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Review Article

AN OVERVIEW ON IMMUNOMODULATION

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ABSTRACT

The immune system is a complex and highly developed system, yet its mission is simple: to seek and kill invaders. Immunomodulation is the process of modifying an immune response in a positive or negative manner by administration of a drug or compound. Many proteins, amino acids, and natural compounds have shown a significant ability to regulate immune responses, including interferon-γ (IFN-γ), steroids, DMG. This review comprises a summary on immunomodulation introduction, immunodeficiency and drug therapy.

Keywords: Immunity, Immunodeficiency, Immunology, Hypersensitivity

1. INTRODUCTION

Immune system is a remarkably sophisticated defence system within vertebrates, to protect them from invading agents. It is able to generate varieties of cells and molecules capable of recognizing and eliminating limitless varieties of foreign and undesirable agents. Modulation of the immune system denotes to any change in the immune response that can involve induction, expression, amplification or inhibition of any part or phase of the immune response. Thus, immunomodulator is a substance used for its effect on the immune system. There are generally of two types immunomodulators based on their effects: immunosuppressants and immunostimulators. They have the ability to mount an immune response or defend against pathogens or tumors. Immunopharmacology is a comparatively new and developing branch of pharmacology aims at searching for immunomodulators. The potential uses of immunodulators in clinical medicine include the reconstitution of immune deficiency (e.g. the treatment of AIDS) and the suppression of normal or excessive immune function (e.g. the treatment of graft rejection or autoimmune disease). Specific immunomodulators administered together with antigens known as immunological adjuvants to boost the immune response to the vaccine constituents. For instance, a plant origin saponin used in veterinary medicine whereas, the non-specific immunostimulators offer a generalized state of resistance to pathogens or tumors. Fungal product cyclosporin A selectivelyblock the function of T lymphocyte and used to prevent graft rejection [1].

Immunity: It refers to the ability of the body to identify and resist microorganisms that are potentially harmful. This ability enables the body to fight or prevent infectious disease and inhibit tissue and organ damage. The immune system is not confined to any one part of the body. Immune stem cells, formed in the bone marrow, may remain in the bone marrow until maturation or migrate to different body sites for maturation. After maturation, most immune cells circulate into the body and exert specific effects [2].

The immune system has two distinct, but overlapping, mechanisms which help to fight invading organisms:

- Cell-mediated defences (cellular immunity)
- Antibody-mediated defences (humoral immunity)

Cell-mediated immunity (CMI): It is the result of the activity of many leukocyte actions, reactions, interactions that range from simple to complex. This type of immunity is dependent on the actions of the T (Thymus) lymphocytes, which are responsible for a delayed type of immune response. The T lymphocyte becomes sensitized by its first contact with a specific antigen.

Humoral immunity: In humoral immunity special lymphocytes (white blood cells), called B (Bone cell) lymphocytes, produce circulating antibodies to act against a foreign substance. This type of immunity is based on the antigen–antibody response [3].

2. HISTORY OF IMMUNOLOGY

Immunology is a science that examines the structure and function of the immune system. It originates from medicine and early studies on the causes of immunity to disease. The earliest known mention of immunity was during the plague of Athens in 430 BC. Thucydides noted that people who had

recovered from a previous bout of the disease could nurse the sick without contracting the illness a second time [4]. In the 18th century, Pierre-Louis Moreau de Maupertuis made experiments with scorpion venom and observed that certain dogs and mice were immune to this venom [5]. This and other observations of acquired immunity were later exploited by Louis Pasteur in his development of vaccination and his proposed germ theory of disease [6]. Pasteur's theory was in direct opposition to contemporary theories of disease, such as the miasma theory. It was not until Robert Koch's 1891 proofs, for which he was awarded a Nobel Prize in 1905, that microorganisms were confirmed as the cause of infectious disease [7]. Viruses were confirmed as human pathogens in 1901, with the discovery of the yellow fever virus by Walter Reed [8].

