Chapter

Role of Dendritic Cells in Pathogen Infections: A Current Perspective

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Abstract

Dendritic cells (DC) represent an important link between innate and adaptive immunity, which play an important role during the immune response against pathogens. There are several populations and subpopulations of DC, but mainly two subpopulations are characterized: the classic DC specialized in the processing and presentation of the antigen; and the plasmacytoid DC that have a high phagocytic activity and capacity for the production of cytokines. This chapter aims to present the current aspects related to the most relevant characteristics and functions of DC, as well as their role in host defense against infections by viruses, parasites, bacteria, and fungi.

Keywords: dendritic cells, pathogen infections, innate immune response, inflammation

1. Introduction

DCs represent an important link between innate and adaptive immunity. 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 [1]. All the DCs are continuously renewed by hematopoietic stem cell progenitor cell located in bone marrow, except of Langerhans cells (LCs) that develop from embryonic macrophages in the yolk sac and fetal liver, that are recruited in the epidermis during embryonic life. The process is not clearly, but hematopoietic stem cell is differentiated into granulocyte-macrophage progenitors (GMP) and multilymphoid progenitors (MLP), that have the potential to differentiate into macrophage-dendritic precursor (MPD) or common dendritic cell progenitor (CDP) like progenitor. These progenitors are subsequently differentiated into common monocyte progenitor (cMoPs), plasmacytoid dendritic cells (pDCs) and human equivalent of pre-DC, those are the most important to differentiate all subsets of DCs. cMoPs develop into blood monocytes, which differentiate into monocyte-derived DCs (MoDCs) in inflamed tissues, and

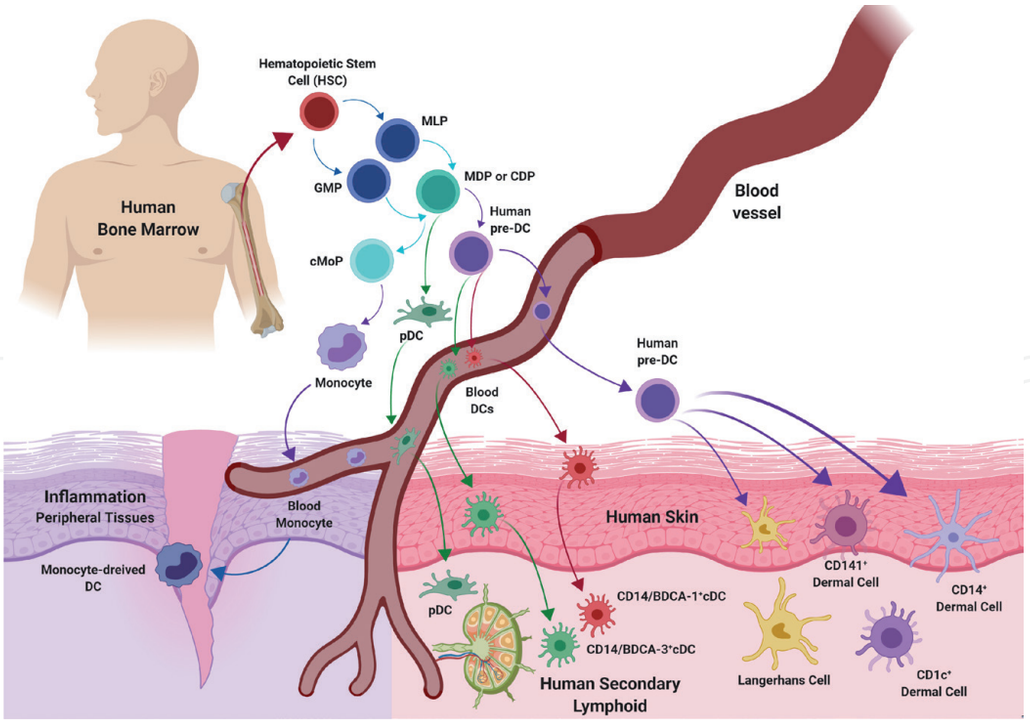

Figure 1.
Dendritic cell lineage development. The hematopoietic stem cell located in bone morrow is the progenitor of all DCs. Here the differentiation in multi-lymphoid progenitor and granulocyte-macrophage can become the human equivalent of macrophage-dendritic precursor (MPD) or dendritic cell progenitor (CDP). From this cell arise three important progenitor cells (cMoPs), pDCs and pre-DC, these last cells migrate to bloodstream or target tissue/organ to maturate and differentiate to become one of the different subsets of DCs. Explanation in the text. Figure modified by the authors from reference [3] and authorized to be published by bio-Techne (figure created by Muñoz-Carrillo et al.*, with BioRender.com).*

fully mature pDCs along with unmatured pre-DCs migrate through the blood tissue. Immature human pre-DCs differentiate either in the bloodstream or in tissues following migration, developing thus in different DCs subsets (**Figure 1**) [2–4].

2. Dendritic cell subsets

The DCs are present in lymph organs and non-lymphoid organs, also in blood stream, afferent lymph, and mucous membranes. There are different ways to classify DCs, by its linage, as mentioned above there are cMoPs and pDCs. The cMocPs express typical myeloid antigens as CD11c, but lack of CD14 or CD16 and may be split in CD1c + and CD141+ fractions. While pDCs have expression of CD123, CD303 and CD304, with high or low expression of CD123, CD303 or CD304; the cluster of differentiation is determined in the differentiation of their precursor. These cells cMoPs and pDCs are classified into blood DCs [5, 6].

Inflammatory DCs derived from classical CD14+ blood monocytes, using granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin (IL)-4. Monocytes are highly plastic, and they differentiate into DCs or different forms of macrophages (M1/M2). Human inflammatory exudates contain distinct inflammatory DC-like and macrophage-like cells and transcriptional profiling suggests a common monocyte origin. Key features of these cells are the expression of CD1c, CD1a, CD206, FcεR1, Sirpα but lack of CD16 and CD209. Non-classical monocytes and antigen 6-Sulpho LacNac DCs are a heterogeneous population and CD16+ monocytes possess distinct characteristics including higher major histocompatibility complex (MHC) class II and co-stimulatory antigen expression, classify as a type of blood DCs [5].

The functional-anatomical classification of DCs is widely vast, the classification of DCs are dependent of anatomical location or function, for example, DCs in heart are known as interstitial cells, in ganglia are known as interdigitating cells, but when DCs are in the afferent lymph are called veiled cells. Also, the function of these are different but sequential [5, 6]. Intestinal DCs are found in small intestine, lamina propia and gut associated lymphoid tissue. This DCs express CD103 and Sirpα in three different ways, such as CD103 + Sirpα- DCs, The CD103 + Sirpα+ DCs and CD103- Sirpα+ DCs. Most of these cells are located deeper into lamina propia, and express CD45, human leukocyte antigen-DR isotype (HLA-DR), CD14, CD64 and high levels of CX3C chemokine receptor 1(CX3CR1), and since these cells do not migrate to the lymph nodes, they have been depicted as intestinal macrophages. In the mesenteric lymph node DCs are a mixture of cells found in the peripheral blood. Such as peripheral blood, where soluble food bioactives may also be directly available for internalization by DCs in the draining lymph nodes *via* the conduit system [7].

LCs and microglia are two specialized self-renewing DCs, found them in stratified squamous epithelium and parenchyma of the brain, respectively. The LCs differentiate into migratory DCs, whereas microglia are considered as a type of specialized macrophage. There are DCs found in tissues and lymph nodes with marker CD14+, a subset of CD11c+, found in interstitial DCs; but they are more monocyte-like or macrophage-like, that may arise from classical monocytes [5].

