Chapter 4

Role of Dendritic Cells in Parasitic Infections

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http://dx.doi.org/10.5772/intechopen.79491

Abstract

Dendritic cells comprise a complex array of cell populations that play a leading role in immune defense. In an immature state, they have the capacity to sense and uptake different antigens. Upon capturing antigens, they become activated, mature, and migrate to lymph nodes where they present antigen-derived peptides to naïve T cells. Due to these excellent surveillance properties, dendritic cells play an important role against parasitic infections. Also, dendritic cells are an important source of IL-12, which is a fundamental proinflammatory cytokine in the control of intracellular parasites. The aim of this chapter is to review the most important characteristics and functions of dendritic cells and their role in the control of infection by parasites.

Keywords: dendritic cells, pattern recognition receptors, pathogen-associated molecular patterns, protozoan parasites

1. Introduction

1.1. Generalities of dendritic cells (DC)

Dendritic cells (DC) were discovered by Paul Langerhans in 1868 when he described dendritic, nonpigmentary cells in the epidermis that he considered intraepidermal receptors for extracutaneous signals of the nervous system [1]. Afterwards, Langerhans discovery fell into oblivion and almost 100 years elapsed until, in 1973, Steinman and Cohn described a cell population in the spleen of mice similar to the one described by Langerhans that had appearance and behavior different from monocytes and macrophages and were named as dendritic

cells [2]. They observed that this new cell population had a great capacity to initiate and modulate the immune response [3, 4] and expressed high levels of MHC-II and CD11c [5, 6].

Currently, DC are recognized as a heterogenous cell population whose members differ in ontogeny, anatomic localization, migration, and due to the great repertoire of functions they perform, make them key participants in the immune response. DC are localized in lymphoid and nonlymphoid tissues including blood. At the periphery, they capture antigens through the recognition of pathogen-associated molecular patterns (PAMPs) by PAMPs recognition receptors (PRRs), migrate, and transport them to lymphoid organs where they are specialized in antigen processing and efficiently present endogenous and exogenous antigen-derived peptides in both MHCI and MHCII contexts. DC also have the unique capacity of presenting exogenous noncytosolic antigen-derived peptides in the context of MHCI by cross presentation [7], a critical mechanism for the immune response against viruses and intracellular bacteria [8]. In addition to the primordial role of DC in antigen processing and presentation, their participation has been broadly documented, along with other immune cells, in the production of cytokines that modulate the immune response toward a Th1 or Th2 response, in the regulation of cytotoxic T lymphocytes, and in immunologic tolerance [9–15]. The crucial role of DCs in the initiation and regulation of adaptive immunity has led to their use in dendritic cell-targeted vaccination [16]. It has been documented that following loading with pathogenic antigens and adoptive transfer, DC mediate protection against a wide spectrum of infectious diseases [17–19]. However, it has been shown that the employment of *ex vivo* antigen-loaded DC for first-line prophylactic vaccination is not adequate. Targeting dendritic cells *in situ* through antigen-DC receptors has circumvented this obstacle. Indeed, this new strategy has proven to be effective against different infections, including parasitic infections [20] and can be explained by the facility of exposing antigens to DC and their regulated presentation pathways. The outcome of these studies emphasizes that targeted delivery of antigens to DC surface endocytosis receptors such as C-type lectins increases antibody and cell-mediated immunity [21].

Due to their complexity, the establishment of the origin of DC and their classification has encountered some difficulties; nevertheless, researchers have reached a consensus on these topics, which is discussed next.

1.2. Origin and subpopulations of DC

The origin of DC has been more precisely deciphered in the murine model as compared to humans. It has been established that during their differentiation, hematopoietic precursors $CD34^+$ in the bone marrow give rise to common myeloid progenitors (CMP) characterized for the expression of Lin^- $CXCR1^+$ $CD11b^-$ $cKit^+$ $CD135^+$ [22]. These CMP give rise to the common progenitor of monocytes and dendritic cells (MDP) [9, 15, 23, 24], which in turn originate the precursors of plasmacytoid DC (pre-pDC) and conventional DC (pre-cDC). These cells abandon the bone marrow to the circulation to later colonize the tissues as immature DC where they develop and differentiate to DC [23, 25–29]. It has been shown that the growth factor FMS-like tyrosine kinase 3 ligand (Flt3L) [30–32] is essential for the process of differentiation of mouse DC, while M-CSF and GM-CSF are indispensable for the development of progenitors, but not for their maturation [33].

In relation to the origin of human DC, for years it has been difficult to establish their ontogenic pattern. Nevertheless, the culturing of human hematopoietic stem cells $CD34^+$ performed by Lee and colleagues [34] shed important information about their origin. They showed that these precursors give rise to the human progenitor of granulocytes, monocytes, and DC (hGMDP), which in turn originate the progenitor of human DC and monocytes (hMDP). The hMDP gives rise to monocytes and the common progenitor of DC (hCDP). Differently from GMP (granulocytes and macrophages progenitor), hCDP are found not only in cord blood and bone marrow, but also in peripheral blood and lymphoid tissues and originate the different types of DC [34]. These cells are characterized for a high expression of MHCII, but lack the typical markers of CD3 lineage (T lymphocytes), CD19/20 (B lymphocytes), and CD56 (NK cells), reason why DC have been traditionally named as $HLA\text{-}DR^+$ $lineage^-$-cells. There are two principal subtypes of DC: conventional DC (cDC), also called myeloid DC (mDC), and plasmacytoid DC (pDC) [15].

