

## Review Article

# Leishmaniasis as a model of chronic immunopathology: From the intracellular niche to the failure of immune control

Daniel Navarro Morales<sup>1\*</sup>, Álvaro Calvo Mondragon<sup>2</sup>, Katherine Maroto Monge<sup>3</sup>, Fabiola Alvarez Mora<sup>4</sup>, Heizel Trejos Quiros<sup>5</sup>

<sup>1, 2, 3, 4, 5</sup>Independent Researcher and General Physician, Cartago, Costa Rica

\*Corresponding author email: [506navarro@gmail.com](mailto:506navarro@gmail.com)

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## Abstract

Leishmaniasis represents a paradigmatic model of chronic immunopathology in which persistent intracellular infection results from a finely balanced interaction between parasite survival strategies and host immune dysfunction. Following transmission by the sand fly vector, *Leishmania* undergoes differentiation from the promastigote to the amastigote form, adapting to the acidic, nutrient-limited environment of the phagolysosome. This adaptation is mediated by specialized transporters, lysosomal sensing mechanisms, and protein kinase A-dependent signaling pathways that enable intracellular survival and replication. Within macrophages, the parasite actively remodels the phagolysosomal niche, alters iron metabolism, and interferes with host signaling cascades, promoting a shift toward a parasite-permissive phenotype. Innate immune evasion is achieved through inhibition of reactive oxygen and nitrogen species, modulation of pattern recognition receptor expression, and suppression of dendritic cell activation and migration, leading to defective priming of adaptive immunity. Persistent antigen exposure subsequently drives T cell exhaustion, characterized by diminished effector function and increased expression of inhibitory receptors, particularly in visceral leishmaniasis and in the context of human immunodeficiency virus coinfection. Concurrently, cytokine imbalance, marked by impaired interferon gamma production and dominance of immunosuppressive mediators such as interleukin 10 and transforming growth factor beta, further compromises immune control. Chronic inflammation emerges as a double-edged sword, contributing

both to partial parasite containment and to progressive tissue damage in cutaneous and visceral disease. Metabolic reprogramming of macrophages, involving shifts toward glycolysis and altered redox balance, supports parasite persistence while shaping immune responses. The limitations of conventional antiparasitic therapies, including toxicity, resistance, and restricted accessibility, highlight the need for alternative approaches. Host-directed therapies targeting immune regulation and immunometabolic pathways offer promising avenues to restore immune control, reduce pathological inflammation, and limit long-term parasite persistence.

## Key words

Leishmaniasis, Chronic immunopathology, Immune evasion, T cell exhaustion, Immunometabolism, Host-directed therapy.

## Introduction

Leishmania parasites have evolved sophisticated mechanisms to manipulate host immune responses in order to ensure their survival and replication, thereby establishing chronic infection. A central aspect of this process is the modulation of local immune responses at the very early stages of infection, influenced by factors such as sand fly salivary proteins and the host microbiota. These elements contribute to increased disease susceptibility and facilitate parasite dissemination by shaping a permissive immunological environment [1].

The persistence of *Leishmania major* is further reinforced by the establishment of an immunosuppressive microenvironment characterized by the recruitment of regulatory T cells. These cells suppress effector immune responses directed against the parasite, limiting the capacity of the host to achieve sterile immunity and thereby promoting chronic infection [2]. This immunosuppressive state becomes particularly evident in individuals with compromised immune systems. In patients receiving tumor necrosis factor antagonists or methotrexate, immune regulation is further impaired, resulting in more severe clinical manifestations and an increased risk of disease relapse [3].

As infection persists, chronic leishmaniasis becomes closely associated with T cell exhaustion, a progressive loss of effector

function that develops during sustained antigen exposure. Exhausted T cells are characterized by the expression of inhibitory receptors, including programmed cell death protein 1 and T cell immunoreceptor with immunoglobulin and ITIM domains. This phenotype is particularly prominent in chronic visceral leishmaniasis and is exacerbated in patients coinfecting with human immunodeficiency virus, in whom immune dysfunction is more pronounced [4].

Experimental models have further revealed that T cell exhaustion in leishmaniasis is not a uniform process but involves distinct subsets of exhausted T cells with differing functional capacities. Subpopulations expressing markers such as CXCR5 and TIM-3 exhibit variable degrees of exhaustion, reflecting a balance between residual immune protection and the inability to fully eliminate the parasite. While these subsets may contribute to the maintenance of long-term immune responses, they simultaneously support parasite persistence and the chronic nature of the infection [5].

