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Chapter 1

A Brief Outline of the Immune System

Namrata Tomar and Rajat K. De

Abstract

The various cells and proteins responsible for immunity constitute the immune system, and their orchestrated response to defend foreign/non-self substances (antigen) is known as the immune response. When an antigen attacks the host system, two distinct, yet interrelated, branches of the immune system are active—the nonspecific/innate and specific/adaptive immune response. Both of these systems have certain physiological mechanisms, which enable the host to recognize foreign materials to itself and to neutralize, eliminate, or metabolize them. Innate immunity represents the earliest development of protection against antigens. Adaptive immunity has again two branches—humoral and cell mediated. It should be noted that both innate and adaptive immunities do not work independently. Moreover, most of the immune responses involve the activity and interplay of both the humoral and the cell-mediated immune branches of the immune system. We have described these branches in detail along with the mechanism of antigen recognition. This chapter also describes the disorders of immune system in brief.

Key words Immune response, Immune system, Adaptive immunity, Innate immunity, Antibody, T cells, B cells, Allergy, Antigen, Humoral immune system, Cell-mediated immune system

1 Introduction

The defense system consists of a wide variety of cells and molecules that have evolved to protect animals from invading pathogenic microorganisms and cancer. Recognition and response are two major activities of immune system. Immune recognition is quite specific. Moreover, it is able to discriminate between foreign molecules and the body's own cells and proteins. After the recognition of a foreign organism, it mounts an effector response through recruiting a variety of cells and molecules to eliminate the invader organism. Later exposure to the same foreign organism induces a memory response, characterized by a more rapid and heightened immune reaction that serves to eliminate the pathogen and prevent disease.

Historical perspective: The discipline of immunology developed through the observation when individuals who had recovered from certain infectious diseases were thereafter found to be protected

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from the disease. The term "immunity" originated from the Latin term "immunis," meaning "exempt," that is, the state of protection from infectious disease. The earliest literary reference to immunology goes back to 430 bc in writings of Thucydides, where he wrote that only those who had recovered from the plague could nurse the sick because they would not contract the disease a second time [1]. In 1798, Edward Jenner found that some milkmaids were immune to smallpox as they had earlier contracted cowpox (a mild disease). The next major advancement in immunology came with the induction of immunity to cholera by Louis Pasteur. He demonstrated the possibility of administrating a weaken pathogen as a vaccine through a classic experiment. In 1881, he first vaccinated one group of sheep with heat-attenuated *Bacillus anthracis* and then challenged the vaccinated sheep and some unvaccinated sheep with a virulent culture of the bacillus. All the vaccinated sheep lived, and all the unvaccinated animals died. In 1885, after applying weakened pathogen to animals, he administered a dose of vaccine to a boy bitten by a rabid dog and later found that the boy survived. However, Pasteur could not explain its mechanism. In 1890, experiments of Emil Von Behring and Shibasaburo Kitasato led to the understanding of the mechanism of immunity. Their experiments described how antibodies present in the serum provided protection against pathogens. These experiments are described as milestone as the beginnings of the discipline of immunology.

2 Types of Immune System: A Layered Defense System

This line of defense against foreign invader microbes has been divided into two general types of immune responses: innate immunity and adaptive immunity. These two differ in time taken and duration of response, effector cell types, and its specificity for different classes of foreign microbes. Innate immune system represents a nonspecific response to a potentially harmful foreign particle; and the adaptive immune system displays a high degree of memory and specificity. Types of immune system have been shown through line diagram in Fig. 1. Table 1 provides the differences between the innate and adaptive immunity. Below is the brief description of innate immunity.

