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Recognition of Pathogens and Their Inflammatory Signaling Events

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Abstract

The innate immune system is the main and first line of defense mechanism present in the human body, which acts against a foreign antigen. To function it utilize several mechanisms, among those are the primary one is recognizing the foreign antigen which is accomplished via decidedly complicated group of molecules termed as pattern recognition receptors (PRRs), which perceive various diverse structures present on the pathogen known as pathogen-associated molecular patterns (PAMPs). PRPs include several classes of receptors', functions, and nature of these receptors vary from each other depending upon the molecular composition of PAMPs they detect. However, the Toll-like receptors (TLRs) are among the class of PRPs, which are studied widely. In this review, we have presented the contemporary understanding of pathogens recognition by various receptor classes including PRRs. In addition, we also discuss PRPs associated signaling pathways associated with antimicrobial immune response triggering.

Introduction

Immune system is a defense mechanism which responds against foreign structures termed as an antigens [1]. These antigens are composed of a wide variety of objects that include living microorganisms [2], such as bacteria, virus, fungi, and protozoa to nonviable structures such as pollen grain and dust particles. Immune system consists of two main parts, an innate immune system and an adaptive immune system [3]. Innate immune system is present at birth and serves as the first line of defense against antigens. It acts by recognizing the infectious agent and then with the aid of immune cells an inflammatory response is generated in which pro-inflammatory molecules such as cytokines and interleukin plays an essential role [4]. In the innate immune response the phagocytic cell which includes neutrophils and macrophages, other granulocytes such as Eosinophils as well as natural killer cells mainly play role. On the other hand, adaptive immunity which is also called acquired immunity takes a certain duration of time to respond against a specific antigen. More specifically, it involves a complex role lymphocytes and antibodies [5].

The first step for the innate immune system to act against an antigen is to recognize it. This fundamental step is accomplished by certain receptors called as pattern recognition receptors (PRPs) [6].

These protein receptors are present on various cells, for example, neutrophils, dendritic cells, monocytes, macrophages, and epithelial cells [7] and are proficient in recognizing certain molecules termed as pathogen-associated molecular patterns (PAMPs) that are present in pathogens as well as specific molecules which are released when cells are damaged hence called as the damage-associated molecular patterns (DAMPs) [8]. These includes ATP, uric acid, cytokine IL1α, the calcium-binding, cytoplasmic proteins S100A8 and S100A9, and the DNA-binding, and nuclear protein HMGB [9]. PRRs are classified into four main types which includes the Toll like receptors (TLRs), the nucleotide binding oligomerization domain (NOD), the retinoic acid inducible gene 1 like receptors (RLR), and the C-type lectin receptors (CLRs) [6]. On recognizing the microbial molecules or stress responses from dying or damaged cells by PRPs leads to activation of various inflammatory caspases that cause cleavage and activation of vital inflammatory cytokines such as interleukin-1 as well as activation of the signaling pathway that results in production of inflammatory molecules that contribute in an early immune response against the infectious agent [10]. Previously a decade back innate immune system was considered as primitive and weak defense system which just played an initial nonspecific role to counter the infection, proposing supplementary credit to adaptive immune system. However, now recent studies have proved that the innate immune system has a major role in eliminating infectious agents and works side by side along with adaptive immune system by not only recognizing the pathogen but also playing a remarkable role in activating the adaptive immune system. In this review, we have discussed the mechanisms of pathogen recognition and pro-inflammatory signal transduction in immune defenses along with the interference of pathogen-induced inflammatory responses by endogenous mechanisms. We also discussed the therapeutic implications of PRRs in primary immunodeficiency as well as in pathogenesis of infectious diseases.

Immune System and the Role of PRRs

Innate immunity refers to nonspecific defense mechanisms that come into play immediately or within hours of an antigen's appearance in the body. Innate (natural) immunity is named so because it is present at birth and does not have to be learned through an exposure by an invader [11]. The innate immune system is comprised various components which includes the physical barriers such as skin and mucous membrane, cellular barriers, and humoral factors (Figure 1). The complement system is also part of the innate immune system and includes over

