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Cellular responses to pathogens and immune modulators

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Abstract

Parasites, fungi and bacteria enter human and animal body systems causing chronic infections after evading the immune system of the host using diverse mechanisms and techniques. Responses to parasitic, fungal and bacterial pathogen invasion triggers specific immunoglobin response that elicit immune activation through receptors on macrophages, natural killer cells and dendritic cells, mast cells, eosinophils, and basophils that bind such pathogens and eventually prevent infections. The review highlights cellular level responses to pathogenic organisms and their pathogenesis, and immune modulators as biological agents that stimulate specific and non-specific immune responses thus making weak immune system more effective.

Keywords: *Parasites, Infection, Immune system, Receptors, Modulators*

1. Introduction

The immune system encompasses the protection of the body from invasion by microorganisms (bacteria, viruses and fungi) and other internal and external threats that may lead to abysmal functioning of the body and disease conditions. These pathogenic microorganisms and parasitic agents access the body through skin, sexual and oral channels, respiratory tracts and other body openings (wounds, ulcers). The two main defense systems in the body are the innate and adaptive immunities. Cellular immunity is a mechanism of the adaptive immunity that is mediated by T lymphocytes inside an infected host cell. It is a defense system against intracellular pathogens, and acts by lysing infected cells. Cellular immunity is not antibody mediated but acquire activation of specialized lymphocyte cells (phagocytes, antigen-specific cytotoxic T lymphocytes) to respond to the antigen presenting cells on cell surface of pathogens (Kaiser, 2021). This type of immune response is directed at microbes that survive against phagocytes as compared to those that invade non-phagocytic cells (Marshall *et al.*, 2018). Responses to bacteria, parasitic agents and other microorganisms are a type 1 immunity that deals with curtailing infections.

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1.1. Cellular response to pathogens

Cellular immune response to parasites, bacteria and fungi trigger responses. Steps involved in cellular response to a pathogen are:

1. Recognition of the antigen of the pathogen as a nonself.
2. MHC complex formation which activates T cell receptors
3. Activation of macrophages and natural killer cells
4. T cell secretion of cytokines
5. Cytokines spurs production of more T cells

1.2. Cellular response to bacterial invasion

Responses to bacteria invasion is usually by cell mediated immunity as bacteria cannot be detected and destroyed through complement or antibody response systems. Most of the cells responsible for cellular response in bacteria arise from the hematopoietic system and they lack somatic recombined antigen-receptors and immunological memory (Van der Meer *et al*., 2015). These include blood monocytes, Dendritic Cells (DCs), tissue macrophages, Nk cells. Pathogenic bacteria that invade the host cell is recognized by receptors complementary to the bacteria antigen factor. The bacterial factor is recognized and eliminated by cell-mediated response. Toll-like receptor, NOD-like receptor and Triggering receptor are the three types of receptors known as Pattern Recognition Receptors (PRR) (Giamarellos-Bourboulis and Raftogiannis, 2012).

Toll-like receptors: They are innate immune cells that recognizes pathogen invasion and coordinate systemic defense against the pathogen. It also activates signals critical to the effective functioning of the adaptive immune responses. The receptors are found on blood monocytes and macrophages.

NOD-like receptors (NLRs): Nucleotide-bonding oligomerization domain-like receptor as it is known are intracellular sensors that reside within the cytoplasm and detect microbial agents that enters the cell.

Triggering receptors: They are pro-inflammatory receptors located mainly on the cell wall of neutrophils and monocytes and RIG-like receptor (RLRs) (Xu *et al*., 2020).

Responses to intracellular bacteria is usually by macrophages with multiple receptors to recognize and destroy such bacteria (Carrillo *et al*., 2017). Invading bacteria are recognized by Toll-like and NOD-like receptors that activate phagocytosis. Macrophages, natural killer cells and DCs all promote bacteria cell death.

