Review

Dendritic cells in Leishmania infection

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Abstract

Dendritic cells (DCs) are key elements of the immune system, which function as sentinel in the periphery and alert T lymphocytes about the type of invading antigen and address their polarisation, in order to mount an efficacious immune response. Leishmania spp. are parasitic protozoa which may cause severe disease in humans and domestic animals. In this work, the main studies concerning the role of DCs in Leishmania infection are reviewed, in both the murine and human models. In particular, the importance of the genetic status of the hosts and of the different Leishmania species in modulating DC-mediated immune response is examined. In addition, different approaches of DC-based vaccination against experimental leishmaniasis, which could have important future applications, are summarised.

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1. Introduction

Dendritic cells (DCs) are a family of professional antigen-presenting cells, which sit in an immature state, capable of antigen uptake and processing, in all peripheral non-lymphoid tissues and therefore function as sentinel of the immune system. After contact with microorganisms or substances associated with infection or inflammation, DCs undergo a process of maturation and migrate to the T-cell areas of lymphoid organs. There they present antigens to naive T cells and modulate their responses [1]. The maturation process consists of (1) increased expression of major histocompatibility complex (MHC) and costimulatory or adhesion molecules such as CD40, CD80, CD86 and CD54; (2) down-regulation of antigen-capture and phagocytic capacity; (3) enhanced cytokine secretion; (4) different patterns of chemokine receptor expression and chemokine production, enabling DC migration and recruitment of other cell types (see in Ref. [2,3]).

DCs take up antigens via different groups of receptor families, such as Fc receptors for antigen–antibody complexes, C-type lectin receptors (CLRs) for glycoproteins [4] and pattern-recognition receptors (PRRs) such as Toll-like receptors (TLRs), which enable DCs to recognise a wide range of microbial stimuli [5].

The information is passed from DCs to T cells via a complex structure, named immunological synapse, which is a specialised molecular organisation that occurs at the contact region between DCs and T cells. It is essentially composed of the T-cell receptor and the MHC molecule, which present the antigenic peptide, but also includes costimulatory and adhesion molecules (mainly CD40–CD40L and CD28–CD80) and cytokine–cytokine receptors [6]. In addition, DCs are essentially flexible and can promote T helper (Th)1, Th2 or regulatory T-cell phenotypes, instructed by the priming signals from microbial and tissue-derived factors. Activated DCs can produce IL-12p70, which regulates Th1 proliferation, interferon (IFN)-γ production and parasiticidal ability of activated macrophages; this is a critical process for the containment of infections caused by intracellular pathogens, even including Leishmania infection. However, it is a specific, tightly regulated mechanism requiring the signal mediated by CD40L, in order to protect the host against the...
potential harmful Th1-mediated immunopathological reactions. The secretion by DCs of anti-inflammatory cytokines, like IL-10, can also prevent the induction of an exaggerated immune response [6].

Human and mouse DCs can be divided into several subtypes on the basis of surface antigen differences. In humans, they include CD11c+ myeloid DCs (DC1) circulating in the blood, CD11c− plasmacytoid DCs (DC2), which are also found in lymphoid organs, and Langherans’ cells (LCs) in the skin. In mouse, high surface expression of the β2 integrin p150/95 (CD1c) is a characteristic of mature DCs. On the basis of the expression of CD8, CD4, CD205 and CD11b surface markers, several murine DC subtypes can be characterised [7]. Human and mouse myeloid and plasmacytoid DC subsets show partly different functions. However, even if different DC subsets may have different functions in terms of Th1/Th2 induction, cytokine production, and antigen recognition and presentation, these functions rather than being intrinsic, are often related to different stimuli and the cytokine milieu [3]. In addition, immature DCs are considered keepers of peripheral T-cell tolerance to self. 

*Leishmania* is a parasitic protozoan, which causes severe diseases in humans and dogs. Its life cycle includes an infective flagellated promastigote stage transmitted by phlebotomine sandfly vectors and an aflagellated amastigote stage in vertebrate hosts. Control measures for leishmaniasis include evaluation of new diagnostic tests [8], screening of new compounds for chemotherapy [9] and development of an affordable and effective vaccine for humans and dogs. For the latter purpose, the precise knowledge of the protective immune response against the parasite, including the role of DCs in the course of the infection, plays a fundamental role.