1.2.1. Conventional (cDC) or myeloid DC (mDC)

cDC or mDC share an ontogenical origin with monocytes and macrophages, and thus, GM-CSF is essential for their differentiation *in vitro*. These cells are characterized for the expression of typical myeloid antigens such as CD11c, CD13, CD33, and CD11b. CD11c is also expressed in human cDC and monocytes, but cDC lack CD14 or CD16 and may be subdivided into cDC $CD1c^+$ and cDC $CD141^+$ fractions. These two fractions share homology with mouse classical DC expressing either CD11b ($CD1c^+$ DC) or CD8/CD103 ($CD141^+$ DCs) [35]. cDC are also characterized for the expression of different Toll-like receptors (TLR) such as TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, and TLR10 [36]. Additionally, human mDC have been subdivided according to their anatomical localization into three groups: (1) peripheral tissue-resident, (2) secondary lymphoid organ-resident, and (3) circulating blood mDC [35]. In particular, peripheral tissue resident DC encompass different mDC subsets localized in human skin. These include Langerhans cells (LC) and dermal interstitial DC (intDC). The origin of these two cell populations is still controversial, since some authors suggest that the precursor is of myeloid origin and one of the intermediaries is the monocyte [37]. Contrarily, other authors have proposed that the origin of LC and intDC proceeds from a fetal progenitor that also originates the glia in the central nervous system [38]. LC are localized in the epidermis and express CD1a, langerin, and E-cadherin. intDCs are localized in the dermis and express DC-SIGN, CD11b, XIIIa factor, and CD14. Besides, these cell populations differ in the response to certain stimuli and production of cytokines and chemokines. For example, the stimulation with CD40L induces the production of IL-10 by intDCs, but not by LC. On the other hand, intDCs produce IL-6 and IL-12 that induce the differentiation of B cells toward IgM-producing plasma cells and stimulate Th cells for the production of Th1 cytokines, favoring this type of response. LC stimulate Th cells for the secretion of IL-4, IL-5, and IL-13, resulting in a Th2 response [35].

1.2.2. Plasmacytoid dendritic cells (pDC)

These cells owe their name to their similar appearance to plasma cells and to the fact that they proceed from a lymphoid progenitor, reason why they require IL-3 instead of GM-CSF for

their differentiation *in vitro*. pDC are characterized for the production of type I IFN in response to viral recognition through TLR7 and TLR9. Apart from these TLR, they also express TLR1 and TLR10 [36]. In mice, pDC are localized in bone marrow, blood, and lymphoid organs and are characterized for the expression of CD11c, CD45RA, CD317, and CD172 with a low expression of MHCII and negative for CD11b. They also show a significant expression of Ly6C, Ly49Q, and Siglec-H [39–41]. It has been shown that mouse pDC are not as efficient in antigen presentation and T cell priming as cDC, even when activated. Instead, murine pDC participate in peripheral tolerance through the induction of regulatory T cells (T regs), which has been proposed to occur by two mechanisms. In one case, it has been suggested that T regs are generated via the production of IDO and subsequent T cell tryptophan starvation upon CD200R engagement. On the other hand, the suggestion is that T regs generation is dependent on IL-10 and TGF-β production by pDC. Other studies have also demonstrated that pDC induce T cell anergy or deletion [42–44]. In relation to human pDC, it has been established that they are strong activators of T cells and share the capacity of their murine counterparts to induce tolerance. Some characteristic markers of human pDC are BDCA-2 (CD303), BDCA-4 (CD304), $CD123^{hi}$, and $CD1c^{low}$ (BDAC-1) [41], and they have been divided into two populations based on CD2 expression [45]. Both pDC subsets demonstrate strong activation and cytokine production in response to viruses, but CD2hi pDC express IL-12p40 during influenza infection, are better stimulators of naïve T cells, and have a better survival rate in response to stress and glucocorticoid treatments [46–48].

1.2.3. Dendritic cells that respond to specific microorganisms: tip-DC

It has been shown that some populations of DC develop in response to specific microorganisms. Such is the case of Tip-DC ($CD11b^{int}$, $CD11c^{int}$, $Gr\text{-}1^{+}$, $DEC\text{-}205^{-}$, $CD14^{-}$, $F4/80^{-}$) that produce TNF and iNOS/NO upon the infection with some microorganisms such as *Listeria monocytogenes* and *Brucella melitensis*, which results in an effective mechanism against infection. Nevertheless, in some cases, this response has been associated with tissue damage [49–51].

It has also been demonstrated that during infection with the intracellular parasite *Trypanosoma brucei*, tip-DC represent the major pathogenic M1 liver subpopulation. $CD11b^{+}$ $Ly6C^{+}$ monocytic cells migrate from bone marrow to the liver of infected mice through CCR2 interactions, then differentiate to immature inflammatory DC ($CD11c^{+}$ $CD80/CD86/MHC\text{-}II^{low}$) in an IFN-γ and MyD88 signaling-independent, and finally mature to functional Tip-DC, whose signaling depends on IFN-γ and MyD88. Interestingly, IL-10 dampens Tip-DC function during *T. brucei* infection by limiting their differentiation and maturation and CCL2 expression [52].

1.2.4. DC $CD14^{+}$

DC $CD14^{+}$ are a group of myeloid DC $CD11c^{+}$ localized in diverse nonlymphoid tissues as well as in lymph nodes. They were originally described as interstitial DC and are characterized by the presence of CD14, which suggests that they probably originate from monocytes with which they share more features than with $CD11c^{+}$ and $CD141^{+}$ DC [35].