Regulatory T cells play a pivotal role in sustaining this chronic state by exerting antigen-specific suppression of immune responses. Through the production of interleukin 10, these cells inhibit the generation of pro-inflammatory cytokines, including interferon gamma, which are essential for effective parasite clearance. This suppression dampens macrophage activation and limits the host's ability to control intracellular parasite replication [2].

The accumulation of regulatory T cells at the site of infection therefore represents a key determinant of parasite persistence. By modulating the immune response, these cells help prevent excessive tissue damage associated with uncontrolled inflammation, yet this protective effect comes at the cost of allowing continued parasite survival. This delicate balance between immune regulation and pathogen persistence illustrates how leishmaniasis serves as a compelling model of chronic immunopathology, in which failure of immune control arises not from immune inactivity, but from tightly regulated immunosuppression that ultimately favors chronic infection [2].

The aim of this article is to examine leishmaniasis as a model of chronic immunopathology by highlighting the mechanisms of immune evasion, T cell dysfunction, and regulatory immune pathways that drive parasite persistence and failure of immune control.

## **Methodology**

For the development of this narrative review on leishmaniasis as a model of chronic immunopathology, a comprehensive analysis of the scientific literature was conducted with the aim of examining the immunological mechanisms underlying parasite persistence, including immune evasion strategies, establishment of the intracellular niche, regulatory immune pathways, and failure of effective immune control. Emphasis was placed on host–parasite interactions, T cell dysfunction, regulatory T cell activity, and the immunological determinants of chronic infection.

The review was based on the consultation of well-established scientific databases, including PubMed, Scopus, and Web of Science, selected for their relevance in immunology, infectious diseases, parasitology, and translational medicine. Inclusion and exclusion criteria were applied to ensure methodological rigor and relevance. Articles published between 2020 and

2025 in English or Spanish were included if they addressed key topics such as immune evasion mechanisms of *Leishmania*, host immune responses, T cell exhaustion, regulatory immune networks, and immunopathological consequences of chronic infection. Studies lacking peer review, presenting incomplete immunological data, or containing duplicated content were excluded. Keywords used in the search strategy included: *Leishmaniasis*, *chronic immunopathology*, *immune evasion*, *T cell exhaustion*, *immunometabolism*, *host-directed therapy*.

The initial search yielded relevant sources, comprising original research articles, experimental studies, narrative and systematic reviews, and consensus documents from recognized scientific societies in immunology and infectious diseases. These sources were critically analyzed to extract data related to intracellular survival mechanisms, immune regulatory pathways, and the immunological basis of parasite persistence.

Artificial intelligence tools were used as complementary support for literature synthesis, thematic organization, and identification of conceptual relationships among studies. This approach facilitated coherent integration of complex immunological concepts and enhanced structural consistency across sections.

The analysis followed a qualitative and integrative approach. Findings were organized thematically to delineate key immunopathological mechanisms, identify convergent pathways of immune failure, and highlight translational implications for therapeutic strategies targeting host immune regulation. This methodology allowed for a structured and evidence-based overview of leishmaniasis as a paradigm of chronic immunopathology.

## **Biology of *Leishmania* and establishment of the intracellular niche**

Leishmania undergoes a complex life cycle transition from the promastigote form within the sand fly vector to the amastigote form inside the mammalian host. This transformation is a critical step for parasite survival and is driven by the need to adapt to the markedly different intracellular conditions encountered after transmission. Upon phagocytosis by host cells, the parasite is exposed to the acidic, nutrient-limited environment of the phagolysosome. Successful adaptation to this hostile compartment is mediated by specific transmembrane transporters that are essential for maintaining nutrient acquisition and ionic homeostasis, allowing the parasite to withstand metabolic stress and sustain intracellular viability [6]. Environmental sensing within the lysosome plays a decisive role in this process, with protein kinase A acting as a key molecular sensor that detects lysosomal cues and initiates the differentiation program leading to the amastigote stage [7].

Following transmission, cell invasion represents another pivotal step in the establishment of infection. Leishmania displays remarkable flexibility in its capacity to invade both professional phagocytes, such as macrophages, and non-professional phagocytes, including fibroblasts. This invasion is not a passive process but involves active manipulation of host cell endocytic pathways, enabling the parasite to enter cells through mechanisms that vary according to the infecting Leishmania species [8]. A central factor in this process is lipophosphoglycan, a major surface virulence molecule that facilitates parasite entry while simultaneously subverting host antimicrobial defenses. By interfering with host signaling and phagosome maturation, lipophosphoglycan enhances parasite internalization and early survival within host cells [9].

