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Innate Immune Responses to *Leishmania* in Dogs and Cats: Mechanisms of Evasion and Host Defense

Sajede Asghari[1], Mostafa Kami[2*], Najva Zivdari[3], Masoud Abedi[4], Fatemeh Sabeti[5]

1. Department of Clinical Sciences, Bab.C., Islamic Azad University, Babol, Iran.
2. The Health of Plant and Livestock Products Research Center, Mazandaran University of Medical Sciences, Sari, Iran.
3. Faculty of Veterinary Medicine, Lorestan University, Khorramabad, Iran.
4. Faculty of Veterinary Medicine, Shahid Bahonar University of Kerman, Kerman, Iran.
5. Faculty of Veterinary Medicine, Urmia University, Urmia, Iran.

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ABSTRACT

Background: Leishmaniasis is an infection transmitted by arthropod vectors and is caused by protozoan parasites of the genus *Leishmania*. Primarily, dogs function as reservoirs. Emerging evidence points to cats as secondary hosts. This study aimed to review innate immune responses and parasite evasion mechanisms in canine and feline leishmaniasis.

Materials and Methods: This narrative review synthesized peer-reviewed studies on innate immune responses to *Leishmania* infection in dogs and cats, identified through searches of major biomedical databases (including PubMed, Scopus, and Web of Science) from 1990 to 2025. Eligible articles reported immunological data on innate cells, cytokine profiles, or parasite evasion; non-English publications, case reports, and studies without immune outcomes were excluded. Key findings were qualitatively integrated to compare species-specific responses and associated clinical outcomes.

Results: Dogs with progressive disease show mixed Th1-Th2 responses, with IL-10 and TGF-β promoting parasite persistence. Cats more often exhibit dominant Th1 responses, with elevated IL-12 and IFN-γ correlating with greater suppression of parasite growth and subclinical infection. *Leishmania* evades immunity by inhibiting phagolysosome maturation, modulating Toll-like receptor signaling, and suppressing reactive oxygen and nitrogen species. Cats display lower antibody production than dogs, contributing to their resistance; however, co-infections with retroviruses increase feline susceptibility. -12/IFN-γ-inducing vaccines and therapies targeting IL-10/TGF-β pathways show potential.

Conclusion: Distinct innate immune responses shape disease outcomes in dogs and cats, necessitating tailored diagnostic and therapeutic approaches and inclusion of feline leishmaniasis in One Health surveillance.

*** Corresponding Author:**
Mostafa Kami, DVM.
Address: *The Health of Plant and Livestock Products Research Center, Mazandaran University of Medical Sciences, Sari, Iran.*
Phone: *+98 (911) 269 8152*
E-mail: *m.kami@mazums.ac.ir*

Introduction

Leishmaniasis is an arthropod-borne infection caused by protozoan parasites of the genus *Leishmania*. This condition poses substantial challenges to animal healthcare and human well-being alike. In dogs, infection with *Leishmania infantum* may result in canine leishmaniosis (CanL), a severe systemic disease common in many regions globally [1, 2]. Dogs act as the primary reservoir for zoonotic transmission, significantly contributing to the maintenance of parasite circulation and the risk of human infection. While leishmaniasis in cats had been thought to be uncommon, current research indicates that it may be more frequent than previously assumed. Cats are susceptible to both dermal and visceral clinical manifestations, suggesting a possible involvement in the parasite's transmission cycle and infection epidemiology [3, 4].

The pattern and severity of disease in these companion animals are influenced by a dynamic interaction between parasite virulence and host immunological responses. As the host's first defensive arm, the innate immune system directs the early identification and response to parasites after inoculation by the sandfly vector. Early after infection, neutrophils, macrophages, and dendritic cells (DCs), as phagocytic effectors, act promptly to restrict parasite multiplication and produce pro-inflammatory molecules, followed by antigen processing and presentation that shapes the ensuing adaptive immune response [5, 6].

Despite host defenses, *Leishmania* spp. have learned to outmaneuver innate immunity through a range of clever strategies, allowing them to establish infection and persist. The parasite establishes a favorable environment within host cells by modifying phagocytic cell function, fine-tuning toll-like receptor (TLR) signaling pathways, and suppressing the generation of oxygen- and nitrogen-derived radicals that would normally aid in its elimination. The balance between host-mediated regulation and parasite evasion determines whether an infection is eradicated, subclinical, or progresses to clinical disease. Macrophages in dogs with advancing CanL typically adopt an M2 profile. Th2 cytokines trigger this anti-inflammatory activation. It fosters immunoregulation and helps parasites persist by releasing mediators, including interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), thereby creating a more permissive environment and promoting parasite survival [7, 8].

Understanding the early crosstalk occurring between innate host defenses and *Leishmania* parasites is critical, as it influences disease progression and severity. Recent studies suggest that cats' innate immune responses may be more effective in limiting parasite replication, leading to a decreased incidence of clinical disease [4, 9]. This review consolidates current knowledge on the processes of innate immune recognition and effector functions in dogs and cats, along with the strategies employed by *Leishmania* to evade these responses. Highlighting these intricate host-parasite interactions helps explain leishmaniasis immunopathogenesis and suggests potential treatment targets for companion animals.