3. IMMUNSYSTEM

The immune system is composed of many interdependent cell types that collectively protect the body from bacterial, parasitic, fungal, viral infections and from the growth of tumor cells. Many of these cell types have specialized functions. The cells of the immune system can engulf bacteria, kill parasites or tumor cells, or kill viral-infected cells. Often, these cells depend on the T helper subset for activation signals in the form of secretions formally known as cytokines, lymphokines, or more specifically interleukins.

The Innate Immune System

Innate immunity comprises a series of host defenses including barrier function, cytokines, complement, phagocytes, natural killer (NK) cells, and gamma-delta (gd) T cells to provide the initial (nonspecific) response to a pathogen or injury. These responses are phylogenetically ancient and have been developed to cope with pathogens thatare encountered regularly but that rarely cause disease. Unlike the adaptive (specific) immune system, responses are generic and leave no memory; nonetheless the innateimmune system functions effectively to keep organisms healthy. Indeed a failing ininnate immunity is hypothesized to contribute to secondary infections in critical illnessand death in sepsis [9-13]. Stimulation of the active components of the innate immune system occurs by way of pathogen-associated molecular pattern (PAMP) receptors or damage-associated molecular pattern (DAMP) receptors. PAMPs are recognized by membrane bound or vesicular pathogen recognition receptors (PRRs) including the Toll-like receptors (TLRs), nucleotide binding oligomerization domain (NOD)-like receptors, and RIG-Ilike receptors. Bacteria stimulate these PRRs to activate various intracellular signalling cascades, leading to a proinflammatory response. For example, the gram-negative bacterial endotoxin, lipopolysaccharide, binds to TLR 4, whereas the gram-positive peptidoglycan binds to TLR 2 In the setting of tissue damage from an infection or trauma, DAMPs activate the innate immune system through these PRRs. Indeed there is significant overlap in mechanisms stimulated by PAMPs and DAMPs. As sedatives are frequently administered during infection and surgery, investigation of their immune effects on these mechanisms of immune stimulation would seem prudent.

The Adaptive Immune System

Adaptive or acquired immunity differs from the innate response as it is specific, has an element of memory, and is unique to vertebrates. The humoral component involves the proliferation of antigen-stimulated B lymphocytes into antibody-secreting plasma cells. The cellular component is mediated by T lymphocytes, the predominant cell types being helper T cells (Th) and cytotoxic T cells. Recently, regulatory T cells that likely dampen the immune response have been identified. T cells recognize antigens bound to major histocompatibility complex (MHC) proteins by way of T cell receptors that are antigen specific. Th lymphocytes act through secretion of cytokines to elaborate andprime the immune response. This action includes inducing immunoglobin classswitching of B cells, activation of Tc, and optimization of bactericidal capacity ofphagocytes. Th lymphocytes are characterized by expression of CD4 proteins andare activated when MHC type II molecules, expressed on professional antigen-presentingcells (dendritic cells, macrophages, and B cells), activate the specific T cellreceptor.Th1 cells are regarded as ''proinflammatory,'' secreting cytokines such as interferon-g and interkeukin (IL)-12, and stimulate macrophage function and cytotoxic Tcell function. Th2 cells have an ''anti-inflammatory'' phenotype and secrete cytokine such as IL-4 and IL-10, acting cooperatively to activate B cells. Further, Th cells include the regulatory T cells that act to dampen the immune response and the Th17 class that modulates neutrophil function. A shift from Th1 to Th2 cells has been observed in the latter stages of sepsis, possibly induced by the apoptotic cell death of lymphocytes, and the subsequent anti-inflammatory phenotype has been associated with secondary infections in these patients [9].

The Organs of the Immune System [14-16].