### 2. *Leishmania*-DC interactions: studies in mice

#### 2.1. A silent phase in the skin

Moll et al. [10] first demonstrated that murine LCs can ingest *Leishmania major* and migrate in lymph nodes, where DCs harbour persistent parasites and enable the maintenance of T-cell memory. However, a recent paper indicates that although parasites can be detected in mouse lymph nodes a few hours after infection, none of the DC emigrants from the skin harbours parasites. The authors conclude that DCs could not be the vehicle that ferries the parasites from the skin to the lymph nodes [11].

Importantly, after *L. major* infection of C57BL resistant mice with low parasite dose into a dermal site, there was a prolonged silent phase of parasite amplification in the skin, lasting 4–5 weeks, before the onset of lesions and immunity [12]. The establishment of the infection can be favoured through different evasion mechanisms, like the inhibition of DC maturation (see below) or induction of regulatory T cells. In fact, during infection by *L. major* in mice, CD4+ CD25+ regulatory T cells accumulate in the dermis, where they suppress, in part by IL-10 production, the ability of effector T cells to eliminate the parasite [13].

#### 2.2. IL-12 production

An impairment of IL-12 production was demonstrated in bone marrow-derived (BMD) *Leishmania*-infected macrophages and was selectively observed in infected cells [14]. In contrast, DCs are the main source of IL-12 in early *Leishmania* infection. In fact, murine C57BL/6 skin-derived DCs were recognised as the main source of IL-12p40 immediately after dermotropic *L. major* infection [15,16], whereas IL-12p70 release by DCs required IFN-γ and prolonged (72 h) incubation [15] or addition of CD40L [17]. After viscerotropic *Leishmania donovani* infection in BALB/c mice, splenic DCs that are localised in the periarteriolar lymphoid sheath are the critical source of early IL-12p40 production [18,19].

The effect of *Leishmania* infection on IL-12 induction and DC maturation may vary according to DC subtype and to *Leishmania* species. In fact, infection in vitro of murine BMD DCs with *L. mexicana* promastigotes failed not only to induce IL-12 release, but also to activate immature DCs. The importance of additional stimuli is underlined in this work, since the addition of IFN-γ plus LPS restored DC maturation and IL-12 production in infected cells [20].

Murine splenic DC subsets can vary in their ability to produce IL-12 and carry out phagocytosis of *L. major* amastigotes in mice. In fact, CD4+ CD8− DCs were the most permissive cells, followed by CD4− CD8− DCs; CD4− CD8+ cells were the least permissive but the best IL-12 producer in response to infection [21].

Moreover, it was found that resting murine and human myeloid cells, including DCs, contain preformed, membrane-associated IL-12p70 stores, which are released within minutes after in vitro or in vivo contact with *L. donovani* [22].

#### 2.3. The role of genetic susceptibility/resistance

DC responses can also vary according to the genetic susceptibility or resistance of mice, on the basis of studies performed mainly in the murine model of *L. major* infection.

Skin-DCs from *L. major*-infected C57BL/6 resistant mice or BALB/c susceptible mice both exhibit up-regulation of surface markers (MHC class I and II antigens, CD40, CD54, and CD86) and release IL-12p70, thus suggesting that genetic susceptibility to *L. major* is not dependent on DC inability to respond to the parasite [23]. However, an increased expression of IL-4R was observed on LCs infected with *L. major* from susceptible but not resistant mice [24], and the expression of the costimulatory molecule CD80 was down-regulated on LCs from susceptible but not resistant mice [25].

Moreover, in lymph node DCs from susceptible, but not resistant mice in vivo infected with *L. major*, a decreased CD40 activity was observed, which correlated with under-production of IL-12p40 and IL-12p40 mRNA expression [26].
In addition, in a model of *L. amazonensis* infection, it was shown that in both BALB/c and C3H/HeJ (resistant) mice, amastigotes enter and activate BMD DCs, but in the former, infection fails to induce CD40-dependent IL-12 release and rather potentiates IL-4 production: transfer of infected BALB/c DCs into syngeneic resistant recipients induces release of IL-4 and IL-10 by primed Th cells [27].

Susceptible and resistant mice infected with *L. major* were also analysed for amastigote load and cell surface phenotype of lymph node DCs [28]. Cells expressing the DC specific marker CD11c were the most frequently infected cells in draining lymph nodes of all mice tested. CD11c+ infected cells from C57BL/6 mice displayed a weak parasitic load, a typical dendritic morphology and frequently expressed CD11b or F4/80 myeloid differentiation (MyD) markers. In contrast, some CD11c+-infected cells from BALB/c mice were multinucleated giant cells, which presented a dramatic accumulation of parasites without differentiation markers at their surface.