1.2.5. Monocyte-derived dendritic cells (moDC)

As already mentioned, DC originate from precursors present in the bone marrow; nevertheless, some of them can differentiate from other cells, as is the case of moDC. In humans, there are three types of monocytes: classic ($CD14^+$, $CD16^-$), intermediate ($CD14^+$, $CD16^+$), and non-classic ($CD14^{low}$, $CD16^+$). Currently, it has not been accurately defined from which monocyte subtype moDC derive *in vivo* [53]. According to transcriptomic analysis, it has been suggested that in humans, skin DC $CD14^+$ as well as DC $CD103^-$ $CD172a^+$ from intestine are related to monocytes [54, 55], reason why they are considered authentic moDC. On the other hand, in inflamed tissues, inflammatory DC express $CD11c^+$, $CD1a^+$, and $CD14^+$ that are most probably derived from monocytes and therefore are also considered moDC [56, 57].

DC are one of the most important effectors in the immune response due to the multiple functions they play such as recognition of PAMPs and activation to produce proinflammatory and regulatory cytokines, phagocytosis of pathogenic organisms, migration to spots where danger and pathogenic signals exist, and processing and presentation of antigens through with MHCII and CD1 to T lymphocytes. In the next section, we will discuss the receptors present in dendritic cells that interact with pathogenic organisms [58].

2. Pattern recognition receptors (PRRs) present in dendritic cells

As already mentioned, DC are the surveillance cells that need to distinguish between self and nonself. They are able to recognize different molecules such as proteins, lipids, carbohydrates, and nucleic acids of bacterial, viral, fungal, or protozoan origin known as PAMPs. To achieve this surveillance task, DC possess distinct types of receptors among, which are: Toll-like receptors (TLR), RIG-I-like receptors (RLR), NOD-like receptors (NLR), and C-type lectin receptors (CLR) [59].

2.1. Toll-like receptors (TLRs)

Innate immunity is the first line of host defense against pathogen infection, and infected hosts need to detect the invasion of pathogens to prevent their spread. TLRs are transmembrane proteins that present two principal domains, leucine-rich repeats (LRR) and a Toll/IL-1R (TIR), which recognize PAMPs and initiate signaling pathways, respectively. Currently, 15 mammalian Toll-like receptors are found (TLR1-15), of which 10 are in humans. TLR3, 7, 8, and 9 are intracellular receptors and the other ones are extracellular [59–61]. The binding partners of the recently discovered TLR10, TLR12, TLR13, and TLR15 are unknown. TLR11 is only expressed in mice, and recent studies suggest that it associates with molecules originating from uropathogenic bacteria and *Toxoplasma gondii* [62, 63]. TLRs exert their functions through the formation of homo- or heterodimers. To date, five dimers have been described that are: TLR1/TLR2, TLR2/TLR6, TLR4/TLR4, TLR5/TLR5, and TLR10/TLR10 [64]. The TLR1/2 heterodimer recognizes bacterial triacyl lipopeptides, and TLR2/6 recognizes bacterial diacyl lipopeptides. In addition, each TLR in individual

form recognizes different ligands and induces the production of various cytokines and chemokines [65–67]. TLR1 and TLR2 recognize triacyl lipopeptides, TLR2 and TLR6 sense diacyl lipopeptides, lipoteichoic acid, and zymosan. Also, TLR2 recognizes peptidoglycans, lipoarabinomannan, porins, glycosylphosphatidylinositol-anchored mucin-like, and hemagglutinin. TLR3 recognizes double-stranded RNA, TLR4 senses LPS and envelope proteins. TLR5 recognizes flagellin, TLR7 and 8 can recognize single-stranded RNA and finally TLR9 recognizes DNA CpG and malaria hemozoin [68]. DCs show different expression levels of TLRs and respond dissimilarly to TLR ligands. The expression of TLRs varies with species, DC subtype, and maturation stage. All human TLRs are present in immune cells, specifically in DC, TLR1, 2, 3, 4, 7 and 9 have been shown to be present [69]. TLR10 is not present in human dendritic cells; nevertheless, it has been recently demonstrated that this receptor could be found intracellularly in endosomes and can recognize dsRNA [70]. When TLRs bind their ligands (PAMPs), this (among another variables) can trigger changes in the maturation, migration, and actions of DC. This phenomenon initiates an inflammatory response characterized by the production of cytokines, cellular migration, and directly or indirectly the activation and generation of Th1, Th2, Th17, Treg, and even B lymphocyte responses [71].

2.2. RIG-I-like receptors (RLRs)

Retinoic acid-inducible gene-I-like receptors (RLRs) are intracellular receptors and, to this date, are a family of three members, which are RIG-I, melanoma-differentiation-associated gene 5 (MDA5), and laboratory of genetics and physiology 2 (LGP2). The ligand for RIG-I is RNA (5′ -PPP single-stranded RNA and short double-stranded RNA), MDA5 recognizes RNA (poly IC and long double-stranded RNA) and LGP2 recognizes RNA [72]. All three receptors are composed of a central DExD/H box helicase domain, which coordinates RNA binding and a C-terminal regulatory domain that is implicated in RNA binding. In addition, RIG-I and MDA5 contain two CARD domains (caspase activation and recruitment) that have critical signal activity and are involved in the innate immune and inflammatory responses upon RNA detection [73]. The activation of these receptors induces the production of type I IFN characterized by its antiviral and antibacterial activity; thus, RLRs are an important complement of the immune response, particularly, with intracellular pathogens, and could be important in the response against antigenic RNA from intracellular protozoa. It has been showed that RLRs responses are independent of TLRs responses [74].

