Chapter 6

Physiology and Pathology of Innate Immune Response Against Pathogens

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Abstract

Pathogen infections are recognized by the immune system, which consists of two types of responses: an innate immune response and an antigen-specific adaptive immune response. The innate response is characterized by being the first line of defense that occurs rapidly in which leukocytes such as neutrophils, monocytes, macrophages, eosinophils, mast cells, dendritic cells, etc., are involved. These cells recognize the pathogen-associated molecular patterns (PAMPs), which have been evolutionarily conserved by the diversity of microorganisms that infect humans. Recognition of these pathogen-associated molecular patterns occurs through pattern recognition receptors such as Toll-like receptors and some other intracellular receptors such as nucleotide oligomerization domain (NOD), with the aim of amplifying the inflammation and activating the adaptive cellular immune response, through the antigenic presentation. In the present chapter, we will review the importance of the main components involved in the innate immune response, such as different cell types, inflammatory response, soluble immune mediators and effector mechanisms exerted by the immune response against bacteria, viruses, fungi, and parasites; all with the purpose of eliminating them and eradicating the infection of the host.

Keywords: innate immune response, eosinophils, mast cells, cytokines, inflammatory response, bacteria, fungi, viruses, parasites

1. Introduction

The immune system consists of a series of effector mechanisms capable of destroying pathogenic organisms such as bacteria, fungi, viruses, and parasites [1]. The immune system consists

of two types of responses: an antigen-specific adaptive immune response and an innate immune response, also called natural, which recognizes pathogen-associated molecular patterns (PAMPs) [2]. These PAMPs are recognized by pattern recognition receptors (PRRs), mainly expressed in the innate immunity cells. PRRs can also recognize host molecules containing damage-associated molecular patterns (DAMPs), molecules that are often released from necrotic cells damaged by invading pathogens [3].

The innate immune system is composed mainly of physical barriers, such as skin and mucous membranes, chemical barriers, through the action of antimicrobial peptides and reactive oxygen species [4], innate immune cells, and soluble mediators such as the complement system, innate antibodies, and associated cytokines [2].

The main purpose of the innate immune system is: (1) to prevent the entry of pathogens into the body through physical and chemical barriers [4]; (2) to avoid the spread of infections through the complement system and other humoral factors; (3) to remove pathogens through phagocytosis and cytotoxicity mechanisms [5]; and (4) to activate the adaptive immune system through the synthesis of several cytokines and antigen presentation to T and B cells [6].

2. Innate immune system cells

The cells of the innate immune system have several functions that are essential for defense against pathogens. Some cells form physical barriers that impede infections. Several cell types express the various PRRs that recognize PAMPs and DAMPs, which respond by producing inflammatory cytokines to kill microbes or infected cells. These cells include nonmyeloid cells, myeloid cells, and some lymphoid cells.

2.1. Nonmyeloid cells

Nonmyeloid cells include epithelial cells, fibroblasts, etc., that basically form a barrier between the internal and external environment. These cells produce antimicrobial substances that hinder the entry of pathogens [1, 2]. These antimicrobial substances are called antimicrobial peptides (AMPs), and they are essential components of the innate immune response, which contribute to the first line of defense against infections [7]. In humans, AMPs are classified into three main families: defensins (α and β), cathelicidin, and statins. AMPs have a wide spectrum of antimicrobial activity, exerting their functions through electrostatic interactions between their positive charge and the negative charge that certain pathogens have on their cell wall. AMPs mediate the inflammatory response allowing cytokine release, cell proliferation, angiogenesis, wound healing, and chemotaxis [8]. Currently, their synergistic activity with antibiotics used in the clinic has been demonstrated. Therefore, their study on potent adjuvants in the eradication of bacterial infections continues to be studied [9].

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2.2. Myeloid cells

Myeloid cells include monocytes, macrophages, dendritic cells (DCs), neutrophils, eosinophils, basophils, mast cells, and platelets. All these cells have specialized functions for defense against invading pathogens [2, 10].

2.2.1. Monocytes

Monocytes are cells that develop in the bone marrow, and they are released into the bloodstream to circulate for approximately 72 hours and then emigrate to different tissues where they differentiate into macrophages or DCs. They represent the major type of mononuclear phagocytes found in blood and are members of the myeloid cell family [11]. In humans, monocytes are classified into classical and nonclassical depending on their surface expression of cluster of differentiation (CD)-14 and CD16. Classical monocytes with phenotype $CD14^{+}CD16^{-}$ are considered inflammatory cells representing more than 92% of total monocytes. In contrast, nonclassical monocytes with $CD14^{+}CD16^{+}$ phenotype can eliminate debris from the vascular system and produce low levels of proinflammatory cytokines, as well as high levels of anti-inflammatory factors. Several studies have shown both subpopulations under inflammatory conditions; the inflammatory response is a gradual process which starts with the main appearance of classical monocytes, and a few days later, nonclassical monocytes appear [12]. Among the main monocyte functions, is their involvement in the innate immune response against pathogens and during inflammatory processes, in which blood monocytes migrate to the infection site, where the process occurs, and they mature into macrophages or DCs to participate as phagocytes as either by digesting pathogens or cellular debris [13]. In addition, monocytes are antigen-presenting cells (APCs) known for their participation in the antigenic presentation through major histocompatibility complex (MHC) to T cells, also cooperating in the activation of the adaptive immune response [14].

2.2.2. Macrophages

Monocytes are precursor cells that are produced in the bone marrow, which are mobilized into the bloodstream and then differentiate into macrophages at the site of inflammation [15]. Macrophages are a very heterogeneous cell population, such as effector cells of the innate immune system, which play an important role in a host's defense and inflammation. In general, macrophages can be divided into two populations: resident and inflammatory macrophages [16]. Resident macrophages are found in almost all tissues and contribute to their development, as well as immunological surveillance, homeostasis, and tissue repair [17, 18]. On the other hand, inflammatory macrophages are derived from circulatory monocytes and rapidly infiltrate tissues compromised by injury or infection. In response to several signals from the microenvironment, macrophages can be activated and adopt different functions: M1 macrophages (classically activated macrophages) and M2 macrophages (alternatively activated macrophages) [19, 20]. M1 macrophages have proinflammatory functions and participate in a host's defense against pathogens and tumoral cells [21], and it is considered that

they promote the Th1 immune response. When M1 macrophages are activated by interferon (IFN)-γ, granulocyte macrophage colony-stimulating factor (GM-CSF), or other ligands of Toll-like receptor, these macrophages produce proinflammatory cytokines such as interleukin (IL)-1β, IL-12, and tumor necrosis factor (TNF)-α, chemokine (C–C motif) ligand (CCL)-15, CCL20, C-X-C motif chemokine (CXC)-8-11 and CXCL13 and reactivate species of nitrogen and oxygen [22], increase the complement-mediated phagocytosis as their main purpose is to kill intracellular pathogens. In contrast, M2 macrophages are associated with tissue remodeling and tumor progression and have an immunoregulatory effect. M2 macrophages express IL-10, IL-1 receptor antagonist, chemokines (e.g., CCL22 and CCL17), transforming growth factor (TGF)-β, mannose, and galactose receptors and possess efficient phagocytic activity. M2 macrophages are considered to promote the Th2 immune response and antagonize the inflammatory response and its mediators [23, 24].