2.1 Morphology

Immatures and matures DCs have different morphologic, immatures DCs monocyte-derived are spherical, irregular shape, with little cytoplasmatic projections, also abundant phase-dense granules (birbeck's granules or bodies) and irregular nucleus with small nucleoli. Once the DCs maturates shows stellate process, giving veiled appearance, with more extended dendrites projecting in many directions from the body cell [6, 8].

2.2 Maturation

The DCs have 3 stages precursor, immature and mature stage, but some authors do not count the precursor phase [6, 9]. Precursor phase course with any of the principal precursor as cMoPs, pDCs or Human equivalent of pre-DCs. It migrates from bone morrow to specific tissue or area, process leaded by chemokine chemoreceptors such as C-C chemokine receptor type 1 (CCR1), CCR5 and CCR6 and by adhesion molecules CD26P ligand. When the cell arrives to the corresponding tissue or place, it becomes immature DC. The immature DC express CCR1 and CCR3, where its ligand is in endothelium and inflammatory cells, promoting its migration to different organs and inflammatory tissues. This immature DC is capable of capture antigens by different receptors like Fc receptor, integrins, type C lectin and scavenger receptors such as lectin-type oxidized LDL receptor 1 (LOX-1) and CD91. Immature DC is characterized for various amounts of chemokines, so it can be extravasated to inflammatory tissue [6].

Once the DC has captured the antigen, this one is degraded to peptides that will get bind to MHC class I or class II. The endogenous antigens are processed by MHC class I, while exogenous antigens are processed by MHC class II. The lipidic antigens are presented by different molecules CD1(a-d) to T cell receptor (TCR) or natural killer T (NKT) cell. The differentiation process of immature DC to mature DC needs different signals to complete the process. To the immature DC gets mature, needs to stimulate T lymphocyte. This is possible when the

antigen is presented to T lymphocyte by MHC class I or class II to TCR receptor and interaction of costimulatory molecules (CD28, CD40, CD54, CD58, CD80, CD83 and CD86) to activate T lymphocyte. Other molecules like adhesion (CD58, CD54) danger signal (CD40 ligand, tumor necrosis factor (TNF)-α, IL-1, IL-6, Interferon (INF)-α and Toll-like receptors (TLRs) agonist) [6, 8]. When the DC becomes mature, decreases the chemokine receptor expression of CCR1 and CCR5, whereas CCR7 increases. The CCR7 ligand is in ganglia walls and ganglionic paracortical zone. There, the mature DC secretes chemokines such as thymus and activation-regulated chemokine (TARC), macrophage-derived chemokine (MDC) or interferon gamma-induced protein 10 (IP-10), which recruits different types of T lymphocytes, monocytes, regulated on activation, normal T cell expressed and secreted (RANTES), macrophage inflammatory protein (MIP)-1α and MIP-β, to the local microenvironment [6].

2.3 Functions

DCs cells have many functions, but these can be globed within three functions. The first one is the main function as antigen presentation and activation of T lymphocytes as inducing adaptative immunity, with important release of cytokines for example IL-12 to differentiate T lymphocytes in T helper cell or cytotoxic lymphocytes. DCs have a wide range of properties including potent stimulation of native CD4+ T cells, cross-presentation to $CD8^+$ T cells and production of pro-inflammatory cytokines IL-1, IL-6, TNF-α, IL-12 and IL-23 [5, 9, 10]. The second function to induce tolerance. There are 2 types of tolerance central and peripheral. Central tolerance develops in thymus where a tolerance upon our own antigens occurs, and the reactive T lymphocytes to those antigens are destroyed, this also happen in bone morrow for B lymphocytes. The peripheral tolerance occurs when costimulatory molecules, last step of antigen presentation is not complete, there is a failure in activation of T lymphocyte, so the T lymphocyte become tolerogenic [6, 9, 10]. The third function to maintain immune memory in tandem with B cells. As mentioned before, there are population of DCs in ganglia, in the germinal center are found the follicular DCs which seems to be a reservoir of antigen and antibody complexes, that last an exceptionally long time up to months or years. This allows a constant stimulation of B cells to maintain memory [9].

There are others important functions of DCs, as their role in innate immunity, the DCs have pattern recognition receptor (PRR) and pathogen-associated molecular pattern (PAMPs) [10]. These receptor patterns activate TLR pathways, type C lectins and release pro-inflammatory cytokines to activate innate immunity system [8]. Also, DCs have been related to B lymphocytes proliferation and induction of T lymphocytes to suppress the immune response by missing of costimulatory molecules without IL-12, inducing T lymphocytes to secrete IL-10 and transforming growth factor (TGF)-β [6, 9].

3. Role of dendritic cells in viral infection

Since the discovery of DCs [11], the knowledge of the innate and adaptive immune response has been increasing significantly. At present, DCs are considered a key cell in immune response activation with multiple functions including the virus recognition, processing of viral antigen and as antigen-presenting cells to cells of specific immune response, serving as a bridge between innate and adaptive response [12]. DCs are bone marrow-derived cells and they can be found in different parts of the organism including mucous membrane, the skin, and

lymphoid tissue [13]. Depending on surface markers, DCs can be classified as immature or mature myeloid DCs and plasmacytoid DCs [14, 15].

Immature DCs are inactive cell with high capacity to capture viral antigen. They are present in virtually all tissue with high probability to capture invading viruses. Immature DCs lack the capacity of antigen presentation. On the other hand, mature MDC is generated by an immature DC that was activated when recognized and processed viral antigen. Mature DCs function as antigen presenting cells (APCs). They express MHC-II molecules and different co-stimulators surface molecules that give them the antigen presentation capacity. Mature DCs also produce different cytokines to initiate antiviral immune response [16].

Likewise, plasmacytoid DCs also sense viral pathogen. They are called plasmacytoid DCs by its high resemblance to plasma cells. Although pDC has the ability of antigen-presenting, this function is low compared with MDC. However, pDCs contribute to both inflammatory process and antiviral state. They are specialized DCs that produce proinflammatory cytokines and high levels of IFN type I [17]. Both MDC and pDCs are present in lymphatic nodes where they are capable to present viral antigen to naïve T cell [18, 19].

3.1 From immature to mature cDCs in viral infection

Immature DCs are considered the sentinels of the immune response. These cells are distributed in practically all the body where they have the capacity of interact with the invading virus. They carry out the function against viral infection by different mechanisms. They can be infected by viruses or they can respond to molecules produced and secreted by other virus infected cells. When they are infected, DCs can respond in various ways, firstly, DCs have different receptors distributed on cell surface, cytoplasm, and specialized endosomes. TLRs and C-type lectins receptors (CLRs) are present in cell surface and some TLRs in endosomes, while retinoic acid-inducible gene (RIG), melanoma differentiation-associated protein 5 (MDA5) and nucleotide-binding oligomerization domain 2 (NOD2) are only present in cytosol [20–22]. TLRs have N-terminal ectodomains (ECDs) which recognize molecules of viruses. This ECDs are constructed by a tandem motif of leucine-rich repeats (LRRs) and forms a horseshoe structures [23]. Binding of TLRs with their ligand depends on these structures [24]. However, diverse receptors respond to an extensive repertoire of viral PAMPs. These viral PAMPs can be glycoproteins present on the viral external surface, viral genome, or replication intermediates formed during viral replication [25].