Once established within the intracellular compartment, Leishmania undergoes further adaptations to ensure long-term persistence and replication. The parasite actively induces

metabolic reprogramming of the host cell, including stimulation of mitochondrial biogenesis, thereby reshaping cellular metabolism to favor its own growth and energy demands [8]. In parallel, Leishmania modulates host cell death pathways to preserve the integrity of its intracellular niche. By inhibiting apoptosis and pyroptosis, the parasite prevents premature host cell death, ensuring a stable environment for sustained replication [10]. These adaptive strategies are tightly linked to lysosomal sensing mechanisms, in which temperature shifts and pH changes serve as essential signals regulating intracellular development and survival of the amastigote form [7].

### **The macrophage as a permissive niche**

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Leishmania establishes its intracellular niche within the phagolysosomes of macrophages, where it adapts to acidic conditions and temperature shifts that act as critical signals for differentiation into its intracellular amastigote form. Rather than being eliminated by this hostile environment, the parasite exploits lysosomal cues to initiate its developmental program. In this context, protein kinase A functions as a pivotal regulator, acting as a molecular gatekeeper of lysosomal signaling pathways that govern parasite differentiation and intracellular survival. The capacity of Leishmania to actively modulate the phagolysosomal environment is therefore fundamental to its ability to persist and replicate within host cells [7].

Beyond environmental sensing, Leishmania profoundly alters iron metabolism within infected macrophages. Iron represents a critical resource for both parasite survival and effective host immune responses, making its regulation a central aspect of host–parasite interaction. By competing with macrophages for iron availability, Leishmania disrupts key antimicrobial functions and favors conditions that support its intracellular persistence. This competition has prompted the exploration of novel therapeutic approaches aimed at restoring

macrophage antimicrobial capacity. In this regard, iron oxide nanoparticles have emerged as a potential strategy to reprogram macrophages from a parasite-permissive M2 phenotype toward a leishmanicidal M1 phenotype, thereby enhancing host defense mechanisms against intracellular parasites [11].

In parallel, *Leishmania* interferes with macrophage signaling pathways through the action of specific virulence factors that modulate kinase and phosphatase activities. Molecules such as eEF-1 $\alpha$  and LmjF\_36\_3850 alter intracellular signaling cascades, leading to changes in the production of key cytokines, including interleukin 12 and interleukin 10, which are central regulators of immune activation and suppression [12]. By skewing this cytokine balance, the parasite further weakens effective antimicrobial responses. Additionally, *Leishmania* exploits host regulatory proteins such as Yin Yang 1 within macrophages, co-opting host cell biology to promote its own survival and replication. Through this multifaceted manipulation of intracellular signaling networks, the parasite reinforces a cellular environment that favors immune evasion and chronic infection [13].

### **Evasion of innate immunity**

*Leishmania* parasites employ multiple strategies to subvert the microbicidal functions of phagocytic cells, particularly macrophages, as part of their capacity to establish persistent infection. A central mechanism of this immune evasion involves the inhibition of reactive oxygen and nitrogen species, which are key effector molecules in the innate immune response and are essential for the intracellular killing of pathogens. By attenuating the production of these reactive intermediates, *Leishmania* significantly reduces the leishmanicidal capacity of macrophages, thereby creating a permissive intracellular environment that favors parasite survival and long-term persistence [14].

In addition to impairing macrophage effector functions, *Leishmania* alters pathogen recognition mechanisms by modulating the expression of pattern recognition receptors on dendritic cells. These receptors are fundamental for sensing microbial components and initiating effective immune responses. *Leishmania donovani* has been shown to downregulate the expression of C-type lectin receptor 2 on dendritic cells, a change that compromises their ability to migrate to regional lymph nodes. As a consequence, antigen presentation to naïve T cells is impaired, leading to defective priming of adaptive immunity and delayed or insufficient immune activation [15].

Dendritic cell dysfunction is further reinforced by direct interference with signaling pathways that regulate their activation and maturation. *Leishmania donovani* suppresses dendritic cell activation through engagement of the TIM-3 receptor, resulting in reduced expression of costimulatory molecules and diminished capacity to stimulate antileishmanial T cell responses [16]. This inhibitory signaling contributes to an immune environment that favors tolerance rather than effective pathogen clearance. Moreover, the parasite induces the secretion of transforming growth factor beta from dendritic cells, a cytokine with potent immunosuppressive effects. Increased transforming growth factor beta production further inhibits dendritic cell function and migration, amplifying defects in antigen presentation and immune coordination [14].