Macrophages possess a wide range of surface receptors, which gives them an ability to recognize a wide range of endogenous/exogenous ligands to respond adequately, which is critical in these cells. These receptors include Toll-like receptors (TLRs), NOD-like receptors, retinoic acid-inducible gene (RIG)-I family, lectins, and scavenger receptors, which recognize PAMPs, DAMPs, foreign substances, and dead or damaged cells [25–27]. During the inflammatory response by pathogens, macrophages activated with an inflammatory phenotype produce several inflammatory mediators, such as TNF-α, IL-1, IL-6, and INF-γ, which are involved in the activation of microbicidal mechanisms contributing to the pathogen elimination. The inflammatory response of macrophages comprises mainly four stages: (1) recognition of the infectious agent through the macrophages PRRs; (2) in situ recruitment and proliferation of macrophages into infected tissue; (3) elimination of the infectious agent; and (4) the conversion to M2 macrophages to restore damaged tissue [28].

2.2.3. Dendritic cells

Monocytes circulate in the blood, bone marrow, and spleen [29, 30] and represent immune effector cells equipped with chemokine and adhesion receptors that mediate cell migration from blood to tissues during infection. Monocytes produce inflammatory cytokines and phagocyte, both cells and toxic molecules. Monocytes can differentiate into inflammatory DCs during inflammation. Migration to tissues and differentiation to inflammatory DCs depend on the inflammatory environment and PRRs [31]. These PRRs, including the TLR family, are capable to recognize PAMPs, on the surface of bacteria, viruses, fungi, and parasites [29].

DCs represent an important link between innate and adaptive immunity [2]. DCs are heterogeneous population of antigen-presenting cells that are crucial to initiate and polarize the immune response. Although, all DCs are capable of capturing, processing, and presenting antigens to T cells, DCs subtypes differ in origin, location, migration patterns, and specialized immunological roles [32]. There are mainly two subtypes of DCs: classical DCs and plasmacytoid DCs. The classical DCs are cells specialized in the processing and presentation of antigens, with high phagocytic activity as immature cells and high cytokine-producing capacity as mature cells [26]. Classical CDs are highly migratory cells that can move from tissues to the T cell and B cell zones of lymphoid organs. Classical DCs regulate T cell responses both at steady state and during infection. They are usually short-lived and replaced by blood-borne precursors [33, 34].

On the other hand, plasmacytoid DCs differ from classical DCs in that they are relatively long-lived [35]. Plasmacytoid DCs are present in the bone marrow and in all peripheral organs, and they are specialized to respond to viral infection with massive production of type I interferons (IFNs). However, they can also act as antigen presenting cells and control T cell responses [36].

2.2.4. Neutrophils

In humans, about 100 billion neutrophils enter the bloodstream each day [37]. Neutrophils originate from hematopoietic stem cells in response to both extracellular stimuli and intracellular regulators. They come from the myeloid cell line in the formation of granulocytes. The granulopoyesis that occurs in the bone marrow is initiated when the neutrophils myeloblasts (MB) develop in promyelocytes (PM), characterized by a round nucleus and presence of azurophil granules. Subsequently, they mature into myelocytes with specific granules, maturing to metamyelocytes (MM), cells composed by a nucleus with kidney form. Metamielocitos mature to band cells (CB) and in segmented cells (CS) also known as polymorphonuclear cells (PMNs). The PMNs are then called from their segmented nucleus, which are finally released into the bloodstream [38, 39]. Neutrophils play a major role in the resolution of microbial infections. After pathogens break into epithelial barriers, neutrophils are the first cell line of defense for the innate immune response, which are recruited from the bloodstream to the site of infection. Neutrophils cross the blood vessels and migrate to the infection site with the help of chemotactic factors and cytokines, which are produced as inflammatory signals during the tissue damage caused by the invading pathogens. Neutrophils reach the infection site and initiate the phagocytosis process through recognition of PAMPs by their receptors such as TLRs. Neutrophils exert their antimicrobial actions through the release of reactive oxygen species and cytotoxic components contained in their granules such as AMPs [40]. Likewise, neutrophils using a mechanism called extracellular traps (NETs) composed of DNA fibers, which are formed and released into the extracellular space, are used by the innate immune system to destroy and eliminate pathogens [41]. However, studies have shown that neutrophils NETs are involved in the development of several pathologies [42–44]. Finally, neutrophils can also regulate the adaptive immune response, as they mediate suppression of T cells proliferation as well as their activity. Neutrophils can also stimulate and activate splenic B lymphocytes [45].

2.2.5. Eosinophils

Eosinophils are produced in the bone marrow from pluripotent stem cells, which first differentiate into a precursor for basophils and eosinophils and then differentiate into an eosinophilic lineage [46]. IL-3, IL-5, and GM-CSF are particularly important in regulating the eosinophils development [47–50]. Of these three cytokines, IL-5 is the most specific for the eosinophilic lineage and is responsible for the selective differentiation [51] and release of eosinophils from the bone marrow into the peripheral circulation [52]. IL-5 plays a critical role in the eosinophils production, as the overproduction [53, 54] and neutralization [55–57] of this cytokine are associated with a significant increase or decrease in eosinophilia, respectively.

Eosinophils are multifunctional leukocytes involved in the pathogenesis of numerous inflammatory processes [58], including parasitic helminths infections and allergic diseases [59–61]. Under basal conditions, most eosinophils traffic into the gastrointestinal tract where

they normally reside within the lamina propria, whose production is independent of lymphocyte production [62]. Recruitment of gastrointestinal eosinophils is regulated by the constitutive expression of eotaxin-1 [63], a chemokine involved in allergen-induced eosinophil responses [64].

In response to several stimuli, such as immunoglobulins, cytokines, and complement system, eosinophils are activated and recruited from the circulation to the site of inflammation [65]. The trafficking of eosinophils into inflammatory sites involves various cytokines derived from a Th2 immune response such as IL-4, IL-5, and IL-13 [66, 67], adhesion molecules (e.g., β1, β2, and β7 integrins) [68] and chemokines (e.g., eotaxins) [69]. Once at the site of inflammation, eosinophils can modulate the immune response through the secretion of several proinflammatory mediators such as IL-2, IL-6. IL-8, TGF-α/β, GM-CSF, TNF-α, INF-γ, as well as chemokines and lipid mediators, such as platelet-activating factor (PAF) and leukotriene (LT)-C4 [70], which exert proinflammatory effects as positive regulation of adhesion systems, modulation of cellular trafficking, activation and regulation of vascular permeability, mucus secretion, and smooth muscle constriction. In addition, eosinophils can serve as effector cells, which can induce tissue damage by releasing a diverse of cationic proteins from their cytotoxic granules, major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil peroxidase (EPO), and neurotoxin derived from eosinophils (EDN) [59]. These proteins are very important, because they are directly related to the effector functions of eosinophils. For example, ECP is involved in the suppression of T cell proliferative responses, and the synthesis of immunoglobulins by B cells induces mast cell degranulation and stimulation of mucus secretion in the airways, as well as the production of glycosaminoglycans by human fibroblasts [71], while EPO is associated in the formation of reactive oxygen species and reactive nitrogen metabolites. These molecules promote oxidative stress and subsequent cell death by apoptosis and necrosis [72–74].

In addition to the multiple effector actions of eosinophils, these cells can initiate antigen-specific immune responses by acting as APCs [75, 76], as they can process and present a variety of bacterial [77], viral [78], and parasitic [79] antigens. Although investigations demonstrated a direct association of eosinophils with parasitic helminths infections, establishing the hypothesis that eosinophils are the classic effector cells in a host's defense [80]. Several studies have also shown that the eosinophils absence during parasitic helminths infections protects the host [81], so that eosinophils may influence the immune response in a manner that supports chronic infection and ensures survival of the parasite in the host [82–84].