2.3. NOD-like receptors (NLRs)

One important family of receptors found in DC is the nucleotide-binding oligomerization domain-containing receptors (NLRs), which are a family of 22 protein members in humans that can be classified into five subfamilies according to their structure: NLRA (CIITA), NLRB (NAIPs), NLRC (NOD1, NOD2 and NLRC3-5), NLRP (NLRP 1-14), and NLRX [74]. Their basic structure consists of a central nucleotide-binding domain (NBD), a carboxy-terminal leucine-rich repeats (LRR), and an amino-terminal effector domain. Some of the ligands that bind to these receptors are iE-DAP, MDP, RNA, ATP, bacterial toxins, uric acid, CPPD, amyloid-b, and anthrax lethal toxin [68]. NLRs are linked to different functions, as is the case of

NOD1, NOD2, CIITA, and NLRP10 that are signaling receptors and are associated to adaptive immunity. NLRC4 and NLRP3 are linked to the formation of the inflammasome and finally NLRP1, NLRP6, NLRP12, and NLRC5 participate both in signaling as well as in the formation of the inflammasome [75]. In relation to the formation of the inflammasome, NLRP 1, 2, 3, 6, 7, 12, NLRC4/N, and AIP 2, 5 have been found to participate when those receptors sense PAMPs or DAMPs (damage-associated molecular patterns). Also, it has been documented that CIITA and NLRC5 can be activated by cytokines that lead to the transcription of MHC I and II, and NOD1-2 have TLR-like activity with the recognition of PAMPs and triggering of inflammatory signaling cascades. Other members such as NLRP 2, 4, 6, 11, 12, NLRX1, NLRC3, etc. participate in the inhibition of the NF-κB pathways [76, 77]. Finally, NLRP 10 and 12 participate in cellular migration. In particular, NLRP10 plays a critical role in antigen-primed DC migration in draining lymph nodes [78], and NLRP-12 regulates migration of DC to a CCR7 chemokine gradient, thus resulting in a reduced T cell response to antigen [79].

In conclusion, this large family of intracellular receptors can recognize viral, bacterial, protozoan, and fungal antigens that trigger cellular innate and adaptive immune responses.

2.4. C-type lectin receptors (CLRs)

Myeloid cells, including DC and macrophages, express a large number of C-type lectin receptors that are one of the most important PRRs that recognize carbohydrates [80]. They can have a transmembrane or soluble localization and can trigger phagocytic and inflammatory responses through the recognition of PAMPs, DAMPs, and tumor-associated molecular patterns (TAMPs) [81]. The common structure in these receptors is the carbohydrate recognition domain (CRD), which can be found in different numbers and arrangements. They also present an ITAM (immunoreceptor tyrosine-based activation) like motif or an ITIM (immunoreceptor tyrosine-based inhibition) motif [82]. A wide array of carbohydrates are recognized by CLRs, among those that can be found are high mannose glycans, mannose, mannosyl fatty acids, fucose glycans, Lewis antigens, glucans, among others. The recognition of the ligand by a CLR can activate or inhibit responses dependent or independent of the Syk signaling pathway [83]. This family of receptors has been classified according to their structure in 17 groups that comprise almost 50 proteins. The groups that comprise the soluble receptors are: I (proteoglycans), III (collectins), VII (free CTLD), IX (tetranectin), and XII (CTLD/acidic neck). On the other hand, transmembrane receptors are grouped as follows: II (type 2 receptors), IV (selectins), V (NK cell receptors), VI (MMR), X (polycystin), XI (attractin), and XIV (endosialin) [82]. Several CLRs are present in DC and the best characterized are DCIR, DCSIGN (CD209), Dectin1, Langerin, and MMR (CD206). Langerin (CD207) on LC in the epithelial layer of the skin has unique carbohydrate specificity for high mannose and LeY carbohydrates and is involved in the recognition of various viruses [84]. DEC 205 has extensively been employed for target delivery of antigens to DC in murine and human studies [16]. It has been shown that targeting antigen to the DEC205 receptor improves humoral and cellular immune responses when DC are stimulated with activating agents or adjuvants such as poly I:C [85]. In mice, this receptor is expressed on cortical thymic epithelium, thymic medullary DC ($CD11c^+$, $CD8\alpha^+$), and subsets of peripheral DC (splenic, lymph node DC, dermal, interstitial DC, and Langerhans cells) [86]. In contrast, DC-SIGN (CD209) is merely expressed on moDCs and

on CD14+ dDCs in dermal layers of the skin and has specificity for mannose and all Lewis type carbohydrates (Lewis A, B, X, and Y) [87]. This receptor is often endosialin with the MR (CD206) and shares mannose specificity [88]. DCIR (for DC immunoreceptor) (CLEC4a) has broad carbohydrate specificity for mannose and fucose [89, 90] and has been shown to participate in T cell responses. Different from other CLRs, DCIR contains an ITIM motif and, upon triggering with Abs, inhibits the production of inflammatory cytokines and, thus, has been associated with homeostatic control and control of inflammation [91–93]. Also, it has been shown that DCIR can participate in the capture of HIV-1 and promote infection in trans and in cis of autologous $CD4^+$ T cells from human immature monocyte-derived DCs [94].

Finally, these receptors can recognize (and opsonize) pathogens and the responses to these events are phagocytosis for antigen uptake, cell migration, cell adhesion, inhibition of cytokine production, and interaction between DC and T lymphocytes [95]. In conclusion, CLRs are key participants in the immune response that spot important signals of PAMPs, DAMPs, and TAMPs with which immune cells (e. g., dendritic cells) sense and recognize the environment. Its interactions and intersections trigger, adapt, and regulate immune responses [96].

In addition to the PRRs just mentioned, it is important to note that some orphan receptors have been described for which a ligand has not been found, as well as the family of ALR intracellular receptors (AIM2-like receptors) and another family of lectins (I-lectins) Siglecs (sialic acid binding Ig-like lectins) [97].

3. Role of dendritic cells in the infection with parasites

Due to a wide variety of functions that dendritic cells display both in the innate immune response as well as in the adaptive immune response, they are key participants in the defense against parasites. DC have the capacity to recognize different molecules in the surface of parasites and are efficient phagocytes; thus, several intracellular parasites reside inside DC. Once DC 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, DC process antigens for presentation to T cells. DC have the unique property to migrate to regional lymph nodes where they activate naïve T cells, as well as produce cytokines and participate in the modulation of the immune response, the amplification of the innate immune response, and can also participate in immunological tolerance.

