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Parasitic Adaptive Mechanisms in Infection by *Leishmania*

Anna C. Cunningham

Department of Pathology, The University of Tennessee, Memphis, Tennessee 38163

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Leishmania are a resilient group of intracellular parasites that infect macrophages. The resultant complex of diseases, or leishmaniases, caused by the parasites affect over twelve million people worldwide. *Leishmania* have developed unique adaptive mechanisms to ensure their survival in the harsh environments faced throughout their life cycle. These parasites must not only contend with the hostile digestive conditions found within the sand fly vector, but they must also avoid destruction by the host immune system while in the bloodstream, before entering the macrophage. To do so, *Leishmania* express unique lipophosphoglycan (LPG) molecules and the metalloprotease gp63, among other proteins, on their cell surface. To enter the macrophage, *Leishmania* utilizes a variety of cellular receptors to mediate endocytosis. Once inside the macrophage, *Leishmania* is protected from phagolysosome degradation by a variety of adaptations to inhibit cellular defense mechanisms. These include the inhibition of phagosome–endosome fusion, hydrolytic enzymes, cell signaling pathways, nitric oxide production, and cytokine production. While other parasites can also infect macrophages, *Leishmania* is distinctive in that it not only relies on its own defenses to survive and reproduce within the macrophage phagolysosome, but *Leishmania* also manipulates the host immune response in order to protect itself and to gain entry into the cell. These unique adaptive mechanisms help promote *Leishmania* survival.

Key Words: Leishmania; leishmaniasis; macrophage; sand fly; parasite; adaptive mechanisms.

INTRODUCTION

Leishmania are intracellular protozoan that infect host mononuclear phagocytes. It has been estimated that over 12 million people suffer from leishmaniasis, a complex of diseases caused by *Leishmania*, with an additional estimated 2 million individuals infected annually (1, 2). Leishmaniasis is widely distributed in the tropics and subtropics, ranging from the rain forests of Central and South America to the deserts of West Asia (2). Growing interest in leishmaniasis has occurred in recent years due to the increasing number of overseas travelers, U.S. Gulf War veterans, and AIDS patients who have developed the disease. Economic development, environmental changes, and an increased number of worldwide travelers have led to the increased incidence of the disease (1). The parasite exists in two morphological forms, as an intracellular amastigote found in vertebrate hosts (including humans, dogs, cats, lizards, gerbils, squirrels, and other rodents) and as a promastigote found in sand fly vectors (1, 3). There are approximately 21 species of *Leishmania*, transmitted by about 30 phlebotomine sand fly species (4–7). *Leishmania* parasites have developed a variety of adaptive mechanisms not only to live inside the insect vector, but also to evade the vertebrate host immune responses, including survival within the host macrophage.

Five major *Leishmania* species (*L. tropica, L. major, L. donovani, L. braziliensis*, and *L. mexicana*) cause the three main forms of the disease in humans, dermal cutaneous leishmaniasis, visceral leishmaniasis, and mucocutaneous leishmaniasis (3). The form and severity of the disease greatly depend on the infecting *Leishmania* species and the immune status of the host (8).

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DERMAL LEISHMANIASIS

Leishmania tropica and *Leishmania major* cause dermal leishmaniasis, consisting of cutaneous ulcers usually localized to the initial site of the *Phlebotomus* sand fly bite (3). There the amastigotes replicate in the reticuloendothelial system and lymphoid cells of the skin (3). *L. tropica* is found in Ethiopia, Kenya, North Africa, the Middle East, the European Mediterranean, and India, where it is predominantly confined to densely populated areas (3, 9). Transmission normally occurs between sand fly and man, with the dog being a possible reservoir host (3). In contrast, *L. major* is found in the sparsely inhabited regions of North Africa, the Middle East, West India, and Sudan, where the parasite cycles mainly through gerbils and other small rodents, with humans an incidental host (3,9). The incubation period for dermal leishmaniasis can last from a few days to months (3, 9). A small, red papule appears first at the site of the bite, showing an infiltration of plasma cells, lymphocytes, and macrophages (1, 3). A thin crust usually develops, hiding a spreading ulcer underneath (3, 9). In uncomplicated cases, the ulcer will heal spontaneously within 2 months to a year; however, secondary infections, such as yaws and myiasis, are common and can result in permanent disfiguration (3, 9).