2.2.6. Basophils

Basophils are cells derived from the myeloid hematopoietic progenitors in the bone marrow, and they are phenotypically and functionally distinct from other leukocytes, including mast cells, since mast cells reside in tissues while basophils reside in the circulation and can be recruited to the tissues [85–89]. Basophils have the ability to bridge innate and adaptive immunity, including the capacity to induce and propagate Th2 immune responses [90]. Basophils are important in all allergic diseases, including anaphylaxis, allergic rhinitis, asthma, urticaria, and food allergies. Basophils rapidly release histamine and synthesize LTC4 after that immunoglobulin (Ig)-E binds to their receptor FcεRI and subsequently produces Th2

cytokines such as IL-4 and IL-13 [91–95], causing the clinical symptoms of immediate hypersensitivity, also promoting delayed hypersensitivity reactions [96–99]. The role of basophils in protective immunity against helminths is well known [96, 100]. However, recently, basophils have also been implicated in the initiation of immune responses against bacterial respiratory infection [101].

2.2.7. Mast cells

Mast cells are granulated tissue-resident cells from $CD34^+$ hematopoietic progenitor cells [102, 103]. Mast cells circulate as immature cells and migrate to vascularized tissues, where they complete their differentiation. Mast cells represent, together with dendritic cells, the first immune cells that interact with environmental antigens, pathogens, and toxins. Therefore, they can be considered "sentinels" of the innate immune system [104]. Mast cells are activated by danger stimuli, which they react by rapidly releasing a wide range of mediators, both preformed and newly produced. Some of these mediators (e.g., histamine, TNF-α, vascular endothelial growth factor, VEGF) contribute to local vascular permeability and edema at the site of inflammation [105], while chemokines (e.g., IL-8/CXCL8, eotaxin) induce the recruitment of other immune cells [106], such as neutrophils, natural killer (NK) cells, and eosinophils. It is important to note that mast cells may also be involved in the defense against pathogens by different mechanisms, such as phagocytosis, antimicrobial peptide release, or the production of extracellular traps similar to those described in neutrophils [107, 108]. Mast cells detect these invading pathogens through PRRs, such as TLRs [109]. Investigations have shown that bacterial and viral proteins can activate mast cells through specific receptors [110, 111].

Mast cells express the high affinity receptor for IgE (FcεRI) [90, 112]. Cross-linking of the FcεRI by IgE-antigens and/or allergens complexes induces mast cell activation and rapid release of proinflammatory mediators via degranulation. Due to this property, together with circulating basophils, mast cells are known primarily as effector cells for IgE-mediated (Th2-like) responses [113], an arm of the adaptive immune system against helminths infection [114], and as primary effector cells in hypersensitivity reactions [115]. In addition to their functions as effector cells, recent evidence suggests that mast cells are capable to modulate both the innate and adaptive immune response, acting as immunomodulatory cells [116, 117].

2.2.8. Platelets

Platelets are cytoplasmic fragments (1 to 4 μm in diameter) produced as a result of fragmentation from megakaryocytes that are cells from bone marrow. Platelets are non-nucleated organelles that have functional characteristics like complete cell, since they possess cytoskeleton, mitochondria, Golgi residues, and endoplasmic reticulum involved in the synthesis of enzymes, storage of calcium ions, as well as storage granules [118, 119]. These storage granules are δ-granules [120], α-granules, and lysosomal granules [121], which play an important role in homeostasis, inflammation, wound healing, and cell-matrix interactions. During the inflammatory response, platelets can be activated through their receptors, which act as adhesion molecules that interact with damaged endothelium, other platelets and leukocytes,

playing an important role in the coagulation process for repairing the damaged blood vessel and restoring its integrity [122–124].

2.3. Lymphoid cells

Lymphoid cells include the NK cells, natural killer T (NKT) cells, and innate lymphoid cells (ILCs). ILCs are a novel family of hematopoietic effectors that serve protective roles in innate immune responses to infectious microorganisms, in lymphoid tissue formation, in tissue remodeling after damage inflicted by injury or infection and in the homeostasis of tissue stromal cells [125].

2.3.1. Innate lymphoid cells (ILCs)

ILCs represent the innate version of helper and cytotoxic T cells as part of the innate immune system, which play essential roles in the early immune response [126, 127]. All members of the ILCs family are characterized by a classical lymphoid cell morphology and the expression of IL-7Ra (CD127) and CD161, but they lack the expression of cell surface molecules that characterize other types of immune cells such as T cells (CD3, TCR$\alpha\beta$, and TCRδ), B cells (CD19), NK cells (CD16 and CD94), myeloid cells (CD1a, CD14 and CD123), granulocytes (FcεR1α and CD123), stem cell hematopoietic (CD34), and plasmacytoid dendritic cells (BDCA2 and CD123), so they are defined as cells that do not express lineage markers (Lin-) [128]. ILCs can be classified based on their phenotypic and functional characteristics in three groups: Group 1 (ILC1) comprises cells that have the ability to produce IFN-γ as their major effector cytokine and express the T-bet transcription factor. The prototype cell of this group is the NK cell. Group 2 (ILC2) are cells that require IL-17 for their development. These cells are characterized by cytokine production associated with the Th2 immune response, in response to stimulation with IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) and shows a GATA3 and RORα phenotype for their development and function. Group 3 (ILC3), includes cell subtypes that produce IL-17 and/or IL-22 and IFN-γ, and these cells depend on the RORγt transcription factor for their development and function [129]. Recent studies have identified various functions of ILCs cells: (1) ILCs promote a host's defense against infections and regulate interactions with the microbiota; (2) as well as orchestrate wound healing and tissue repair and (3) in other circumstances, ILCs may promote inflammation and tumor progression [130]. ILCs are poorly represented in lymphoid tissues, but they are found to be important in parenchymal tissues, especially mucosal surfaces. Therefore, the subtypes of ILCs play an important role in the innate immune response to viruses, bacteria, fungi, and intracellular and extracellular parasites in this type of tissue, and they have a rapid activation through cytokines and growth factors [125, 131].

2.3.2. Natural killer cells

NK cells are derived from cellular lymphoid progenitors. However, they do not mediate the conventional adaptive immune response because they lack antigen-specific receptors such as T and B lymphocytes [132]. Previously, it was believed that the development of NK cells

in humans occurred exclusively in the bone marrow. However, recent studies have shown that NK cells also develop in secondary lymphoid organs [133]. The dominant population of the NK cells in blood circulation has a $CD56^{dim}CD16^{+}$ phenotype corresponding to its final maturation stage, whereas the NK cells with phenotype $CD56^{bright}$ are considered as relatively immature cells [134]. NK cells are important effector lymphoid cells of the innate immune system, since they represent a key element in the rapid recognition and death of both infected or tumorigenic cells, which can cause damage to the integrity of host tissues. NK cells identify target cells (cells that have some damage) through complex combinations of signals from the activation or inhibition of receptors, which interact with ligands that are expressed on the surface of stressed or normal cells, respectively [135]. The decision to eliminate or not eliminate these cells depends on the result of the balance between positive (activation) and negative (inhibition) signals. Also, the activation of NK cells is regulated through cooperation with other immune cells, including DCs [136], which allows that NK cells to acquire potent cytotoxic activity, the ability to produce cytokines such as IFN-γ and contribute to the adaptive immune response by triggering the T cell–mediated response [137].