Materials and Methods

This narrative overview was based on a systematically designed search across leading biomedical bibliometric databases, such as MEDLINE/PubMed, Scopus, Web of Science, and CAB Abstracts, supplemented by targeted searches in Google Scholar and manually screening the bibliographies of key original research articles and reviews. The search strategy combined controlled vocabulary and free-text terms related to the parasite, host species, and innate immunity (e.g. "*Leishmania*", "*Leishmania infantum*", "leishmaniasis", "canine", "dog*", "feline", "cat*", "innate immunity", "macrophage*", "neutrophil*", "dendritic cell*", "natural killer cell*", "Toll-like receptor*", "cytokine*", "IL-10", "IL-12", "interferon-gamma"), linked with Boolean operators and adapted to each database. Searches were limited to articles published between January 1990 and June 2025, with filters for relevant species (dogs, cats, or directly comparable mammalian models) and publication type (original research and reviews). Studies were eligible if they reported data or substantial discussion on innate immune mechanisms during *Leishmania* infection, including innate cell functions, pattern-recognition pathways, early cytokine or chemokine responses, or parasite evasion strategies. Exclusion criteria comprised studies restricted to humans or vectors without translational relevance, non-canine/feline models, case reports, conference abstracts, letters, and non-English publications. An initial screening of titles and abstracts was performed, after which potentially relevant articles underwent full-text evaluation. Findings were synthesized narratively and grouped thematically to compare species-specific responses and identify consistent mechanisms and gaps.

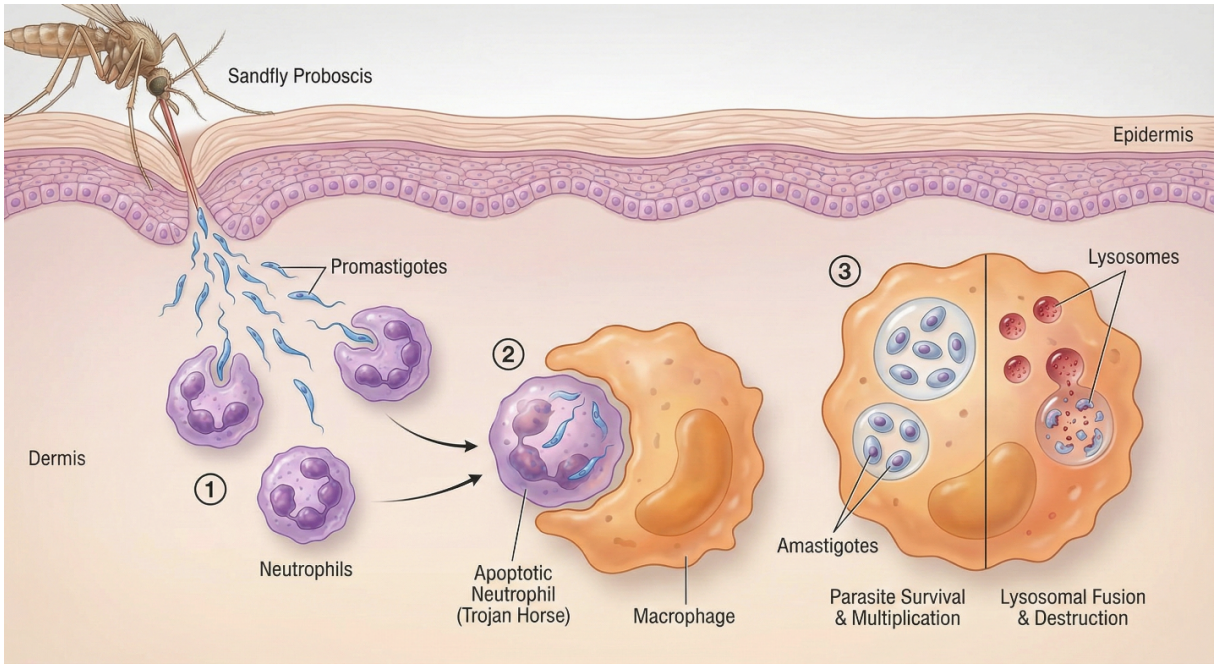

Figure 1. The "Trojan horse" mechanism of *Leishmania* immune evasion

Note: Neutrophils initially phagocytose promastigotes at the infection site. The parasites subsequently transfer to macrophages via the uptake of apoptotic, infected neutrophils, allowing them to enter their definitive host cells undetected by the immune system.

Overview of Innate Immunity in *Leishmania* Infection

Innate immune responses represent the earliest layer of host defense against invading pathogens and is crucial for determining the fate of a *Leishmania* infection. This system uses cellular and molecular mechanisms to recognize pathogen-associated molecular patterns (PAMPs) and mount a rapid anti-parasite response [10].