1.3. Cellular response to fungal invasion

Response to fungal infection resulting from inhalation of spores and yeast cells is by Toll-like receptors that recognizes Pathogen-Associated Molecular Pattern (PAMP) during infection (Romani, 2011). TLRs are proteins that detect PAMPs during fungal infection. Toll-1 receptor (TLR 1 to 4, 9 and 9) are involved in the recognition of the complementary antigens during fungi invasion. TLR-2 recognizes conidia, hyphae and β-glucans of the pathogenic Coccidioides, which activate and induces oxidative pathway in polymorphnuclear cells where inflammatory cytokines and gelatinases are released from *Candida* species. Toll-like receptor six aids the synthesis of interleukin-25 (involved with the internal safety of adaptive immunity and production of cytokines) and 17A (mediates protective innate immunity to pathogens) and promotion of activity of Th17 secretory signature (Williams *et al*., 2016; and Taghavi *et al*., 2017). Th17 causes inflammatory responses which aid microbe killing capacity of macrophages and recruitment of other immune cells to the infected area of the body. NLRs are involved in the activation of IL1β and IL-18 to produce inflammasomes that induce inflammation in response to fungal infection (Saïd-Sadier *et al*., 2010). Responses resulting from these receptors' recognition of fungal antigens aid and promotes phagocytosis, production of cytokines and other processes involved in fungal death (Kimura *et al*., 2014).

1.4. Cellular response to parasitic infection

An important aspect of pattern recognition is to be able to differentiate pathogenic microbes from non-pathogenic microbes because all parasites are pathogenic to human (Medzhitov, 2007). Parasitic infection induces a different type of immune response due to their structure and heterogeneities. PAMP types activated in reaction to parasitic infection known as Dangers Associated Molecular Patterns (DAMPs). DAMPs are a group of endogenous biomolecules that induces the innate immune response. They are released from damaged or dying (Tang *et al*., 2012).

2. Protective mucosa immune responses and tolerance

Mucosa immune responses to invading pathogens is an important part of the immune system being distinct as it encompasses the production of immunoglobin and the innate responses. The innate responses involve macrophages, neutrophils that phagocytize to destroy invading pathogens. The mucosa immune system is directly involved in providing protection at the site of an attack by invading microbes (Russell *et al*., 2020), while commensals that colonize the GIT spurs the immune system to be activated in response to pathogenic strains of microorganisms (Kabat *et al*., 2014).

The body devised strategies to maintain the mucosa tolerance level to prevent hypersensitivity reaction that could lead to chronic infection or disease (Wiedermann, 2003). This tolerance balances the responses to foreign antigens and the components of the mucosa surfaces. Mucosa tolerance is established when a foreign antigen is not suppressed or attacked by either the humoral or cellular component of the immune system. Tolerance is induced by prior introduction of the antigen through the oral and nasal routes (Moorman *et al*., 2021). The mucosal immune system also encounters what is referred to as dietary antigenic load and the immune system has to respond appropriately to this antigen (oral tolerance). The immune system through antigen exclusion capabilities regulate penetration of harmful toxins.

3. Immunopathogenesis of bacterial, parasitic and fungal pathogens

Immunopathogenesis is the process of disease development resulting from immune cell response or components. Immunopathogenesis of bacteria, parasite or fungi pathogens is the development of a disease or disease condition as a result of an infection from either of the listed pathogen or a combination involving an immune response or components of the immune system (Innate or adaptive).

3.1. Immunopathogenesis of bacteria

The main stages of the immune pathogenesis include exposure, adhesion, invasion, infection, and transmission. Immunopathogenesis can be via complement-mediated lyses, phagocytosis or cell-mediated immunity.

i. **Complement-mediated lysis –** Whenever a bacterium invades the body cell thus disrupting the integrity of immune system to cause infection, a receptor immune protein called complement proteins binds it and kill the bacterium. Killing of the bacterium can be through (a) the complement system, (b) the alternative complement system, or (c) the lectin system. In the complement system, bacterial antigen is bound by complementary antibody become potential target for a complement protein complex C1 to C1. The binding of C1 causes a cascade of complement complex to form cleavage and reformation. The complexes formed cause a membraneous attack or labeling of the bacterium for destruction. Some other bacteria create pores and acquire the complement complex into their cell membrane but are destroyed by osmotic lysis.