2.3.3. Natural killer T cells

NKT cells constitute a small subpopulation of lymphocytes that are characterized by the markers expression of the NK cell lineage, as well as receptors of the $\alpha\beta$ T lineage. NKT cells develop in the thymus and have the same common lymphoid precursor of conventional T cells, but they have phenotypic and functional characteristics different of T cells [138]. Four subpopulations of NKT cells $CD4^{+}$, $CD8^{\alpha\beta+}$, $CD8^{\alpha\alpha+}$, and double negatives ($CD4^{-}CD8^{-}$) were identified in human peripheral blood [139], which differ in the cytokine secretion profile and the expression of chemokines receptors, integrins, and NK receptors [140]. In addition, NKT cells recognize glycolipid antigens that are presented through CD1d molecules, MHC-like molecules that are constitutively expressed by antigen presenting cells such as DCs, B cells, and macrophages. NKT cells also have the ability to respond to cells participating in innate immunity with minimal involvement of the T cell receptor (TCR), and memory cells through a portion of the TCR, which makes them capable to be a bridge between the innate and adaptive immune response [141].

3. Pattern recognition receptors in innate immunity

Pathogens that invade a human host are controlled by the immune system, both innate and adaptive. The adaptive immune system, which is mediated by T and B cells, recognizes pathogens with high affinity through the rearrangement of certain receptors. However, the establishment of this adaptive immune response is often not fast enough to eradicate pathogens, and it also involves cell proliferation, genetic activation, and protein synthesis [142]. Thus, the fastest defense of a host mechanism is provided by the innate immune system, which has developed the ability to recognize invading pathogens and thus effectively eliminate them so that they do not cause damage to host cells.

The recognition of pathogens occurs through cells involved in the innate immunity response by nonspecific molecules that are commonly shared by most pathogens called PAMPs. PAMPs are highly conserved products and are produced by numerous microorganisms. These PAMPs do not show specific structures with antigenic variability, and host cells do not share the same molecular patterns with pathogens, resulting in recognition of the immune system, capable to discriminate between self and nonself [143]. Among the PAMPs that present the pathogens are lipopolysaccharide (LPS), peptidoglycan (PGN), lipoteichoic acid, unmethylated cytosine phosphor-guanine (CpG) motifs, double-stranded RNA virus, and the cell wall component of yeast called manan. LPS represents the major component of Gram-negative bacteria, as PGN represents the major component of Gram-positive bacteria [144]. Recognition of these PAMPs is mediated through PRRs, primarily attributed to the family TLRs [142].

However, pathogens are not the only cause of cell and tissue damage. A trauma, a vascular event, even in physiological states as well as in disease states, are other causes of damage, and when this occurs, intracellular proteins called "alarminas" are released, which are considered in a subgroup of a large quantity of DAMPs [145]. This occurs by identifying changes in the host's own structures that show signs of damage and then repairing and removing damaged tissue. DAMPs include any endogenous molecule that experiences a change of state in association with a tissue injury, which allows the immune system to be informed that any damage has occurred [146].

When these DAMPs are released from damaged or necrotic cells, together with PAMPs, are recognized by certain PRRs for their subsequent activation and induction of a potent acute inflammatory response [147]. These PRRs include Toll-like receptors (TLRs), nucleotide-binding domain and leucine-rich repeat containing receptors (NLRs), and retinoic acid-inducible gene-I (RIG-)-like receptors (RLRs).

TLRs are evolutionarily conserved proteins that detect PAMPs. They were originally identified in the *Drosophila* fly as an important gene for its ontogenesis and its immunological resistance against fungal infections. In addition, it was found that during microbial infections of flies, Toll receptors induce the production of antimicrobial peptides [148]. In humans, the first protein structurally related to the *Drosophila* Toll receptor was identified and called the Toll-1 receptor (TLR-1). These proteins are characterized by the presence of an extracellular domain formed by leucine-rich repeats, in which the recognition of the PAMPs is given; and an intracellular region called intracellular Toll/IL-1R (TIR), which is responsible for the signals transmission that culminates in the activation of nuclear factor (NF)-κB, which induces the synthesis of proinflammatory cytokines [149]. Currently, 10 TLRs have been identified (TLR-1 to TLR-10), the TLR-1, TLR-2, TLR-4, TLR-5, and TLR-6 expressed on the cell surface; while TL-3, TLR-7, TLR-8, and TLR-9 are found intracellularly in endosomes [150].

Different TLRs specifically recognize distinct PAMPs and DAMPs [151]. TLR-2 forms heterodimers with TLR-1 or TLR-6. The TLR-1/TLR-2 complex mainly interacts with lipopeptide triacyl ligands in contrast to the TLR-2/TLR-6 complex, which binds only to diacyl lipopeptides. TLR-3 recognizes double-stranded RNA ligands, which are produced by most viruses in replication stages. TLR-4 requires binding with the MD-2 co-receptor and is specific for

interacting with LPS ligands, which comes from Gram-negative bacteria. TLR-5 responds to bacterial flagellin ligands. Both TLR-7 and TLR-8 recognize single-stranded ARN. TLR-9 binds to ligands containing CpG motifs [152]. TLRs are a family of transmembrane receptors that are key in the response and regulation of both innate and adaptive immunity [151], since they recognize diverse pathogens and help to eliminate them.

There are other receptors such as NLRs, which are a family of 23 members that have been identified in humans. They are intracellular receptors that are structurally composed of caspase recruitment domains (CARDs), as in the case of members called NODs, a pryin domain, as in the case of NLRP members. Among the most important members of these receptors are NOD1 and NOD2, which recognize specific ligands from various pathogens. This family is involved in increasing the proinflammatory events caused by cell death, pyroptosis and pyronecrosis, and several more proinflammatory processes [153].

Another family of receptors is the RIGs. They are intracellular recognition receptors for patterns involved in the recognition of viruses by the action of the innate immune system. There are three members: RIG-1, MDA-5, and LGP2. They act as sensors for viral replication within human host cells necessary to mediate antiviral responses [154].

4. Soluble mediators of the innate immune system

In innate immunity, a large number of soluble mediators such as cytokines, chemokines, and the complement system participate. All these mediators provide protection in the initial phase of contact with pathogens and are responsible for preventing potentially harmful infections.

4.1. The complement system

The complement system has been considered as an effector response of the innate immune system capable of eliminating a great diversity of pathogens including bacteria, viruses, and parasites [155]. The complement system is composed of plasma proteins, which are present as inactive proteins [156]. After activation, the products that are generated from the complement system facilitate the recruitment of cells from the immune system to the site of damage to eliminate the pathogen through opsonization or direct destruction [157]. Activation of the complement system occurs through three pathways: (1) the classical pathway for the antigen–antibody complex; (2) the alternating pathway through the spontaneous hydrolysis of C3; and (3) the lectin pathway where certain sugars are recognized on the surface of the pathogens through mannose-binding lectin (MLB). Once activated, the pathway of the complement system generates a multimolecular enzyme complex that cuts to C3 and forms C3a and C3b. The C3b fragment that is generated binds to C3 convertase to form the C5 convertase, and once formed, this complex cuts to C5 to form C5a and C5b [155]. Then, C5b begins to recruit complement components C6, C7, C8, and C9 to form the membrane attack complex which is a lytic pore inserted into the membrane of the pathogen [158]. Since the complement system uses multiple activation pathways, it has the ability to maximize the number of pathogens that it

can recognize and thus eliminating a great diversity of these. In addition, it is responsible for eliminating apoptotic cells, this occurs through depositing a low amount of C3b molecules which facilitates the removal of these cells by macrophages [159].