Depending on the activated receptor, DCs can produce proinflammatory cytokines or IFN. During maturation process DCs interact with the antigen and upregulate MHC-II to present antigen to naïve $CD4^{+}$T cells. In addition, DCs produce diverse surface molecules such as CCR7 which is necessary in trafficking into lymphatic nodes and CD40, CD80, and CD86 which are co-stimulatory surface factors that enable them to activate T naïve cell to initiate the adaptive immune responses [26, 27].

3.2 Differential PRR activation on dendritic cells

DCs is the main cell used to establish an effective immune response. At present, four subsets with different functions have been identify in human. Each subset of DC has different markers and a functional distinction that enable them to participate in different states to orchestrate an antiviral immune response. Each type of DC expresses different receptors that can be membrane-associated molecules or free in the cytoplasm. Activation of these receptors ends in different cytokine-proinflammatory

production and interferon. Depending on cytokine produced, naïve $CD4^{+}$T cells is differentiated into T helper effector cell [14].

Myeloid DCs, called classical or conventional DCs (cDCs) detect viral proteins through expression of membrane surface receptors such TLR-4 and DC-specific intercellular adhesion molecule 3 (ICAM3)-grabbing non-integrin (DC-SIGN) (see **Figure 2**) [28]. DC-SIGN support the initial immune response between T cells and DCs, but when DC-SIGN have contact with viral glycoproteins results in activation of signal transduction pathways than cause modulation of immune responses [29]. The signaling pathway triggered by DC-SIGN recruits Ras and the subsequent phosphorylation of the kinase RAF1 which is mediated by p21-activated kinases (PAKs) and Src Kinases. The activation of RAF1 induces phosphorylation of nuclear factor (NF)-κB increasing the transcriptional activation from IL-18, IL-10 and IL-12 promoter [29, 30].

The association of viral proteins through concave surface of TLR4-ECD induces two different pathways [31]. Myeloid differentiation primary response 88 (MyD88)-Dependent Pathway initiates with the recruitment of MyD88 adapter and subsequent activation of tumor necrosis factor receptor (TNFR)-associated factor 6 (TRAF6). Then TRAF6 activates the NF-κB essential modulator (NEMO), which is the regulatory subunit IKK complex and activates NF-κB causing its translocation to the nucleus, where induces gene expression such as IL-6 and IL-12 [21]. MyD88-Independent pathway recruits TIR-domain-containing adapter-inducing interferon-β (TRIF) [32]. TRIF activates TRAF3 and finally induce interferon regulatory transcription factor (IRF-3) activation and the subsequent IFN-β expression [21].

In addition to membrane surface receptors cDCs also have endosomal TLRs such as TLR-3 and TLR-7/TLR-8 which sense dsRNA and ssRNA respectively. Each receptor has a specific signaling pathways [14]. TLR-3 sense viral dsRNA through its largely uniform and flat horseshoe structure of TLR-ECD [33]. TLR3 has the same MyD88-Independent pathway with the activation of TRAF3 and subsequent IFN-β expression [32]. Viral ssRNA are sense by TLR-7 and TLR-8, these receptors activate MyD88 pathway with the recruitment of TRAF6 and TRAF3. Finally, activation of IRF-3 and IRF-7 induces IFN-β and IFN-α expression respectively (see **Figure 2A**) [21, 34].

In addition to DC-SIGN and TLRs, the viral genome can be exposed in the cytoplasm during the replicative processes or during direct penetration into the cell. NOD2 and RNA helicases such melanoma differentiation-associated protein 5 (MDA5) and RIG-1 detect dsRNA in the cytoplasm [35]. Interferon promoter

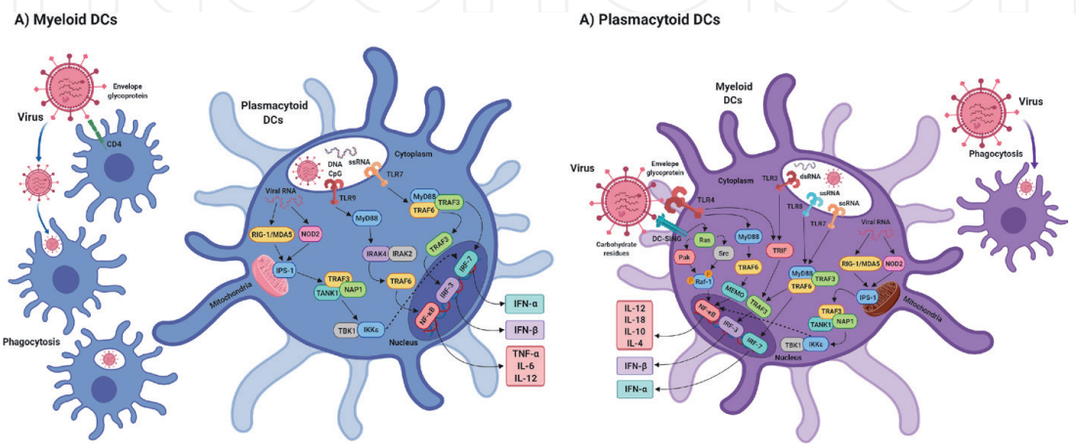

Figure 2.
Signaling pathway and cytokines production of DCs during viral infection. (A) Myeloid DCs and (B) Plasmacytoid DCs. Description in the text (figure created by Muñoz-Carrillo et al.*, with BioRender.com).*

stimulator-1 (IPS-1) interacts with MDA5, RIG-1 and NOD2 *via* caspase activation and recruitment (CARD) domain. IPS-1 localizes in mitochondria and interacts with TRAF3. TRAF family member associated NF-κB activator (TANK) is recruited from TAF3 and interacts with TANK Binding Kinase 1 (TBK1) and the kinase IKKε [36–38]. Finally, TBK1 and IKKε interact *via* their C termini with NFκB activating kinase (NAK)-associated protein 1 (NAP1) [39]. This signaling pathway activates NFκB, IRF-3 and IRF-7 to express IL-12, IFN-β and IFN-α [38, 39].

On the other hand, pDCs not express DC-SIGN but express CD4 that can sense glycoproteins of viruses as human immunodeficiency virus (HIV). The viruses can enter through direct fusion with the cell membrane or through receptor-mediated endocytosis and activates different signaling pathways (see **Figure 2B**) [40, 41]. The endosomal receptors TLR-7 and TLR-9 are selectively express in pDCs and sense RNA or DNA respectively. This engage activates downstream signaling pathway [42]. TLR-9 and TLR-7 activates IRF-3 and IRF-7 like in cDCs signaling with final IFN-β and IFN-α expression respectively [43]. TLR-9 signaling pathways include the recruitment of Interleukin-1 receptor-associated kinase 4 (IRAK4) through its death domain. Activated IRAK4 interacts with IRAK2. This complex associates with TRAF6 to final activation and nucleus translocation of NF-κB and leads TNF-α and IL-6 production [17, 44, 45]. pDCs can also be infected by direct penetration of virus and the viral genome can be sense by RIG-1, MDA5 and NOD2. The signaling in the pDCs is through IPS-1 pathways as the same way that on cDCs [20, 22]. This pathway activates NFκB, IRF-3 and IRF-7 to express IL-12, IFN-β and IFN-α respectively [38, 39].

Other subsets of DCs are the LCs and Interstitial DCs (IDCs), these kinds of DCs are commonly the first DCs that have contact with some virus [46]. LCs are localized in mucosal stratified squamous epithelium and skin epidermis. LCs express different CLR: CD207 or Langerin. Moreover, LC has a low expression of TLR4 and expression of TLR-3, –7 and – 8 [14, 47]. LCs activated finally express IL-8, IL-6, TNF-α [48]. On the other hand, the IDCs are localized in the epidermis and express similar receptors that cDCs like DC-SIGN and TLR-3, -4, -7 and -8 and have similar signaling pathways [14].