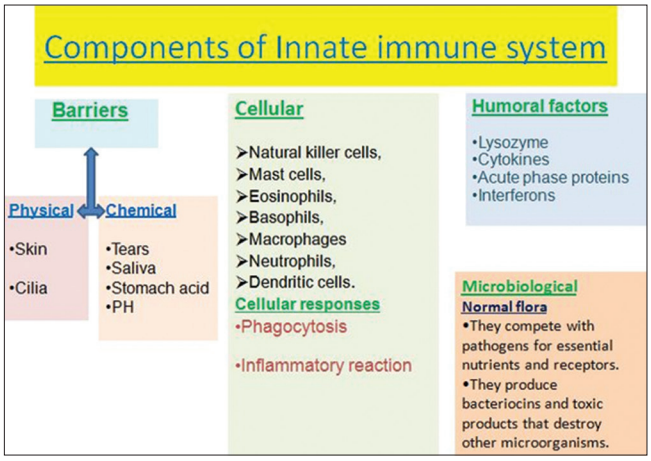

Figure 1: Updated details of innate immune system components

20 functionally linked proteins that are synthesized by the liver. Complements circulates in the blood as inactive precursor forms and is activated directly by pathogens or indirectly by pathogen bound antibody. The complement system helps antibodies and phagocytic cells to clear pathogens from body [12], [13], [14]. Pattern recognition receptors (PRRs) are protein receptors present on cells of the innate immune system and these receptors identify two classes of molecules that includes pathogen-associated molecular patterns (PAMPs), which are present on microorganisms and damage-associated molecular patterns (DAMPs) which are they are released from damaged or dying cells. Phagocytes recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular pattern (DAMPs). The first event in the uptake and digestion of a microorganism by the professional phagocyte involves the attachment of the microbe to the surface of the cell due to presence of pathogen-associated molecular patterns (PAMPs) on the microbe that is recognized by pattern recognition receptors (PRRs) present on the phagocyte surface [6], [15].

Types of PRPs

Toll like receptors (TLRs)

These receptors are named for their similarity to Toll, a receptor first identified in the fruit fly Drosophila melanogaster [16], [17]. TLR family members are expressed by: Various immune cells that include Neutrophils, Macrophages, Dendritic cells., endothelial, and epithelial cells. TLRs are composed of a unique structural shape, the Leucine rich repeats (LRR), which furnish their specific facade and are also responsible for their function [17], [18]. Binding of infectious agents through Toll-like receptors results in phagocytosis and the release of inflammatory cytokines such as IL-1, TNF-α, and IL-6 by the phagocytes [19].

Various TLRs can recognize specific antigens as listed below in Table 1. The details of innate immune system components are summarized in Figure 1.

Table 1: Toll-like receptors (TLR) types

TLR 1: Lipoprotein and cell wall peptidoglycan of bacteria
TLR 2: Peptidoglycan present in cell wall of bacteria
TLR 3: Double stranded ribonucleic acid
TLR 4: Lipopolysaccharide mainly present in cell membrane
TLR 5: Flagella
TLR 6: Bacterial lipoprotein
TLR 7: Single stranded ribonucleic acid present in virus and bacteria
TLR 8: Single stranded ribonucleic acid present in virus and bacteria as well as phagocytized bacterial RNA.
TLR 9: Deoxyribonucleic acid of bacteria and other microorganisms

Nod-like receptors (NLRs)

NLRs are types of PRRs present intercellularly and sense PAMPs that enter the cell through phagocytosis or pores, and damage-associated molecular patterns DAMPs [20]. NLRs can cooperate with TLRs and regulate inflammatory and apoptotic response. They are located in lymphocytes, macrophages, and also in non-immune cells, for example, in epithelium. These receptors recognize endogenous or microbial molecules or stress responses by damaged cells resulting in formation of oligomers that leads to activation of numerous inflammatory caspases that cause cleavage and activation of vital cytokines along with activation of NF-κB signaling pathway that results in release if of inflammatory molecules.

The RIG-like receptors (RLRs)

The RIG-like receptor (RLR) is a type of PRP that can recognize viruses and can induce antiviral immune responses. RLRs are located in various cell types and within the cytoplasm. However, recent studies showed that RIG-I may also be localized in the nucleus of the cell. RLRs, are composed of RNA helicases, which play role in intracellular recognition of double-stranded and single stranded viral RNA which recruit factors through twin N-terminal CARD domains resulting in activation of antiviral gene programs [21]. Studies have revealed that the principle antiviral program that is initiated by RLR is relies on activity of ATPase. RLRs also have a role in regulation of acquired immune response. Recent studies have also demonstrated that RPRs also interact with TLRs [22].

Cytosolic DNA sensors (CDS)

These include various structurally related proteins that recognize deoxyribonuclease present within the cytoplasm and generate an immune response mainly through producing interferon beta. In healthy cells, DNA is present within the nucleus and mitochondria. The presence of DNA in the cytoplasm is a sign that is linked to abnormality such as tumorigenesis, viral, and intracellular bacterial infection.