Bone Marrow: All the cells of the immune system are initially derived from the bone marrow. They form through a process called hematopoiesis. During hematopoiesis, bone marrow-derived stem cells differentiate into either mature cells of the immune system or into precursors of cells that migrate out of the bone marrow to continue their maturation elsewhere. The bone marrow produces B cells, natural killer cells, granulocytes and immature thymocytes, in addition to red blood cells and platelets.

Thymus: The function of the thymus is to produce mature T cells. Immature thymocytes, also known as prothymocytes, leave the bone marrow and migrate into the thymus. Through a remarkable maturation process sometimes referred to as

thymic education, T cells that are beneficial to the immune system are spared, while those T cells that might evoke a detrimental autoimmune response are eliminated. The mature T cells are then released into the bloodstream.

Spleen: The spleen is an immunologic filter of the blood. It is made up of B cells, T cells, macrophages, dendritic cells, natural killer cells and red blood cells. In addition to capturing foreign materials (antigens) from the blood that passes through the spleen, migratory macrophages and dendritic cells bring antigens to the spleen via the bloodstream. An immune response is initiated when the macrophage or dendritic cells present the antigen to the appropriate B or T cells. This organ can be thought of as an immunological conference center. In the spleen, B cells become activated and produce large amounts of antibody. Also, old red blood cells are destroyed in the spleen.

Lymphnodes: The lymph nodes function as an immunologic filter for the bodily fluid known as lymph. Lymph nodes are found throughout the body. Composed mostly of T cells, B cells, dendritic cells and macrophages, the nodes drain fluid from most of our tissues. Antigens are filtered out of the lymph in the lymph node before returning the lymph to the circulation. In a similar fashion as the spleen, the macrophages and dendritic cells that capture antigens present these foreign materials to T and B cells, consequently initiating an immune response.

The Cells of the Immune System [17-20]

T-Cells: T lymphocytes are usually divided into two major subsets that are functionally and phenotypically (identifiably) different. The T helper subset, also called the CD4+ T cell, is a pertinent coordinator of immune regulation. The main function of the T helper cell is to augment or potentiate immune responses by the secretion of specialized factors that activate other white blood cells to fight off infection. Another important type of T cell is called the T killer/suppressor subset or CD8+ T cell. These cells are important in directly killing certain tumor cells, viral-infected cells and sometimes parasites. The CD8+ T cells are also important in down-regulation of immune responses. Both types of T cells can be found throughout the body. They often depend on the secondary lymphoid organs (the lymph nodes and spleen) as sites where activation occurs, but they are also found in other tissues of the body, most conspicuously the liver, lung, blood, and intestinal and reproductive tracts.

Natural Killer Cells: Natural killer cells, often referred to as NK cells, are similar to the killer T cell subset (CD8+ T cells). They function as effector cells that directly kill certain tumors such as melanomas, lymphomas and viral-infected cells, most notably herpes and cytomegalovirus-infected cells. NK cells, unlike the CD8+ (killer) T cells, kill their targets without a prior "conference" in the lymphoid organs. However, NK cells that have been activated by secretions from CD4+ T cells will kill their tumor or viral-infected targets more effectively.

B Cells: The major function of B lymphocytes is the production of antibodies in response to foreign proteins of bacteria, viruses, and tumor cells. Antibodies are specialized proteins that specifically recognize and bind to one particular protein that specifically recognize and bind to one particular protein. Antibody production and binding to a foreign substance or antigen, often is critical as a means of signaling other cells to engulf, kill or remove that substance from the body.

Granulocytes or Polymorphonuclear (PMN) Leukocytes: Another group of white blood cells is collectively referred to as granulocytes or polymorphonuclear leukocytes (PMNs). Granulocytes are composed of three cell types identified as neutrophils, eosinophils and basophils, based on their staining characteristics with certain dyes. These cells are predominantly important in the removal of bacteria and parasites from the body. They engulf these foreign bodies and degrade them using their powerful enzymes.

