JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

THE IMMUNOLOGY AND IMMUNOTHERAPY: AN UPDATE

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Abstract

Beyond structural and chemical barriers to pathogens, the immune system has two fundamental lines of defense: innate immunity and adaptive immunity. Innate immunity is the first immunological mechanism for fighting against an intruding pathogen. It is a rapid immune response, initiated within minutes or hours after aggression, that has no immunologic memory. Adaptive immunity, on the other hand, is antigen-dependent and antigen-specific; it has the capacity for memory, which enables the host to mount a more rapid and efficient immune response upon subsequent exposure to the antigen. There is a great deal of synergy between the adaptive immune system and its innate counterpart, and defects in either system can provoke illness or disease, such as inappropriate inflammation, autoimmune diseases, immunodeficiency disorders and hypersensitivity reactions. This article provides a practical overview of innate and adaptive immunity, and describes how these host defense mechanisms are involved in both heath and illness.

Keywords:

Immune system, Innate and adaptive Immunity, Phagocytosis, Dendritis, T cells, APCs, B cells

Introduction

he immune system refers to a collection of cells, chemicals and processes that function to protect the skin, respiratory passages, intestinal tract and other areas from foreign antigens, such as microbes (organisms such as bacteria, fungi, and parasites), viruses, cancer cells, and toxins. Beyond, the structural and chemical barriers which protect us from infection, the immune system can be simplistically viewed as having two “lines of defense”: innate immunity and adaptive immunity. Innate immunity represents the first line of defense to an intruding pathogen (1,2). It is an antigen-independent (non-specific) defense mechanism that is used by the host immediately or within hours of encountering an antigen. The innate immune response has no immunologic memory and, therefore, it is unable to recognize or “memorize” the same pathogen should the body be exposed to it in the future. Adaptive immunity, on the other hand, is antigen-dependent and antigen-specific and, therefore, involves a lag time between exposure to the antigen and maximal response. The

hallmark of adaptive immunity is the capacity for memory which enables the host to mount a more rapid and efficient immune response upon subsequent exposure to the antigen. Innate and adaptive immunity are not mutually exclusive mechanisms of host defense, but rather are complementary, with defects in either system resulting in host vulnerability or inappropriate responses (3).

Innate immunity

Humans are exposed to millions of potential pathogens daily, through contact, ingestion, and inhalation. Our ability to avoid infection depends in part on the adaptive immune system (discussed in Chapter 24), which remembers previous encounters with specific pathogens and destroys them when they attack again. Adaptive immune responses, however, are slow to develop on first exposure to a new pathogen, as specific clones of B and T cells have to become activated and expand; it can therefore take a week or so before the responses are effective. By contrast, a single bacterium with a doubling time of one hour can produce almost 20 million progeny, a full-blown infection, in a single day. Therefore, during the first critical hours and days of exposure to a new pathogen, we rely on our **innate immune system** to protect us from infection.

Innate immune responses are not specific to a particular pathogen in the way that the adaptive immune responses are. They depend on a group of proteins and phagocytic cells that recognize conserved features of pathogens and become quickly activated to help destroy invaders. Whereas the adaptive immune system arose in evolution less than 500 million years ago and is confined to vertebrates, innate immune responses have been found among both vertebrates and invertebrates, as well as in plants, and the basic mechanisms that regulate them are conserved. As discussed in Chapter 24, the innate immune responses in vertebrates are also required to activate adaptive immune responses (1).