TLRs Activation by IKK and MyD88-Dependent TAK1

There is a direct attachment of TLR5, TLR7, TLR8, TLR9, TLR10, and TLR11, heterodimeric TLR1-TLR2 and TLR2-TLR6, and the IL1Rs with the adaptor MyD88 whereas, TLR1-TLR2, TLR2-TLR6, and TLR4 engage in combination with the adaptor TIRAP/Mal. Serine/threonine kinase IRAK4MyD88 interact with death domain (DD) as well as with TIR domain [23]. Autophosphorylation results due to IRAK4 clustering within the receptor complex. Polyubiquitin chains on lysines can be formed when TRAF6 and Ubc13 play role in formation of polyubiquitin in which isopeptide bond is formed by carboxyl terminus of one ubiquitin. The complete details are summarized in Figure 2.

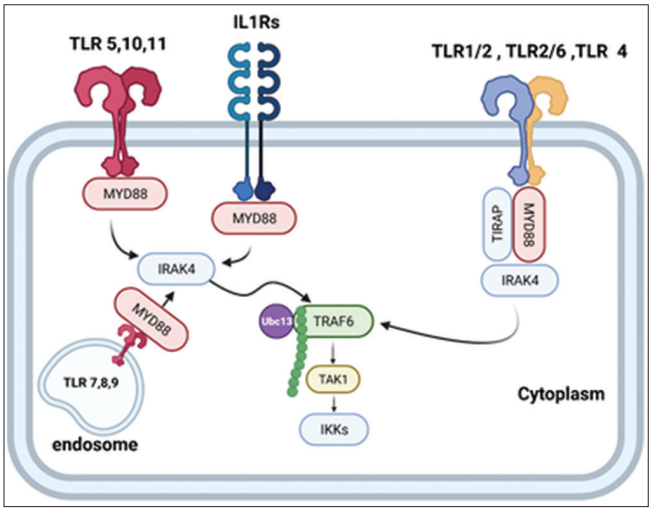

Figure 2: TLRs activation by IKK and MyD88-Dependent TAK1

Recognition of Microorganisms by Pattern Recognition Proteins (PrPs)

The details of recognition of microorganisms such as viruses, bacteria, fungi, and parasites by PrPs are summarized in Figure 3 and specifically provided in the following sections.

Viruses

Viruses are obligate intracellular pathogens and are composed of a genome which can be either a RNA or DNA. The clinical symptoms due to a viral infection vary from person to person depending on his immune status, past infection as well as the viral load. The viral envelope, capsid proteins as well as surface proteins serve as a source of PAMPS which are recognized by specialized PRRs present on various cells. DNA of the virus is recognized by DAI, and TLR9

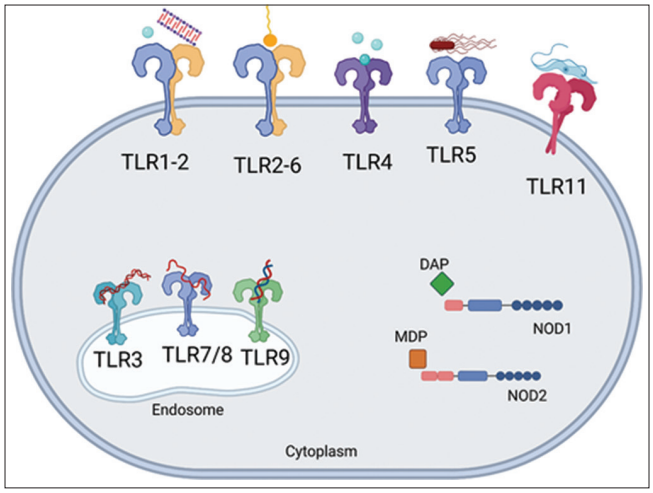

Figure 3: Recognition of microorganisms by the PrPs

whereas recognition of RNA depends on whether it is single stranded or double stranded. Dingle stranded RNA genome is recognized by TLR7 and TLR8 whereas double stranded RNA os detected by TLR3, PKR, and RLRs [24]. Moreover, various different PRPs are responsible to recognize various virus such as RIG-I detect dsRNA of certain RNA viruses such as influenza A virus, HCV, present in the cytoplasm.MDA5 located in the cytoplasm detects dsRNA of certain viruses such as picorna- and noroviruses. TLR7/8 located in the endosome detect the ssRNA of RNA viruses that had infected a cell. Moreover, TLR3 present on cell surface as well as on endosomes recognize dsRNA viruses [25].