2.1 Innate Immunity (Nonspecific)

The innate immunity is an evolutionarily older defense system that is a dominant one in plants, fungi, insects, and primitive multicellular organisms [2, 3]. The innate system represents the first line of defense to an intruding pathogen. Innate immune systems are found in all plants and animals. The response evolved is therefore rapid and is unable to memorize. It comprises four types of defensive barriers, namely anatomic (e.g., skin and mucous membranes), physiological (e.g., temperature, low pH), phagocytic (e.g., blood

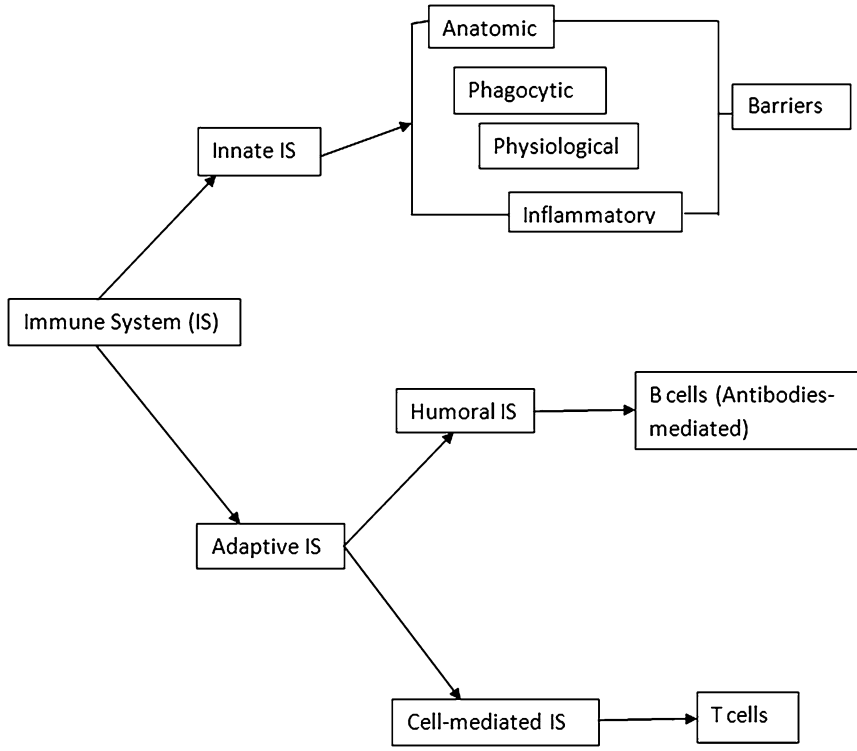

Fig. 1 Types of immune system (IS)

Table 1
Difference between innate and adaptive immune systems

Innate immune system	Adaptive immune system
Nonspecific response	Specific response
Immediate response	Lag time between antigen exposure and response
Retains no immunological memory	Retains immunological memory
Found in nearly all forms of life	Found in only jawed vertebrates

monocytes, neutrophils, tissue macrophages), and inflammatory (e.g., serum proteins).

Cells of the innate immune system: Phagocytes, neutrophils, macrophages, natural killer cells, mast cells, basophils, dendritic cells, eosinophils.

2.2 Adaptive Immunity (Acquired/ Specific Immunity)

The adaptive immune system is activated by innate immunity. The components of the adaptive immune system possess slower temporal dynamics with high degree of specificity and a more potent secondary response. The adaptive immune system frequently incorporates

cells and molecules of the innate system in its fight against harmful foreign bodies. For example, complement system (molecules of the innate system) may be activated by antibodies (molecules of the adaptive system). The cells of the acquired immune system are T and B lymphocytes that we will describe later. It is of two types: (1) humoral (antibody-mediated system) and (2) cell mediated. Below is the brief description of the types of adaptive immune system.

2.2.1 Humoral Immune System (Antibody-Mediated Immune System)

It involves substances found in the humors, or body fluids; therefore, the name is humoral immune system. This kind of immunity is mediated by macromolecules found in extracellular fluids such as secreted antibodies, complement proteins, and certain antimicrobial peptides.

Complement system: The complement system is involved in the responses of both innate immunity and acquired immunity. It is named so as it helps or "complements" the ability of antibodies and phagocytic cells to clear pathogens from an organism. It is a biochemical cascade of the innate immune system that helps clear pathogens from an organism. Activation of this system leads to cytolysis, chemotaxis, opsonization, immune clearance, and inflammation. Three biochemical pathways activate the complement system: the classical complement pathway, the alternate complement pathway, and the mannose-binding lectin pathway [3].