Protozoan infections that persist in urban environments including leishmaniasis, Chagas disease, malaria, and zoonotic diseases such as toxoplasmosis are a matter of great concern due to their prevalence, morbidity, and mortality [98]. Our best hope to counteract them is the development of new and innovative technologies. For this development, the better understanding of the biology of these parasites and their interaction with their host is of outmost importance. We chose the above-mentioned diseases and analyzed their interaction with DC that are one of the most important participants of the immune response.

3.1. Interaction of dendritic cells with *Leishmania*

3.1.1. Generalities of Leishmania

Leishmania is an obligate intracellular parasite that presents two morphological stages: the flagellated promastigote that is found in the salivary glands of the insect vector and the aflagellated amastigote that is the intracellular form found in the vertebrate host. This genus of parasites is constituted by diverse species that are morphologically indistinguishable and are grouped in three subgenera: *Leishmania*, *Viannia*, and *Sauroleishmania*. The species that cause infection in humans and other mammals are found in the subgenus *Leishmania* and *Viannia*. *Sauroleishmania* has been only found to infect some reptiles. Species belonging to *Leishmania* are characterized for having a suprapyloric development and among these are: *donovani, chagasi (infantum), major, tropica, aethiopica, mexicana (pifanoi), amazonensis,* and *venezuelensis.* On the other hand, the species of the subgenus *Viannia* have a peripyloric development and are *braziliensis, guayanensis, peruviana,* and *panamensis*. *Leishmania* is transmitted by Diptera belonging to the family Psychodidae, specifically, by females of the genus *Lutzomyia* and *Phlebotomus* [99, 100]. *Lutzomyia* is the transmitter of leishmaniasis in America, and *Phlebotomus* transmits this pathology in Africa, Asia, and Europe [101, 102].

3.1.2. Leishmania life cycle

Leishmania life cycle starts when the insect vector feeds blood from the vertebrate host and inoculates promastigotes in the superior dermis [103]. Then, promastigotes are recognized through different receptors such as CR3 [104], C-type lectin receptors, and FcγR and are phagocytosed by dermal macrophages, where they transform to amastigotes [105] and also infect neutrophils. Thanks to a series of events such as the inhibition of phagocytosis, resistance to microbicidal mechanisms, and inhibition of host cells apoptosis, amastigotes manage to survive inside macrophages and duplicate until they lyse them and infect new surrounding cells, such as dendritic cells. If the parasite is not able to inhibit the different microbicidal mechanisms of macrophages, they will be able to destroy them mainly through the production of nitric oxide and induce the activation and recruitment of proinflammatory cells such as cutaneous mast cells, neutrophils, and inflammatory monocytes that lead to the development of a focus of chronic inflammation in the site of infection, which will be evident in the patient [105, 106]. The female sand fly when ingests blood from an infected host draws infected cells as well as free amastigotes and in this form the life cycle continues.

3.1.3. Interaction of Leishmania major with macrophages and DC

One of the most studied interactions of DC with a parasite is the interaction with the intracellular parasite *Leishmania.* In the murine model of infection and using *Leishmania major*, it has been shown, as already mentioned, that promastigotes infect macrophages and neutrophils that are localized near the site of inoculation. Promastigotes are phagocytosed by macrophages mainly through CR3 [104], which permits parasites to enter to this host cell without activating it [107]. Interestingly, the infection with *Leishmania* downregulates the capacity of macrophages to produce IL-12. Even the stimulation of macrophages with IFN-γ/LPS does not

elicit the production of IL-12 when cells are infected with *L. major* [108]. Once promastigotes enter to macrophages without activating them, they differentiate into amastigotes and start dividing in the parasitophorous vacuoles. Then, amastigotes are released to the extracellular milieu where they are phagocytosed by neighboring cells such as DC. DC phagocytose amastigotes mainly through FcγRI and FcγRIII, inducing DC maturation, migration to lymph nodes, and IL-12 production [109]. It has also been shown that *Leishmania*-infected DC upregulate the levels of costimulatory molecules such as CD40, CD54, CD80, and CD86, as well as of MHCII; that is, the maturation of DC enables them to initiate the activation of T lymphocytes [110]. Other authors have demonstrated that during the course of chronic infection of C57BL/6 mice with *L. major*, the main producers of iNOS are inflammatory DC, which are recruited in a CCR2-dependent manner and the induction of iNOS depends on the development of a local Th1 microenvironment [111]. In addition to the analysis of the infection of murine DC with *L. major*, other authors have shown that in the case of human DC infected with *L. major* metacyclic promastigotes, the production of high amounts of IL-12 needs the interaction of CD40-CD40L, although infected DC are able to produce some IL-12. Also, the infection of human DC with *L. major* promastigotes does not inhibit the process of maturation [112].

