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Role of the C-type lectins DC-SIGN and L-SIGN in \textit{Leishmania} interaction with host phagocytes

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Abstract

Leishmaniasis is a parasitic disease that courses with cutaneous or visceral clinical manifestations. The amastigote stage of the parasite infects phagocytes and modulates the effector function of the host cells. Our group has described that the interaction between \textit{Leishmania} and immature monocyte-derived dendritic cells (DCs) takes place through dendritic cell-specific ICAM-3-grabbing nonintegrin (DC-SIGN), a C-type lectin that specifically recognizes fungal, viral and bacterial pathogens. The DC-SIGN-mediated recognition of \textit{Leishmania} amastigotes does not induce DC maturation, and the DC-SIGN ligand/s on \textit{Leishmania} parasites is/are still unknown. We have also found that the DC-SIGN-related molecule L-SIGN, specifically expressed in lymph node and liver sinusoidal endothelial cells, acts as a receptor for \textit{L. infantum}, the parasite responsible for visceral leishmaniasis, but does not recognize \textit{L. pifanoi}, which causes the cutaneous form of the disease. Therefore, DC-SIGN and L-SIGN differ in their ability to interact with \textit{Leishmania} species responsible for either visceral or cutaneous leishmaniasis. A deeper knowledge of the parasite-C-type lectin interaction may be helpful for the design of new DC-based therapeutic vaccines against \textit{Leishmania} infections.

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\textbf{Leishmaniasis}

Leishmaniasis is a vector-borne parasitic disease whose clinical manifestations range from local cutaneous lesions (cutaneous leishmaniasis, CL) to life-threatening visceral disease (visceral leishmaniasis, VL), mainly as a result of differences among \textit{Leishmania} species. \textit{L. pifanoi} is responsible for CL, characterized by a localized infection at the site of inoculation by the
vector, while *L. infantum* causes VL due to parasite dissemination into internal organs. *Leishmania* parasites exist in two developmental stages. The flagellated promastigote is transmitted with the bite of the sand fly (insect vector) to the mammalian host, where it transforms into the amastigote stage. *Leishmania* amastigotes infect mononuclear phagocytes, where their intracellular location allows them to subvert the effector and regulatory functions of these cells (Duclos and Desjardins, 2000). Since epidermal Langerhans cells and dermal dendritic cells (DCs) contribute to immunosurveillance of the skin (Banchereau and Steinman, 1998; Mellman and Steinman, 2001) and are located in proximity to the site of parasite delivery, their role in the initiation of *Leishmania*-specific immune responses is an active area of research.

**Leishmania** host cells

To attain a successful infection, *Leishmania* needs to subvert the host immune response from the early steps after its inoculation. In the natural course of infection, these events occur in the dermis, where DCs may act as host cells for *Leishmania*, independently of the pathological outcome of the infection (McDowell et al., 2002). In this regard, Langerhans cells within cutaneous lesions are parasitized by *Leishmania* in vivo in both human and experimental murine CL (Blank et al., 1993; Moll, 1993). Studies on the interactions of *Leishmania* with murine or human DC have not yet clearly determined the range of parasite forms that these cells can internalize (Ampray et al., 2004; Bennett et al., 2001; Blank et al., 1993; Konecny et al., 1999; Marovich et al., 2000; Moll, 2000; Moll and Flohe, 1997; Qi et al., 2001; Sacks and Sher, 2002; Udey et al., 2001; von Stebut et al., 1998, 2000) or their influence on parasite survival.