Activation of the antiviral response generated by immune system depends largely on the activation of dendritic cells. Each subtype of this family of antigen-presenting cells have an important role by processing viral antigens that trigger different signaling pathways through their distinct receptors. The consequence of this signaling pathway results in the expression of various cytokines involved in the activation of immune cells. For this reason, a better knowledge about how different immune cells subtypes can induce distinct pathways is required for a better vision of whole antiviral response.

4. Role of dendritic cells in parasitic infection

In parasitic infections is difficult to generalize about the mechanisms of anti-parasitic immunity because there is a great variety of different parasites that have different morphology and reside in different locations of tissues and hosts during their life cycles [49]. For this reason, we will talk about the role of dendritic cells in protozoa and helminths infection, two of the main parasites of medical importance for human health.

DCs have the capacity to recognize different molecules in the surface of parasites and are efficient phagocytes; thus, several intracellular parasites reside inside DCs. Once DCs phagocytose intracellular parasites, they can exert their microbicidal capacities, although it has been shown that they are not as efficient in the

destruction of microorganisms as other phagocytes such as macrophages and neutrophils. Once internalized, DCs process antigens for presentation to T cells [50].

4.1 Parasitic protozoan infections

Protozoan parasites are pathogens that have developed additional and sophisticated strategies to escape the immune attack of the host. This is because their life cycles generally involve several stages of specific antigenicity, which facilitates their survival and propagation within different cells, tissues, and hosts [51]. Frequently, the host is unable to eliminate protozoan infections, which often results in chronic disease or irreparable infections, in which the host continues to act as a reservoir of parasites, a cause of great concern due to their prevalence, morbidity and mortality [52, 53]. This host resistance to protozoa infections depends mainly on the development of a T helper type 1 (Th1) response and on the production of IL-12 by APCs [54]. Therefore, the classical reaction of the host to infections by protozoan parasites is the maturation of different subsets of DC, and in some cases, the activity of these cells leads to a response that is effective in controlling the infection [55].

Among the most important protozoan parasites are those that living in human blood and tissues, which can cause fatal diseases. The immune response against protozoan infections involves a strong innate immune response followed by predominantly a Th1 response. The innate immune system is comprised of several cell types, including DCs. Recognition of pathogens by these cell types leads to phagocytosis in some cases, and the production of pro-inflammatory cytokines, which assist in shaping the subsequent adaptive immune response (see **Figure 3**) [56].

During the parasitic protozoan infections different PRRs present in DCs are involved in the recognition PAMPs of parasites. In trypanosomiasis, the

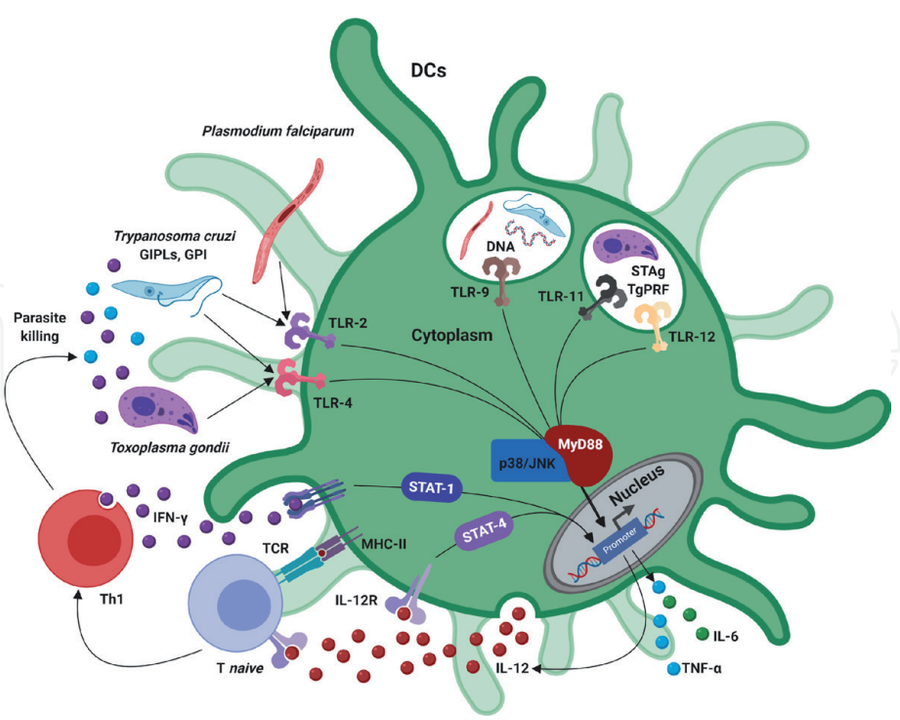

Figure 3.
Role of DCs in protozoan infections. Polarization of Th1 response through interactions between PAMPs and PRRs (TLR-2, -4, -9, -11 and -12), which in a signal-dependent manner (involving the activation of MAPKs p38/JNK and MyD88) induce the expression of Th1 cytokines such as IL-12, Il-6, IFN-γ and TNF-α. the PRRs from protozoa induce the presentation of antigens, the co-stimulation, and the expression of the cytokine IL-12, IFN-γ production by DCs during Ag presentation, by signaling pathway STAT-4. Description in the text. (figure created by Muñoz-Carrillo et al.*, with BioRender.com).*

glycoinositolophospholipids (GIPLs) and glucosylphosphatidylinositol (GPI) anchors from Trypanosoma cruzi are recognized by TLR-4 and TLR-2, respectively, inducing the inflammatory cytokines production [57, 58]. Likewise, the DNA of *T. cruzi* stimulates the production of cytokines in a manner dependent on TLR-9 and synergizes with the GPI anchor of TLR-2 in the induction of cytokines [59], such as IL-12 by activation of the p38 pathway [60].

Toxoplasma gondii is a parasite that can infect any nucleated host cell, but it has a preference for cells of the immune system, including DCs [61]. Currently, the participation of TLRs in the recognition of *T. gondii* is not very clear. On the one hand, studies have shown that the soluble parasite extract (STAg) of *T. gondii* induces the production of IL-12 through the binding of *Toxoplasma profilin* (TgPRF) with TLR11 in DCs, signaling pathway MyD88 [62–65]. In fact, it has been shown that TgPRF is not required for the intracellular growth of *T. gondii*, but it is indispensable for host cell invasion and active egress from cells [65], and it is critical for the IL-12 production, especially in plasmacytoid DCs [66]. On the other hand, studies show that the absence of either TLR-2 or TLR-4 in DCs does not modify the production of IL-12 in response to STAg [62]. Other authors have reported the involvement of the TLR4-dependent signaling pathway in *T. gondii* independent of the MyD88 pathway [67]. However, reports have shown that mice deficient for TLR-2, TLR-4 or TLR-11 survive *T. gondii* infection, suggesting that *T. gondii* recognition may be associated with an additional signaling pathway MyD88-TLR-dependent. This additional signaling pathway could be by binding of TgPRF with TLR-12, since it has been observed that TLR-12-deficient mice succumb rapidly to *T. gondii* infection [62, 63, 66, 68]. On the other hand, *T. gondii* is capable to activate the JAK/STAT signaling pathway to facilitate survival within the host, blocking IFN-γ-mediated-STAT1-dependent proinflammatory gene expression in APCs. This is through sustained STAT-1 phosphorylation and nuclear translocation in bone marrow-derived DCs (BMDCs). However, in combination with IFN-γ, T. gondii simultaneously blocks IFN-γ-induced STAT-1 transcriptional activity avoiding the DCs activation by IFN-γ [69].