### **Dysfunctional adaptive immune response**

*Leishmania* establishes its intracellular niche within the phagolysosome, an acidic compartment of macrophages that is essential for parasite survival and for the differentiation from promastigote to amastigote forms. Rather than being eliminated by this hostile environment, the parasite exploits the acidic conditions of the phagolysosome as a developmental signal. The low pH acts as a trigger for stage conversion, a process in which protein kinase A plays a central role by sensing lysosomal cues and initiating the

molecular programs required for amastigote differentiation [7, 17].

The acidic milieu of the phagolysosome also has important implications for ion homeostasis and drug accumulation. Low pH conditions facilitate the so-called ion trapping mechanism, which promotes the intracellular accumulation of leishmanicidal compounds such as quinolines within the phagolysosomal compartment [14]. At the same time, this environment profoundly influences iron metabolism, a critical factor for both host and parasite survival. *Leishmania* actively competes with macrophages for iron, a nutrient required for essential metabolic processes, thereby modulating macrophage activation status and influencing cellular phenotype [11].

Beyond metabolic adaptation, *Leishmania* interferes with key macrophage signaling pathways to further secure its intracellular survival. The parasite deploys virulence factors that modulate host kinase and phosphatase activities, leading to broad alterations in immune signaling cascades and dampening of effective antimicrobial responses [12]. Because of this signaling interference, macrophage polarization is shifted away from a pro-inflammatory M1 phenotype toward an anti-inflammatory M2 phenotype. This phenotypic reprogramming creates an intracellular environment that is more permissive to parasite survival and replication, reinforcing chronic infection and immune evasion [11].

### **Chronic inflammation and tissue immunopathology**

Persistent antigen exposure represents a central mechanism driving immune dysfunction in leishmaniasis. In visceral leishmaniasis, chronic infection is associated with progressive T cell exhaustion, a state characterized by reduced effector function and an impaired capacity to respond to antigenic restimulation. This phenomenon is largely driven by sustained parasite burden and prolonged infection, which

together promote continuous antigen presentation and the upregulation of inhibitory receptors on T cells, ultimately undermining effective immune control [18].

In parallel, *Leishmania* actively modulates inflammasome activation as part of its immune evasion strategy. By interfering with inflammasomal signaling pathways, the parasite is able to sustain its presence within the host while maintaining a state of low-grade but persistent inflammation. This altered inflammasome activity contributes directly to the chronicity of infection, as it allows continued immune stimulation without effective pathogen elimination [19].

The host immune response plays a dual and paradoxical role in this context. While inflammation is essential for parasite control, sustained activation of inflammatory pathways contributes significantly to tissue damage. Inflammasomal markers are consistently activated in both visceral leishmaniasis and post-kala-azar dermal leishmaniasis, reflecting an ongoing inflammatory response that targets parasite-containing tissues but also drives local pathology [19].

CD8 T cells exemplify this dual role of the immune response. Although these cells are critical for controlling intracellular pathogens, their effector functions can also promote immune-mediated tissue injury. Cytotoxic activity and pro-inflammatory cytokine production by CD8 T cells can exacerbate inflammation, particularly in cutaneous leishmaniasis, where excessive immune activation correlates with increased tissue damage [20, 21].

In cutaneous leishmaniasis, tissue damage is closely linked to a highly inflammatory microenvironment characterized by a pronounced CD8<sup>+</sup> T cell immunosenescence signature. Senescent T cells and natural killer cells contribute to the maintenance of chronic

inflammation, thereby intensifying lesion severity and impairing tissue repair mechanisms [21].

Similarly, in visceral leishmaniasis, prolonged immune activation and persistent parasite survival lead to significant damage to visceral organs. The combined effects of ongoing inflammation and sustained antigenic stimulation contribute to progressive pathology in organs such as the liver and spleen, underscoring the central role of host-mediated immune responses in disease progression [1].

### **Failure of immune control**

Functional depletion of T cells represents a central mechanism underlying the failure of immune control in visceral leishmaniasis. Chronic infection is associated with progressive T cell exhaustion, a state characterized by diminished effector capacity and an impaired ability to respond to antigenic restimulation. Sustained parasite persistence and prolonged antigen exposure drive this dysfunctional immune profile, ultimately weakening cellular immunity and favoring disease chronicity [18].

This phenomenon is particularly pronounced in patients coinfecting with visceral leishmaniasis and human immunodeficiency virus. In this population, profound immunosuppression is reflected by low CD4<sup>+</sup> T cell counts and high expression of inhibitory receptors such as programmed cell death protein 1 on T cells. These immunological alterations are strongly associated with disease relapse, underscoring the critical role of sustained T cell function in long-term disease control rather than solely clinical or parasitological factors [22].