Initial encounter and skin immunity

After sandfly transmission, *Leishmania* promastigotes first encounter skin keratinocytes, Langerhans cells, and dermal DCs [11, 12]. Comprising 90–95% of the epidermis, keratinocytes secrete early pro-inflammatory mediators, notably interleukin-6 (IL-6), IL-4, IL-1β, and tumor necrosis factor-alpha (TNF-α) that shape subsequent immune responses. Although only 1-3% become infected, their cytokine production and apoptosis, mediated through the death receptors Fas/Fas ligand (FasL) and TNF–related apoptosis-inducing ligand (TRAIL), amplify local inflammation and influence disease evolution [12].

Humoral defense: The complement cascade

The complement system, also referred to as the complement cascade, is a key early humoral defense. Its initiation through any of the three routes, classical, lectin, or alternative (APs), causes C3b deposition, opsonization, and the generation of a membrane attack complex (MAC) for pathogen elimination. *Leishmania* evades this by using mechanisms, such as glycoprotein 63 (GP63)-mediated cleavage of C3b to inactive C3b (iC3b), recruitment of host factor H, lipophosphoglycan (LPG) steric hindrance, secretion of serine peptidase inhibitors (serpins), and salivary complement suppression. These pathways avoid lysis and allow silent phagocytic entry via receptors, such as complement receptor 3 (CR3), thereby reducing inflammation [13, 14].

Key innate immune cells

Neutrophils act as "Trojan horses" to infect macrophages, even though they are early responders that phagocytose promastigotes (Figure 1). Despite producing reactive oxygen species (ROS) and neutrophil extracellular traps (NETs)—both of which are often ineffective—the parasite uses factors like inhibitor of serine peptidases 2 (ISP2) to prolong neutrophil lifespan, inhibit apoptosis, and evade NET-mediated killing [10, 12].

Macrophages act as the main effector and reservoir cells. After phagocytosis, promastigotes differentiate into amastigotes within phagolysosomes. Principal cellular participants include neutrophils, macrophages, and DCs. NO synthesis is arginine-dependent and regulated by cytokines, including TNF-α, interferon-gamma (IFN-γ), IL-4, IL-10, and TGF-β [10, 11, 13].

DCs integrate innate immune sensing with adaptive responses. In addition to phagocytosing parasites, they also migrate to lymph nodes and induce protective T helper 1 (Th1) differentiation by producing IL-12. Impaired DC migration or antigen presentation is associated with severe disease [10, 12].

Roles of other innate immune cells

Other innate immune cells also contribute. Gamma delta (γδ) T cells release IL-4 and IL-17, which affect disease outcomes. Eosinophils and mast cells contribute to local inflammatory circuits by producing IL-4 and IL-5, which regulate macrophage activation and lesion progression. Natural killer (NK) cells release IFN-γ and TNF-α to boost macrophage activity, but these responses can be influenced by parasite virulence factors [12].

Disease outcome and comparative susceptibility

In dogs, an effective innate response, involving keratinocyte cytokines, complement, neutrophils, DCs, and macrophage NO, promotes protective Th1 polarization [11, 14, 15]. Disease progression is linked to TLR downregulation and impaired effector functions [10]. Species-specific immune differences may explain the lower clinical disease prevalence in cats versus dogs. Cats display comparable innate systems, indicating that these reactions impact the course of infections and species-specific vulnerability [9, 12, 14].

Innate Immune Responses in Dogs

Overview of innate and adaptive immunity in dogs

The immune system consists of two fundamental branches: Innate and adaptive immunity. Innate immunity serves as the body's immediate defense, relying on physical barriers, like the skin and immune cells, such as neutrophils, macrophages, and NK cells. Conversely, adaptive immunity, mediated by B and T lymphocytes, operates with a slower response but exhibits high specificity toward particular pathogens [16].

Newborn puppies acquire most of their passive immunity through colostrum rich in maternal antibodies. Although innate immune elements, such as phagocytes are active at birth, the functional maturity of antigen-presenting cells (APCs) remains unclear [16, 17]. The neonatal immune system develops progressively after birth, with its maturity strongly influenced by gestational duration—shorter pregnancies often leading to weaker immune responses [18].

DCs and IL-12-driven Th1 polarization

DCs serve as key mediators linking innate and adaptive immune responses [19]. They function by capturing antigens, migrating to lymph nodes, and activating naïve T cells. In vitro, DCs can be generated from bone marrow or peripheral blood mononuclear cells (PBMCs) and are identified by their distinct morphology and surface markers, including major histocompatibility complex class II (MHC-II) and CD11c [20]. When stimulated, such as by lipopolysaccharide (LPS), they upregulate co-stimulatory molecules CD80 and CD86 [21].

IL-12 is essential for protective immunity, especially against *Leishmania major*. It activates NK and $CD8^+$ T cells while promoting a Th1-type immune response characterized by IFN-γ production. Research using genetically susceptible mouse strains, such as BALB/c, demonstrates that IL-12 increases resistance to lethal infection. Structurally, IL-12 is a heterodimer consisting of p35 and p40 subunits, and knockout models for these components confirm its pivotal role. In the absence of IL-12, both early NK cell activation and IFN-γ secretion are markedly reduced [22].