Macrophages: Macrophages are important in the regulation of immune responses. They are often referred to as scavengers or antigen-presenting cells (APC) because they pick up and ingest foreign materials and present these antigens to other cells of the immune system such as T cells and B cells. This is one of the important first steps in the initiation of an immune response. Stimulated macrophages exhibit increased levels of phagocytosis and are also secretory.

Dendritic Cells: Another cell type, addressed only recently, is the dendritic cell. Dendritic cells, which also originate in the bone marrow, function as antigen presenting cells (APC). In fact, the dendritic cells are more efficient apcs than macrophages. These cells are usually found in the structural compartment of the lymphoid organs such as the thymus, lymph nodes and spleen. However, they are also found in the bloodstream and other tissues of the body. It is believed that they capture antigen or bring it to the lymphoid organs where an immune response is initiated. Unfortunately, one reason we know so little about dendritic cells is that they are extremely hard to isolate, which is often a prerequisite for the study of the functional qualities of specific cell types. Of particular issue here is the recent finding that dendritic cells bind high amount of HIV, and may be a reservoir of virus that is transmitted to CD4+ T cells during an activation event.

4. IMMUNOMODULATION

Immunomodulators are substances that have been shown to modify the immune systems response to a threat upon it.

They modulate and potentiate the weapons of your immune system keeping them in a highly prepared state for any threat it may encounter. With this balancing effect, all subsequent immune responses improve. When your immune system is in this highly prepared state, the invading organisms do not have the time to build up force and strength before the immune system attacks, destroys and/or weakens the invader. Immunomodulation is the process of modifying an immune response in a positive or negative manner by administration of a drug or compound. Many proteins, amino acids, and natural compounds have shown a significant ability to regulate immune responses, including interferon-γ (IFN-γ) [21-23], steroids [24, 25], DMG [26-29]. These are biological or synthetic substances, which can stimulate, suppress or modulate any of the immune system including both adaptive and innate arms of the immune responce. Clinically immunomodulators can be classified into following three categories [30].

Immunoadjuvants: These agents are used for enhancing vaccines efficacy and therefore, could be considered specific immune stimulants 31 example in this regard is of Freund's adjuvant 32. The immunoadjuvants hold the promise of being the true modulators of immune response. It has proposed toexploit them for selecting between cellular and humoral, Th1 (helper T1 cells) and Th2, (helper T2 cells) immunoprotective and immunodestructive, and reagenic (IgE) versus immunoglobin G (IgG) type of immune responses, which poses to be a real challenge to vaccine designers [31].

Immunostimulants: These agents are inherently non-specific in nature as they envisaged to enhance body's resistance against infection. They can act through innate immune response and through adaptive immune response [32]. In healthy individuals the immunostimulants are expected to serve as prophylactic and promoter agents i.e. as immunopotentiators by enhancing basic level of immune response, and in the individual with impairment of immune response as immunotherapeutic agents [33].

Immunosuppressants: These are a structurally and functionally heterogeneous group of drugs, which are often concomitantly administered in combination regimens to treat various types of organ transplant rejection and autoimmune diseases [34].

Methods for Testing Immunological Factors [35]

The routine process for screening is to extract single ingredient or single distilled fraction from herbal drugs, determine its bioactivity by the classic pharmacological means. The whole animal model is the most classic pharmacological screening model, which is very important at the aspect of medicine evaluation because it can apparently respond to the efficacy, side effect and toxicity of medicines in whole. Although this method is high cost and low efficient, at present it is still a primary way to drug discovery and evaluation. Several *in vitro*, *in vivo* methods of pharmacological screening of medicinal plants having immunomodulatory activity has been listed.