3.1.4. Role of DC in the adaptive immune response against Leishmania major

Once DC capture *Leishmania* parasites, they migrate to the lymph nodes were they activate naïve CD4 and CD8 T lymphocytes in order for them to respond specifically against the parasite with an immune response dominated by the presence of IFN-γ and cytotoxic T lymphocytes species specific in what has been called a type Th1/Tc1 immune response. This type of response permits mice to control infection and eliminate the parasite [113]. IL-12-producing DC have been observed until week 4 postinfection with a peak in week 6 just before the Th1/Tc1 IFN-γ-producing response develops completely [114]. Nevertheless, the reason for the delay in DC maturation still remains to be clarified. Iborra and colleagues have described a route that attempts to understand this delay in the maturation of DC after *Leishmania* infection. They found that *L. major* parasites secrete a soluble factor that binds to the soluble macrophage c-type lectin receptor (Mincle) of DC, which inhibits its maturation. They showed that Mincle deficiency favored stronger DC activation represented by a higher expression of costimulatory molecules, migration to dLNs and priming of a Th1 response. Thus, mice deficient in Mincle receptor are capable of controlling parasite replication and indeed had smaller lesions [115]. It has been shown that in the infection of mice with *L. major* metacyclic promastigotes, Langerhans cells induce the activation of regulatory T lymphocytes [116]. Murine $CD103^+$ dermal DC have been shown to be responsible of inducing a protective immune response against *L. major* since mice lacking this DC subtype develop an immune response dominated by regulatory and Th2 lymphocytes infection [117].

3.1.5. Interaction of DC with L. mexicana

While *L. major* is an etiologic agent of cutaneous leishmaniasis (CL) in the Mediterranean region, *L. mexicana* is in Mexico and Central America. Although both species cause CL, the case of *L. mexicana* is of particular interest due to the fact that this species can cause localized cutaneous leishmaniasis (LCL) and diffuse cutaneous leishmaniasis (DCL). Different studies

have shown that the interaction of *L. mexicana* and its principal host cells, macrophages and DC, are substantially different as compared to what has been observed with the *L. major* model. It has been observed that in DC infected with *L. mexicana,* the parasite manages to be internalized without the initiation of cell maturation or the production of IL-12. Although the infection inhibits IL-12 production, *L. mexicana* does not eliminate the capacity of DC to produce it and, indeed, when an external stimulus such as LPS is used, infected DC are capable of producing and secreting IL-12. In addition it was observed that the internalization of the parasite is independent of opsonization [118]. In relation to the recognition of *L. mexicana* by DC, the information about the receptors involved is scarce. On one hand, it has been reported that DC-SIGN is capable of binding *L. mexicana* LPG [119]. Recently, our group showed that DC-SIGN participates in an important manner in the internalization of *L. mexicana* promastigotes since the blockade of the receptor with a specific antibody diminished significantly the interaction of monocyte-derived dendritic cells with *L. mexicana* promastigotes [120]. Using the same strategy of blocking DC-SIGN with an antibody, its role in the infection of DC with *L. pifanoi* amastigotes was shown to be relevant since it dramatically diminished the interaction of DC with amastigotes [121].

3.1.6. Interaction of DC with other species of Leishmania

It has been observed that DC can interact with both *L. infantum* y *L. pifanoi* amastigotes and promastigotes through DC-SIGN and that it binds more avidly the infective metacyclic forms. Interestingly, the interaction of DC with *L. major* metacyclic promastigotes does not depend on DC-SIGN [122]. Also, it has been shown that plasmacytoid DC do not internalize *L. infantum* promastigotes, although contact of the parasites with these cells induces the secretion of IFNα/β, but not of IL-12 [123]. Also, it has been described that in the early stages of *Leishmania* infection, the inflammatory milieu that is produced is ideal for the induction of monocytes toward Tip-DC.

3.1.7. Molecular mechanisms involved in the modulation of DC by Leishmania

The molecular mechanisms involved in the modulation of DC during the infection with *Leishmania* have not been fully analyzed. In the murine model of infection with *L. major*, it has been clearly established that susceptible mice (Balb/c) mount a Th2-type response that enables them to eliminate the parasite while resistant mice (C57/BL6) mount a Th1 response that permits the elimination of the parasite. In contrast, C57/BL6 mice infected with *L. mexicana* metacyclic promastigotes do not resolve infection and it becomes chronic, what has been associated with a decrease in the recruitment of monocytes, a reduction in inducible nitric oxide synthase (NOS2) synthesis in moDC along with a reduction in the migration to the lymph node, which results in an insufficient activation of a Th1 response [124]. *Leishmania* parasites possess an extraordinary capacity to manipulate host cells. In particular, it has been shown that the infection of murine DC with *L. mexicana* promastigotes rapidly affects DC molecular mechanisms necessary for the development of a protective immune response, among them, an increase in tyrosine phosphatases, which translates in an inactivation of mitogen-activated protein kinases (MAPK), and decrease in the translocation of transcription factors such as

NF-κB and AP-1. In addition, parasites also modulate DC maturation markers decreasing the surface expression of antigen-presenting and costimulatory molecules [125]. Our group has worked for several years in the modulation of DC by *L. mexicana*. We have shown that LPG purified from *L. mexicana* promastigotes induces a major secretion of IL-12 and NF-κB translocation in human DC as compared with monocytes [126]. We also showed that the infection of murine DC with *L. mexicana* amastigotes downregulates NOS2 and thus diminishes NO production [127]. On the other hand, we have also shown that the infection of human DC with *L. mexicana* amastigotes and promastigotes inhibits the activation of MAPK JNK and p38, and the infection of human DC with *L. mexicana* amastigotes activates AKT during camptothecin-induced apoptosis [128, 129].

In addition to the modulation of DC biology exerted by *Leishmania* that has just been described, another intracellular parasite whose interaction with DC has been deeply studied is *Toxoplasma gondii.*

3.2. Dendritic cells in the infection with *Toxoplasma gondii*

3.2.1. Generalities of T. gondii

Toxoplasma gondii is an intracellular parasite that causes toxoplasmosis, and it can be hosted by diverse warm-blooded animals and is present in two interconvertible stages: the lytic, invasive, and active tachyzoites and the slow-growing, encysted bradyzoites. The oocysts present in the definitive host, a feline, are highly infective and long-lived and are shed in the feces for a limited time [130]. The infection initiates with direct contact with oocysts or by consumption of undercooked meat containing bradyzoite cysts. Bradyzoite cysts convert to tachyzoites in the small intestine of the intermediate host and can infect almost all nucleated cells. Here, they replicate within a parasitophorous vacuole (PV), egress by lysing the cell, and infect neighboring cells. Tachyzoites elicit a potent immune response that eliminates most parasites. However, some tachyzoites can evade this response, convert back to bradyzoites, and persist mostly in nonreplicative cells such as those in the brain or heart of their intermediate host [131].