Neutrophil responses and the "Trojan horse" strategy

During *Leishmania* infection, DCs not only present antigens but also engulf promastigotes, actively contributing to disease progression. Neutrophils, the body's initial defenders, eliminate pathogens through phagocytosis, ROS, and lysosomal enzymes, and can also form NETs to restrain pathogens. The early immune response to *Leishmania* relies on complement activation and recognition through pattern recognition receptors, like TLRs. Approximately 90% of stationary-phase promastigotes are destroyed by complement, while the remaining parasites become opsonized with C3b and internalized by APCs via complement receptor 1 (CR1) and CR3 receptors. This uptake, however, occurs in a "silent" manner, without triggering an oxidative burst or IL-12 production, thereby restricting macrophage activation and DC migration. Consequently, T-cell activation is thought

to result mainly from antigen drainage to lymph nodes rather than direct presentation [23].

Remarkably, *Leishmania* uses a "Trojan horse" mechanism, infecting neutrophils and then transferring to macrophages after the neutrophils undergo apoptosis, allowing the parasite to escape immune detection [24]. *Leishmania* manipulates neutrophils in a two-step process. Initially, it attracts them while avoiding activation of their antimicrobial mechanisms by imitating apoptotic signals, such as phosphatidylserine exposure. It then prolongs neutrophil survival and induces macrophage recruitment through chemokines, like macrophage inflammatory protein-1β (MIP-1β), also known as chemokine (C-C motif) ligand 4 (CCL4) [25]. Ultimately, the parasite is transferred to macrophages in a stealthy manner, a phenomenon humorously termed the "Trojan Horse" strategy [26].

Macrophage activation, nitric oxide, and cytokine balance

In visceral CanL, the immune response is highly complex. Research has shown that the number of iNOS$^+$ (inducible nitric oxide synthase) cells in lymphoid tissues is inversely related to parasite load but positively associated with IFN-γ levels, indicating that elevated iNOS activity enhances control of *Leishmania* infection. Moreover, vaccination using killed *Leishmania* promastigotes has been found to boost nitric oxide (NO) production and strengthen macrophage-mediated parasite destruction, emphasizing the critical role of NO in parasite clearance [27].

In canine leishmaniasis, *L. infantum* triggers a mixed Th1–Th2 immune response, with infection outcomes dependent on their balance. While IFN-γ supports parasite control, IL-10 correlates with higher parasite loads and acts as a key regulator of Th1 activity and macrophage function [28]. In CanL, the immune response exhibits a combination of Th1 and Th2 characteristics. IFN-γ contributes to infection control, whereas the anti-inflammatory cytokine IL-10 correlates with greater parasite loads and disease severity by suppressing macrophage activity. Interestingly, asymptomatic dogs commonly produce both IFN-γ and IL-4, indicating a balanced immune response that limits disease progression [29].

Resistance to CanL is linked to a strong Th1 immune response characterized by the activity of IFN-γ, IL-2, and TNF-α, which stimulate macrophages to eliminate intracellular amastigotes through the L-arginine–NO pathway. Increased NO production and enhanced parasite clearance have been documented in both vaccinated dogs and experimental models. IL-12 supports this Th1 profile, as the combined expression of IL-12, IL-2, and IFN-γ is associated with delayed disease progression. Likewise, IL-18 appears to contribute similar immunoprotective effects [30-32]. In CanL, the role of Th2 cytokines is not fully defined, and infection outcomes depend largely on the cytokine balance, especially IL-10's regulatory effects [29, 33].

Innate Immune Responses in Cats

Evidence of feline resistance to clinical disease

Cats demonstrate remarkable natural resistance to *L. infantum* infection compared to dogs, with the majority of infected felines remaining asymptomatic despite parasite exposure in endemic areas [34]. This resistance is characterized by spontaneous healing of cutaneous lesions and minimal pathological changes, suggesting an inherent capacity for parasite control [35]. The subclinical nature of feline leishmaniasis is prevalent, with infected cats frequently showing no clinical manifestations even when parasites are detectable through molecular methods [34]. Unlike canine leishmaniasis, where progressive disease is common, feline infections with *L. infantum* usually do not show prominent clinical symptoms, and their infection remains subclinical [36]. This natural resistance is attributed to species-specific differences in innate and adaptive immune responses that enable cats to mount more effective parasite containment mechanisms than dogs [37].