ii. **Phagocytosis** – Phagocytes destroy bacterial cell by opsonization. Opsonization is marking of a pathogen with immune proteins and antibodies to make them more susceptible for phagocytosis. The marker proteins coats the bacterium in compounds that phagocytic cells detect and react to. Opsonized bacteria are ingested and killed by phagocytic cells. Helper T cells are activated by bacterial fragments, which results in the release of cytokines. Th1 helper cells produce interferon-g (IFN-g) which enhances cell-mediated immune processes, while Th2 helper cells release interleukin-4 (IL-4), which activates B cells and enhances humoral immunity. Antibodies produced by B cells bind to external bacteria, stopping them from growing and surviving.

iii. **Cell-mediated immunity** – Intracellular bacteria that evade phagocytic killing are target for macrophages and destroyed by cell mediated responses.

3.2. Immunopathogenesis of parasitic pathogens

T-helper cells are activated by Antigen-Presenting Cells (APC), leading in the production of chemical substances known as cytokines that stimulate activation of other immune cells. One of the anti-inflammatory proteins produced by these regulatory T cells called interleukins. Interleukins suppresses the activity of innate immunity and the body immune system's reactions to allergens through suppression of immunologic response, severity of autoimmune illnesses and reduction in inflammation in the entire body.

3.3. Immunopathogenesis of fungal pathogens

Type I, III and IV antibodies can all be produced by fungi responses of hypersensitivity, which may all work together to mediate the pathophysiology of various allergic diseases. The ability of fungi to colonize the host and germinate actively can predispose the host to immune-related illnesses. Fungal inflammatory responses are triggered by fungal proteases, which activates cellular and leukocytes (eosinophil) response. The process triggers production of eosinophil-derived neurotoxin associated with mucociliary clearance, change epithelial barrier permeability, and activation of innate immune responses which all contribute to the development of asthma.

4. Innate immunity against bacterial, parasitic, and fungal pathogens

Innate immunity uses natural barriers to destroy and prevent pathogen entrance into the body. Humans relate with microorganisms always and some live on the skin surface, gut and other openings into the body. Innate immunity limits host invasion by the normal flora on body surface and against harmful non-infectious microorganisms. A number of elements inherent in both the organisms and the host influences the outcome of the association between these microorganisms and human host. Infection occurs when an organism crosses its normal anatomical barrier and causes pathological injury to the host. Innate immunity is a non-specific, natural immune system that prevent hazardous things from entering into the body. Interleukin-1, interferons, tears, skin oil, mucus membranes and skin all make up the innate immune system (Aristizábal and González, 2013).

Parasites evade host immunity by adopting series of mechanisms to ensure its survival and a successful infection process. These parasites adopts (i) taking residency in anatomical sites not accessed host immunological agents such hollow organs, (ii) covering themselves with host proteins or glycoconjugates (antigenic disguise), (iii) parasites exixting in different developmental forms, (iv) antigenic variation capability common to blood-borne protozoan, and (v) molecular sharing of a sequence or structural similarities with the host's self-antigens (Chulanetra and Chaicumpa, 2021).

5. Immune modulators and therapeutics in the pathogenesis of human diseases

Immune modulators are biological or synthetic substances designed to suppress, stimulate, or modulate both the innate and adaptive immune response (Agarwal and Singh, 1999). The term modulation as it applies to the immune system suggests specific changes within the immune system complex, which can result in induction, addition, or repression of any component of the immune reaction. Conventionally, immunomodulators are employed because of their inherent effects on the immune system (Quinn, 1990). Generally, the immune system is a complex or sophisticated defense mechanism used by the body to protect itself from foreign invasion (Janeway *et al.*, 2001).