Bacteria

Bacteria are single cell organisms and are classified in prokaryotes. They are divided into two main groups, on the basis of peptidoglycan present in their cell wall. Gram-positive bacteria have a thick layer of peptidoglycan making it hard to decolorize during the process of Gram staining whereas Gram-negative bacteria have a thin layer of peptidoglycan present in their cell wall [26]. Beside the cell wall, the Gram-positive and Gram-negative bacteria have differences in other structures such as Teichoic acid and lipoteichoic is present in Gram-positive bacteria and serves numerous function, most important of which is adherence. These lipoteichoic acids serve as PAMPS and are recognized by TLR2 [27]. Bacterial DNAs also serve as a PAMP and are recognized by TLR9. NOD1 is present in cytoplasm and aids in recognizing diaminopimelic acid of Gram-negative bacteria whereas NOD2 detects cytoplasmic MDP of both Gram-positive and Gram-negative bacteria. In certain Gram-positive bacteria and Mycoplasma Diacyl lipopeptides and lipoteichoic acid serve as PAMPS and are recognized by TLR2 and TLR6 present on cell surface. Porins are cell membrane proteins that serve as transport channels in bacteria primarily responsible for passive transport of hydrophilic molecules of different size and charge across the cell membrane [28]. These porins also serve as PAMPS and are recognized by TLR2 receptors present on the cell membrane. Similarly flagella are whip-like structures that can be present in both Gram-positive and Gram-negative bacteria and the main function of flagella is in motility. These structures are composed of a protein termed as flagellin which also serves as a PAMP and is recognized by TLR5 present on cell surface [29].

Fungi (Yeast and molds)

Fungi are eukaryotes, so they have well defined membrane bound organelles present within the cytoplasm and are surrounded by a cell membrane. Above the cell membrane, a cell wall composed of chitin is also present [30]. The relationship in between PRPs and PAMPs related to various fungi have been studied and the result revealed that TLR2 and TLR4 are the two most vital PRPs that play a vital part in recognition of various PAMPS associated with clinically important fungi such as s *Candida albicans, Aspergillus fumigatus,* and *Cryptococcus neoformans* [31]. The cell wall of majority of yeast is composed of structures called as galactomannans. A study conducted on Candida albicans, which is a frequent cause of infection particularly in immunocompromised patients and those patients who are on total parenteral nutrition, found that TLR4 can recognize the mannans present in *C.albicans* [32]. Professional phagocytic cells like macrophages signify a grave role in immunity through their specialized ability of endocytosis and digestion of extracellular milieu. The degradative and microbicidal functions of phagocytes depend on the fusion of lysosomes with phagosomes, liberating the lysosomal enzymes in the endosomes that result in the digestion of the material present within. Despite these efforts, various pathogens can resist digestion and often survive and even can proliferate within the phagosome [33]. It has been revealed in a study that TLR2 can detect the fungi present in the phagosome [34]. Few studies also found out that dectin-1 can recognize beta glycan present in various fungi [35].

Parasite

Parasites are a hefty group of microorganisms and range structurally from being unicellular to multicellular. The main PAMPs that are present in protozoa are glycosylphosphatidylinositol anchors [36]. The PRPs which recognize it include TLR2, TLR4 and TLR9 [37]. A study conducted on plasmodium that is responsible for causing malaria revealed that hemozoin acts as an effective PAMP and is detected by TLR9 [38]. Toxoplasmosis is a disease transmitted by *Toxoplasma gondii* which is a protozoa. The IL-12 inducer profilin-like protein released by Tachyzoites form *T. gondii* is a potent PAMP that is detected by non-functional TLR [39].

Conclusions

In this review, we have highlighted vital rudiments by which our innate immune system identifies and initiates an immune response by various signaling pathways and release of immune mediators against various pathogens. Identifying a pathogen is the first step required to encounter them. This task is executed by the innate immune system by PRPs; hence, their contribution in the immune system is of extreme significance. PRPs in the immune system are not only limited to recognizing the pathogen but it is much more complex, ranging from production of various inflammatory cytokines to antipathogenic activity. Moreover, PRPs serve as a bridge for our immune system to step from the innate immune system to the adaptive immune system. Hence, the understanding of pathogen recognition and pro-inflammatory signaling is a vital prerequisite for knowing the pathogenesis of different infectious as well as various immune related diseases; moreover, it can play a fundamental role in the formation of novel therapeutic intervention and strategies.

Authors' Contributions

All authors performed literature search, review design, literature coordination, and drafting of the review article. All authors have read and approved the final article.

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