Plasmodium falciparum is capable to activate DCs through TLR-2 [58, 70, 71] and TLR-9, inducing the production of proinflammatory cytokines [72]. Depending on the DCs population that are activated during Plasmodium infection, it will be the type of cellular immune response that the host will mount against the infection. On the one hand, it has been observed that DCs subpopulations such as $CD8^+CD11b^-$DC (located in the peripheral lymph nodes), mature ($CD40^+$) spleen DC and ($CD8\alpha^+CD11b^-$ and $CD8\alpha^-CD11b^+$) DCs [73, 74], are associated to the protective effect of $CD8^+$ T-cells, which produce INF-γ and induce parasite death, reducing the parasite burden in hepatocytes [75–78]. On the other hand, during the acute phase of infection $CD8\alpha$-$CD11b^+$DC activates $CD4^+$ T-cells, inducing the production of IL-12, IL-6, IFN-γ and TNF-α [79–83].

4.2 Parasitic helminth infections

Helminth parasites, like protozoan parasites, have significant differences in their biological life cycles, which are reflected in the differences in clinical outcomes seen among helminth parasites. Pathological consequences of most helminth infections have been associated with both with the parasite intensity (or burden) and the relative acuteness or chronicity of the infection, because the helminth parasites modulate/regulate the host response to themselves (parasite-specific immunoregulation) [84].

The immune response against helminths is characterized by the induction of an early immune response of type Th1, with subsequent predominance of a Th2 type

immune response, resulting in a mixture of both Th1/Th2 responses [85, 86], which are dependent on the immune responses mediated by $CD4^+$ T cells [87]. These $CD4^+$ T cells can function as APCs and play a key role in establishment the cytokine environment, thus directing their differentiation either by suppressing or favoring the inflammatory response at the intestinal level, which is crucial for the expulsion and elimination of the parasite (see **Figure 4**) [88].

This implies that the helminths have developed strategies, such as the evasion or suppression of the host immune response, which prevent their expulsion and allow their long-term survival. It is believed that the modulating effects of the immune system arise from the ability of the helminth to regulate the host immune response, developing mechanisms for the modulation of DCs as key players in the initiation and polarization of adaptive immune responses [89–91].

During the intestinal infection by helminths, the polarization of the cellular immune response to a Th1 type immune response depends on the type of signal derived from DCs. For example, *Trichinella spiralis* larvae group (TSL-1) antigens induce the DCs maturation [92], leading to the expression of MHC II [93, 94], promoting the development of a Th1 type cellular immune response [95]. Several studies, both *in vitro* and *in vivo*, have shown that during the early stage of intestinal infection by *T. spiralis* there is a significant increase of Th1 cytokines such as IL-12 [96, 97], INF-γ [95–98], IL-1β [97–99] and TNF-α [96, 97, 100]. It is possible that this Th1 response is mediated through the TLR-4 activation in DCs by TSL-1, through the signaling pathway TLR4/MyD88/NF-κB [101, 102]. Another example is double-stranded RNA from schistosome eggs has been implicated in the activation of DCs *via* TLR-3, resulting in a Th1-polarized response [103, 104].

Intestinal DCs are classified according to their unique or combined expression of CD11b and CD103, as well as the dependence on either interferon regulatory factor 4 or 8 (IRF4 or IRF8) for their development and/or survival. The intestinal DCs are

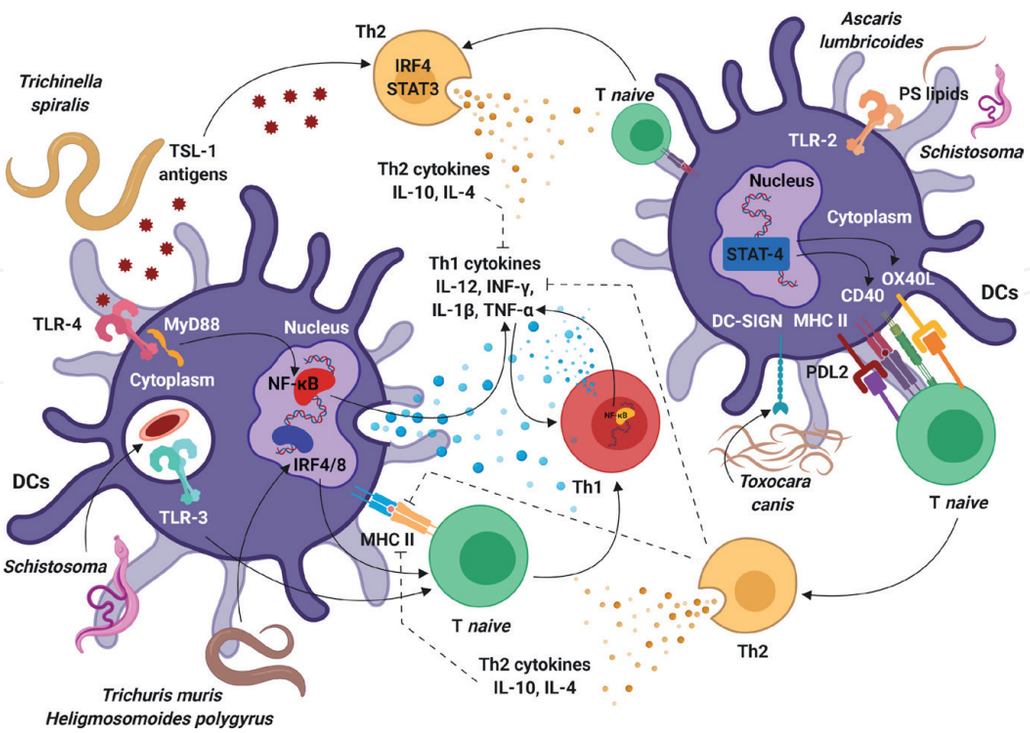

Figure 4.
Role of DCs in helminth infections. The immune response against helminths is characterized by the induction of an early immune response of type Th1, with subsequent predominance of a Th2 type immune response, resulting in a mixture of both Th1/Th2 responses. The polarization of the cellular immune response to a Th1/Th2 type immune response depends on the type of signal derived from DCs. Description in the text. (figure created by Muñoz-Carrillo et al.*, with BioRender.com).*

capable of process antigens, migrating to mesenteric lymph nodes upon activation, and priming naive T cells. However, IRF8-dependent $CD103^+$ DCs are important for the generation of type 1 responses of both helper and cytotoxic T cells, thus promoting *Trichuris muris* and *Heligmosomoides polygyrus* chronicity. In contrast, IRF4-dependent $CD11b^+$ DCs in the induction of Th2 immunity, notably during infection with *Nippostrongylus brasiliensis*, *T. muris*, and the parasitic trematode *Schistosoma mansoni* [105].

On the other hand, the PRRs from helminths can also activate the DCs for the induction of the Th2 response by interacting with the TLR and CLR. This interaction may promote Th2 responses by suppressing antigen presentation, co-stimulation and/or expression of Th1-promoting cytokines by directly interfering with these pathways. DCs that drive Th2 responses typically exhibit specialized markers, such as CD301b, PDL2, and CD11b, and several receptors for the Th2-related cytokines IL-4R, IL-13R, IL-25R, TSLP-R, and IL-33R. Additionally, the extracellular signal-regulated kinase (ERK) and signal transducer and activator of transcription 4 (STAT4) pathway upregulates the costimulatory molecules, CD40, OX40L, and Jagged. Activation of the major transcription factors interferon regulatory factor 4 (IRF4) and KLF4 inhibits IL-12 production and increased IL-10 secretion. These factors typically act individually or in concert to orchestrate Th2 responses in helminth infections [106–108].