Cell	Image	% in adults	Nucleus	Functions	Lifetime	Main targets
Macrophage*		Varies	Varies	• Phagocytosis • Antigen presentation to T cells	Months – years	• Various
Neutrophil		40-75%	Multi-lobed	• Phagocytosis • Degranulation (discharge of contents of a cell)	6 hours – few days	• Bacteria • Fungi
Eosinophil		1-6%	Bi-lobed	• Degranulation • Release of enzymes, growth factors, cytokines	8-12 days (circulate for 4-5 hours)	• Parasites • Various allergic tissues
Basophil		< 1%	Bi- or tri-lobed	• Degranulation • Release of histamine, enzymes, cytokines	Lifetime uncertain; likely a few hours – few days	• Various allergic tissues
Mast cell		Common in tissues	Central, single-lobed	• Degranulation • Release of histamine, enzymes, cytokines	Months to years	• Parasites • Various allergic tissues
Lymphocytes (T cells)		20-40%	Deeply staining, eccentric	T helper (Th) cells (CD4+): immune response mediators Cytotoxic T cells (CD8+): cell destruction	Weeks to years	• Th cells: intracellular bacteria • Cytotoxic T cells: virus infected and tumour cells • Natural killer cells: virus-infected and tumour cells
Monocyte		2-6%	Kidney shaped	Differentiate into macrophages and dendritic cells to elicit an immune response	Hours – days	• Various
Natural killer (NK) cell		15% (varies) of circulating lymphocytes and tissues	Single-lobed	• Tumour rejection • Destruction of infected cells • Release of perforin and granzymes which induce apoptosis	7-10 days	• Viruses • Tumour cells

Fig 1: **Characteristics and function of cells involved in innate immunity**

Dendritic cells also phagocytose and function as APCs, initiating the acquired immune response and acting as important messengers between innate and adaptive immunity. Mast cells and basophils share many salient features with each other, and both are instrumental in the initiation of acute inflammatory responses, such as those seen in allergy and asthma. Mast cells also have important functions as immune "sentinel cells" and are early producers of cytokines in response to infection or injury. Unlike mast cells, which generally reside in the connective tissue surrounding blood vessels and are particularly common at mucosal surfaces, basophils reside in the circulation. Eosinophils are granulocytes that possess phagocytic properties and play an important role in the destruction of parasites that are often too large to be phagocytosed. Along with mast cells and basophils, they also control mechanisms associated with allergy and asthma. Natural killer (NK) cells play a major role in the rejection of tumours and the destruction of cells infected by viruses. Destruction of infected cells is achieved through the release of perforins and granzymes (proteins that cause lysis of target cells) from NK-cell granules which induce apoptosis (programmed cell death) [4].

Adaptive immunity

The development of adaptive immunity is aided by the actions of the innate immune system, and is critical when innate immunity is ineffective in eliminating infectious agents. The primary functions of the adaptive immune response are: the recognition of specific "non-self" antigens, distinguishing them from "self" antigens; the generation of pathogen-specific immunologic effector pathways that eliminate specific pathogens or pathogen-infected cells; and the development of an immunologic memory that can quickly eliminate a specific pathogen should subsequent infections occur [2]. Adaptive immune responses are the basis for effective immunization against infectious diseases. The cells of the adaptive immune system include: antigen-specific T cells, which are activated to proliferate through the action of APCs, and B cells which differentiate into plasma cells to produce antibodies.

T cells and APCs

T cells derive from hematopoietic stem cells in bone marrow and, following migration, mature in the thymus. These cells express a series of unique antigen-binding receptors on their membrane, known as the T-cell receptor (TCR). Each T cell expresses a single type of TCR and has the capacity to rapidly proliferate and differentiate if it receives the appropriate signals. As previously mentioned, T cells require the action of APCs (usually dendritic cells, but also macrophages, B cells, fibroblasts and epithelial cells) to recognize a specific antigen.

The surfaces of APCs express a group of proteins known as the major histocompatibility complex (MHC). MHC are classified as either class I (also termed human leukocyte antigen [HLA] A, B and C) which are found on all nucleated cells, or class II (also termed HLA DP, DQ and DR) which are found only on certain cells of the immune system, including macrophages, dendritic cells and B cells. Class I MHC molecules present endogenous (intracellular) peptides, while class II molecules on APCs present exogenous (extracellular) peptides to T cells. The MHC protein displays fragments of antigens (peptides) when a cell is infected with an intracellular pathogen, such as a virus, or has phagocytosed foreign proteins or organisms [2, 3].