Although *Leishmania* species might differentially subvert DC effector function (Antoine et al., 2004; Brandonisio et al., 2004; Chaussabel et al., 2003; Ghosh and Bandyopadhyay, 2004; Jebbari et al., 2002; Konecny et al., 1999; Ponte-Sucre et al., 2001; Scott and Hunter, 2002; von Stebut et al., 1998), the receptors involved in the *Leishmania*–DC interaction remain largely undefined and could be critical for this process. In contrast, several macrophage receptors have been identified which mediate binding and subsequent uptake of *Leishmania* promastigotes (Blackwell, 1985; Russell and Talama-Rohana, 1989). In this regard, lipophosphoglycan (LPG) and the metalloproteinase gp63 bind to complement receptor type 3 (CR3), mannose-fucose, and fibronectin receptors on macrophages (Blackwell, 1985; Da Silva et al., 1989; Guy and Belosevic, 1993; Mosser, 1994; Talama-Rohana et al., 1990; Wilson and Pearson, 1988). However, the receptors implicated in amastigote uptake by DC and macrophages are poorly characterized, mainly due to the fact that isolation or in vitro culture of this intracellular form is difficult. The availability of axenic cultures has now opened the possibility of addressing the identification of *Leishmania* amastigotes receptors on macrophages and DCs (Armson et al., 1999; Bates et al., 1992; Debrabant et al., 2004; Doyle et al., 1991; Gupta et al., 2001; Hodgkinson et al., 1996).

**Leishmania** interaction with dendritic cells: exploiting DC-SIGN

Macrophages and DCs express a wide variety of pathogen-associated molecular pattern receptors, including numerous C-type lectin and lectin-like receptors (Engering et al., 2002; Figdor et al., 2002; McGreal et al., 2004). Since *Leishmania* spp. display an abundance of mannose-rich glycoconjugates on their surface that are important for parasite virulence (Ilgoutz and McConville, 2001; Garami and Ilg, 2001), a reasonable hypothesis is that lectin–oligosaccharide interactions are involved in parasite recognition by mononuclear phagocytes. DC-specific ICAM-3-grabbing nonintegrin (DC-SIGN, CD209) is a type II transmembrane C-type lectin expressed on DCs and macrophages, and was initially described as involved in cell–cell interactions through its capacity to bind ICAM-3 and ICAM-2 (Geijtenbeek et al., 2000a,b; van Kooyk and Geijtenbeek, 2002). The DC-SIGN extracellular domain comprises eight 23-residue tandem repeats and a C-terminal carbohydrate-recognition domain (Mitchell et al., 2001). DC-SIGN is now known to be a receptor for HIV (Geijtenbeek et al., 2000c; Pohlmann et al., 2001), *Ebola* virus (Alvarez et al., 2002), *Schistosoma mansoni* (van Die et al., 2003), *Sindbis* virus (Klimstra et al., 2003) *Candida albicans* (Cambi et al., 2003) *Mycobacterium tuberculosis* (Geijtenbeek et al., 2003), Hepatitis C (Wang et al., 2004), *Helicobacter pylori* (Bergman et al., 2004) and the fungal pathogen *Aspergillus fumigatus* (Serrano-Gomez et al., 2004).

Most *Leishmania* amastigote-DC studies have been carried out with tissue-derived opsonized parasites, which might be bound via Fc and complement receptors, thus precluding the identification of opsonization-independent binding mechanisms. To analyze the participation of the receptor DC-SIGN in binding and internalization of *Leishmania*, we used axenic amastigotes (Armson et al., 1999; Pan and McMahon-Pratt, 1988), which are devoid of opsonizing antibodies. We first analyzed the interaction of *L. pifanoi* (that causes CL) axenic amastigote with K562-DC-SIGN transfec-
tants and demonstrated that they are specifically recognized by DC-SIGN (Colmenares et al., 2002).
Subsequently, L. pifanoi amastigotes were found to bind DC-SIGN on the surface of immature monocye-derived dendritic cells (IMDCs), an interaction that was dramatically reduced in the presence of anti-DC-SIGN blocking antibodies (Colmenares et al., 2002). This set of results suggested an important role for DC-SIGN in the early stages of infection of DCs by Leishmania.