VISCERAL LEISHMANIASIS

Visceral leishmaniasis, also known as kala-azar (Hindi for black sickness) or Dum-Dum fever, is predominantly caused by *L. donovani* but also by *L. infantatum* (4, 9). *L. donovani* has been found in Mediterranean Europe, North and East Africa, India, and China, where it is transmitted by the *Phlebotomus* sand fly, as well as in South America, particularly Brazil, where it is transmitted by the *Lutzomyia* species (*L. chagasi*) (3). The 2- to 3-μm amastigotes reside within the reticuloendothelial cells of the viscera, including the spleen, lymph nodes, liver, and intestine (3, 9). Normally, the incubation period is 2 to 4 months (3). Symptoms include a slow developing low-grade fever, general malaise, a progressive wasting seen with anemia, and protrusion of the abdomen, due to enlargement of the liver and spleen (3). Clinical signs also include edema, especially of the face, bleeding mucous membranes, difficulty breathing, and diarrhea (3). If left untreated, death can occur within 2 to 3 years; however, in more acute forms, death may occur within 6 to 12 months (3).

MUCOCUTANEOUS LEISHMANIASIS

Mucocutaneous leishmaniasis is caused by *L. braziliensis*, which is found in Central and South America and spread by the *Lutzomyia* sand fly (3). The primary lesion occurs at the initial site of the bite on the skin, similar to other *Leishmania* species, but the infection also involves the mucosal system of the nasal and buccal cavity, causing degeneration of the cartilaginous and soft tissues (3, 9). These ulcerations are often quite disfiguring to the lips, nose, hard and soft palates, and vocal cords (1, 3). Death is often due to secondary bacterial infections or malnutrition (1, 3).

L. mexicana, found in North and Central America, including Mexico and Texas, and transmitted by the *Lutzomyia* species of sand fly, is largely responsible for a cutaneous form of leishmaniasis (3). However, on some occasions it can affect the mucocutaneous regions of the body. It normally heals spontaneously within a few months, but if the infection is in the ear, disfiguration or almost total destruction of the external ear can occur (1,3). The disease can last up to 40 years (1,3).

DIAGNOSIS AND TREATMENT

Leishmania infections are often diagnosed by the detection of amastigotes through microscopy or cultured parasite growth (1). Stained blood smears can show the amastigotes within the macrophages, known as Leishman-Donovan (LD) bodies (3). PCR amplifications of *Leishmania* genes from tissue biopsies can be used in diagnosis (1). *In vitro* culture of infected tissue or inoculation into animals (e.g., golden hamsters) is also performed (4). Identification of the *Leishmania* species is carried out by isoenzyme analysis of cultured promastigotes by various molecular methods or with monoclonal antibodies, which can also be used for *in situ* diagnosis (4, 10, 11).

Leishmaniasis is often treated with the systemic or local use of pentavalent antimony compounds and aromatic diamidines (1). However, these drugs can have severe toxic side effects (3). Developed in the late 1940s and early 1950s, the most widely used form of treatment includes the antimonials sodium stibogluconate and meglumine antimoniate (1). However, 10–25% of leishmaniasis treatments fail or a relapse occurs, in which case the drugs pentamidine and amphotericin B are used (1). Vaccine trials are currently being conducted in South America and the Middle East, with mixed

success (3). Vaccine candidates include killed or attenuated whole promastigotes, synthetic and recombinant peptides (e.g., LPG or gp63), and recombinant live vectors, administered with or without cytokines or other adjuvants (1, 3, 4, 12). While leishmaniasis is treatable, the complexities of the disease and the inadequacies of what is known about it make treatment difficult (4).

LIFE CYCLE

The life cycle of *Leishmania* consists of two different developmental stages. In vertebrates *Leishmania* exists as a nonmotile, spherical amastigote, approximately 2.5 to 5 μm in diameter, which proliferates inside the phagolysosome of host macrophages (3, 13, 14). The amastigote is transmitted to other vertebrate hosts by blood sucking sand flies of the "Old World" *Phlebotomus* or "New World" *Lutzomyia* genera (1). The sand fly ingests amastigote-containing macrophages and monocytes in its blood meal. These amastigotes are released into the sand fly midgut, where they differentiate into flagellated, procyclic promastigotes and attach to the midgut epithelium (13). The promastigote goes through a process called metacyclogenesis, where the dividing, noninfective procyclic form acquires virulence capabilities and is transformed into a nondividing, infective metacyclic form (13, 15). The metacyclic promastigotes detach from the midgut epithelium and migrate into the pharynx and buccal cavity (13). During the next blood meal, the infective metacyclic promastigotes are passed into the vertebrate host. Once inside the host, the promastigotes must evade destruction by the host immune system in order to enter macrophages through receptor-mediated phagocytosis (13). Promastigotes are incorporated into phagolysomes, where they differentiate into the amastigote form. The amastigotes proliferate, eventually rupturing the infected macrophages, and are released to infect neighboring macrophages, and the cycle begins again (13).