However, data from a recent paper argue against a relevant genetic difference in the DCs initiating the anti-parasite Th cell response in C57BL/6 and BALB/c mice, but rather underline the importance of DC turnover during the infection. In fact, in both strains there were two different waves of antigen-containing DCs in vivo in experimental *L. major* infection. In the first wave, DCs presented leishmanial antigens, produced IL-12 but were not infected, whereas DCs of the second wave were able to ingest the parasites [29].

2.4. TLR involvement: studies in null mice

After the demonstration that TLR2 is essential for the pro-inflammatory activity of the protozoan parasite *Trypanosoma cruzi* (the causative agent of Chagas’ disease) and that the glycosylphosphatidylinositol (GPI) anchor of this parasite activates TLR2 [30], studies have been undertaken to evaluate a possible involvement of TLRs in *Leishmania* infection. Firstly, studies were performed on a murine macrophage cell line transfected with a dominant-negative version of the MyD88, which is a protein adaptor involved in TLR-signalling pathways and production of inflammatory cytokines [5]. Transfection inhibited activation of the IL-1α promoter, which is selectively activated by *L. major* infection. Furthermore, stimulation of IL-1α RNA expression by *L. major* was inhibited in peritoneal macrophages from MyD88−/−, compared to MyD88+/+ mice, thus indicating that the parasite stimulates IL-1α promoter activity and mRNA expression in macrophages through MyD88- and TLR-dependent pathways [31].

Similar results showing that MyD88-dependent pathways are essential for the development of the protective IL-12-mediated Th1 response against *L. major* were obtained by Muraille et al. [32] and de Veer et al. [33]. Following inoculation of *L. major*, MyD88−/− C57BL/6 mice presented large footpad lesions containing numerous infected cells. In response to soluble leishmanial antigens (SLAs), cells from lesion-draining lymph nodes showed a typical Th2 profile, similarly to infected BALB/c mice. Moreover, IL-12p40 plasma levels collapsed in infected MyD88−/− mice compared with infected wild-type C57BL/6 mice. Importantly, administration of exogenous IL-12 rescues *L. major*-infected MyD88−/− mice, demonstrating that the susceptibility of these mice is a direct consequence of IL-12 deficiency [32].

Furthermore, among leishmanial major surface glycoconjugated molecules, a role for promastigote lipophosphoglycan (LPG) in TLR2 activation was demonstrated [33]. In fact, LPG, but not LPG without the lipid portion nor glycoinositolphospholipids (GIPs) or proteophosphoglycan, activates IL-12p40 and tumour necrosis factor (TNF)-α synthesis in macrophages from wild-type but not from MyD88-null mice, thus indicating that LPG signals through a TLR pathway. In this work, human kidney 293T cells were also transfected with seven different human TLR expression constructs and evaluated for NFκB and IL-8 promoter activation after addition of LPG. LPG stimulated both IL-8 and a synthetic NFκB-luciferase reporter only in cells transfected with TLR2 [33].

As regards DCs, recent data on mice suggest that MyD88-dependent receptors are implicated in their maturation in response to *Leishmania* infection. In fact, *L. donovani*-induced DC maturation in terms of up-regulated expression of MHC II and costimulatory receptors (CD40, CD80/86, and CD86) was partially abolished in MyD88-deficient mice [34]. Interestingly, in this work the use of a green fluorescent protein-expressing parasite showed that DCs undergoing maturation in vivo display no parasite internalisation, thus indicating that *Leishmania*-induced maturation results from direct recognition of *Leishmania* by DCs, and not from DC infection [34].