4.2. Cytokines

Cytokines form a molecular network that is synthesized and released by different cell types. These molecules act in a paracrine and endocrine way through their receptors that express the target cell. These molecules are synthesized and released in response to some damage or recognition of specific structures of the pathogens through their receptors (e.g., PAMPs and TLRs) [160]. Initially, the cytokines were defined based on the activity they performed, among these activities are regulating the immune system but also exerting an effector function on the cells, these effects not only occur at local level but also occur through the tissues or systems. Cytokines are involved in regulating the homeostasis of the organism but when its production or its signaling pathway in the cell is not regulated, this homeostasis is altered, which can trigger in a pathology [161, 162]. Cytokines can be classified into five groups: type I cytokines (include cytokines from IL-2 to IL-7), type II cytokines (interferons and cytokines of the IL-10 family), type III cytokines (the TNF family), type IV cytokines (IL-1 family, such as IL-1, IL-18, IL-36, IL-37, and IL-38), and type V cytokines (the IL-17 family that includes IL-17E) [162]. Cytokines may increase systemic level during some pathological condition, either acute or chronic, these molecules exert their effect by binding to their receptors, where the signal translation is given, which leads to the gene expression and finally can regulate the function of the target cell. The cytokine pattern that is released from the cell depends primarily on the nature of the antigenic stimulus and the type of cell being stimulated. Cytokines compromise leukocytes to respond to a microbial stimulus, through regulating positively the expression of adhesion molecules on endothelial cells and amplifying the release of molecules such as reactive oxygen species and nitrogen, histamine, serotonin, as well as arachidonic acid derivatives, which regulate the release of the cytokines. On the other hand, cytokines can promote apoptosis by binding to receptors that contain death domains, for example TNF receptor 1(R1) [163].

4.3. Chemokines

Chemokines or chemotactic cytokines are small molecules which constitute a large family of peptides (60–100 amino acids) structurally related to cytokines. Their main function is to stimulate leukocyte migration. They are secreted in response to some signals such as proinflammatory cytokines, where they play an important role in selectively recruiting monocytes, neutrophils, and lymphocytes [164, 165]. These molecules are defined by the presence of four conserved cysteine residues that form two disulfide bonds (Cys1-Cys3 and Cys2-Cys4) and are classified into four families based on the number of amino acids between the first two cysteines: CXC-(α), CC-(β), CX3C-(δ), and C-(γ) according to the systematic nomenclature [166]. The chemokines CXC and CC are distinguished according to the position of the first two cysteines, which are adjacent (CC) or separated by an amino acid (CXC) [167]. The CC chemokine family is the largest and can be subdivided into several subfamilies. One is monocyte chemotactic protein (MCP), this subfamily is characterized by recruiting monocytes to damaged tissue after

ischemia, which is conformed for five members: CCL2 (MCP-1), CCL8 (MCP-2), CCL7 (MCP-3), CCL13 (MCP-4), and CCL12 (MCP-5). Another chemokine in this group is the macrophage inflammatory protein (MIP)-1α (CCL3), MIP-1β (CCL4), and RANTES (CCL5) [168]. The second family consists of CXC chemokines; the prototype of these chemokines is IL-8 (CXCL8); mainly this chemokine attracts polymorphonuclear cells to the site of acute inflammation. Also, CXCL8 activates monocytes and can recruit these cells to vascular injury. The third family, consisting of a single member is Fraktalkine (CX3CL1) which is one of the two transmembrane chemokines and has two isoforms, one binds to the membrane and the other is a soluble form. According to its isoform, it may have different functions, the form that is anchored to the membrane serves as adhesion molecule for cells expressing CX3CR1, while the soluble form possesses a potent chemotactic activity [169]. The fourth family has only one member lymphotoxin (XCL1); this chemokine is similar to members of the CC and CXC families, but the lack of two of the four cysteine residues are characteristic of this chemokine. Its chemotactic function is for lymphocytes and not for monocytes and neutrophils as do other chemotactic chemokines [170].

5. Immune response against pathogens

Inflammation is a protective response to extreme challenges to homeostasis, such as infection, tissue stress, and injury [171], which is characterized by its cardinal signs: redness, swelling, heat, pain, and disrupted function [172]. A typical inflammatory response consists of four components: (1) inflammatory inducers: depending on the type of infection (bacterial, viral, fungi or parasitic) [173]; (2) sensors that detect the inflammatory inducers: these sensors are receptors of the innate immune system such as TLRs, NLRs and RLRs [153, 174]; (3) inflammatory mediators induced by the sensors, such as cytokines, chemokines and the complement system [175]; (4) target tissues that are affected by the inflammatory mediator. Each component comes in multiple forms and their combinations function in distinct inflammatory pathways.

The inflammatory reaction is characterized by successive phases: (1) silent phase, where cells reside in the damaged tissue releases in the first inflammatory mediators, (2) a vascular phase, where vasodilation and increased vascular permeability occur, (3) cellular phase, which is characterized by the infiltration of leukocytes to the site of injury [176], and (4) resolution of inflammation, which is the process to return tissues to homeostasis [177, 178].

5.1. Immune response against bacteria

In an infection by extracellular bacteria, the host triggers a series of responses to combat the pathogen and prevent its spread. The main mechanism of the innate immune response to eradicate bacteria is activation of the complement system, phagocytosis, and inflammatory response (**Figure 1**). Both the alternative and the lectin pathways of the complement system participate in the bacteria opsonization and potentiate their phagocytosis. To perform the correct phagocytosis, activation of several surface receptors in phagocytes, including scavenger receptors, mannose, Fc, and mainly TLRs is required. Activation of these receptors