In *T. spiralis* infection, the initial exposure of TSL-1 antigens of *T. spiralis* activated $CD4^+$ T cells, as well as DCs, leading to the secretion of large amounts of IL-10. IL-10 suppress cell markers, the proliferation and antigen presentation by DCs and inhibition of IL-12 secretion. In addition, TSL-1 increased the both IL-4 and IL-10 production derived from Th2 cells with a decrease in INF-γ production, polarizing the immune response to a strong Th2 cellular immune response, protective and responsible for the *T. spiralis* expulsion [109]. In addition, it has been shown that phosphatidylserine (PS) lipids derived from schistosomes and ascaris worms, which carry TLR2-activating molecules, promote Th2 responses through DCs [110]. Further, it was found that antigens of *Toxocara canis* were recognized by DC-SIGN expressed on DCs [111], and the induction of a Th2 response *in vivo* by antigens of the parasitic nematode *Brugia malayi*, as well as the free-living nematode *Caenorhabditis elegans*, was found to be dependent on intact glycans [112]. These findings together suggest that certain helminth glycans can serve as PAMPs that instruct DCs through CLR to boost polarized Th2 responses [113].

5. Role of dendritic cells in bacterial infection

Activated DCs are involved in the response to infections, which induces an increase in MHC expression, adhesion, and costimulatory molecules. The recognition of intracellular pathogens derived from mycobacterial cell wall components (lipids/glycolipids) such as phosphatidyl-myo-inositol mannoside, lipo-mannan, lipoarabinomannan, mycolic acids, lipopeptides, and phosphoinositol-containing lipids is given through the TLR-2, TLR-4, TLR-9, TLR-8 and the TLR1/TLR6 that heterodimerize with the TLR-2 [114, 115]. The signaling pathway that occurs in almost all TLRs is through MYD88, while for TLR4 the signaling pathway can be through MYD88 and TRIF [116, 117]. The activation of these receptors induces the activation of mitogen-activated protein kinase (MAPK) and NF-κB producing proinflammatory cytokines in DCs (see **Figure 5**). Other antigens derived from *Mycobacterium tuberculosis* such as lipoamide dehydrogenase C (Rv0462) induce the maturation and activation of DCs, increasing the expression of costimulatory molecules, MHC II and proinflammatory cytokines such as TNF-α, IL-1β, IL-6,

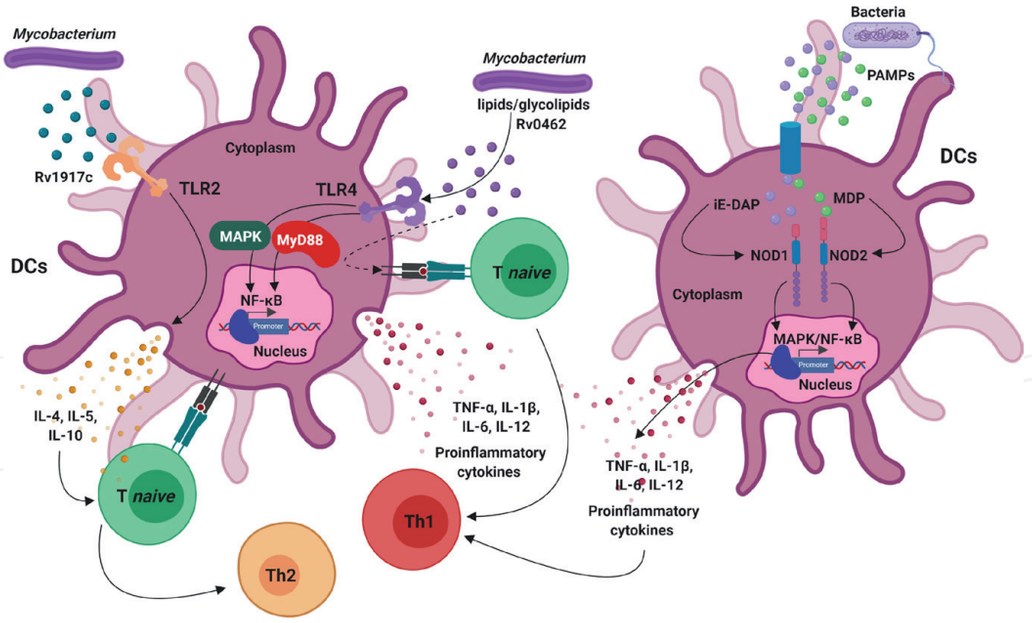

Figure 5.
Role of DCs in bacterial infections. The TLRs are involved in the recognition of mycobacterial antigens. The activation of TLR-4 and TLR-2 by these antigens leads to an intracellular signaling pathway, leading to a Th1 and Th2 response, respectively. NOD-like receptors (NOD 1 and NOD 2) recognize bacterial peptidoglycans (DAP and MDP), the downstream signaling activates NF-κB and MAPK generating a Th1 response. Description in the text (figure created by Muñoz-Carrillo et al.*, with BioRender.com).*

and IL-12, which leads to a Th1 immune response [118, 119]. Another protein that induces the maturation of DCs is RV2220 is a glutamine synthetase (GS) type I enzyme derived from M. tuberculosis, which induces the upregulation of MHC I and MHC II as well as CD80 and CD86, which leads to a Th1 response or Th2 or to regulatory T cell, through the secretion of cytokines such as, TNF-α, IL-6, IL-1β, IL-12 or IL-10, activating the MAPK and NF-κB pathway [120]. Different proteins that derive from *M. tuberculosis* trigger different responses, as cell wall-associated/secretory Rv1917c antigen acts as a ligand of TLR-2, which induces the maturation of DCs secreting IL-10 and inducing the production of IL-4, IL-5 and IL-10 in CD4+ T cell which leads to a Th2 response (see **Figure 5**) [121].

On the other hand, DCs infection with other bacteria of the type *Listeria monocytoges*, *Shigella flexneri*, *Salmonella typhimurium* and *Francisella tularensis*, can activate inflammasome receptors [122]. The inflammasome is a multiprotein complex that contains one or more Nod-like receptors (NLRs) and regulates caspase-1 activity [123, 124], this complex is formed by at least three elements: (1) an inflammatory caspase (caspase-1, caspase- 11); (2) an adapter molecule such as apoptosis-associated speck-like protein containing a CARD, caspase recruitment domain (ASC); and (3) a sensor protein such as NLR Family Pyrin Domain Containing 1 (NLRP1), NLRP3, NLRP12, NAIP1, NAIP2, NAIP5, or absent in melanoma 2 (AIM2) [125]. The NLRP1 inflammasome is activated by anthrax lethal toxin, a toxin produced by *Bacillus anthracis* [126]. The toxin is composed of a protective antigen and lethal factor, the protective antigen generates pores in the membrane of the host while the lethal factor enters the cell and short NLRP1b and leads to inflammasome activation [127]. The NLRP3 inflammasome is activated by ligands derived from pathogens such as microbial cell wall components, nucleic acids, and pore-forming toxins [128]. Activation NLRP3 inflammasome require two signals: the priming which occurs when cells are activated by a PRR and activates the NF-kB, that induce the production of NLPR3, pro-IL-1β and pro-IL-18 and cytokines proinflammatory drugs such as IL-6, IL-8 and TNF-α. Subsequently the second signal carrying the assembly for inflammasome activation of caspase-1 occurs, which gives rise to the production of