3. Leishmania–DC interactions: studies in humans

The importance of CD40–CD40L interaction for IL-12p70 production, which is also investigated for immunotherapy of infections, is underlined in a study on human myeloid-derived human DCs [35]. The IL-12p70 production by L. major-harbouring myeloid-derived human DCs showed a CD40/CD40L-dependent process. In fact, DCs which have ingested metacyclic promastigotes of *L. major* up-regulated HLA-DR, CD86 and CD40 surface molecules, thus suggesting a process of maturation. However, these cells were unable to produce IL-12p70, IL-1β, IL-6, IL-10 or TNF-α, while the addition of CD40 ligand trimer 8–10 h after infection resulted in a marked IL-12p70 production. IL-12 production by DCs in vitro required opsonisation of parasites with 5% normal human serum, mimicking the in vivo infection. Interestingly, flow cytometry analysis by an anti-IL12 and anti-LPG mAbs showed that IL-12 was co-localised to LPG+ (i.e., *Leishmania*-infected) DCs. In addition, when autologous primed T cells were co-cultured with these infected cells, they were able to proliferate and produce IFN-γ [35].
The effect of infection on DCs may vary according to Leishmania species in the human model also. In fact, monocyte-derived DCs, infected with metacyclic promastigotes (i.e. parasites at infectious stage) and then stimulated with CD40L, showed a different ability to secrete IL-12p70, according to the Leishmania species employed for the infection. In fact, L. major, which is responsible for self-healing cutaneous leishmaniasis, induced IL-12p70 release, differently from L. tropica, which may cause persistent cutaneous lesions and from the viscerotropic species L. donovani [36]. These opposite effects may be related to the difference in leishmanial surface molecules LPG and GIPLs, which show a great diversity between the various species.

The response to different Leishmania species of monocyte-derived DCs and macrophages from blood donors was also investigated in a study assessing gene expression profiles by microarray analysis [37]. Human DCs and macrophages shared a vast majority of genes expressed at baseline, but each cell type responded very distinctly to infection with diverse pathogens. In particular, after infection with metacyclic promastigotes of L. major or L. donovani, a small number of genes, notably IFN-γ-induced genes, were differentially regulated by the two species in macrophages and DCs [37].

As regards TLRs, studies in humans were performed on natural killer (NK) cells, which can also express these receptors. Interestingly, purified L. major LPG up-regulates both mRNA and the membrane expression of TLR-2 in human NK cells, and enhances IFN-γ and TNF-α production and nuclear translocation of NFkB. The activation effect was more intense with LPG purified from infectious metacyclic promastigotes than from non-infectious procyclic parasites. Since the difference between the molecules derived from these two stages lies exclusively in the number of phosphosaccharide repeat domains and in the composition of glycan side chains that branch off these domains, TLR-2 could distinguish between phosphorylated glycan repeats on LPG molecules [38].

4. Evasion of Leishmania parasites from DC presentation

4.1. Inhibition of DC migration

The inhibition of DC migration could represent a stratagem for the pathogens to escape the host immune system. Products secreted by L. major promastigotes inhibit the motility of murine splenic DCs in vitro [39], and L. major LPG inhibits migration of murine LCs [40]. The chemokine–chemokine receptor pathway may be involved in this inhibition. In fact, DCs can be selectively recruited due to their expression of different chemokine receptors: chemokines that arise under inflammatory conditions and act on CCR1, CCR2, CCR5 and CCR6 attract immature DCs to the affected sites. After antigen uptake, during maturation, chemokine receptor expression changes: CCR1, CCR2 and CCR5 are down-regulated and replaced by CCR7 and CXCR4, thus enabling DCs to migrate in the draining lymph nodes in response to corresponding chemokines [41].

Absence of CCR2 shifts the L. major-resistant phenotype to a susceptible state dominated by Th2 cytokines [42]. Furthermore, Leishmania infection can differently modulate chemokine receptor expression on host cells [43]. Interestingly, after chronic infection with L. donovani in mice, there was IL-10-mediated inhibition of CCR7 expression and inhibition of DC migration from the marginal zone to the T-cell areas of the spleen, which may contribute to the development of visceral leishmaniasis [44].

4.2. Inhibition of DC maturation

Results from different investigations suggest that Leishmania parasites tend to delay DC maturation to favour the establishment of the infection before the onset of the acquired immune response.

As described above, after L. major infection in C57BL resistant mice with low parasite dose into a dermal site, there was a prolonged silent phase of parasite amplification in the skin, before the onset of lesions and immunity, suggesting an impairment of DC activation [10]. In mouse BMD DCs in vitro infected with L. mexicana, an impairment of maturation and IL-12 secretion was selectively induced by uptake of parasites, whereas infected cells retained the capacity of full activation after addition of LPS plus IFN-γ [20] and retained the capacity of exogenous antigen presentation [45].

In addition, metacyclic promastigotes of L. amazonensis phagocytosed by murine DCs did not induce DC maturation, which was instead elicited if parasites were previously opsonised with specific antibodies [46].