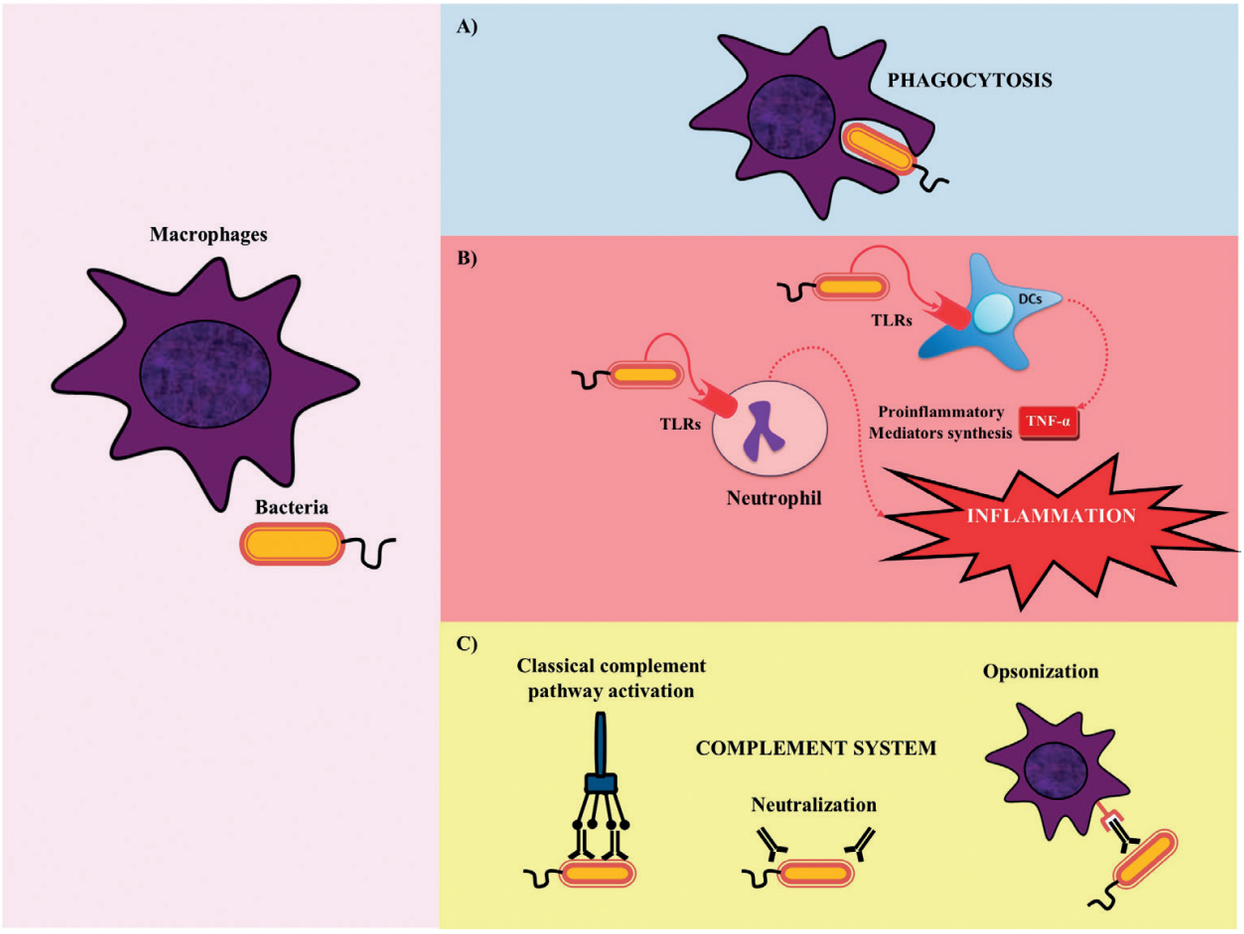

Figure 1. Immune response against bacteria. Mechanisms of the innate immune response to eradicate bacteria are (A) phagocytosis, (B) inflammatory response, and (C) participation of the complement system. Description in the text.

results in inflammation, by recruiting leukocytes to the site of infection [152]. On the other hand, the humoral adaptive immune response is the main protective against extracellular bacteria. Its primary function is to block infection, through the release of antibodies that are directed against the antigens of the bacterial cell wall, as well as of the toxins secreted by certain extracellular bacteria. The effector mechanisms used by the antibodies include neutralization, opsonization, and classical complement pathway activation, which allow bacteria phagocytosis. In the case of neutralization, IgG, IgM, and IgA participate; while in the opsonization, the IgG participates; and in complement activation, the IgM and some subclasses of IgG participate. Protein antigens from extracellular bacteria also activate the cellular adaptive immune response, which is mediated by $CD4^+$ T cells. These $CD4^+$ T cells produce cytokines that induce local inflammation, increase phagocytosis, as well as microbicidal activities of macrophages and neutrophils. The Th17 cells are also involved in recruiting monocytes and neutrophils, promoting local inflammation. Similarly, there is an induction of the Th1 immune response that contributes to the macrophages activation with ample phagocytic capacity and the production of the cytokines, such as IFN-γ [179].

In the case of infection by intracellular bacteria, they have the ability to survive and replicate within phagocytic cells, which causes the circulating antibodies to be inaccessible to intracellular

bacteria. The innate immune response against these bacteria is mediated primarily by phagocytes and NK cells [180]. Among the phagocytes involved are neutrophils and then macrophages. However, these pathogens are resistant to degradation, but their products are recognized by TLRs and NLR receptors that are responsible for activating more phagocytes. NK cells are also activated in this type of infections and participate by stimulating the production of cytokine IL-12 by DCs and macrophages. Also, the NK cells produce IFN-γ, which promotes the death of phagocytic intracellular bacteria. But usually this immune response is ineffective against infection. In contrast, the adaptive immune response against infections by intracellular bacteria is mediated by $CD4^+$ T cells that help recruit and activate phagocytes that kill the pathogen, and the response of cytotoxic $CD8^+$ T cells that kills the infected cells. Both subpopulations of T cells respond through the antigen presentation by MHC type I and II. All this to eradicate the infection of the host [181].

5.2. Immune response against fungi

Most fungi are present in the environment, so animals including humans are exposed and then can inhale spores or yeasts [182]. The mechanisms for defense against the fungi comprise of both innate and adaptive immune responses. TLRs recognize several PAMPs, so that TLR1, TLR2, TLR3, TLR4, TLR6, and TLR9 have been implicated in the recognition of PAMPs from fungi. Activation of TLR4 and CD14 by recognition of conidia derived from some fungi has been shown to increase the production of inflammatory molecules such as TNF-α. Meanwhile, the TLR2 may recognize conidia and hyphae, as well as β-glucans from pathogenic fungi *Coccidioides*. TLR2 activation induces oxidative pathways in polymorphonuclear (PMN) cells with the release of gelatinases and inflammatory cytokines. TLR6 is involved in the recognition of *Candida albicans*, which is involved in the production of IL-23 and IL-17A, which promote Th17 responses. TLRs can be combined to recognize a large number of fungal structures and thus generate a broader response against the various fungal structures [183, 184].

The NLRs are involved in detection of fungal structures, such as *Aspergillus fumigatus* hyphal fragments, and once activated the production of IL-1β and IL-18 is induced by the formation of a multimeric complex known as inflammasome [182, 185].

Type C lectin receptors (CTLRs) make up a receptors family that can recognize several molecules like proteins, carbohydrates, and lipids. Among these receptors, the best studied are dectin-1, dectin-2, dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN), macrophage inducible C-type lectin, and mannose receptor (MR) involved in the recognition of some structures of the fungi [186]. Dectin-1 recognizes β-glucan and promotes its phagocytosis, it can also interact with TLR2 to induce the activation of NF-κB and the production of reactive oxygen species [187]. Dectin-1 activation can also induce mast cells to produce proinflammatory and TH2-polarizing cytokines, such as IL-4 and IL-13. Dectin-2 also activates NF-κB. In addition, dectin-2 promotes Th17 polarization by inducing IL-17A, which is crucial in neutralizing some fungi. The MR recognizes mannose, fucose, or N-acetylglucosamine residues present in fungi. MR generates a Th17 response and promotes fungi phagocytosis [183]. The response that occurs through the activation of these receptors includes the binding to fungi and their phagocytosis, the induction of antifungal effector mechanisms and the production of soluble mediators such as cytokines, chemokines, and inflammatory lipids [187].

The immunity against fungi requires the recruitment and activation of phagocytosis, which is mediated through factors that induce inflammatory molecules such as proinflammatory cytokines and chemokines. The PRRs interaction with fungal structures plays an important role in the control of infections against these pathogens, since this interaction is determinant for the generation of the profile of cytokines or chemokines that influence the immune response. For example, the interaction of *Candida albicans* with TLR4 or TLR2 generates a Th1 or Th2 response, respectively. Therefore, these interactions of the different fungal structures and the PRRs generate different responses polarizing toward one or the other depending on the cytokine profile that could be generated after these interactions (**Figure 2**) [188].

