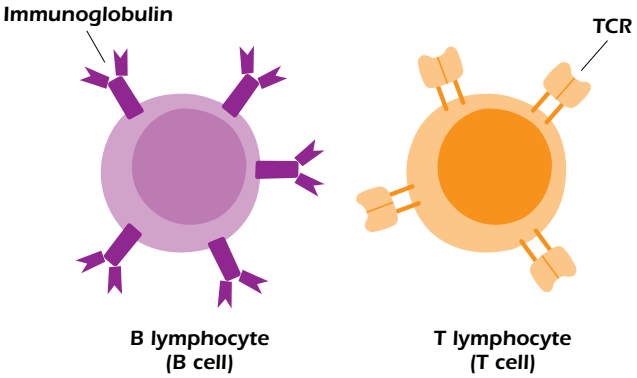

Figure 1.4. Antigen receptors expressed as transmembrane molecules on B and T lymphocytes.

- ***Regulatory effects***. In contrast with T_C cells, T_H cells play a significant role in regulating immune responses. The other distinguishing feature of T_H cells is their expression of membrane molecules called CD4 (hence, they are $CD4^+$ cells). They 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 (e.g., 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 T cells, the T_{reg} cells, co-express CD4 and a molecule called CD25 (CD25 is part of a cytokine receptor known as the interleukin-2 receptor α chain). 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.

For many years, immunologists recognized that cells activated by antigen manifest a variety of effector phenomena. It is only in the past few decades that they 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 the cell. In fact, 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 APCs. Signal 2 involves co-stimulators that include certain cytokines such as interleukin (IL)-1, IL-4, and IL-6 (Chapter 11) as well as cell-surface molecules expressed on APCs, such as CD40 and CD86. The term ***co-stimulator*** 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 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.

IMMUNE BALANCE

Although the humoral and cellular arms of immune responses have been considered as separate and distinct components, it is important to understand that the response to any particular antigen, be it a pathogen or other foreign molecular structure, may involve a complex interaction between them, as well as the components of innate immunity. All this with the purpose of ensuring 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. As was pointed out at the beginning of this introductory chapter, the normally tuned immune system continuously aims to maintain homeostasis in the context of host defenses. A complex set of factors influences how our immune system achieves homeostasis or immune balance. These include an individual's genotype, diet, and environmental conditions, as well as neurological influences related to how we respond to stress and even potential consequences of mental health disorders on immune homeostasis.

The significance of the ***microbiome*** on gut–brain–immune system homeostasis has become a major area of study. The community of microbes that reside in our gut significantly impacts the integrity of our mucosal (gut) immune system. For example, when gut barrier integrity is the norm, we live symbiotically with our gut microbiome. In contrast, under abnormal conditions of gut barrier permeability, we can experience gut–brain–immune system dysregulation or microbiome dysbiosis. The latter can occur during periods of high stress, changes in diet, or other lifestyle changes. These conditions lead to immune imbalance that can manifest as chronic inflammation, autoimmunity, and allergic disease. Specific examples of disease associated with increased gut permeability include type 2 diabetes, inflammatory bowl disease, and mood disorders, just to name a few.

It is important to note that in addition to the impact of the gut microbiome on immune homeostasis, we are becoming increasingly aware of the importance of the early gut microbiome for neonatal immune system development and disease pathogenesis. The increase in allergies and other immune-mediated diseases in industrialized countries has been hypothesized to be a result of deficiencies in early life exposure to microbial organisms and their products, resulting in impaired immune system development. This concept was first introduced as the hygiene hypothesis. The first six months after birth are considered the window of opportunity during which contact with specific microbe-associated molecular patterns triggers a cascade of reactions crucial for infant gut maturation, including the developing mucosal immune system.

GENERATION OF DIVERSITY IN THE IMMUNE RESPONSE

The most recent tidal surge in immunological research represents a triumph of the marriage of molecular biology and immunology. While cellular immunology had delineated the cellular basis for the existence of a large and diverse repertoire of responses, as well as the nature of the exquisite specificity that could be achieved, arguments abounded on the exact genetic mechanisms that enabled all these specificities

to become part of the repertoire in every individual of the species.

Briefly, the arguments were as follows.

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

The pioneering studies of Susumu Tonegawa (1987 Nobel laureate) and Philip Leder, using molecular biological techniques, finally addressed these issues by describing a unique genetic mechanism by which B-cell immunological receptors (BCRs) of enormous diversity could be produced with a modest amount of DNA reserved for this purpose.

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 is discussed in detail in Chapter 7.

Although this mechanism was first elucidated to explain the enormous diversity of antibodies that are not only released by B cells but that, in fact, constitute the antigen- or epitope-specific receptors on B cells (BCRs), it was subsequently established that the same mechanisms operate in generating diversity of the antigen-specific TCR. Mechanisms operating in generating diversity of BCRs and antibodies are discussed in Chapter 9. Those operating in generating diversity of TCRs are discussed in Chapter 10. Suffice it to say at this point that various techniques of molecular biology, that permit genes not only to be analyzed but also to be moved around at will from one cell to another, have continued to provide impetus to the onrushing tide of progress in the field of immunology.

BENEFITS OF IMMUNOLOGY

While we have thus far discussed the theoretical aspects of immunology, its practical applications are of paramount importance for survival and must be part of the education of students.