***In vitro* methods:**

1. Inhibition of histamine release from mast cells
2. Mitogen induced lymphocyte proliferation
3. Inhibition of T cell proliferation
4. Chemiluminescence in macrophages
5. PFC (plaque forming colony) test *in vitro*
6. Inhibition of dihydro-orotate dehydrogenase

***In vivo* methods:**

1. Spontaneous autoimmune diseases in animals
2. Acute systemic anaphylaxis in rats
3. Anti-anaphylactic activity (Schultz-Dale reaction)
4. Passive cutaneous anaphylaxis
5. Arthus type immediate hypersensitivity
6. Delayed type hypersensitivity
7. Reversed passive arthus reaction
8. Adjuvant arthritis in rats
9. Collagen type II induced arthritis in rats
10. Proteoglycan-induced progressive polyarthritis in mice
11. Experimental autoimmune thyroiditis
12. Coxsackievirus B3-induced myocarditis
13. Porcine cardiac myosin-induced autoimmune myocarditis in rats
14. Experimental allergic encephalomyelitis
15. Acute graft versus host disease (GVHD) in rats
16. Influence on SLE-like disorder in MRL/lpr mice
17. Prevention of experimentally induced myasthenia gravis in rats
18. Glomerulonephritis induced by antibasement membrane antibody in rats
19. Auto-immune uveitis in rats
20. Inhibition of allogenic transplant rejection.

5. IMMUNOSUPPRESSANT DRUGS [36]

These drugs have major role in organ transplantation and auto immune diseases. The drugs are:

1. Calcineurin inhibitors (Specific T-cell inhibitors)

Cyclosporine (Ciclosporin): It is a lipophillic cyclic polypeptide composed of 11 amino acids. The drug is extracted from a soil fungus. It profoundly and selectively inhibits T lymphocyte proliferation, IL2 and other cytokine production and responce to inducer T-cells. Lymphocytes are arrested in G_0 to G_1 phase. KDT 837 Cyclosporine is used to prevent rejection of kidney, liver and cardiac allogeneic transplanted.

Tacrolimus: (TAC)-it is a newer immunosuppressant, macrolide. TAC exerts its immunosuppressive effect in the same manner as C_SA except that it binds to a different

immunophillin, FKBP-12 (fk-binding protein). Tacrolimus is used in prevention of rejection of liver and kidney and is given with a corticosteroids and antimetabolites.

2. Antiproliferative drugs (Cytotoxic drugs)

Azathioprine: It is a purine antimetabolite.its selective uptake into immune cells and intracellular conversion to the active metabolite 6-mercaptopurine, which then undergoes further transformation to inhibit de novo purine synthesis and damage to DNA. It is approved for prevention of renal and other graft rejection.

Cyclophosphamide: This drug has more effect on B cells and humoral immunitycompared to that on t cells and cell-mediated immunity. It is used in bone marrow transplant.
Other drugs of this category are
Methotrexate,
Chlorambucil,
Mycophenolate mofetil (MMF)

3. Glucocorticoids

Prednisolone: The steroids are used to suppress acute rejection of solid allograft and in chronic graft versus host disease. The steroids are able to rapidly reduce lymphocyte populations by lysis or redistribution. On entering cells, they bind to the glucocorticoid receptor and the complex passes into the nucleus and regulates the translation of DNA.

4. Antibodies

Muromonab CD3-muromonab cd3 is a murine monoclonal antibody against the CD3 glcoprotein located near to the T cell receptor on helper T cells.It is used for treatment of acute rejection of renal allografts as well as cardiac and hepatic transplantation.
Antithymocyte globin (ATG): It is a polyclonal antibody purified from horse or rats immunized with human thymice lymphocytes. It binds to T-lympocytes and depletes them. It is a potent immunosuppressant used for suppress acute allograft reject episodes.

Other drugs of this category are:
Rho (D) immuneglobin,
Efalizumab

6. IMMUNOSTIMULANT DRUGS

They stimulate the immune system to fight against immunodeficiencies (like AIDS), infections and cancers.