5.3. Immune response against viruses

In an infectious process, the most common host response is to generate inflammation. Viruses in the absence of cytopathologic damage at early stages of infection inhibit the induction of acute phase protein response because early monocytes are not activated. By contrast, the participation of NK cells against the virus play an important role in the host's defense, they recognize cells infected by viruses in an antigen-independent manner, exert cytotoxic activities and rapidly produce large amounts of IFN-γ that participate in the activation of the adaptive immune cell [5]. Type I interferons are the major cytokines responsible for defending the human host against viral infections. It has been shown that interferons

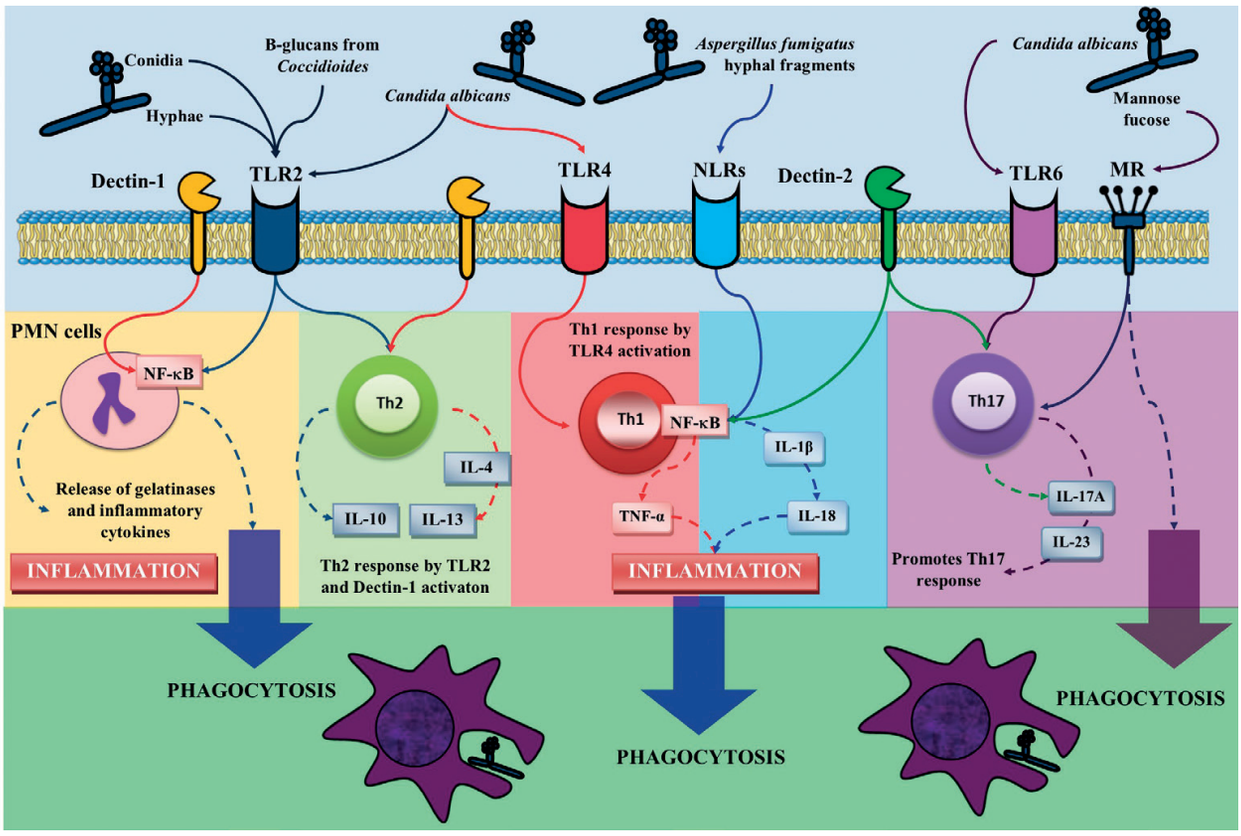

Figure 2. Immune response against fungi. PRRs, such as TLR2, 4, 6, NLRs, dectins-1 and 2, and RM, are involved in the recognition of some structures of the fungi. The activation of these receptors includes the binding to fungi and their phagocytosis. Description in the text.

do not exert their antiviral effects by direct action on viruses, but they help in the gene activation that results in the production of antiviral proteins, which participate as mediators in the inhibition of viral replication, as well as mediating the effects of suppressor T cells [189].

The adaptive immune response against this type of infection is primarily composed of the humoral immune response with the antibody production directed against viral antigens. However, the cellular immune response is the most important for virus eradication. T $CD4^+$ cells recognize antigens presented by MHC-II molecules on the surface of APCs [190]. Subsequently, T $CD4^+$ cells perform multiple effector functions including direct activation of antigen-specific macrophages and B cells, as well as cytokine-dependent activation of T $CD8^+$ cells. T $CD8^+$ cells eliminate virus-infected cells and secrete cytokines such as TNF-α and IFN-γ, which also participate in the inhibition of viral replication. Thus, both the innate immune response and the adaptive immune response in their cellular and humoral involvement eradicate viral infections in most cases (**Figure 3**). However, certain viruses have developed mechanisms of immune evasion to survive longer and thus be able to replicate without any problem until causing serious damage to the host [191].

5.4. Immune response against parasites

Due to there being a large variety of parasites and that each of their life cycles are very complex, in this section, we will focus on the immune response against helminth parasites. This is