Since infection of immature dermal DCs is a common step shared by all Leishmania species, we next analyzed the capacity of IMDCs to bind other Leishmania life cycle forms and species. Our results (Colmenares et al., 2004) underscored the relevance of the DC-SIGN–Leishmania interaction in both VL (L. infantum) and CL (L. pifanoi), as amastigotes and promastigotes from both species exhibited DC-SIGN-interaction capacity. Since the membrane composition of the parasite changes throughout its life cycle (Bahr et al., 1993; Wright and el Amin, 1989), we tested the ability of DC-SIGN to bind the three main life cycle forms of the parasite (amastigotes, procyclic promastigotes and metacyclic promastigotes). Amastigotes and metacyclic promastigotes showed the strongest DC-SIGN-dependent interaction with IMDDC (Fig. 1). Moreover, the avidity for DC-SIGN increased in the transition from procyclic (non-infective) to metacyclic (infective) promastigotes (i.e., procyclic and metacyclic promastigotes, respectively) (Fig. 1). Hence, the avidity of the different forms of the parasite for DC-SIGN appears to correlate with their virulence. On the other hand, a much lower ability for DC-SIGN recognition was observed in Leishmania promastigotes (Fig. 1).

**DC-SIGN ligands on Leishmania:** LPG is one of the most abundant glycoconjugates exposed on the cell surface of promastigotes, but scarcely expressed on amastigotes, and plays a pleiotropic role through the life cycle of Leishmania (Aebischer et al., 2005; Cunningham, 2002; Kamhawi et al., 2000; Naderer et al., 2004; Sacks et al., 2000; Turco and Descoteaux, 1992; Turco et al., 2001). This molecule is characterized by a high mannose content, and has been proposed to mediate promastigote interaction with DCs via DC-SIGN (Appelmelk et al., 2003). However, our results indicate that LPG is not an important Leishmania ligand for DC-SIGN because: (1) LPG is strongly down-regulated in amastigotes (Ilg et al., 1999; Ilgutz and McConville, 2001; Turco and Descoteaux, 1992), which exhibit the highest DC-SIGN-binding ability; (2) LPG was unable to block Leishmania binding to DC-SIGN for all species and parasite developmental stages assayed; and (3) the LPG-defective L. donovani promastigotes (R2D2) bind to DC-SIGN-expressing cells. Furthermore, since LPG-defective promastigotes bound DC-SIGN with higher avidity than their wild-type counterparts, LPG might in fact mask other promastigote membrane ligands with affinity for DC-SIGN (Colmenares et al., 2004). Leishmania ability to modulate the DC maturation state: Conflicting results have been obtained on the ability of various Leishmania species to induce DC maturation (Antoine et al., 2004). It is currently unknown whether this variability is due to variations in the experimental conditions or truly reflects species-specific or strain-specific interactions between Leishmania and DC. Since Leishmania spp. express highly polymorphic cell surface molecules, the DC response might vary according to the Leishmania species examined (Bennett et al., 2001; Flohe et al., 1998; Henri et al., 2002; Konceny et al., 1999; McDowell et al., 2002; von Stiebut et al., 1998, 2000). We have evaluated the ability of L. infantum to alter the maturation state of IMDCD. Unlike LPS, L. infantum amastigotes, which bind to IMDC via DC-SIGN, did not affect the cell surface expression of CD83, CD86 or MHC II, commonly considered as DC maturation parameters. Therefore, our results suggest that non-opsonized L. infantum amastigotes are unable to induce IMDCD maturation, at least during a 48-hour period (Fig. 2A). Moreover, LPS induced maturation of IMDCs infected with L. infantum amastigotes (Fig. 2A), indicating that the parasites do not inhibit the capacity of DCs to be matured by other pathogen-derived products. The failure of IMDCD to mature in response to Leishmania capture and entry might represent a parasite strategy to avoid immunosurveillance and to allow their establishment and multiplication before the onset of immune responses. On the other hand, L. infantum amastigotes did not induce CCR7-directed IMDC migration but...
inhibited the CCR7-dependent migration induced upon LPS maturation (Fig. 2B). These data are in agreement with previous results demonstrating that cytokines abundantly produced during *Leishmania* infection (e.g., IL-10) down-regulate CCR7 expression (Antoine et al., 2004). Therefore, *Leishmania* might prevent the establishment of T cell-mediated immunity by interfering with the migratory properties of DCs.

