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Biology of Innate Immune Response

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ABSTRACT

Higher and complex organisms have developed a robust and sophisticated immune system which helps in elimination of invading pathogens from the system. There are two types of immunity: innate and adaptive. Innate immunity was the earliest immune response which developed in organisms before the development of adaptive immunity. Innate immunity can be broadly classified into humoral immunity and cellular immunity. Both these arms have different purpose and recognize different set of antigens. However, to have a potent immune response, a successful synchronization of both the branches is necessary. Deregulation of innate immune system can cause pathological symptoms as observed in various infectious and non-infectious diseases. It is utmost important that the response triggered is properly controlled and channeled to the target area, otherwise it will cause damage to the host cells. In this chapter we discuss about the biology of innate immunity, the types of innate immunity and the key players which orchestrate the whole process. We also discuss the physiological roles of these components in the context of elimination of pathogens.

Keywords: Innate; Adaptive; Pathogens; Antigens; Complement; Humoral; Cellular

Abbreviations: MBL-Mannose binding lectin; MASP: MBL associated serine protease

INTRODUCTION

The immune system in humans consists of two branches, adaptive immunity and innate immunity. Innate immune system is quick in its response as the functioning of this system is already programmed in the genetic material, DNA. It is the first line of defence against invading pathogens. Adaptive immune response on the other hand is slow and requires exposure to specific antigens to get activated. This requires genetic rearrangements to target a particular antigen.

The evolution of innate immunity occurred much before the development of adaptive immunity [1]. Innate immune response started during the emergence of first multi-cellular organisms on earth. The innate immunity has evolved over a long time and is quite complex in its mechanisms. RNA interference (RNAi) is one of the oldest immune responses against the nucleic acids of pathogens [1]. Another mechanism is that of anti-microbial peptides. As the multicellular organisms diversified, the need for a immune response that could act intracellular as well as extracellular was felt. Thus innate immunity developed two branches; humoral response targeting the circulating antigens and pathogens and the cellular response which targeted the intracellular pathogens. Both the pathways act through specific receptors against antigens/pathogens. These receptors recognise specific pathogen patterns.

HUMORAL INNATE IMMUNE REPONSE

The humoral immunity consists of a large of chemokines, cytokines, defensins and complements. These molecules provide protection against pathogens at the site of infection. Complement system directly interacts with the pathogens and opsonises them. Complement system is an enzymatic cascade which has four main functions, cell lysis, triggering inflammation, opsonisation of pathogens and immune clearance. The opsonised pathogens which are taken up by phagocytic cells through complement receptors and are destroyed through lysosomal degradation. Activation of the complement pathway is important for chemotaxis and inflammation. Upon activation by pathogens, the complement factor C3 is activated to C3b. The activated factor C3b along with its fragment C3d gets covalently coated on to the surface of the pathogen. These coated pathogens are recognized by dendritic cells and B lymphocytes which triggers a humoral adaptive response resulting in production of antibodies. Complement system also cause cell lysis by forming a membrane attack complex (MAC) on the cell surface of the pathogens. This complex lyses the cell and kills the pathogen.

There are three pathways of complement activation, namely, classical, alternative and lectin pathways. Figure 1 depicts the different pathways for complement activation and the various factors involved in each step. The pathways are mostly activated through proteolytic cleavage of complement factors. The classic complement pathway is triggered when antibody-antigen complex interact with C1-complex, which consists of C1q, two molecules of C1r, and two molecules of C1s. The C1-complex cleaves C2 and C4, which then form C3 convertase (C4b2a). C3 is then cleaved by the C3 convertase, and forms C5 convertase in association with C4b and C2a.

The generation of C5 convertase is the end of the classical pathway. The lectin pathway is very similar to the classical pathway. It is stimulated when the mannose-binding lectin (MBL) binds to mannose residues on the pathogen surface. The MBL-associated serine proteases, MASP-1, and MASP-2, are activated and cleave C4 and C2, which then form the C3 convertase as in the classical pathway. The alternative complement pathway begins with the activation of C3 and requires factor B and factor D. All three pathways merge at C3, which is then converted into C3a and C3b. C3b binds to C5 convertase which forms C5b. The C5b in association with C6, C7, C8 and C9 forms the membrane attack complex causing cell lysis. Depletion of complement system in rats results in drastically reduced antibody response [2].