The field of immunology has been in the public limelight since the successful use of polio vaccines in the mid-twentieth century. Today, vaccines almost completely eliminate a host of childhood diseases in the United States and other industrialized nations, including those that prevent measles, mumps, chickenpox, pertussis (whooping cough), polio, and tetanus. Advances in the field of immunology with expanded knowledge regarding mechanisms of organ and tissue rejection and tolerance have ushered in successful life-saving efforts in transplantation of major organs such as heart, liver, pancreas, and kidney, just to name a few. More recently, public interest in immunology has intensified with the use of monoclonal antibodies used in a variety of clinical applications including diagnostic, surgical mapping, and direct (e.g., tumor specific) or indirect (immune system targeted) therapy. It is noteworthy that the Nobel Prize was awarded in 1984 to Köhler and Milstein for their technological advances in the development of monoclonal antibodies and them in 2018, James Allison was awarded the Nobel Prize for launching an effective new way to attack cancer by treating the immune system rather than the tumor.

The innate and adaptive 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. Metchnikoff was the first to propose in the 1800s 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 are encountered in the daily lives of most individuals. 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 19 presents information concerning how our immune systems respond to microorganisms and how methods developed to exploit these mechanisms are used as immunoprophylaxis.

Vaccination against infectious diseases has been an effective form of prophylaxis. Immunoprophylaxis against the virus that causes poliomyelitis has significantly reduced the incidence of this dreadful disease. Indeed, the previously widespread disease smallpox has been eliminated from the face of the Earth. The last documented case of natural transmission of smallpox virus was in 1972. Unfortunately, the threat of biological weapons has prompted new concerns regarding the reemergence of certain infectious diseases, including smallpox. Fortunately, public health vaccination initiatives can be applied to prevent or significantly curtail the threat of weaponized microbiological agents.

DAMAGING EFFECTS OF THE IMMUNE RESPONSE

The enormous survival value of the immune response is self-evident. Adaptive 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 a result of the accumulation of components with nonspecific

effects. This damage is generally temporary. As soon as the invader is eliminated, the situation at that site reverts to normal.

There are instances in which the power of the immune response, although directed against foreign substances—some innocuous such as some medications, inhaled pollen particles, or substances deposited by insect bites—produces a response that may result in severe pathological 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 and, in addition, has contributed much to our knowledge of the normal immune response. The latter is true because both utilize essentially identical mechanisms; however, in hypersensitivity, these mechanisms are misdirected or out of control (see Chapters 13–15).

Given the complexity of the immune response and its potential for inducing damage, it is self-evident that it must operate under carefully regulated conditions, as does any other physiological system. These controls are multiple and include feedback inhibition by soluble products as well as 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 perturbed by a foreign invader, 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, its memory of that particular invader is retained so that a more rapid and heightened response will occur should the invader return.

Disturbances in these regulatory mechanisms may be caused by conditions such as congenital defects, hormonal imbalance, or infection, any of which can have disastrous consequences. AIDS may serve as a timely example: it is associated with an infection of T lymphocytes that participate in regulating the immune response. As a result of infection with the human immunodeficiency virus (HIV), which causes AIDS, there is a decrease in occurrence and function of one vital subpopulation of T cells, which leads to immunological deficiency and renders the patient powerless to resist infections by microorganisms that are normally benign. An important form of regulation concerns the prevention of immune responses against self-antigens. As discussed in Chapter 12, this regulation may be defective, thus causing an immune response against self to be mounted. This type of immune response is termed ***autoimmunity*** and is the cause of diseases such as some forms of arthritis, thyroiditis, and diabetes, which are very difficult to treat.

THE FUTURE OF IMMUNOLOGY

For the student, a peek into the world of the future of immunology suggests many exciting areas in which the application of molecular and computational techniques promises significant dividends. To cite just a few examples, let us focus on vaccine development and control of the immune response. In the former, 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 candidate immunogenic peptides that can be tested as vaccines. 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 portions thereof (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 the characterization and synthesis of cytokines that enhance and control the activation of various cells associated with the immune response as well as with other functions of the body. Techniques of gene isolation, clonal reproduction, the polymerase chain reaction, and biosynthesis have contributed to rapid progress. Powerful and important modulators have been synthesized by the methods of 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, and probably one of the most exciting areas, is the technology to genetically engineer 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 the final chapter (Chapter 20). They allow the immunologist to study the effects of such traits on the immune system and on the body as a whole with the aim of understanding the intricate regulation, expression, and function of the immune response, and with the ultimate aim of controlling the trait to the benefit of the individual. Thus our burgeoning 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 orient the reader about the complex yet fascinating subject of immunology. In the following chapters we provide a more detailed account of the workings of the immune system, beginning with its cellular components, followed by a description of the structure of the reactants and the general methodology for measuring their reactions. 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. A discussion of the control mechanisms that regulate the scope and intensity of immune responses completes the description of the basic nature of immunity. Included in this section of the book is a chapter on cytokines (Chapter 11), the soluble mediators that regulate immune responses and play a significant role in hematopoiesis. Next are chapters that deal with the great variety of diseases involving immunological components. These vary from ineffective or absent immune responses (immunodeficiency) to those produced by aberrant immune responses (hypersensitivity) to responses to self-antigens (autoimmunity). This is followed by chapters that describe the role of the immune response in transplantation and discuss antitumor reactions. Chapter 19 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 is a discussion of immunoprophylaxis using vaccines that protect us from 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 microorganisms and viruses (most notably HIV and the novel coronavirus responsible for the recent COVID-19 pandemic), as well as those that have been engineered as potential biological weapons, or have yet to be identified.

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 the reader's interest has been aroused, 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 flesh out the details on the scaffolding provided by this book.

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