T cells have a wide range of unique TCRs which can bind to specific foreign peptides. During the development of the immune system, T cells that would react to antigens normally found in our body are largely eliminated. T cells are activated when they encounter an APC that has digested an antigen and is displaying the correct antigen fragments (peptides) bound to its MHC molecules. The opportunities for the right T cells to be in contact with an APC carrying the appropriate peptide MHC complex are increased by the circulation of T cells throughout the body (via the lymphatic system and blood stream) and their accumulation (together with APCs) in lymph nodes. The MHC-antigen complex activates the TCR and the T cell secretes cytokines which further control the immune response. This antigen presentation process stimulates T cells to differentiate primarily

into either cytotoxic T cells (CD8+ cells) or T-helper (Th) cells (CD4+ cells) (see Fig. 2). CD8+ cytotoxic T cells are primarily involved in the destruction of cells infected by foreign agents, such as viruses, and the killing of tumor cells expressing appropriate antigens. They are activated by the interaction of their TCR with peptide bound to MHC class I molecules. Clonal expansion of cytotoxic T cells produces effector cells which release substances that induce apoptosis of target cells. Upon resolution of the infection, most effector cells die and are cleared by phagocytes. However, a few of these cells are retained as memory cells that can quickly differentiate into effector cells upon subsequent encounters with the same antigen [2, 3].