Fig. 2. Effect of *Leishmania* infection on dendritic cells maturation and migration. Immature monocyte-derived DCs were left untreated or pretreated for 1 h with LPS before adding or not *L. infantum* axenic amastigotes, and then incubated for 48 h. Afterward, cells were phenotypically characterized (A), and subjected to migration assays towards the CCR7 ligand CCL19 (B). Three independent experiments were performed with similar results, and a representative experiment is shown.
L-SIGN: a receptor implicated in VL: L-SIGN is a close homologue of DC-SIGN (77% amino acid sequence identity) that is expressed on human liver and lymph node sinusoidal endothelial cells (Soilleux et al., 2000). Like DC-SIGN, L-SIGN recognizes and binds high-mannose glycans, binds to ICAM-3 (Bashirova et al., 2001), and recognizes carbohydrate structures on pathogens such as ManLAM on M. tuberculosis (Koppel et al., 2004) and high-mannose moieties on HIV-1, HCV and Ebola. Besides, L-SIGN has been described as a receptor for severe acute respiratory syndrome coronavirus (Jeffers et al., 2004). Unlike DC-SIGN, L-SIGN does not bind to the fucosic-containing Lewis 
³ antigens, suggesting that L-SIGN-expressing liver endothelial cells and lymph node are not involved in capture and internalization of Lewis 
³-containing pathogens such as H. pylori and S. mansoni (Van Liempt et al., 2004). Besides, binding to L-SIGN is not reversible at low pH, suggesting that L-SIGN does not release internalized ligand in low-pH vesicles and that L-SIGN is degraded upon internalization (Guo et al., 2004). Because of their similar ligand specificity but differential tissue location, we have compared the capacity of DC-SIGN and L-SIGN to bind axenic amastigotes from L. pifanoi (responsible for CL), and L. infantum (responsible for VL). Binding experiments with Jurkat cells stably transfected with DC-SIGN or L-SIGN indicated that L. infantum amastigotes specifically bound to both DC-SIGN and L-SIGN, whereas L. pifanoi amastigotes were unable to bind to L-SIGN (Fig. 3). Therefore, only VL-causing parasites (L. infantum) appear to be recognized by L-SIGN. These results suggest that L-SIGN recognition of the distinct Leishmania species might play a role in the outcome of the parasite infection (CL vs. VL).

To further evaluate the relevance of L-SIGN in binding of Leishmania species causing VL, human hepatic sinusoidal endothelial cells (HSEC) were isolated from hepatic surgery donors, using a modification (Iñigo Martinez and Fernando Vidal-Vanaclocha, unpublished information) of previously described isolation procedures (Daneker et al., 1998; Heuff et al., 1994). Incubation of HSEC with axenic amastigotes showed that L. infantum amastigotes bound strongly to HSEC, whereas no binding was observed with L. pifanoi amastigotes (Fig. 4). In addition, the HSEC-L. infantum
amastigote interaction was reduced in the presence of a blocking monoclonal antibody against L-SIGN (Fig. 4). These results confirmed the ability of VL-causing amastigotes to interact with L-SIGN. Given the mechanism described for the hepatitis C virus (Cormier et al., 2004), it is tempting to speculate that L-SIGN-mediated capture of *L. infantum* by HSEC could result in transinfection of Kupffer cells, which are the final targets of VL-causing *Leishmania* parasites (el Hag et al., 1994; Murray, 2001).

**Concluding remarks**

Taken together, the present work demonstrates that the C-type lectins DC-SIGN and L-SIGN are broad *Leishmania* receptors that differentially bind the distinct infective forms and species of the parasite. A deeper knowledge of the *Leishmania*–DC/L-SIGN interactions, and the subsequent immune consequences, may pave the way for the design of new therapeutic approaches against leishmaniasis. The recent description that macrophage treated with IL-4 (alternatively activated macrophages) also express DC-SIGN (Puig-Kroger et al., 2004) could be of major importance, due to the fact that the expression of this cytokine correlates with the pathology of the disease, and hence increases the potential relevance of these C-type lectins in leishmaniasis.

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