IMMUNOLOGY

Immunity against *Leishmania* is cell-mediated (1). The parasites escape the humoral immune response of hosts by residing in the phagolysosomes of macrophages (1). Therefore, antibodies have no effect on the infection and may even be detrimental to the host (1). Macrophages employ a number of defense strategies against the infecting parasites. Phagocytosis of a foreign body by the macrophage results in an oxidative burst. NAD(P)H oxidase in the plasma membrane is activated, transferring protons to molecular oxygen and forming highly reactive superoxide, hydrogen peroxide, and hydroxyl radicals at the site of phagocytosis, which interact with pathogen phospholipid membranes (1). Another macrophage defense mechanism is the acidification of the vesicle formed by the fusion of the phagosome and endosome by a proton ATPase (1). The acidic environment promotes protein denaturation, which leaves the protein, as well as DNA, RNA, and carbohydrates, susceptible to degradation by acid hydrolases (1).

T helper cells also play a role in the immune response. The expansion of T_H1 clones protects during infection, while T_H2 cell expansion exacerbates the disease (1). IL-12 production by dendritic cells and macrophages causes naïve T cells to differentiate into T_H1 cells and induces the production of IFN-γ by T cells and natural killer (NK) cells (4, 8, 16–18). IFN-γ in conjunction with TNF-α, produced by the infected macrophages, activates the inducible nitric oxide synthetase (iNOS) gene, resulting in the production of nitric oxide (NO), which is toxic to the parasite (1, 8). While T_H1 cell expansion is occurring, T_H2 cell expansion must be kept in check. IL-4 regulates T_H2 cell differentiation, which confers susceptibility to *Leishmania* by downregulating IL-12, IFN-γ production, and IL-12 receptor expression and inhibiting macrophage NO production (19–25).

SURVIVAL WITHIN THE SAND FLY

In order to infect its host, *Leishmania* must first survive within the digestive environment of the sand fly midgut. Promastigotes have a unique lipophosphoglycan (LPG) molecule on their surface, consisting of a modified phosphatidylinositol lipid anchor, a glycan core, repeating disaccharide phosphate units, and a small oligosaccharide cap (13). Promastigotes express large quantities of LPG as well as other glycoconjugates, such as the metalloprotease gp63, on their surface, both of which are thought to protect the parasites from the hydrolytic enzymes of the sand fly gut (19, 26, 27). In order to avoid being excreted after digestion of the blood meal, procyclic promastigotes attach to the midgut epithelium through binding interactions involving LPG with lectin and lectin-like molecules in the gut (13, 19, 28–31). As the promastigote differentiates into the metacyclic form, extensive structural modifications involving the size and

expression of terminally exposed sugars are made to the LPG molecules, reducing their binding affinity for the lectins (13). These alterations lead to the detachment of the metacyclic promastigotes from the midgut epithelium, at which point they migrate to the pharynx in preparation for transmission to the vertebrate host.