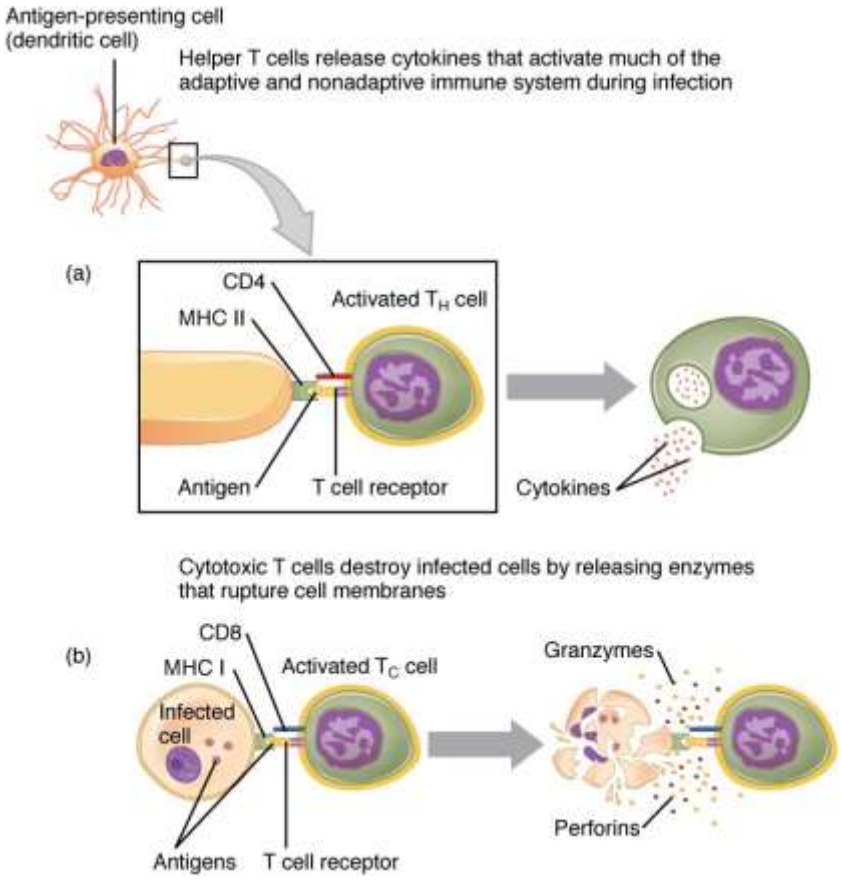

Fig 2. **Adaptive immunity**

B-Lymphocyte Lineage Subsets

Three principal classes of B lymphocytes exist in mice and humans, classified on the basis of their ontogeny and anatomic localization: B1 and B2 B lymphocytes, consisting of the marginal zone (MZ) and follicular (FO) B cells (3). B1 lymphocytes arise from B1 progenitors in fetal liver and persist as a self-renewing population beyond the neonatal period, with little input from the bone marrow (BM) in adulthood, while B2 lymphocytes develop from transitional 2 (T2) B cells that originate from BM precursors with continued output throughout life (5-7). In mice, B1 B cells predominantly reside in the peritoneal and pleural cavities and produce IgM antibodies directed against so-called thymus- or T-independent antigens, usually carbohydrate or phospholipid antigens present on commensal bacteria. They are called T independent because they do not require T-cell help to elicit antibody production. Such antibodies are polyreactive or polyspecific in that they can bind to both self-antigens and microbial antigens.

When activated by foreign antigens to which they have an appropriate antigen specific receptor, B cells undergo proliferation and differentiate into antibody-secreting plasma cells or memory B cells (see Fig. 2). Memory B cells are “long-lived” survivors of past infection and continue to express antigen-binding receptors.

These cells can be called upon to respond quickly by producing antibodies and eliminating an antigen upon re-exposure. Plasma cells, on the other hand, are relatively short-lived cells that often undergo apoptosis when the inciting agent that induced the immune response is eliminated. However, these cells produce large amounts of antibody that enter the circulation and tissues providing effective protection against pathogens.

Antibody Mediated Vs. Cell Mediated Immunity

Five major types of antibodies are produced by B cells: IgA, IgD, IgE, IgG and IgM. IgG antibodies can be further subdivided into structurally distinct subclasses with differing abilities to fix complement, act as opsonins, etc. The major classes of antibodies have substantially different biological functions and recognize and neutralize specific pathogens (8).

Antibodies play an important role in containing virus proliferation during the acute phase of infection. However, they are not generally capable of eliminating a virus once infection has occurred. Once an infection is established, cell-mediated immune mechanisms are most important in host defense against most intracellular pathogens.

Cell-mediated immunity does not involve antibodies, but rather protects an organism through [2]:

- The activation of antigen-specific cytotoxic T cells that induce apoptosis of cells displaying foreign antigens or derived peptides on their surface, such as virus-infected cells, cells with intracellular bacteria, and cancer cells displaying tumour antigens;
- The activation of macrophages and NK cells, enabling them to destroy intracellular pathogens; and
- The stimulation of cytokine (such as IFNγ) production that further mediates the effective immune response.

Cell-mediated immunity is directed primarily at microbes that survive in phagocytes as well as those that infect non-phagocytic cells. This type of immunity is most effective in eliminating virus-infected cells and cancer cells, but can also participate in defending against fungi, protozoa, cancers, and intracellular bacteria. Cell-mediated immunity also plays a major role in transplant rejection.

Immunopathology

As mentioned earlier, defects or malfunctions in either the innate or adaptive immune response can provoke illness or disease. Such disorders are generally caused by an overactive immune response (known as hypersensitivity reactions), an inappropriate reaction to self (known as autoimmunity) or ineffective immune responses (known as immunodeficiency).

Hypersensitivity reactions

Hypersensitivity reactions refer to undesirable responses produced by the normal immune system. There are four types of hypersensitivity reactions [9,10]:

- Type I: immediate hypersensitivity.
- Type II: cytotoxic or antibody-dependent hypersensitivity.
- Type III: immune complex disease.
- Type IV: delayed-type hypersensitivity.