IL-1β and IL-18 responsible for maintaining the inflammatory response [129]. The NLRC4 inflammasome is activated by the bacterial flagellar protein flagellin, as well as the Salmonella type III secretion system, this inflammasome does not interact directly with its activator, the NAIPs proteins do (NLR family), which recognize the ligands and induce activation of the NLRC4 inflammasome [130, 131]. The double chains of microbial DNA present in the cytosol are recognized by the AIM2 inflammasome, this receptor contributes to host defense when pathogens do not have ligands that stimulate PRRs such as flagellin and LPS, such as *Brucella spp* and *Francisella spp*. This receptor binds to DNA and oligomerizes with ASC to then form the caspase-1 activating inflammasome, which leads to the secretion of cytokines such as IL-1β and IL-18 [132]. The cytokines that are produced through the inflammasome not only contribute to the defense of the host against infections, they also induce a Th17 response, this differentiation is driven by IL-1β, and is regulated by the factors NF-κB, activator protein 1 (AP-1) or the signaling way of the MAPK [133]. After the binding of IL-1β to IL-1R, signaling occurs through MYD88 until activating NF-κB, which induces the production of proinflammatory cytokines leading to a Th17 phenotype, in this differentiation IL-1β synergizes with IL-6 which upregulates the master transcription factor of Th17 cells, such as STAT3, IRF4 and RAR-related orphan receptor gamma (RORγt) [134]. The Th17 response is a typical response that occurs against extracellular bacteria such as *Klebsiella pneumoniae*, *Bordetella pertussis*, or *Streptococcus pneumoniae* and is characterized by a vigorous response of neutrophils which is coordinated by the Th17 cells, an alteration in IL-17 signaling increases the susceptibility to infection of these bacteria [135]. Although the defense of the host against extracellular bacteria is considered mainly associated with the

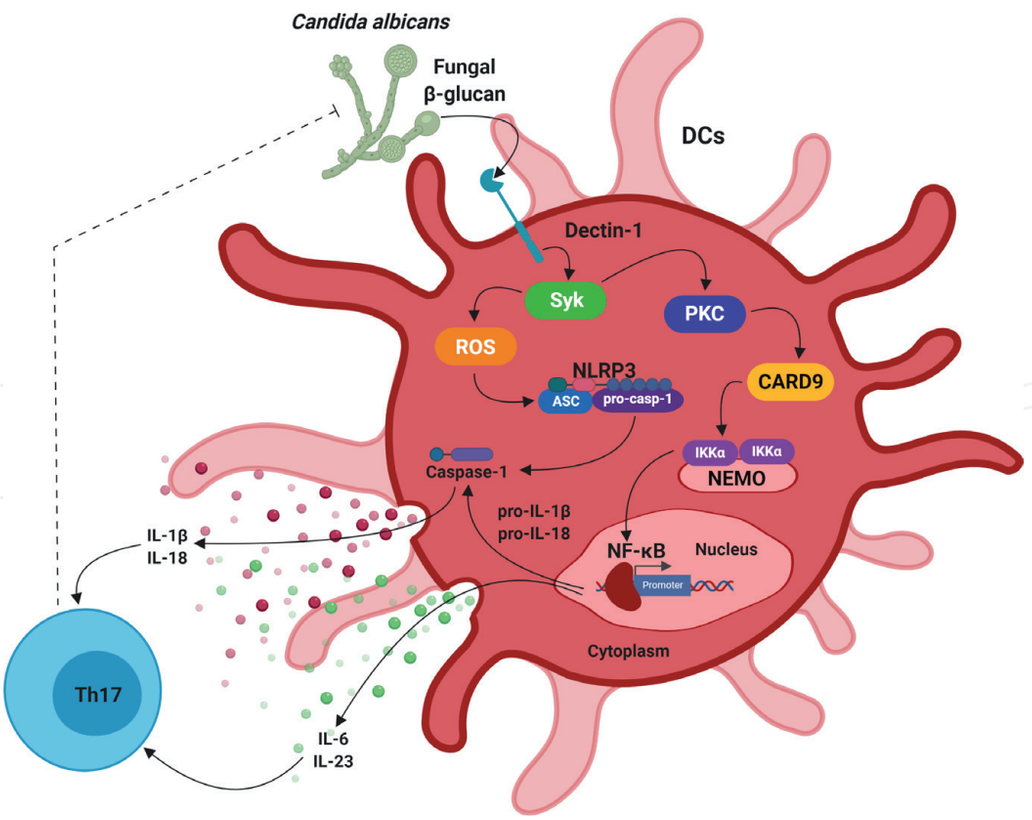

Figure 6.
Role of DCs in fungal infection. Antigens derived from fungi such as b-glucan which are recognized by Dectin-1, this leads to a downstream signaling pathway activating NF-kB producing IL-6 and IL-23 leading to a Th17 phenotype. The union of Dectin-1 whit b-glucan also leads to the activation of ROS, which can NLRP3 inflammasome assembly activating caspase-1 which cuts the pro-IL-1 and pro-IL-18 generating its active forms, which together with IL-23 activates the Th17 phenotype. Description in the text (figure created by Muñoz-Carrillo et al.*, with BioRender.com).*

Th17, some authors indicate that effective protection requires the synergism of Th1 and Th17 cells, as it is for *Bordetella perussis* that induces the production of IFN-γ in the phase maximum infection and decreases its expression as time passes reaching basal levels at 14 days post-infection, however the Th17 response is persistent and production of IL-17 remains high even when the infection has been eliminated [136].

Other receptors involved in the response to pathogens are NOD1 and NOD2 receptors make up the family of NOD-like receptors containing a CARD domain (NLRC) [137]. These receptors are highly expressed in DCs and act as intracellular PRRs that recognize bacterial peptidoglycans [138–140]. NOD1 mainly recognizes γ-D-Glu-meso-diaminopimelic acid (DAP) while NOD2 recognizes muramyl dipeptide (MDP) [141]. Once the activation of these receptors occur, the downstream signaling activates NFκB through the union of its CARD domain to the protein kinase RIP2, which in turn recruits IRAK2, TRAF6, TAK1 binding protein (TAB1) and transforming growth factor-β-activated kinase 1 (TAK1) to activate the IKK complex, these events result in the degradation of IκBα inhibitor which leads to the translocation of NFκB to the nucleus and induce the expression of proinflammatory mediators [142]. In addition to the NFκB pathway, the stimulation of NOD1 and NOD2 leads to the activation of MAP kinases p38, ERK, and JNK pathway *via* RIP2. This event facilitates the formation of a multiprotein complex called "Nodosome" that leads to the production of inflammatory and antimicrobial agents mediated by NFκB and MAPK (see **Figure 6**) [143].

6. Role of dendritic cells in fungal infections

Infections caused by opportunistic fungal pathogens include *Aspergillus fumigatus*, *Cryptococcus neoformans* and thermal dimorphic fungi (*Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Paracoccidioides brasiliensis*, *Coccidioides immitis*, *Penicillium marneffei* and *Sporothrix schenckii*) and *Candida albicans*, the latter being a normal inhabitant of the human intestine, however as a pathogen has been associated with various serious diseases ranging from severe mucocutaneous allergy to bloodstream infections [144, 145].