In lymph node of mice, CD11c+ L. major-infected DCs express low MHC II levels and no detectable CD86 expression, thus suggesting that they might constitute a reservoir of parasites [28].

In addition, L. donovani inhibits expression of the lipid and glycolipid antigen-presenting molecules CD1 on human BMD DCs, thus impairing CD1-mediated presentation of lipid antigens and activation of T cells [47]. CD1 molecules may be involved in the protective immune response against Leishmania species, which harbour abundant glycolipid antigens.

4.3. Inhibition of IL-12p70 production by DCs

As mentioned above, studies in human myeloid DCs have demonstrated the inhibitory effect of infection with L. tropica and L. donovani, but not L. major, on IL-12p70 production after addition of CD40L [36].

4.4. Induction of IL-10

Finally, DCs could be indirectly modulated by Leishmania infection through the induction of IL-10, which can
render DCs tolerogenic through the up-regulation of the inhibitory receptor leukocyte immunoglobulin-like receptor (LIR)-2, resulting in T-cell hyporesponsiveness in vitro [48].

The main escape mechanisms of *Leishmania* parasites from DC-mediated immune-responses are listed in Table 1.

### 5. Targeting *Leishmania*-DC interaction

DC-specific ICAM-3-grabbing nonintegrin (DC-SIGN) is CLR which is expressed almost exclusively on differentiated blood myeloid and tissue monocyte-derived DCs. It is being extensively studied not only as a pathogen-binding receptor, but also as mediator of DC-T-cell interactions and as an escape mechanism for intracellular pathogens, which can target DC-SIGN to shift the protective Th1 towards Th2 cell balance [49]. Interestingly, DC-SIGN was indicated as a major ligand for the amastigote stage of *L. pifanoi* [50] and for LPG of *L. mexicana* [51]. In addition, it was recently demonstrated that DC-SIGN is a receptor for promastigote and amastigote infective stages from both visceral (*L. infantum*) and New World cutaneous (*L. pifanoi*) *Leishmania* species, but not for *L. major* metacyclic promastigotes, an Old World species causing cutaneous leishmaniasis. However, in this work, *Leishmania* binding to DC-SIGN was independent from LPG [52]. Since binding of DC-SIGN by distinct *Leishmania* species and strains can favour parasite survival and persistence, it was suggested that this receptor might be a therapeutic target for both visceral and cutaneous leishmaniasis [52].

### 6. DC-based vaccination and immunotherapy

Several studies suggest the potential of tumour Ag-pulsed DCs or DCs engineered to secrete cytokines such as IL-12 or IL-18 to induce anti-tumour immunity [53,54]. Moreover, DC-based immunotherapy or vaccination is also emerging as a tool to combat infectious diseases, since DCs can be long-lived, thus ensuring the maintenance of an efficient presentation and stimulation for T cells in draining lymph nodes [2,6,55].

The first studies demonstrating that LCs can be used as a natural adjuvant to induce a protective immune response against leishmaniasis were performed in a murine model of *L. major* infection. A single i.v. application of LCs, pulsed with promastigote lysate in vitro, induced protection in susceptible BALB/c mice against subsequent challenge with *L. major* parasites. Development of resistance was paralleled by a reduced parasite burden and a shift of the cytokine expression towards a Th1-like pattern [56]. In a murine BALB/c model of *L. donovani* infection, DCs engineered to secrete IL-12 and pulsed ex vivo with soluble *L. donovani* antigens were potent vaccine [57].

Not only antigen-pulsed, but also *Leishmania*-infected DCs were used for vaccination: in another work *L. major*-infected syngeneic DCs protected BALB/c susceptible mice against *L. major* challenge [23].

Moreover, LCs loaded with a mixture of the recombinant leishmanial antigens LACK, KMP-11, gp63 and PSA or with the single antigen LeIF mediated significant protection against challenge with *L. major* parasites, upon adoptive transfer into naive susceptible mice [58]. In this work, the protection was found to be dependent on IL-12, since in Ag-pulsed LCs from IL-12-deficient mice, the capacity of DCs to mediate protection was completely abrogated.

Another approach to vaccination is to deliver the antigen to endogenous DCs with the aid of molecules, which bind surface receptors on DCs and deliver an activating signal. The importance of CD40L in DC activation and IL-12 production by DCs was obtained by using murine L929 transfected cells expressing CD40L and the *Leishmania* antigen gp63 [17]. Vaccination with these co-transfected cells provided a significant degree of protection against challenge with virulent *L. major* and *L. amazonensis* in genetically susceptible mice.