Type I hypersensitivity is the most common type of hypersensitivity reaction. It is an allergic reaction provoked by re-exposure to a specific type of antigen, referred to as an allergen. Unlike the normal immune response, the type I hypersensitivity response is characterized by the secretion of IgE by plasma cells. IgE antibodies bind to receptors on the surface of tissue mast cells and blood basophils, causing them to be

"sensitized". Later exposure to the same allergen cross-links the bound IgE on sensitized cells resulting in degranulation and the secretion of active mediators such as histamine, leukotrienes, and prostaglandins that cause vasodilation and smooth-muscle contraction of the surrounding tissue. Common environmental allergens inducing IgE-mediated allergies include pet (e.g., cat, dog, horse) epithelium, pollen, house dust mites, and molds. Food allergens are also a common cause of type I hypersensitivity reactions, however, these types of reactions are more frequently seen in children than adults. Treatment of type I reactions generally involves trigger avoidance, and in the case of inhaled allergens, pharmacological intervention with bronchodilators, antihistamines and anti-inflammatory agents. Some types of allergic disease can be treated with immunotherapy (see *Allergen-specific Immunotherapy* article in this supplement). Severe cases of type 1 hypersensitivity (anaphylaxis) may require immediate treatment with epinephrine.

Type II hypersensitivity reactions are rare and take anywhere from 2 to 24 h to develop. These types of reactions occur when IgG and IgM antibodies bind to the patient's own cell-surface molecules, forming complexes that activate the complement system. This, in turn, leads to opsonization, red blood cell agglutination (process of agglutinating or "clumping together"), cell lysis and death. Some examples of type II hypersensitivity reactions include: erythroblastosis fetalis, Goodpasture syndrome, and autoimmune anemias.

Type III hypersensitivity reactions occur when IgG and IgM antibodies bind to soluble proteins (rather than cell surface molecules as in type II hypersensitivity reactions) forming immune complexes that can deposit in tissues, leading to complement activation, inflammation, neutrophil influx and mast cell degranulation. This type of reaction can take days, or even weeks, to develop and treatment generally involves anti-inflammatory agents and corticosteroids. Examples of type III hypersensitivity reactions include systemic lupus erythematosus (SLE), serum sickness and reactive arthritis.

Unlike the other types of hypersensitivity reactions, type IV reactions are cell-mediated and antibody-independent. They are the second most common type of hypersensitivity reaction and usually take 2 or more days to develop. These types of reactions are caused by the overstimulation of T cells and monocytes/macrophages which leads to the release of cytokines that cause inflammation, cell death and tissue damage. In general, these reactions are easily resolvable through trigger avoidance and the use of topical corticosteroids. An example of this is the skin response to poison ivy.

Immunodeficiency

Immunodeficiency refers to a state in which the immune system's ability to fight infectious disease is compromised or entirely absent. Immunodeficiency disorders may result from a primary genetic defect (primary immunodeficiency—see *Primary Immunodeficiency* article in this supplement) which can effect either innate or acquired immune function through inhibition of selected immune cells or pathways, or it may be acquired from a secondary cause (secondary immunodeficiency), such as viral or bacterial infections, malnutrition, autoimmunity or treatment with drugs that induce immunosuppression. Certain diseases can also directly or indirectly impair the immune system such as leukemia and multiple myeloma. Immunodeficiency is also the hallmark of acquired immunodeficiency syndrome (AIDS), caused by the human immunodeficiency virus (HIV). HIV directly infects Th cells and also impairs other immune system responses indirectly [11,12].

Conclusion

Innate immunity is the first immunological, non-specific mechanism for fighting against infections. This immune response is rapid, occurring minutes or hours after aggression and is mediated by numerous cells including phagocytes, mast cells, basophils and eosinophils, as well as the complement system. Adaptive immunity develops in conjunction with innate immunity to eliminate infectious agents; it relies on the tightly

regulated interplay between T cells, APCs and B cells. A critical feature of adaptive immunity is the development of immunologic memory or the ability of the system to learn or record its experiences with various pathogens, leading to effective and rapid immune responses upon subsequent exposure to the same or similar pathogens.

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