SURVIVAL WITHIN THE BLOODSTREAM

Once transmitted into a mammalian host, *Leishmania* must avoid destruction by the host immune system while transiently in the bloodstream before infecting macrophages. An early host immune response against *Leishmania* is the complement system. Metacyclic promastigotes not only resist lysis by complement, but they also use it to their advantage to gain entry into macrophages (13, 32–34). Their resistance to lysis is due in part to the structural modifications of LPG found on metacyclic promastigotes (13, 15, 35). For example, *L. major* metacyclic promastigotes express longer LPG molecules than those found on procyclic promastigotes. The complement factor C_{3b} is deposited on the promastigote cell surface, but the longer LPG molecules found on metacyclic promastigotes prevent access and insertion of the $C_{5b\text{-}9}$ membrane attack complex into the parasite's membrane (13, 35). *L. donovani* promastigotes have adapted a slightly different mechanism to evade destruction. In their case, C_{3bi} cannot be deposited on the promastigote surface and thus cannot function in the formation of C_5 convertase (13, 36). The metalloprotease gp63 on the promastigote cell surface also prevents complement-mediated lysis and enhances promastigote uptake by cleaving C_{3b} to C_{3bi} (19, 37, 38). *Leishmania* promastigotes also interact with other serum proteins to activate complement, thus facilitating their uptake into host macrophages (13). Mannan-binding protein (MBP) can bind to mannose-terminating oligosaccharides in the LPG cap structure (13). This activates complement by allowing the formation of C_3 convertase and the resulting formation of C_{3b}, which helps the promastigote attach to the macrophage (13, 39). *L. donovani* promastigotes use opsonization by the acute phase C-reactive protein, which binds to LPG, to their advantage to enhance their phagocytosis into macrophages (13, 40). Survival of metacyclic promastigotes within the vertebrate blood stream is also assisted by the sand fly itself. Sand fly saliva contains a peptide called maxadilan, a selective agonist of pituitary adenylate-cyclase-activating polypeptide type 1 receptor. Maxadilan inhibits LPS-stimulated macrophages from producing TNF-α, and it reduces their ability to make NO to kill the parasites (19, 41–43). Thus, there are a variety of mechanisms *Leishmania* employs to escape destruction before ever infecting the macrophages.

Leishmania amastigotes that have ruptured from macrophages must also survive in the bloodstream until they infect a new macrophage. *L. major* amastigotes derived from lesions have been shown to activate complement and fix C_3, leading to their reuptake into other macrophages (13, 44, 45). *L. mexicana* amastigotes use a different approach to survive within the bloodstream. While still in the phagolysosome, *L. mexicana* amastigotes secrete large amounts of proteophosphoglycan (PPG) (13, 46). Once the macrophage ruptures, PPG can bind to MBP, activating complement away from the amastigote (13). These mechanisms help prevent lysis of the amastigotes as well as initiate their uptake into surrounding macrophages.

ENTRANCE INTO THE MACROPHAGE

Leishmania enter mononuclear phagocytes by receptor-mediated endocytosis. Metacyclic promastigotes have exploited their opsonization by complement to gain entry into macrophages. Opsonization with C_{3b} and C_{3bi}, which bind to the macrophage receptors CR1 and CR3, respectively, is the predominant way in which metacyclic promastigotes enter the macrophage (19). This method may provide a survival advantage, since CR1 and CR3 promote phagocytosis without prompting an oxidative burst (13, 33, 47). Another benefit to using the CR3 receptor is that it inhibits IL-12 induced cell-mediated immunity, thus protecting the promastigote (13, 48, 49). *L. major* and *L. donovani* amastigotes also use the CR3 receptor (19). *Leishmania* amastigotes also use other receptors to gain entrance into the macrophage. *L. major* and *L. mexicana* amastigotes have both been shown to use immunoglobulin opsonization as a means of entering the macrophage through the Fc receptor (19, 45, 50). *L. amazonensis* can bind to heparin sulfate and a fibronectin receptor because the surface protein gp63 appears to mimic fibronectin (1, 19, 51, 52). *L. donovani* can bind to the mannose–fucose receptor (19, 53). *L. major* can attach through a lectin-like receptor that recognizes LPG (19, 44). These receptors and others, including CR4, the receptor for advanced glycosylation end products, and the C-reactive protein receptor, have been found to facilitate promastigote uptake into host macrophages (19, 40, 54–60). The ability to use a variety of different receptors makes it easier for the promastigote to enter the macrophage. These receptors also

allow the promastigotes to enter Langerhans cells in the epidermis, where they can safely transform into amastigotes (19, 61, 62) Although the parasites cannot replicate here, these cells may offer a safer environment for the transformation into amastigotes because Langerhans cells do not produce inducible nitric oxide synthase (iNOS, NOS2), which might otherwise kill the parasite (19, 63). Multiple routes of entry into macrophages help protect promastigotes and amastigotes from destruction outside the cell.