Immunomodulatory compounds are biological response modifiers that have the potential to interact in a specific way with the immune system, thus modifying the immune processes and create effects that alters its functionality. This is however largely dependent on the quantity of the immunomodulator consumed or administered and the specificity of its association with the immune processes. Immune modulating compounds can be (within the body) or exogenous (outside the body). Growth factors, cytokines, and hormones are a few examples of endogenous immunomodulatory compounds. An important ingredient found in foods or prescribed drugs is classified as exogenous immune modulators. A few of these ingredients are vitamins and minerals required for the proper functioning of the body (Maggini *et al.*, 2018). Several food materials sourced from plants contain immune modulating properties. Food substances like omega 3 and 6 have inflammatory characteristics and are able to scavenge free radicals in the body (Balić *et al.*, 2020)

Immune modulation aid in;

- Induction of coordinated and sustained reaction against infection.
- Ensures quick development of both adaptive and innate immunity at infancy.
- The epithelial cells within the body produce distinct factors that act on DCs, macrophages, and lymphocytes. By this process, the innate and adaptive immune responses are controlled and a better local immunity is achieved.
- Stress conditions when too chronic can cause the immune system to falter. Chronic stress decreases the number of immune cells produced or increasing immunosuppressive mechanisms (Kabat *et al.*, 2014).

Immunomodulators should be able to stimulate specific and non-specific immune responses. The nonspecific immune responses provide general protection against invading foreign microorganisms; while the specific responses are tailored to specific invading microbe. An ideal immunomodulatory substance should act as an adjuvant when introduced to a vaccine. This substance should be compatible with other conventional drugs when administered orally. This is to avoid the side effect associated with drug-to-drug interactions and potential toxicity. A good immunomodulator used as a therapeutic should not induce fever, high blood pressure or cause the recipient to become highly susceptible to other infections (Swaggerty *et al.*, 2019).

5.1. Mode of Action of Immune modulators

Innate immune system fights against invading microbes using **natural killer cells, phagocytes**, and macrophages. This provides a general response against harmful substances (Van der Willik *et al.*, 2019). The adaptive immune (acquired) response takes between 7-10 days to activate, but its response result from the incursion of foreign proteins or microbes (antigen). The antigen-specific response can either be active or passive. Active immunity involves a direct encounter with the foreign agent; whilst, passive immunity occurs without direct contact with the antigen (Kennedy, 2010). The B lymphocyte involved in immune response provides humoral immunity through antibody production and it is involved in antigen-stimulated B-lymphocytes differentiating into antibody-secreting plasma cells. The mechanism of immune response of T-cells receptor is dependent on the complex actions of MHC protein (human leukocyte antigen) (Kennedy, 2010; and NCBI, 2022).

A good example of an immune modulator is the yeast beta-glucan that controls inflammatory and antimicrobial activities of neutrophils and macrophages (Stier *et al.*, 2014). Beta-glucans serve as immune modulators tend to 'train' the immune cells, consequently triggering the needed changes that help to fight against pathogens. The training stimuli experienced by the innate immune cells retain a memory that enables them to respond more rapidly and efficiently when it encounters another pathogenic microorganism of a similar variant (Netea *et al.*, 2020).

5.2. Categorization of immune modulators according to their actions

1. Immune stimulants: These immune potentiators enhance immune responses. They are nonspecific and act through innate and adaptive immune responses. They also act as prophylactics in apparently healthy individuals and as immunotherapeutic agents in immune-compromised patients (Nayak and Mengi, 2009).
2. Immune suppressants: These prevent the immune system from destroying healthy cells and tissue. They are used in synergy with other drugs for the treatment autoimmune diseases and patients with organ transplant rejections.
3. Immune adjuvant: Adjuvants are known for their inherent ability to enhance the cellular or humoral immune response to antigens (Coffman *et al.*, 2010). They are added to vaccines to improve their efficacy and uptake. The immune adjuvant serves as a good modulator of the immune system. They activate the immune system to better recognize and neutralize specific harmful immune cells (Schijns and O'Hagans, 2017; and Virgil *et al*, 2020).

6. Conclusion

The body immune system is a complex properly coordinated conglomerate of many sub-systems and components that ensure destruction, removal of the effects of invading pathogenic microorganisms. Cellular immunity recognizes the antigen of the pathogen as a non-self and quickly put defense machinery in place to prevent infection. Modulators aid the activity of the immune system, which strengthens immune responses and prevent inflammation resulting in allergic reactions by overreacting immune cells.

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