3.2.2. Immune response to T. gondii

Toxoplasma orchestrates a carefully balanced string of events between various cell types including neutrophils, DCs, and macrophages upon first encountering the host innate immune defense. A complex network of molecular signaling pathways leads to the activation and regulation of cytokines and ultimately to the production of effector molecules [132]. Acquired resistance to *T. gondii* infection is mediated by a mucosal and systemic Th1 cellular immunity [133]. The deviation to a Th1 response depends enormously on the production of IL-12 by different cells such as conventional DCs, macrophages, and pDCs. Parasite infection causes damage to the intestinal epithelium resulting in the translocation of microflora and subsequent MyD88-dependent signaling and IL-12 production. IL-12 triggers the proliferation of NK cells, CD4 T cells, and CD8 T cells, which mediate cytotoxicity and the production

of high amounts of IFN-γ [134, 135]. It has been previously showed that DC pulsed with *T. gondii* antigens elicit protective immunity against chronic toxoplasmosis in mice [136, 137].

3.3. Interaction of DC with *T. gondii*

3.3.1. Recognition of T. gondii by DC

DC are crucial participants in the immune response against *T. gondii* and one of the leading roles that they play in the production of IL-12, which, as previously mentioned, promotes the production of IFN-γ and thus deviates the immune response toward a Th1. DC recognize diverse *T. gondii* molecules; in particular, it has been shown that a soluble parasite extract (STAg) has a major capacity of eliciting IL-12 from splenic DC as compared to other PAMPs such as LPS and CpG oligonucleotides [138]. The production of IL-12 induced by *T. gondii* in DC is dependent on MyD88, an adaptor molecule in TLR signaling pathways, and the chemokine receptor CCR5, since the production of IL-12 decreases dramatically in mice lacking MyD88 or CCR5 [139]. Interestingly, CCR5 in DC is induced with cyclophilin-18 from *T. gondii* [139]. The participation of MyD88 in the induction of IL-12 by *T. gondii* presupposes the recognition by TLRs. Indeed, it has been shown a profilin-like protein, which is not required for the intracellular growth of *T. gondii*, but is indispensable for host cell invasion and active egress from cells [139], was identified as a ligand of TLR11 and the profilin-like protein is also recognized by TLR-12 [62], and is critical for IL-12 production, especially in plasmacytoid DCs (pDCs) [140]. TLR11 has been localized intracellularly associated with the nucleic acid-sensing TLR trafficking protein UNC93B1.52. A mutation in this protein impedes TLR intracellular trafficking, which has been shown to cause a reduction in IL-12 production in mice infected intraperitoneally with *Toxoplasma* bradyzoites and increases susceptibility to infection [141, 142].

Both cyclophilin-18 and the profilin-like protein stimulated IL-12 production in $CD8\alpha^+$ DC and $CD8\alpha^-$ DC. Although humans do not express either TLR11 or TLR12, human monocytes produce proinflammatory cytokines in response to *T. gondii* infection, suggesting that other TLRs in humans recognize different compartments of *T. gondii* to produce IL-12 in antigen-presenting cells. Additionally, DC also produce chemokines such as CCL2 and CXCL2 upon recognition of parasite components including virulence factors [143]. These chemokines induce the migration of $Ly6C^{high}CCR2^+$ monocytes and neutrophils to the infection site [144]. Albeit not demonstrated specifically in DC, other TLRs, such as TLR2, can also be activated in response to *Toxoplasma* [145]. TLR2 and TLR4 both signal after binding *Toxoplasma* glycosylphosphatidylinositol (GPI) anchors [146]. However, single absence of either TLR2 or TLR4 in DC did not reduce the production of IL-12 in response to STAg [147].

3.3.2. Effector functions of DC against T. gondii

It is possible that DCs can directly act as effector cells to eliminate *Toxoplasma* as suggested by their ability to display oxygen-dependent microbicidal activity after IFN-γ activation [148]. Moreover, plasmacytoid DCs (pDCs) have been shown to be efficient at autophagy

[149], a process known to eliminate *Toxoplasma* in primed macrophages and to involve the family of p47 GTPases [150]. The various subsets of DC possibly recognize either direct infection with *Toxoplasma* or sense parasite products differently, and are thus important mediators of parasitic elimination and facilitators for the development of an efficient adaptive immune response. Conventional $CD11c^+$ DC have been shown to play key roles in host resistance to *Toxoplasma* bradyzoite cysts administered i.p. [151, 152].

3.4. Role of DC in the infection with *Plasmodium*

3.4.1. Plasmodium life cycle

Malaria is a disease caused by the blood protozoan of the genus *Plasmodium* about which there have been described five species capable of infecting humans that are *P. falciparum, P. vivax, P. malariae, P. knowlesi,* and *P. ovale* [153]. The life cycle of this parasite starts when a hematophagous female mosquito of the genus *Anopheles* introduces its proboscis, containing infective sporozoites into the mammalian host. There is evidence that once the sporozoites have been inoculated, they can remain on the skin for hours and slowly release into the blood [154, 155]. Once sporozoites reach the bloodstream, they migrate to the liver where they infect hepatocytes and transform into merozoites that infect red blood cells. Some of these merozoites transform into male and female gametocytes to finally complete their cycle within the mosquito's digestive tract [156, 157].