B cells: B cells belong to a group of white blood cells known as lymphocytes. The abbreviation "B," in B cell, comes from the bursa of Fabricius in birds, where they mature. In mammals, immature B cells are formed in the bone marrow, which is used as a backronym for the cells' name [5]. There is a random gene rearrangement during B cell maturation in the bone marrow that generates more than 10^{10} number of B cells with different antigenic specificities. Later, there is a selection process to eliminate any B cells with membrane-bound antibody that recognizes self-components. This ensures that self-reactive antibodies (autoantibodies) are not produced.

Somatic hypermutation: When a B cell recognizes an antigen, it starts proliferating. During proliferation, the B cell receptor (BCR) locus undergoes somatic mutation in the hypervariable regions, of 10^5- to 10^6-fold greater than the normal rate of mutation across the genome [6, 7]. Hypermutation enhances the ability of immunoglobulin receptors present on B cells to recognize and bind a specific antigen [3].

Antibodies: The production of antibodies is the main function of the humoral immune system [4]. Antibodies are secreted by plasma cell, a type of white blood cell. These are the large Y-shaped protein molecules secreted by B cells, also known as immunoglobulins (Ig). The antibody recognizes a unique part of the foreign target, called an antigen [2, 3]. Antibody has a "Y"-structured tip for a specific epitope, known as paratope. The structural diagram of antibody has been shown in Fig. 2. Isoforms of Igs have been described in Table 2.

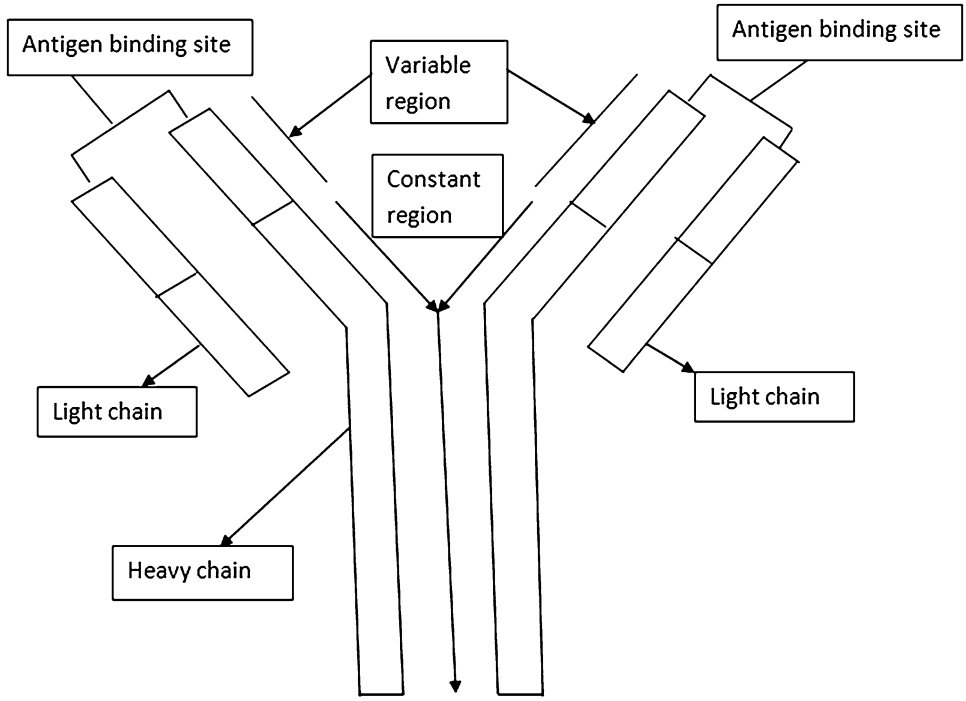

Fig. 2 Antibody structure

Table 2
Antibody isotypes

Type names	Description
IgA	Found in mucosal areas of gut, respiratory tract, and urogenital tract, including saliva, tears, and breast milk
IgD	Functions mainly as an antigen receptor on B cells that have not been exposed to antigens
IgE	Involves in allergy, binds to allergens, and triggers histamine release from mast cells and basophils
IgG	Only antibody that can cross the placenta to give passive immunity to the fetus
IgM	Secreted pentamer form, expressed on the surface of B cells (monomer). Eliminates pathogens in the early stages of B cell-mediated (humoral) immunity before there is sufficient IgG

Class switch recombination (CSR) (immunoglobulin class switching/isotype switching/isotypic commutation): B cell's production of antibody from one class to another can be changed through a biological mechanism called as CSR binding, for example, from an isotype called IgM to an isotype called IgG. During this process,

the constant region portion of the antibody heavy chain is changed, but the variable region of the heavy chain stays the same; hence it does not affect the antigen specificity.