Cytokine responses

Cats exposed to *L. infantum* often mount a cellular response characterized by heightened production of key Th1-associated cytokines, most notably IL-12 and IFN-γ [38]. Clinically healthy cats with natural *Leishmania* infection exhibit increased serum IL12 and IFNγ relative to uninfected counterparts, with IL12 positively linked to IFNγ production, indicating coordinated activation of the Th1 immune response [39]. This cytokine pattern points to IL-12 as a key driver of Th1-type immunity, boosting macrophage activity and facilitating clearance of intracellular parasites [38]. Notably, a significant inverse relationship between IL-12 levels and bone-marrow parasitemia demonstrated its protective effect in feline leishmaniasis [38]. Cats from endemic areas produce IFN-γ in vitro following stimulation with soluble *Leishmania* antigens, confirming cell-mediated immune activation [39]. Functional assessment of feline cellular immunity has confirmed that cats in endemic areas

can mount specific responses to *L. infantum*. Utilizing a whole-blood release assay, Priolo et al. [39] detected specific IFN-γ production in both asymptomatic and sick cats. Notably, the study reported that the median concentration of this pro-inflammatory mediator was significantly higher in clinically affected cats (567.1 pg/ml) compared to healthy infected individuals (116 pg/ml), challenging the assumption that strong cellular immune activation is solely a marker of resistance.

Lower antibody and humoral contribution

Feline leishmaniasis is characterized by a relatively limited humoral immune response compared to canine infections [34]. Unlike dogs, cats typically mount lower antibody responses against *Leishmania* antigens, with antibody levels generally insufficient to indicate active infection through serological methods alone [35, 40]. Infected cats frequently present with low or undetectable anti-*Leishmania* antibody titers despite parasitological confirmation [40, 41]. This pattern suggests that humoral immunity may play a protective role in cats, contrasting with dogs where high antibody production correlates with disease susceptibility [35]. Studies demonstrate that cats with increased antibody titers often show decreased PCR positivity, while higher PCR positivity occurs in cats with reduced antibody levels [42]. This inverse relationship indicates that the humoral response in felines differs fundamentally from dogs, with seroconversion potentially occurring during lesion resolution phases rather than active disease [35]. The immune response in cats appears to favor cell-mediated immunity (Th1) over antibody production, contributing to better parasite control and the spontaneous resolution of lesions [35, 37, 43].

Role of co-infections

Co-infections with feline immunodeficiency virus (FIV) and feline leukemia virus (FeLV) significantly alter immune responses in cats with leishmaniasis, inducing hematological changes, such as monocytosis that reflect a modified inflammatory state [4, 44, 45]. Epidemiologically, this altered immune landscape corresponds with increased susceptibility; FIV-seropositive cats demonstrate a 2.8-fold increased risk of being *L. infantum* antibody-positive compared to their FIV-seronegative counterparts [4]. Approximately 50% of cats with clinical leishmaniasis test positive for FIV or FeLV, indicating that immunocompromised states predispose to disease progression [9]. FIV/FeLV co-infection impairs T cell-mediated immunity, reducing the effectiveness of innate defense mechanisms and promoting clinical manifestation of otherwise controlled infections [4]. Cats co-infected with FIV and *L. infantum* exhibit altered hematological profiles consistent with chronic inflammation, including anemia, monocytosis, and thrombocytosis [44, 46].

Comparative Perspective: Dogs vs Cats

The profile of intrinsic cytokines differs between species, with significant implications for the immune response to *Leishmania* infection. In dogs, increased regulatory cytokines, including IL-10 and TGF-β, are tied to clinical deterioration and increased parasite load, while higher levels of IFN-γ and TNF-α are associated with better infection resistance and control [47]. Furthermore, increased expression of TLR2 is linked to heightened severity within cutaneous and lymphatic tissues of dogs [10, 47]. In contrast, cats are more inclined to Th1 responses involving increased IFN-γ and IL-12, possibly providing natural immunity and more effective control of infection [37]. Although both species share the same set of intrinsic receptors and lymphocytic subgroups, differences in how these components interact lead to different immune responses [37].

Furthermore, patterns of *L. infantum* infection in dogs and cats demonstrate fundamental differences in disease dynamics and clinical immune response. Dogs generally develop a more severe immune response, and the incidence of clinical symptoms is more common, while cats often experience infections that are asymptomatic or mild [4]. It has been demonstrated that both species are capable of producing protective humoral and cellular responses. However, in cats, these responses are less severe and stable, often leading to the preservation of infection at underlying levels. Conversely, the greater severity of the disease in dogs is usually associated with increased parasite load, predominance of Th2 response, and decreased Th1 activity [47-49].

In the domain of reservoir role and disease transmission, the parasite load is found to be higher in dogs, particularly in skin tissues, and these animals possess a heightened capacity to infect sandflies [48, 50, 51]. Dogs are thus recognized as the principal household reservoir in the leishmaniasis transmission cycle [52, 53]. However, under certain conditions, such as the presence of free-roaming populations or the presence of FIV, cats can also be sustainably infected with the parasite and play a significant role in the transmission cycle [49, 52]. While the prevalence of parasites and the severity of the disease in cats are typically lower, the presence of active infection in cat populations in endemic regions underscores their significance in epidemiology [48, 49, 52].