After binding to the macrophage cell surface, promastigotes are endocytosed into a phagosome known as a parasitophorous vacuole, which undergoes a series of fusion events to become a phagolysosome (13, 64). LPG molecules protect the promastigote from the harsh conditions of the maturing parasitophorous vacuole (13). Differentiation of the promastigote into the amastigote form and its subsequent proliferation occur in the acidic and hydrolase-rich environment of the phagolysosome (13). However, LPG levels expressed on the amastigote surface are downregulated, so other phosphoglycan-containing glycoconjugates may also protect the amastigote form (13, 65–67). Once inside the macrophage, *Leishmania* parasites employ a variety of adaptive mechanisms to survive the harsh conditions found there.

INHIBITION OF PHAGOSOME–ENDOSOME FUSION

While amastigotes can survive inside acidic phagolysosomes, promastigotes have adapted survival strategies early during infection before the amastigote transformation occurs. *L. donovani* promastigotes can inhibit phagosome–endosome fusion through their LPG molecules (9). LPG repeating units may inhibit phagosome–endosome fusion by reducing the fusogenic properties of the membranes (13, 68). LPG may prevent this fusion by creating steric repulsion between the phagosome and endosome membranes or by reducing the negative curvature strain in the membrane bilayers, which would increase the energy barrier for forming highly curved fusion intermediates (13). While the degree to which the inhibition of phagosome–endosome fusion enhances the establishment of promastigote infection is not fully understood, delayed maturation of the parasitophorous vacuole may protect the promastigotes from hydrolytic degradation and provide a supportive environment for their differentiation into amastigotes (13).

L. mexicana amastigotes use a different mechanism for survival. These amastigotes are taken up into a phagolysosome that eventually grows into a large parasitophorous vacuole (13, 69). Large amounts of PPG are secreted by the amastigotes into the parasitophorous vacuole, which may promote their survival through an unknown mechanism (13).

INHIBITION OF HYDROLYTIC ENZYMES

While in the phagolysosomes, *Leishmania* amastigotes must be able to either withstand or inhibit host hydrolytic enzymes in order to survive (13). LPG may act as a degradation barrier because of its highly anionic nature and its unique galactose-β1,4-mannose linkages within the repeating units (13). These surface glycoproteins are resistant to host lysosomal enzymes and may destroy them (3). The gp63 protease, which exhibits optimal activity under the acidic conditions of the phagolysosomes, has been shown to degrade lysosomal enzymes, as well (1).

INHIBITION OF CALCIUM CHELATION

Since calcium regulates many cellular activities, chelation by LPG may protect the amastigote while in the phagolysosome (13). Calcium can bind to the LPG repeating units near the phosphate groups without disturbing the structure of the glycan (13, 70). Altered calcium mobilization can lead to impaired signal transduction, which can result in defective PKC activation (8, 71, 72).

INHIBITION OF HOST SIGNALING PATHWAYS

Leishmania may impair host macrophage signaling pathways to disrupt cellular functions. Impaired responsiveness to IFN-γ, lipopolysaccharide (LPS), and activators of protein kinase C (PKC) have been seen in *Leishmania* infections (13, 73, 74). Altering signal transduction through the disruption of cellular phosphorylation, either by an alteration of cellular kinases and phosphatases or by *Leishmania* expressing its own phosphatases that act on macrophage proteins, is used by *Leishmania* to enhance survival (8). *L. donovani* has been shown to impair tyrosine phosphorylation and activation of JAK1, JAK2, and STAT1 in response to IFN-γ, possibly involving the activation of the cellular protein tyrosine phosphatase SHP-1 (75, 76). Activation of

SHP-1 may also be responsible for dephosphorylating MAP kinases 1 and 2 (75). MAP kinases phosphorylate and activate transcription factors such as Elk-1 to regulate gene expression (75, 77). When stimulated with PMA, Elk-1 phosphorylation is reduced in cells infected with *L. donovani* (75). *L. donovani* promastigotes also express an endogenous phosphatase to impair cellular phosphorylation (8, 78).

Leishmania decreases macrophage PKC activity to enhance its survival (8, 79–81). LPG may interact with the regulatory domain of PKC containing the diacylglycerol, calcium, and phopholipid binding sites, or it may inhibit the activation of PKC by preventing its insertion into the membrane (13). MARCKs (myristolated alanine-rich C kinase substrate) and MRP (MARCKs-related protein) are PKC substrates associated with components of the cellular cytoskeleton and involved in regulating the actin network during cytoskeletal rearrangements (8). *Leishmania* promastigotes downregulate MRP, which may affect vacuolar trafficking or maturation, in order to deactivate the macrophages (8, 82). Glycosylinositol phospholipids (GIPLs) found on amastigotes also inhibit PKC, yet this inhibition may involve a different mechanism than that of LPG (13, 83).