1. Levamisole: An antihelmintic drug that also restores functions of B lymphocytes, T lymphocytes, monocytes and macrophages. Hence it has been used in colon cancer along with 5-FU.
2. Thalidomide: Different effects of this old drug have been utilized in conditions such as:

- Erythema nodosum leprosum: Anti-inflammatory effect
- Multiple myeloma: Anti-angiogenesis
- Rheumatoid arthritis: Anti TNF effect.

3. BCG: Used in carcinoma bladder.
4. Recombinant cytokines

- Interferons: In tumors and chronic hepatitis B and C
- Interleukin 2 (aldeslukin): has been used in renal cell carcinoma and melanoma

7. IMMUNODEFICIENCY

Immunodeficiencies occur when one or more of the components of the immune system are inactive. The ability of the immune system to respond to pathogens is diminished in both the young and the elderly, with immune responses beginning to decline at around 50 years of age due to immunosenescence [37, 38]. In developed countries, obesity, alcoholism, and drug use are common causes of poor immune function.[37] However; malnutrition is the most common cause of immunodeficiency in developing countries [37]. Diets lacking sufficient protein are associated with impaired cell-mediated immunity, complement activity, phagocyte function, IgA antibody concentrations, and cytokine production. Deficiency of single nutrients such as iron; copper; zinc; selenium; vitaminsA, C, E, and B_6; and folic acid (vitamin B_9) also reduces immune responses [39]. Additionally, the loss of the thymus at an early age through genetic mutation or surgical removal results in severe immunodeficiency and a high susceptibility to infection [40].

Immunodeficiencies can also be inherited or 'acquired'. Chronic granulomatous disease, where phagocytes have a reduced ability to destroy pathogens, is an example of an inherited, or congenital, immunodeficiency. AIDS and some types of cancer cause acquired immunodeficiency [41].

8. AUTOIMMUNITY

Overactive immune responses comprise the other end of immune dysfunction, particularly the autoimmune disorders. Here, the immune system fails to properly distinguish between self and non-self, and attacks part of the body. Under normal circumstances, many T cells and antibodies react with “self” peptides [42]. One of the functions of specialized cells (located in the thymus and bone marrow) is to present young lymphocytes with self antigens produced throughout the body and to eliminate those cells that recognize self-antigens, preventing autoimmunity [43].

Hypersensitivity

Hypersensitivity is an immune response that damages the body's own tissues. They are divided into four classes (Type I – IV) based on the mechanisms involved and the time course of the hypersensitive reaction. Type I hypersensitivity is an

immediate or anaphylactic reaction, often associated with allergy. Symptoms can range from mild discomfort to death. Type I hypersensitivity is mediated by IgE, which triggers degranulation of mast cells and basophils when cross-linked by antigen. Type II hypersensitivity occurs when antibodies bind to antigens on the patient's own cells, marking them for destruction. This is also called antibody-dependent (or cytotoxic) hypersensitivity, and is mediated by IgG and IgM antibodies.Immune complexes (aggregations of antigens, complement proteins, and IgG and IgM antibodies) deposited in various tissues trigger Type III hypersensitivity reactions [44]. Type IV hypersensitivity (also known as cell-mediated or *delayed type hypersensitivity*) usually takes between two and three days to develop. Type IV reactions are involved in many autoimmune and infectious diseases, but may also involve *contact dermatitis* (poison ivy). These reactions are mediated by T cells, monocytes, and macrophages [44].

9. CONCLUSION

The immune system is a complex organ high specialized cells and even a circulatory system separate from blood vessels. The organ of the immune system poisoned throughout the body called lymphoid organ. Organ and the tissues of the immune system dot the body in a protective network of barrier to infection. Innate and adaptive immunity depends on the activity of white blood cells. Innate immunity largly depends upon granuolocyte and macrophages, while adaptive immune response depends upon lymphocytes, which provide long term immunity. Immunodeficiencies occur when one or more of the components of the immune system are inactive. It included autoimmunity, hypersensitivity and HIV etc.

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