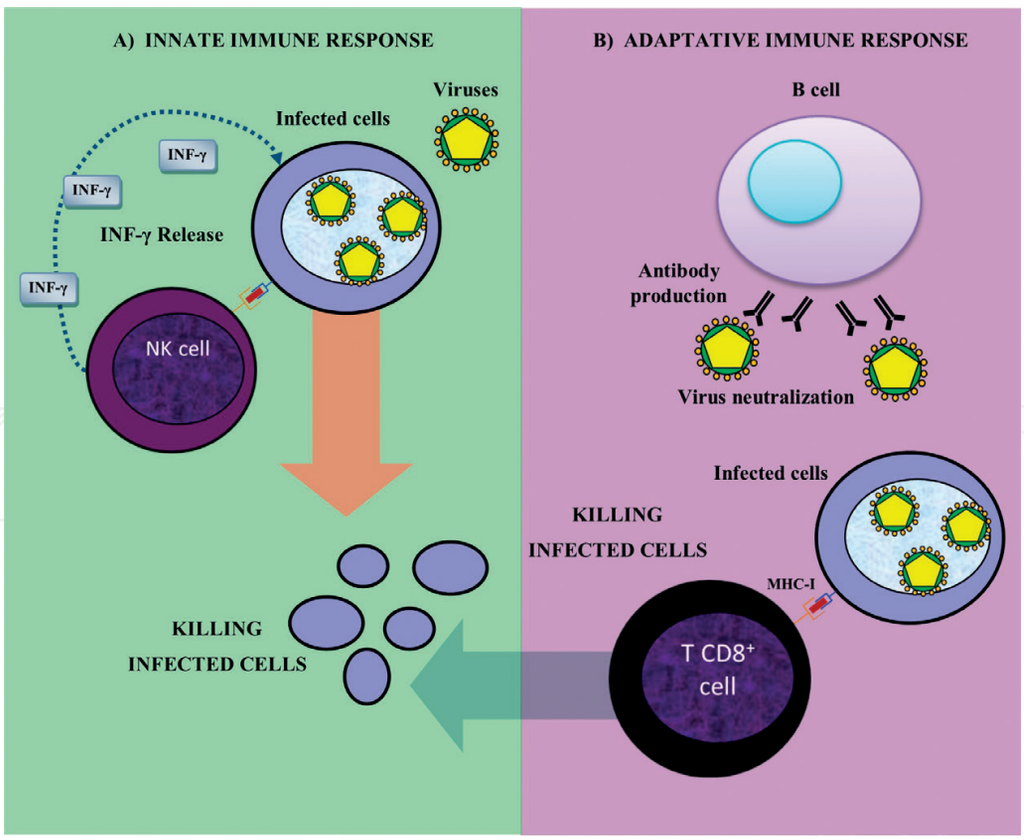

Figure 3. Immune response against viruses. (A) Innate immune response: NK cells recognize cells infected by viruses in an antigen-independent manner, exert cytotoxic activities and rapidly produce large amounts of IFN-γ to eliminate infected cells. (B) Antibody production directed against viral antigens. T $CD8^+$ cells eliminate virus-infected cells and secrete cytokines such as TNF-α and IFN-γ. Description in the text.

because more than 1 billion people are currently infected with helminth parasites worldwide [192], making them one of the most prevalent infectious agents responsible for many diseases in both animals and humans [193]. The investigation of these parasitic infections is not only of direct relevance to human and animal health but also because they present a constant and important challenge to the host immune system, since both in humans and animals, helminth parasites establish chronic infections [194] associated with a significant downregulation of the immune response.

The first defense barrier during intestinal helminth parasites infection is the mucus layer secreted by the host's intestine, either in a larval stage during the early infectious process or as adult parasites during the reproductive phase of infection. Thus, helminth parasites will interact with the mucus layer and in many cases will have to cross it to reach the epithelial layer and thus thrive and reproduce within it [192].

The immune response against helminth parasites involves both the innate and adaptive immune response [195, 196]. Helminth parasite antigens are capable of inducing the DCs maturation, leading to the expression of MHC class II [197, 198], promoting the development of a Th1 type cellular immune response (**Figure 4A**) [199]. Several studies have shown that during intestinal infection by helminth parasites, there is an increase in the levels of

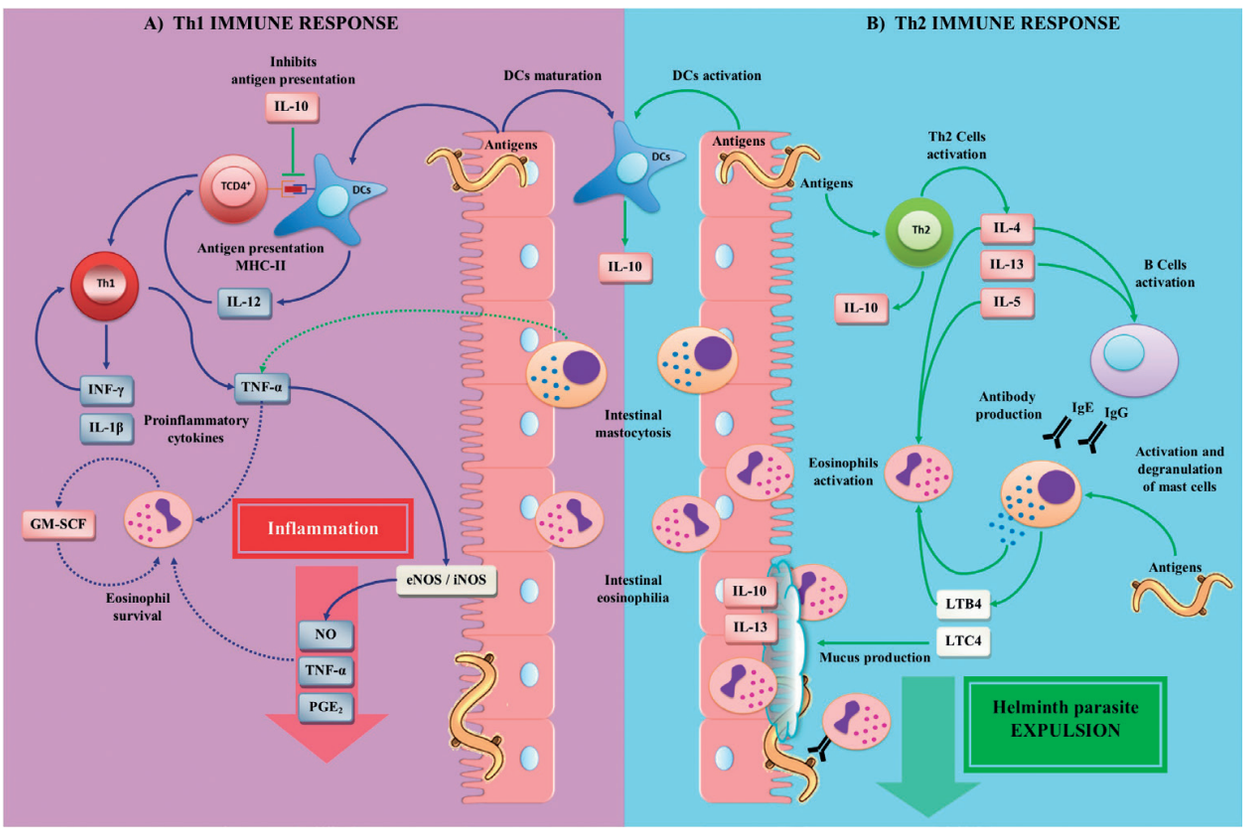

Figure 4. Immune response against parasites. (A) Th1 immune response: helminth parasites antigens induce maturation of DCs by polarizing a Th1 immune response, which is mainly characterized by the release of IL-12, INF-γ, GM-SCF, NO, PGE_2, IL-1β, and TNF-α, which together with eosinophilia (derived from the Th2 immune response) enhance intestinal inflammatory response, resulting in the development of intestinal pathology, creating a favorable environment for the helminth parasites survival. (B) Th2 immune response: helminth parasites antigens activate T cells that together with IL-10 induce a Th2 immune response characterized by the release of IL-4, IL-5, IL-10, and IL-13 favoring helminth parasites antigens expulsion.

gene expression of TLR4 and TLR9 [200], with a significant increase of proinflammatory cytokines such as IL-12, INF-γ, IL-1β, TNF-α, nitric oxide (NO), and prostaglandin (PG)-E_2 [201–207].

Helminth parasite antigens also induce Th2 immune response (**Figure 4B**) trough $CD4^+$ T cells [208], and DCs activation, leading to the secretion Th2 cytokines, such as IL-10 [209], IL-4, IL-5 [210], and IL-13 which stimulate IgE synthesis, inducing mast cell and eosinophil hyperplasia, triggering immediate hypersensitivity reactions, promoting the helminth parasites expulsion from the intestine [197, 208, 211–213]. However, mast cells rapidly expand in the mucosa, where helminth parasites antigens can directly induce their degranulation, releasing effector molecules such as histamine, serine proteases [197], TNF-α, LTC4, LTB4 [213], IL-4, IL-13 [201], which together with the eosinophils contributes to the intestinal inflammation development [214, 215].

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