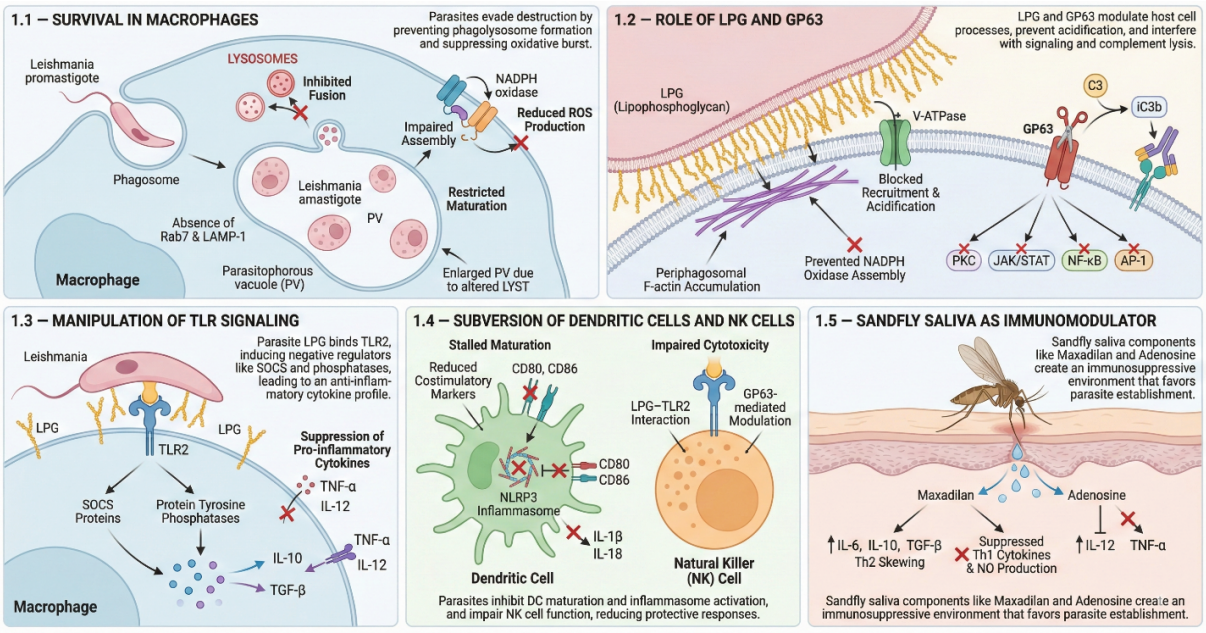

Figure 2. Overview of Leishmania immune evasion and modulation strategies

Note: The figure depicts key mechanisms favoring parasite persistence: (1.1) inhibition of macrophage phagolysosome fusion and oxidative burst; (1.2) disruption of host signaling, complement, and acidification by virulence factors LPG and GP63; (1.3) subversion of TLR pathways to induce anti-inflammatory cytokines (IL-10, TGF-β); (1.4) impairment of dendritic cell maturation and NK cell cytotoxicity; and (1.5) establishment of an immunosuppressive environment by sand fly salivary components, like maxadilan and adenosine.

While dogs remain the primary and most effective reservoirs for the transmission of *Leishmania*, recent evidence suggests that cats should also be considered in disease monitoring and control programs. Cats can act as secondary players in the transmission dynamics and environmental persistence [49, 52].

Parasite Evasion Strategies

Survival in macrophages

Leishmania parasites employ sophisticated mechanisms to survive within the hostile macrophage environment by preventing phagolysosome maturation and suppressing oxidative burst [54]. Upon internalization into phagosomes, promastigotes transiently inhibit the fusion of phagosomes with lysosomes, thereby delaying phagolysosomal formation and preventing the acquisition of lysosomal hydrolytic enzymes [55]. This delay in phagosome maturation is mediated by multiple parasite-derived mechanisms that prevent the recruitment of late endosomal markers, such as ras-related protein Rab-7 (Rab7) and lysosome-associated membrane protein 1 (LAMP-1) [56, 57]. The parasitophorous vacuole (PV) undergoes restricted maturation, creating a specialized intracellular compartment that provides an optimal niche for parasite differentiation and survival [57, 58]. In infections with species, such as *Leishmania amazonensis*, the formation of large parasitophorous vacuoles serves to dilute the intravacuolar concentration of NO, thereby reducing its leishmanicidal efficacy [59]. This vacuolar expansion is critical for parasite survival, as host mechanisms involving the lysosomal trafficking regulator protein (LYST) attempt to restrict PV size to limit parasite growth [60]. Regarding oxidative burst suppression, infected macrophages demonstrate impaired ROS production due to inhibition of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex and its associated signaling cascades [54, 61].