INHIBITION OF NITRIC OXIDE PRODUCTION

Macrophages produce nitric oxide through the induction of iNOS, in response to extracellular signals, including IFN-γ and LPS (13, 84). GIPLs on the amastigote surface can inhibit NO production, reducing leishmanicidal activity (13, 85). The LPG-associated kinetoplastid membrane protein 11 may also downregulate iNOS activity in infected macrophages because it contains a structural analog of L-arginine, an inhibitor of iNOS (86, 87).

INHIBITION OF OXIDATIVE BURST METABOLITES

The repeating units of LPG may help protect promastigotes from toxic oxygen metabolites generated during the macrophage oxidative burst by scavenging hydroxyl radicals and superoxide anions (13, 88–90). LPG may also protect the parasites by attenuation of the PKC-mediated induction of the oxidative burst (13). Gp63 has also been associated with suppression of the oxidative burst (19, 91).

INHIBITION OF CYTOKINE PRODUCTION

Leishmania parasites may also survive by modulating macrophage cytokine production. Both promastigotes and amastigotes have been shown to downregulate macrophage IL-12 production, which is necessary for the T_H1 response (8, 92, 93). Ligations of macrophage phagocytic receptors, including complement receptors and Fcγ receptors that mediate promastigote and amastigote phagocytosis, respectively, have been shown to specifically suppress IL-12 production (8, 49, 50, 94). Fcγ receptor ligation also induces IL-10 production, which has been associated with suppressing macrophage antimicrobial activity, cytokine production, and the expression of costimulatory molecules on macrophages and dendritic cells (8, 87, 95–97). Amastigotes are also responsible for impairing the production of agonist-induced IL-1 through an unknown mechanism (13, 98, 99). LPG inhibits IL-1β gene expression by suppressing transcription through a unique sequence in the IL-1β promoter (13, 100). *L. braziliensis* and *L. major* induce TGF-β production, which has macrophage inhibitory properties, within the first 3 days of infection (86, 101, 102). The manipulation of cytokine production allows *Leishmania* to survive by altering the immune response to the infection (8).

COMPARISON TO OTHER INTRACELLULAR PARASITES AND PROTOZOANS

A variety of intracellular parasites can cause macrophage disruption. Unlike other intracellular protozoans such as *Toxoplasma gondii*, which survives by inhibiting lysosomal fusion with the phagosome, or *Trypanosoma cruzi*, which can escape the parasitophorous vacuole, *Leishmania* relies on its own defense mechanisms to survive and proliferate within the macrophage phagolysosome (3). Other intracellular parasites utilize survival mechanisms that are similar to those of *Leishmania*. *Mycobacteria tuberculosis* infects mononuclear phagocytes and evades destruction by impairing important macrophage functions, such as macrophage activation induced by IFN-γ, through a cell wall glycolipid called lipoarabinomannan (LAM) (75). LAM may also affect cell signaling by modulating the activity of SHP-1 and diminishing the tyrosine phosphorylation of p42 MAP kinase (75, 103). *Mycobacteria* also have a cell wall glycolipid (α,α-trehalose 6,6-dimycolate), which inhibits phospholipid vesicle fusion and is similar to LPG on *Leishmania* (104, 105). While

Leishmania may share similar types of survival mechanisms with other parasites, it has adapted many unique methods that allow it to thrive within the macrophage phagolysosome.

CONCLUSIONS

Leishmania are a diverse group of intracellular pathogens that have efficiently developed adaptive measures to ensure their survival. Not only have they developed strategies to survive inside the sand fly vector, but the parasites have also established means to survive in the vertebrate bloodstream, as well as to flourish within the hostile conditions of the macrophage phagolysosome. *Leishmania* effectively use the immune response of the host to target themselves for engulfment into macrophages. Once phagocytised, they manipulate the harsh environment through the inhibition of hydrolytic enzymes, toxic metabolic products, cell signaling, cytokine production, and other events. These strategies allow *Leishmania* to successfully undermine the host innate and acquired immune responses and promote parasite survival.

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