2.2.2 Cell-Mediated Immune System

It does not involve antibodies, rather activates phagocytes and antigen-specific cytotoxic T lymphocytes and releases various cytokines in response to an antigen attack.

T lymphocytes: Although T lymphocytes arise in the bone marrow, it migrates to the thymus gland to mature unlike B cells [1]. Within the thymus, it expresses a unique antigen-binding molecule on its membrane, called as T cell receptor (TCR). TCRs can recognize only antigen that is bound to cell-membrane proteins called major histocompatibility complex (MHC) molecules, unlike B cells. There are two well-defined subpopulations of T cells: T helper (Th) and T cytotoxic (Tc) cells. It becomes an effector cell (activated) that secretes various growth factors known collectively as cytokines, after a Th cell recognizes and interacts with an antigen–MHC class II molecule complex. The secreted cytokines play an important role in activating B cells, Tc cells, macrophages, and various other cells that participate in the immune response.

TCR–MHC molecule interaction to present antigen to T cell has been shown in Fig. 3.

Under the influence of TH-derived cytokines, a Tc cell recognizes an antigen and MHC class I and further proliferates and differentiates into an effector cell called as a cytotoxic T lymphocyte (CTL). It has cytotoxic activity and usually does not secrete cytokines. The CTL has a vital function in eliminating antigen-displaying cell, such as virus-infected cells, tumor cells, and cells of a foreign tissue graft.

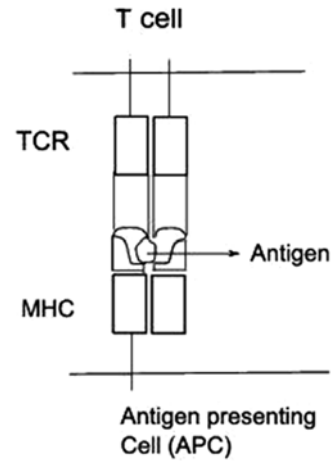

Fig. 3 TCR–MHC interaction for antigen presentation

T cell maturation also includes random rearrangements of a series of gene segments that encode the cell's antigen-binding receptor, like B cell maturation. The random rearrangement of the TCR genes is capable of generating on the order of 10^9 unique antigenic specificities. Each T lymphocyte cell expresses about 10^5 receptors, and all of the receptors on the cell and its clonal progeny have identical specificity for antigen. However, it is later diminished through a selection process to ensure that only T cells with receptors capable of recognizing antigen associated with MHC molecules will be able to mature [1].

The MHC: The MHC is a large genetic complex with multiple loci and encodes for three major classes of membrane-bound glycoproteins: class I, class II, and class III MHC molecules. These molecules do not have fine specificity for antigen characteristic; instead of this, it binds to a spectrum of antigenic peptides derived from the intracellular degradation of antigen molecules. In both class I and class II MHC molecules posses variable regions;, a cleft within which the antigenic peptide binds and is presented to T lymphocytes. As mentioned above, Th cells generally recognize antigen combined with class II molecules, whereas Tc cells generally recognize antigen combined with class I molecules.

Below are the major differences among these three classes: (1) Class I MHC genes encode glycoproteins expressed on the surface of nearly all nucleated cells; the major function of the class I gene products is presentation of peptide antigens to Tc cells. (2) Class II MHC genes encode glycoproteins expressed primarily on antigen-presenting cells (macrophages, dendritic cells, and B cells), where they present processed antigenic peptides to Th cells. (3) Class III MHC genes encode various secreted immune system-related proteins, including components of the complement system and molecules involved in inflammation.