Role of LPG and GP63

The parasite surface LPG, the most abundant glycoconjugate on *Leishmania* promastigotes, plays a critical role in immune modulation [54]. LPG inhibits endosome maturation by inducing periphagosomal filamentous actin (F-actin) accumulation [62] and prevents acidification of the phagosome by interfering with the vacuolar-type H^+-ATPase (V-ATPase) pump [63], allowing promastigotes to differentiate into resistant amasti-

Table 1. Diagnostic biomarkers linked to innate immunity in *Leishmania* infection

Biomarker	Type	Findings	Clinical Relevance	Ref.
IL-12	Cytokine	Elevated IL-12 in asymptomatic cats and dogs correlates with parasite control and resistance to clinical disease; diminished IL-12 is observed during active disease progression	Predicts immune status, correlates with control/resistance	[38, 84]
IFN-γ	Cytokine	Elevated IFN-γ correlates with parasite control, while low levels are observed in advanced disease	A critical indicator of therapeutic response and disease status	[38, 93]
TLR2/*TLR4* gene expression	Gene/protein expression (macrophages)	Higher TLR2 and TLR4 expression is associated with healing lesions and better prognosis; lower expression is found in non-healing disease	Links to effective healing and prognosis	[85]
CRP	Acute phase protein	Elevated CRP levels occur during active infection and decline after treatment; CRP shows high sensitivity and specificity for VL diagnosis	A non-specific but valuable biomarker of disease activity and prognosis	[84, 94]
SAA	Acute phase protein	Increased SAA levels are observed in acute inflammation and infection, with levels dropping post-treatment	Correlates with disease activity, responds to therapy	[84, 94]
Ferritin	Acute phase protein	Ferritin levels increase during active infection and decrease with effective treatment.	Monitors treatment response and inflammation	[84, 94]

Abbreviations: IL-12: Interleukin-12; IFN-γ: Interferon gamma; TLR: Toll-like receptor; TLR2/TLR4: Toll-like receptor 2 and Toll-like receptor 4; CRP: C-reactive protein; VL: Visceral leishmaniasis; SAA: Serum amyloid A.

gotes [58]. Moreover, LPG inserts into the phagosome membrane and destabilizes lipid microdomains [64]. This disruption leads to the exclusion of crucial regulators, such as synaptotagmin V [63] and impairs the assembly of the NADPH oxidase complex [57, 61]. The zinc-metalloprotease GP63, expressed on all *Leishmania* species, directly cleaves complement C3 to escape complement-mediated lysis and generates iC3b, which facilitates attachment to macrophage complement receptors [65, 66]. GP63 modulates host macrophage signaling by altering protein kinase C (PKC) activity to inhibit inflammasome activation [67]. It also inhibits the IFN-γ-mediated JAK/STAT pathway by activating host protein tyrosine phosphatases via direct cleavage [68], and interferes with transcription factors by degrading c-Jun to inactivate AP-1 [69].

Manipulation of TLR signaling and induction of IL-10/TGF-β

Leishmania manipulates TLR signaling to establish infection-permissive conditions [55]. Specifically, the surface molecule LPG acts as a ligand for TLR2 on macrophages and NK cells [70], initiating signaling cascades that can paradoxically contribute to immune suppression through the upregulation of negative regulators, like SOCS proteins [71, 72]. The parasite induces the expression of suppressors of cytokine signaling (SOCS) proteins, specifically SOCS1 and SOCS3, which negatively regulate TLR2-induced cytokine production [71, 73]. Additionally, it activates host protein tyrosine phosphatases (PTPs), such as SHP-1 to inhibit inflammatory responses [68]. *Leishmania* promotes the production of immunoregulatory cytokines IL-10 and TGF-β, which suppress pro-inflammatory responses and enhance parasite survival [55, 74, 75].

Subversion of dendritic cell and NK cell functions

L. amazonensis is an intracellular protozoan parasite endemic to the Americas. It is notable for its ability to subvert DC maturation through multiple mechanisms, including stalled maturation characterized by maintained immature phenotypes despite internal maturation signals [76]. The parasite inhibits inflammasome activation by downregulating NOD-like receptor family pyrin domain containing 3 (NLRP3) expression and prevents IL-1β and IL-18 secretion [76]. In NK cells, while LPG acts as a ligand for TLR2 [70], the surface protease GP63 binds to NK cells and impairs their proliferation and cytotoxic functions, thereby reducing their ability to kill parasites [77].

Sandfly saliva as an immunomodulator

During vector transmission, sand fly saliva significantly enhances *Leishmania* infection establishment [77, 78]. Sand fly salivary proteins, particularly maxadilan from *Lutzomyia longipalpis*, act as potent vasodilators and immunomodulators, upregulating Th2-associated cytokines (IL-6, IL-10, and TGF-β) while downregulating Th1 cytokines and NO production [78-80]. Adenosine in *Phlebotomus papatasi* saliva induces IL-10 and suppresses IL-12 and TNF-α production, creating

an immunosuppressive microenvironment favorable for parasite survival [78, 81, 82]. As illustrated in Figure 2, *Leishmania* employs diverse mechanisms to evade host immunity, including blockade of macrophage killing and ROS generation, subversion of TLR pathways, impairment of dendritic and NK cell responses, and exploitation of sandfly saliva–derived immunomodulators.