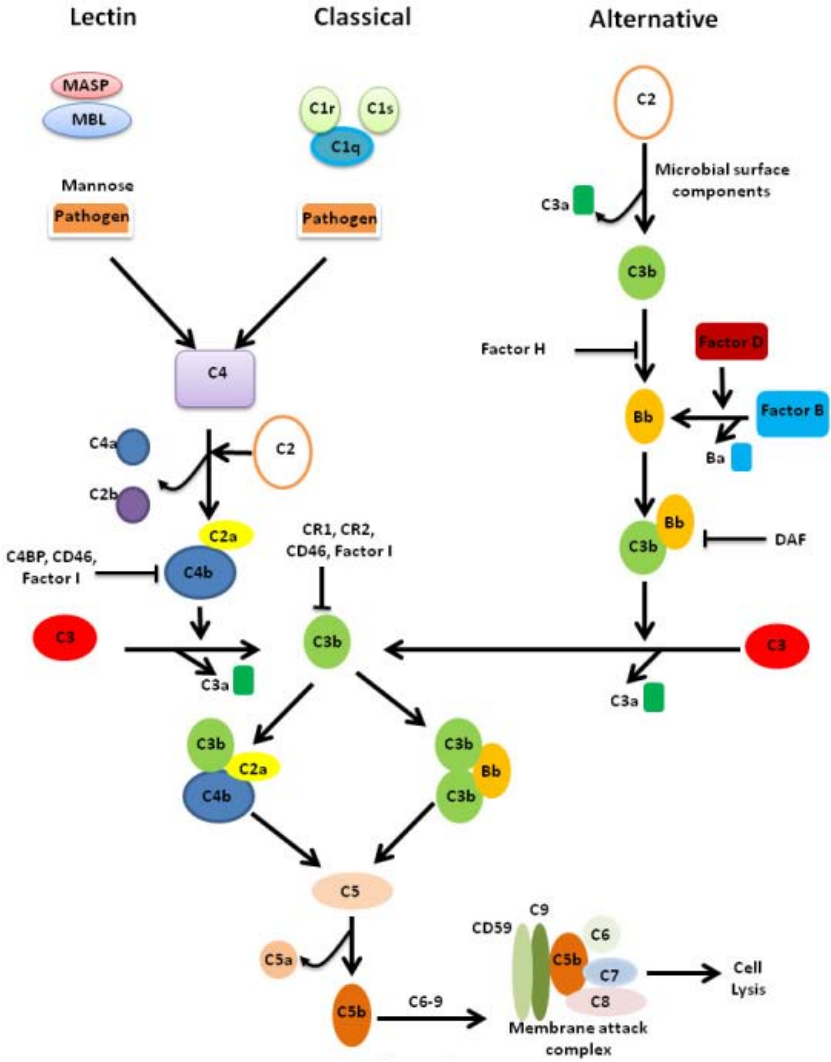

Figure 1: Different A schematic diagram shows different pathways for the activation of the complement system. There are three different pathways for complement activation, namely, classical, lectin and alternative pathways. Lectin and classical pathways are activated

by different mechanisms, both lead to formation of C4 intermediate. Alternative pathway is activated by components present on the surface of microbial pathogens. All three pathways lead to the formation of a common intermediate C3b which is finally converted to C5b in several steps of proteolytic cleavage and protein-protein interactions. C5b then forms a membrane attack complex (MAC) along with C6, C7, C8 and C9. This complex makes a pore on the surface of microbe causing cell lysis.

Deregulation of complement system occurs when auto antibodies develop against C3Bb convertase. These auto antibodies are also known as C3 nephritic factors which stabilize the convertase resulting in prolonged complement activation and tissue damage [3]. The injured tissue can further serve to activate the complement resulting in a vicious feedback loop. Therefore, complement inhibitors play an important role in regulating the intensity and duration of the complement response. Two such inhibitors, Factor H and Factor I, which inhibit alternative and classical/lectin pathways respectively are important in this respect [4].