Another important aspect is their structural features, where class I and class II MHC molecules have common structural features and both have roles in antigen processing. However, the class III MHC region encodes molecules that have little in common with class I or II molecules.

3 Disorders of Human Immunity

Although, the immune system is a remarkably specific and adaptive, however, it may lead to develop autoimmunity, hypersensitivities and immunodeficiencies, upon deregulation.

3.1 Autoimmunity

Autoimmunity arises when immune system fails to distinguish between self and non-self. Here, immune system attacks on self-antigens, instead of reacting against foreign antigens. The result is an inappropriate response of the immune system against

self-components termed autoimmunity. Normal healthy individuals have been shown to possess self-reactive lymphocytes in periphery, where its presence does not inevitably result in autoimmune reactions [1]. However, their activity is regulated through clonal anergy or clonal suppression. Its deregulation can lead to the activation of humoral or cell-mediated responses against self-antigens. These reactions can damage cells and organs, sometimes with fatal consequences. Lymphocytes or antibodies bind to cell-membrane antigens and lead to cellular lysis and/or an inflammatory response in the affected organ. The damaged cellular structure is gradually replaced by connective tissue (scar tissue), and thereby the function of the organ declines.

Many autoimmune diseases are characterized by tissue destruction mediated directly by T cells. For example in rheumatoid arthritis, self-reactive T cells attack the tissue in joints, causing an inflammatory response that results in swelling and tissue destruction. In Hashimoto's thyroiditis, autoantibodies reactive with tissue-specific antigens such as thyroid peroxidase and thyroglobulin cause severe tissue destruction. Other examples include insulin-dependent diabetes mellitus and multiple sclerosis. The immune response is directed to a target antigen unique to a single organ or gland in an organ-specific autoimmune disease. This way, the effects are largely limited to that organ. In case of damage by humoral or cell-mediated effector mechanisms, the antibodies may overstimulate or block the normal function of the target organ.

3.2 Hypersensitivity

The ability of the immune system to respond inappropriately to antigenic challenge is known as hypersensitivity or allergy. It refers to undesirable reactions produced by the normal immune system, including allergies and autoimmunity. The four-group classification was given by Gell and Coombs in 1963 [8]. Table 3 gives brief description of this classification, along with an additional type.

Table 3
Allergy classification

Type	Names	Mediators
I	Allergy, IgE mediated	IgE and IgG4
II	Cytotoxic, antibody dependent	IgM and IgG
III	Immune complex disease	IgG
IV	Delayed-type hypersensitive (DTH)	T cells
V	Autoimmune disease, receptor mediated	IgM or IgG

3.3 Immunodeficiencies

Immunodeficiency is a state in which the immune system compromises or is unable to fight infectious disease. In this case, the system fails to protect the host from diseases or from malignant cells. A condition that occurs from a genetic or a developmental defect in the immune system is called a primary immunodeficiency. Secondary immunodeficiency, or acquired immunodeficiency, is the loss of immune function and results from exposure to various agents. Till date, the most common secondary immunodeficiency is acquired immunodeficiency syndrome, or AIDS, which results from infection with the human immunodeficiency virus 1 (HIV-1) [1].

Primary immunodeficiency: A primary immunodeficiency may affect either adaptive or innate immune functions. Most of the primary immunodeficiencies are inherited, and the genetic defects are determined. The consequences of primary immunodeficiency depend on the number and type of immune system components involved. Defects in components early in the hematopoietic developmental scheme affect the entire immune system. Deficiencies involving components of adaptive immunity, effector T or B cells, while phagocytes or complement, are impaired in innate immunity.

Secondary immunodeficiency: Agent-induced immunodeficiency results from the exposure to any of a number of chemical and biological agents that induce an immunodeficient state. These agents can be immunosuppressive medicines. The drugs that are used to combat autoimmune diseases such as rheumatoid arthritis or lupus erythematosis induce the abovementioned kind of immunodeficiency. Cytotoxic drugs or radiation treatments given to cancer patients damage the immune cells and thereby induce a state of immunodeficiency.

4 Conclusion

We have described immune system and its branches briefly in this chapter. We have described the difference between the two said branches of the immune system in a tabular way. We have also highlighted the immune system disorders.

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