DCs are the only ones capable of decoding information related to fungi [146]. The activation of the various immunity mechanisms is carried out efficiently by the DC that decode the signals sent by the fungi and translate them into an immune response of T helper (Th) *in vitro* and *in vivo* where the DC recognize each fungal morphotype of specific form by means of different recognition receptors which triggers the production and co-stimulation of cytokines [144]. For the immunological processes to be activated against different classes of fungi, the differentiation of the naive CD4 + T cells towards the Th1 or Th17 subtype is essential, which occurs by interaction with dendritic cells through different cytokines, these subsets of cells Th1 and Th17 play an important role in protection against various fungal diseases [147]. To be contained and resistant to fungal infections it is necessary that DC are activated since they produce cytokines of the IL-1 family, such as IL-1β and IL-18 and which activate other innate immune cells, or they modulate the development of the acquired immune response. IL-1β plays an important role in the inflammatory immune response and polarization of Th17 cells, whereas IL-18 participates in the differentiation of Th1 cells, but may also be responsible for the expansion of Th2 cells in the absence of IL-18 [148] IL-12 and IFN-γ promote Th1 differentiation, while TGF-β, IL-6, IL-1, IL-21 and IL-23 promote the differentiation and maintenance of Th17. The release of these cytokines by DCs is in turn regulated by innate receptors activated in response to fungal infection [149]. In order for the effective response of the host to the fungi to occur, the Th17 cells are indispensable [147].

Inflammatory DCs generate the responses of Th17 and Th2 antifungal cells *in vivo* by means of signaling pathways in which the TLR adapter MYD88 participates, while tolerogenic DCs promote regulatory differentiation programs of Th1 and Treg cells through processes in which the signaling adapter TRIF participates. In addition, STAT3, which alters the balance between the canonical and non-canonical activation of NF-κB and, therefore, the expression of the enzyme indoleamine 2,3-dioxygenase (IDO), has a key role to DCs plasticity and functional specialization. The multiple, functionally distinct receptor signaling pathways in DCs affect the balance between $CD4^+$ effector T cells and Treg cells and, therefore, are likely to be harnessed by fungi to allow them to establish commensalism or infection [146]. In contrast some studies have shown that suppressive silencing of cytokine signaling 1 (SOCS1) can induce maturation of DCs and initiate the immune response find *C. albicans in vitro*. In which DC silenced by SOCS1 extend mouse survival and significantly decrease the colonization of fungi in the kidneys and the differentiation of $CD4^+$ T cells producing IL-4 (Th2) or $CD4^+$ T cells producing IL-17 (Th17 cells) are not affected under the same treatment, suggesting that DC silenced by SOCS1 significantly affect the $CD4^+$ producer of IFN-γ cells (Th1). However, in the later stages of infection, when differentiation of Th1, Th2 and Th17 cells decreases in mice treated with DCs silenced with SOCS1, all serum cytokines (IFN-γ, IL-4 and IL-17) also reduced [150].

It has also been reported that NLRP3 linked with ASC and caspase 1, is triggering inflammation activated by pathogenic fungi such as *C. albicans*, *Aspergillus fumigatus* and *Cryptococcus neoformans*. Inflammasome NLRP3 responds to various stimuli, such as crystalline and particulate matter, extracellular ATP, pore-forming toxins, reactive oxygen species (ROS) (see **Figure 6**), endosome destabilization and cathepsin release, changes in intracellular calcium levels and K^+ efflux [148].

Many types of cells, including macrophages and DCs, produce IL-1β induces the differentiation of Th17 cells, which are necessary for effective defense of the host against *C. albicans* when producing IL-17 through the stimulation of PRRs like Dectin-1 and Dectin 2, and both types of cells are indispensable for host defense against *C. albicans*. Dectin 1 is activated through the binding of the b-glucan of the fungal cells, and triggers intracellular signaling recruitment of Syk, activation of NF-kB *via* CARD9, the phosphorylation of IκB is mediated by the IκB kinase (IKK) complex, this complex consists of NF-κB essential modulator (NEMO, or IKKγ), IKKα, and IKKβ, to release the IκBα from NF-κB (see **Figure 6**). In the early stages of candidiasis, DCs are also essential in the antifungal response, since they are responsible for detecting fungal PAMP through their PRR, secreting cytokines and chemokines into the environment, retaining fungal particles by phagocytosis and presenting antigens to T cells to induce an adaptive immune response [147, 151].

7. Dendritic cells and its potential benefits to combat different diseases

DCs are considered key cells as the first line of defense against viruses and to induce adaptive defense. In the innate immune response, they can exert virus phagocytosis and produce cytokines to activate NK cells to eliminate virus infected cells. In adaptive immune response, DCs induce differentiation of Th1-cells that in turn induce activation of antigen specific cytotoxic cells, macrophages, and antibody production to participate in viral clearance.

For the elimination of bacteria, a specific immune response is required, for intracellular bacteria a Th1 response is required as well as cytotoxic T lymphocytes, the latter to produce IFN-γ and can kill the cells that have been infected, in this response the Il –12 is important and its production by DCs requires stimuli derived

from pathogens as well as from $CD4^+$ T-cells; on the other hand, for extracellular bacteria a Th17 response is required, in this response DCs play an important role in producing pro-inflammatory cytokines so that a Th17 response can be given, thus these cells coordinate the recruitment of neutrophils that phagocytize extracellular bacteria and thus eliminate the bacterial infection.

DCs participate in the immune response against different opportunistic fungi, the latter are capable of producing different diseases including vulvovaginal candidiasis, oral candidiasis or disseminated candidiasis (*Candida albicans*), invasive pulmonary asperilosis (*Aspergillus fumigatus*), pneumonia (*Pneumocystis carinii*), cryptococcosis (*Cryptococcosis neoformans*). DCs recognize specific structures of fungi such as carbohydrates, proteins, and nucleic acids. This recognition through the PPR activates signaling pathways that lead the DCs to a state of maturation and secretion of cytokines which play an important role in host defense against fungal infections, generating a response either of the Th1 type or Th17.

During parasitic infections, DCs play an important role, since, through them, the body can mount a specific immune response, mainly mediated by T lymphocytes. The DCs recognize the antigens of the parasites, and in the first instance, they induce a Th1-type immune response, characterized mainly by the production of pro-inflammatory cytokines and mediators. Nevertheless, parasites have the ability to polarize, through the activation of DCs, towards a Th2-type immune response, characterized mainly by the production of anti-inflammatory cytokines, eosinophilia and mastocytosis. However, due to the great diversity of parasites that exist, as well as their phenotypic variability, which involves different stages of antigenicity, conditioned by the life cycle of the parasite itself, these microorganisms have the ability to develop strategies that allow them to evade the immune system and facilitate their survival and spread in the host. Despite the different immune responses that the host assembles in contact with the different diseases caused by these microorganisms, DCs are very important, since they represent the junction point between the innate and adaptive immune responses, allowing the host to differentiate the type of microorganism by which it has been invaded and thus be able to mount a specific immune response.

8. Conclusions

Dendritic cells are a key cell type in the recognition of intracellular and extracellular pathogens through the different receptors that they express. The maturation of the DCs is an important event since through this mechanism these cells acquire the ability to express MHC as well as costimulatory molecules, thus conditioning the presentation of the antigen, producing cytokines and mounting immune in order to kill the invading pathogen. The response can be mediated by the PRRs as they will recognize different structures of the invading microorganism and execute a defensive response with the purpose of eliminating the invading microorganism through the production of antimicrobial cytokines and intermediaries, as well as activating transcription factors to produce cytokines that have an important role in the polarization of the T helper cell during priming by DCs.

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Conflict of interest

We have no conflict of interest related to this work.

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