Several other proteins have been found in the blood that recognizes pathogen associated molecular patterns (PAMPs). Not much study has been done on these proteins to unravel their mechanisms of action. The surfactant proteins might play a role in innate immunity [5]. It was also shown that C-reactive proteins, pentraxins and serum amyloids also play a role in innate immunity [6].

CELLULAR INNATE IMMUNE RESPONSE

The cellular innate immunity involves a wide variety of cells and is very complex. The cells of this branch of innate immunity are classified into myeloid and non-myeloid cells.

Myeloid Cells

Myeloid cells consist of monocytes, macrophages, neutrophils, eosinophils, basophils, platelets. These cells, except the platelets, possess phagocytic properties by which they can ingest pathogens and degrade them intracellularly and present the foreign antigens to B and T lymphocytes for activation of adaptive immunity. These cells have evolved from simple multi-cellular organisms to highly complex species today.

Monocytes

Monocytes are precursors of tissue macrophages. They originate from bone marrow progenitor cells under the influence of different cytokines. Monocytes migrate to different tissues through blood. In the tissue, they differentiate to macrophages under the influence of macrophage colony stimulating factor (M-CSF). Monocytes are less efficient in phagocytosing foreign antigens than macrophages or neutrophils. Monocytes were earlier thought to be a single homogenous population; however recent studies have shown that three different subsets of monocytes are present [7]. They perform different functions in innate immunity by producing cytokines. In acute and chronic inflammation, there is a significant change in the number of monocytes [8].

A significant increase in the number of monocytes in blood is an indication of acute infection or inflammation.

Macrophages

Macrophages originate from differentiation of monocytes. Macrophages can phagocytose pathogens, cellular debris and even aged neutrophils. Upon phagocytosis, the material goes to phagosome which eventually fuses with lysosome. At the low pH of lysosome, the ingested matter is degraded by proteolytic enzymes. Macrophages also present antigens to B and T lymphocytes which triggers the adaptive immune response. They also secrete cytokines like tumor necrosis factor α (TNF- α) and interleukin-10 (IL-10). TNF- α and IL-10 are pro- and anti-inflammatory cytokines and play a vital role in amplification or down regulation of immune response. Macrophages that encourage pro-inflammatory response are called M1 while those that support anti-inflammatory response are M2. Some pathogens like *Mycobacterium tuberculosis* inhibit fusion of phagosome with lysosome which helps the bacilli to prevent degradation and survive intracellularly [9]. Mycobacterial secretory proteins modulate macrophage pathways and function leading to a favorable intracellular niche for bacteria [10-12]. Macrophages also play an important role in muscle regeneration and wound healing.

Neutrophils

Neutrophils are professional phagocytic cells which originate from bone marrow and are present in blood and tissue [13]. They differentiate under the influence of granulocyte colony stimulating factor (G-CSF). Neutrophils are the most abundant white blood cells (50-70%). The nuclei of the neutrophils display multiple lobes and are called polymorphonuclear granulocytes. At the onset of infection, neutrophils are the first to be attracted to the site of inflammation. They are attracted by the large of chemokines and cytokines like interleukin-8 (IL-8), Leukotriene B4, C5a by a process called chemotaxis. Neutrophils have short life span; they are highly mobile and migrate through bloodstream and interstitial tissue. A study has shown recently that that in peripheral blood neutrophils are present for 2-3 days [14]. In humans, reverse migration of neutrophils from tissue to blood and lymph nodes have been observed [15]. A study has shown that trans-differentiation of neutrophils to cells which has dual functionality of dendritic cells and neutrophils [16]. Aged neutrophils are cleared by reticular macrophages. A recent report has challenged this view and shown that neutrophils are cleared at bone marrow and liver also through the CXCL12/CXCR4 chemokine pathway [17].