Clinical and Therapeutic Implications

Diagnostic biomarkers linked to innate responses

Diagnostic biomarkers associated with *Leishmania* infection comprise both serological markers and immunological parameters reflecting innate immune function [83]. Cytokine profiles, particularly IL-12 and IFN-γ, serve as critical indicators of disease status and therapeutic response. In naturally infected asymptomatic cats and dogs, elevated serum IL-12 and IFN-γ levels correlate with parasite control and resistance to clinical disease, whereas diminished production of these cytokines characterizes active disease progression [38]. TLR expression, particularly TLR2 and TLR4 on macrophages, also represents important diagnostic biomarkers; higher *TLR2* and *TLR4* gene expression in peripheral blood macrophages correlates with healing cutaneous lesions and superior disease prognosis [84]. Additionally, acute phase proteins, including C-reactive protein, serum amyloid A, and ferritin, exhibit elevated levels during active infection and decline within 2–3 weeks post-treatment, offering non-specific yet valuable indicators of disease activity [83]. Key diagnostic biomarkers associated with innate immune responses during *Leishmania* infection are summarized in Table 1.

Vaccine development with IL-12/IFN-γ induction

IL-12 demonstrates remarkable efficacy as a vaccine adjuvant for leishmaniasis, promoting robust Th1-mediated cellular immunity [85, 86]. Immunization with *Leishmania* antigens combined with exogenous recombinant IL-12 in experimental models consistently induces protective CD4+ T helper 1 cell responses characterized by elevated IFN-γ and TNF-α production [85]. TLR agonists, including monophosphoryl lipid A (MPL, a TLR4 agonist) and CpG oligodeoxynucleotides (TLR9 agonist), serve as cost-effective IL-12-inducing adjuvants in multisubunit recombinant vaccine formulations [87].

Immunotherapy targeting IL-10/TGF-β pathways

IL-10 receptor (IL-10R) blockade represents a promising immunotherapeutic strategy for visceral leishmaniasis. Anti-IL-10R antibody treatment accelerates granuloma maturation and enhances parasite killing by restoring Th1 cytokine production and macrophage microbicidal activity [74, 88]. In experimental models, IL-10R blockade synergizes with conventional pentavalent antimony chemotherapy, inducing near-cure with reduced drug requirements [74]. Similarly, TGF-β pathway antagonism shows modest therapeutic potential, though IL-10 inhibition remains the primary target among suppressive cytokines [89-91]. Neutralizing anti-IL-10 monoclonal antibodies restore IFN-γ production in anergic peripheral blood mononuclear cells from active visceral leishmaniasis patients, demonstrating clinical relevance for human applications [92].

Research Gaps and Future Directions

Limited data on feline innate immunity

Comprehensive understanding of feline innate immune responses to *L. infantum* remains substantially limited compared to canine infections [4]. While dogs represent the principal reservoir and have been extensively studied, cats remain an emerging concern as potential secondary domestic reservoirs with poorly characterized immune mechanisms against *Leishmania* parasites [34, 94]. To date, comprehensive investigations evaluating innate immune markers beyond cytokine profiling in naturally infected cats are lacking, particularly regarding macrophage activation states, complement pathway contributions, and tissue-specific immune responses [4].

Need for comparative cross-species studies

Substantial knowledge gaps exist regarding mechanistic differences in innate immunity between dogs and cats infected with *Leishmania* spp. [94]. Although both species mount immune responses to *L. infantum*, comparative investigations examining TLR expression patterns, inflammasome activation, and innate lymphoid cell (ILC) populations remain absent [4]. Longitudinal studies in cats are critically needed to clarify early infection phases and adaptive immune maturation trajectories, contrasting with well-documented canine paradigms [4].

One health implications

Current epidemiological evidence suggests cats are emerging as secondary domestic reservoirs, transmit-

ting *L. infantum* to sandfly vectors and potentially to humans in endemic Mediterranean regions [34]. Dogs remain primary reservoirs; however, integrated One Health surveillance networks are needed to understand interspecies transmission dynamics and zoonotic spillover risk [95], particularly given increasing feline infection prevalence and altered host-parasite equilibrium in endemic foci.

Conclusion

L. infantum employs diverse evasion strategies targeting host innate immunity, particularly macrophage functions, to establish infection in dogs and cats. While dogs serve as primary reservoirs with disease progression linked to impaired cell-mediated immunity and elevated regulatory cytokines, cats typically show stronger innate Th1 responses, maintaining subclinical infections with limited clinical signs. This species-specific immune dichotomy emphasizes the importance of tailored diagnostic and therapeutic approaches, including cytokine profiling and TLR analyses, to improve disease management. The emergence of feline leishmaniosis as a potential secondary reservoir requires integrated One Health surveillance to mitigate zoonotic risks. Future research should focus on elucidating feline innate mechanisms, the role of inflammasomes and innate lymphoid cells, and comparative immunopathology with dogs. Advances in vaccines promoting IL-12/IFN-γ responses and immunotherapies targeting IL-10/TGF-β pathways hold promise for improved control. These insights have critical implications for veterinary diagnostics, treatment, and public health strategies addressing this re-emerging zoonosis.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors contribution's

Conceptualization, data curation, formal analysis, visualization, project administration, validation, and supervision: Mostafa Kami; Methodology and writing the original draft: All authors; Investigation, review and editing: Mostafa Kami and Najva Zivdari; Resources: Mostafa Kami, Masoud Abedi, and Najva Zivdari.

Conflict of interest

The authors declared no conflict of interest.

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