Oligodeoxynucleotides (ODNs) which contain immunostimulatory CG motifs (CpG ODN) and activate DCs by promoting Th1 responses were also investigated as adjuvant for vaccination against leishmaniasis in susceptible BALB/c mice. Mice receiving SLA plus CpG ODN showed a highly significant reduction in swelling compared to SLA-vaccinated mice and enhanced survival compared to unvaccinated mice. The modulation of the response to SLA by CpG ODNs was maintained even when mice were infected 6 months after vaccination [59]. CpG ODNs were also able to reduce the pathogenicity of a live *L. major* promastigote vaccine, without reducing its efficacy [60].

### Table 1

<table>
<thead>
<tr>
<th>DC subtype</th>
<th>Function inhibited</th>
<th>Host</th>
<th>Parasite</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCs</td>
<td>Migration</td>
<td>BALB/c mice</td>
<td><em>L. major</em></td>
<td>[40]</td>
</tr>
<tr>
<td>Splenic DCs</td>
<td>Migration</td>
<td>BALB/c mice</td>
<td><em>L. major</em></td>
<td>[39]</td>
</tr>
<tr>
<td>Splenic DCs</td>
<td>Migration and CCR7 expression</td>
<td>C57BL/6 mice</td>
<td><em>L. donovani</em></td>
<td>[44]</td>
</tr>
<tr>
<td>BM-derived DCs</td>
<td>Activation markers expression</td>
<td>CBA mouse</td>
<td><em>L. mexicana</em></td>
<td>[20]</td>
</tr>
<tr>
<td>BM-derived DCs</td>
<td>Activation markers expression</td>
<td>BALB/c mice</td>
<td><em>L. amazonensis</em></td>
<td>[46]</td>
</tr>
<tr>
<td>Lymph node DCs</td>
<td>MHC II and CD86 expression</td>
<td>BALB/c and C57BL/6 mice</td>
<td><em>L. major</em></td>
<td>[28]</td>
</tr>
<tr>
<td>BM-derived DCs</td>
<td>Expression of CD1 molecules</td>
<td>Humans</td>
<td><em>L. donovani</em></td>
<td>[47]</td>
</tr>
<tr>
<td>Monocyte-derived DCs</td>
<td>IL-12p70 production</td>
<td>Humans</td>
<td><em>L. tropica, L. donovani</em></td>
<td>[36]</td>
</tr>
</tbody>
</table>
The mechanism by which CpG ODNs mediate the adjuvant effect in vivo was investigated in BALB/c mice. Vaccination with leishmanial LACK antigen and CpG ODNs led to the presence of CD11c+ DCs in the draining lymph nodes, which were potent producers of IL-12p70 and IFN-γ, and were capable of vaccinating naïve BALB/c mice against L. major infection [61]. However, in another work, IL-12 expression by the immunising DCs was not required for induction of host resistance in mice vaccinated with a single dose of L. major Ag-pulsed BMD DCs, stimulated by prior in vitro exposure to CpG ODN [62].

DCs pulsed with soluble L. donovani antigen were also employed for immunotherapy of murine visceral leishmaniasis together with the conventional chemotherapy with sodium antimony gluconate. This combined treatment potentiates the antileishmanial effect of antimony and results in complete clearance of parasites from both the liver and the spleen [63].

Finally, targeting DCs with antigen-containing liposomes was highly effective in inducing anti-tumour immunity [64] and could be exploited for immunotherapy of leishmaniasis, in which liposomal amphotericin B is the first-line treatment for visceral leishmaniasis [65].

The main investigations concerning DC-based vaccination against experimental leishmaniasis are summarised in Table 2.

7. Conclusions

The possibility of DC-based vaccination against leishmaniasis is exciting, even if further studies are needed. These studies may have practical applications for vaccination purposes after an exact standardisation concerning parasite antigen for an appropriate DC instruction, route of antigen delivery, stage of DC maturation and usefulness of exogenous activating factors like CD40L or cytokines (see also in Ref. [55]).

Possible applications of this type of vaccine include not only human cutaneous and visceral leishmaniasis in hyper-endemic countries, but also canine leishmaniasis in areas, including Mediterranean countries and Latin America, where the dog is the main domestic reservoir of the parasite. In these areas, vaccination of dogs may be an important measure for control of the human disease.

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