Dendritic cells

Dendritic cells are antigen presenting cells that originate from bone marrow. They take up antigens for presentation to T cells. These cells are therefore important for the activation of naive T cells. They have high levels of expression of class II major histocompatibity complex (MHC) at their surface which makes them very efficient in antigen presentation. Dendritic cells are at the border between innate and adaptive immunity. The cells have several subtypes which vary

according to their immunological role, location and pattern of migration [18]. Dendritic cells are either resident or migratory. Resident cells localize to lymphoid tissue where they take up antigens from blood and lymph and present to T cells locally. Migratory DCs move throughout the non-lymphoid tissue where they take up tissue derived antigens to T cells. Based on the expression of cell surface markers, three types of DCs are present in peripheral blood; plasmacytoid DCs and two forms of conventional DCs, CD141/BDAC-3+ and CD1c/BDCA-1+. CD141 DCs constitute 5-10% of total DC population and the plasmacytoid and CD1c types make up the remaining amount in equal share.

Basophils

The role of basophils in the innate immunity is mainly concerned with the development of allergic response. They constitute about 0.01% to 0.3% of white blood cells. The cells contain large cytoplasmic granules and are therefore referred to as granulocytes. Basophils originate from the bone marrow and mature under the influence of interleukin-3 (IL-3). Basophils belong to non-phagocytosing cells since they don't have any capacity to ingest foreign materials. These cells stain with basic dye, hence the name basophils. Basophils play an important role in inflammatory and allergic responses. They secrete histamine which is a vasodilator and a mediator for allergic response. The allergic response is triggered by binding of immunoglobulin E (IgE) on the receptors present on the cell surface. This binding allows release of histamine from the basophils which gives rise to the symptoms associated with allergic response. Basophils also secrete interleukin-4 (IL-4) which helps in generation of IgE antibodies. Basophils also contain the anti-coagulant heparin which prevents quick clotting of blood. These cells are mostly found at the sites of parasitic infections.

Eosinophils

These cells stain with an acidic dye, eosin and hence called eosinophils. Eosinophils make up 1-6% of the total white blood cells and are usually 10-15μm in diameter. Normal life span of eosinophils is about 8-10 days. These cells, like basophils, contain thick granules around the nucleus. The cells contain histamine which plays a important role in allergic and inflammatory responses. Eosinophils act against parasitic infections. They contain cationic protein, peroxidase, ribonuclease, deoxyribonuclease, plaminogen, neurotoxin, major basic protein etc. which are released from the cell following activation of eosinophils. These chemicals are detrimental to the parasite and helps in eliminating them. They also secrete cytokines such as interleukin 1, 2, 4, 6, 8 and 13 and growth factors like transforming growth factor β (TGF-β), vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF). Eosinophils are normally found in ovary, uterus, spleen, lymph nodes, and lower gastrointestinal tract where they act against pathogens. They are not found in skin and lungs.

ROLE OF NERVOUS SYSTEM

The nervous and immune system both play an important role in maintaining physiological

homeostasis. Conventional view was that both the systems are autonomous with no interaction with each other. However, recent studies have shown the contrary; there is an extensive cross talk between the two systems. Nervous system regulates the immune system [19]. Immune system gives feedback to the brain about the events occurring in the periphery of the body and hence acts as a type of sense organ. A study has shown that inflammatory response to endotoxin is attenuated by the stimulation of vagus nerve [20]. Stimulation of vagus nerve also resulted in inhibition of pro-inflammatory cytokine response, rheumatoid arthritis, haemorrhagic shock, myocardial ischemia etc. [21-25]. It is crucial to regulate the exact magnitude of the inflammatory responses; a weak response can lead to systemic spread of the infection while an exaggerated response can lead to tissue damage as in case of autoimmune diseases. This is controlled not only by immune system but also by nervous system. Pro-inflammatory responses were also suppressed by nutritional activation of vagus nerve by chemokines [26].

It has become clear that both immune and nervous system plays a role in maintaining the homeostasis in immune system. The role of immune system in neuronal homeostasis would be an exciting area of research for future. Neurodegenerative diseases have higher levels of inflammatory molecules.

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