3.4.2. Interaction of DC with Plasmodium

Several studies have revealed that DC play an important role during *Plasmodium* life cycle, as well as in the pathophysiology and outcome of the disease. Although *Plasmodium* does not infect DC, it has been shown that the interaction of DC with infected erythrocytes has an effect on DC functions. In particular, it has been shown that erythrocytes infected with *P. falciparum* and co-cultured with human DC manage to induce in them an arrest in the process of maturation, thus inhibiting their ability to stimulate and activate T lymphocytes; however, the effect is dependent on the parasite: DC ratio [158, 159]. Also, during the acute phase of infection with *Plasmodium*, there is an increase in $BDCA3^+$ DC, but not in $CD1c^+$ DC, which correlates with a severe presentation of the disease [160, 161]. Other DC populations that change during *Plasmodium* infection are pDC ($HLA\text{-}DR^+CD123^+$): mDC ($HLA\text{-}DR^+CD11c^+$). It has been reported that the ratio of pDC:mDC diminishes in patients suffering from the acute phase of *P. vivax* infection. In addition to this decrease, there also exists an arrest in DC maturation demonstrated by a reduction in CD86 in patients infected with *P. vivax* and a decrease in CD83 and HLA-DR in individuals in the acute phase of infection with *P. vivax* and *P. falciparum*. This diminution of CD functions in these infections is accompanied by an increase in the number of cells that die by apoptosis, as well as by the decrease in their ability to capture, mature, and present antigens to T cells [162–164].

Other research groups have addressed the role of DC in the induction of the response of T and B cells in *Plasmodium* infection. It has been shown that $TCD8^+$ cells, previously activated by DC, exert their cytotoxic effect by inducing death of *P. vivax* sporozoites housed in

hepatocytes, thus, reducing parasite loads in hepatocytes. There is evidence that suggests $CD8^+$CD11b-DC located in the peripheral lymph nodes near the mosquito inoculation site are the same subtype of DC responsible for the activity of $TCD8^+$ cells [165–168]. The protective response of $TCD8^+$ cells is associated with the production of IFN-γ, which is induced by two subtypes of mature ($CD40^+$) spleen DC and ($CD8\alpha^+CD11b^-$ and $CD8\alpha^-CD11b^+$) D C) [169, 170]. There is evidence that, of these two subtypes, only the $CD8\alpha^-CD11b^+$ DC are responsible for the activation of $TCD4^+$ cells, in the acute phase of the infection, while the $CD8\alpha^+CD11b^-$DC participate in the process of antigen cross presentation throughout the infection [171, 172]. In relation to the activation of $TCD4^+$ cells, in different study models, it has been shown that the presentation of *Plasmodium* antigens by DC to $TCD4^+$ cells expresses MHC-II, CD40, and CD80 and produces IL-12, IL-6, and TNF-α, thus inducing $TCD4^+$ cells to express IL-2, IFN-γ, and TNF-α. Finally, the stimulation of DC with *Plasmodium* antigens also induces their migration of DC to lymphoid organs [173–177].

Apart from the interaction of DC with protozoan parasites that has been discussed, we chose *Trichinella spiralis* as an example of the interaction of a helminth with DC.

3.5. Interaction of *Trichinella spiralis* with DC

Trichinella spiralis is a parasitic helminth that belongs to the group of nematodes. Its biological cycle begins when a mammal (usually mouse, rat, pig, and human) ingests raw or undercooked meat containing cysts (encysted larvae). As it passes through gastric acid and pepsin, the larva is released from the cyst and invades the mucosa of the small intestine, where it matures to the sexually differentiated adult state that initiates reproduction [178]. After 1 week, females release larvae, which migrate to skeletal striated muscle where they encyst and the cycle closes when cysts are ingested by another mammal [178]. In order for *T. spiralis* to remain for long periods in the muscle, the parasite must have mechanisms to evade the immune response and inhibit tissue inflammation. It has been described that *T. spiralis* muscle larvae have structural carbohydrates on their surface that contribute to the activation of the immune response that results in Th2/anti-inflammatory response [179]. It has been shown that *T. spiralis* glycans affect the anti-inflammatory environment and can interfere with the development of inflammatory diseases [180]. On the other hand, *T. spiralis* muscle larvae excrete a molecular complex called excretory-secretory antigen (ES L1) that has been shown to alter DC maturation [180]. In addition, immature DC resulting from the exposure to ES L1 induce a Th2 and regulatory response with the production of IL-10 and TGF-β, but without increasing $CD4^+CD25^+Foxp3^+$ effector T cell population [179]. Thanks to these two mechanisms, the induction of an anti-inflammatory response and the inhibition of DC maturation, *T. spiralis* survives as long as it is the muscular larva without inducing inflammation or an adequate immune response.

4. Conclusion

Dendritic cells represent a wide constellation of cells that perform crucial roles in the immune response covering from recognition and phagocytosis, to antigen processing and presentation

to naïve T cells and immune tolerance. Due to this wide array of functions, they constitute a bridge that connects the innate immune response with the adaptive and are very important against parasites. DC are able to recognize diverse PAMPs present in parasites through different PRRs such TLRs, CLRs, NLRs, and RLRs, some of which, upon binding their respective ligand, induce phagocytosis and/or signal for the production of different molecules. Parasitic infections cause great morbidity and mortality. For the majority of them, there are no vaccines and the treatments that are not always effective. The better understanding and gaining of knowledge on the biology of parasites and their interaction with the immune system, in particular with DC due to the important role that play in the immune responses, will permit the development of new strategies and drugs to effectively treat the pertaining diseases mentioned in this work.

Financial support

This work was supported by grant IN225116 from Papiit, DGAPA, UNAM to LGK.

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