Cytokine dysregulation further contributes to immune failure in visceral leishmaniasis. Cytokines play a dual and context-dependent role, with certain mediators such as interferon gamma and interleukin 12 promoting protective immune responses, while others, including interleukin 10 and transforming growth factor

beta, drive immunosuppression and disease progression [23]. Effective immune control depends on a delicate balance between these opposing signals. In visceral leishmaniasis and human immunodeficiency virus coinfection, the inability to restore antigen-specific interferon gamma production has been directly linked to relapse, highlighting the central importance of cytokine equilibrium in maintaining protective immunity [22].

Beyond immunological dysfunction induced by infection, host genetic and environmental factors also modulate susceptibility and disease outcome. Variations in genes involved in immune regulation can influence both the risk of developing visceral leishmaniasis and the effectiveness of the host immune response once infection is established [24]. Environmental factors, particularly coinfections such as human immunodeficiency virus, further exacerbate immune impairment, amplifying cytokine imbalance, accelerating T cell exhaustion, and increasing the likelihood of relapse [22].

### **Immunometabolism in chronic leishmaniasis**

Infection with *Leishmania* species induces profound metabolic reprogramming in macrophages, reshaping cellular energy pathways in a manner that supports parasite survival within host cells. This reprogramming is characterized by increased energy metabolism, with elevated glycolytic activity and enhanced oxygen consumption rates observed in infected macrophages. These metabolic changes create a cellular environment that accommodates the intracellular demands of the parasite while sustaining its long-term persistence [25].

Among these changes, modulation of the urea cycle, amino acid metabolism, and glutathione metabolism plays a critical role in determining the outcome of infection. These pathways are influenced by the presence or absence of parasite-derived arginase, which directly affects arginine availability and downstream nitric oxide

production, a key effector mechanism in macrophage-mediated parasite killing. Through these metabolic adjustments, *Leishmania* alters redox balance and nitrogen metabolism, thereby weakening antimicrobial responses and promoting intracellular survival [26].

A central feature of macrophage metabolic reprogramming during infection is a shift toward glycolysis. This glycolytic bias supports key antileishmanial functions of innate immune cells, including the production of reactive oxygen species, which are essential for pathogen control. In this context, glycolysis provides rapid metabolic intermediates required for immune activation, mirroring metabolic patterns observed in other activated immune cells such as neutrophils [27].

Oxidative phosphorylation remains important for maintaining cellular redox homeostasis by supplying nicotinamide adenine dinucleotide phosphate, which is required for effective oxidative bursts. Although oxidative phosphorylation does not contribute substantially to adenosine triphosphate generation in infected macrophages, its role in supporting reactive oxygen species production underscores the complexity of metabolic adaptations during infection [27].

Collectively, these metabolic adaptations facilitate immune evasion by *Leishmania*, enabling chronic infection and long-term persistence within the host. By reprogramming macrophage metabolism, the parasite dampens effective antimicrobial responses while maintaining host cell viability [28]. Importantly, experimental evidence indicates that pharmacological targeting of key metabolic pathways can significantly reduce parasite burdens, highlighting metabolic modulation as a promising therapeutic avenue to enhance host immune responses and limit parasitic persistence [29, 30].

## **Therapeutic implications**

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Conventional antiparasitic treatments for leishmaniasis face several important limitations that restrict their effectiveness and broader implementation. Widely used drugs such as antimonials, amphotericin B, and miltefosine are frequently associated with significant toxicity and adverse side effects, which limit their tolerability and complicate treatment adherence, particularly during prolonged therapeutic courses [30, 31].

In parallel, the emergence and spread of drug-resistant *Leishmania* strains have progressively undermined the efficacy of existing pharmacological options. Resistance mechanisms have been increasingly reported across endemic regions, leading to treatment failure and higher relapse rates, thereby complicating disease management and control efforts [30]. This growing resistance highlights the limitations of relying exclusively on parasite-targeted therapies. Furthermore, the high cost and limited accessibility of effective antileishmanial drugs pose additional barriers, particularly in resource-limited settings where leishmaniasis is most prevalent. Financial constraints, supply chain limitations, and the need for hospitalization for certain treatments significantly restrict equitable access to care [31, 32].

In response to these challenges, host-directed therapies have emerged as a promising complementary strategy. Rather than targeting the parasite directly, these approaches aim to modulate the host immune response to enhance intrinsic mechanisms of parasite control. By restoring or strengthening effective immune pathways, host-directed therapies offer the potential to limit infection while reducing selective pressure for drug resistance [33, 34].

An important aspect of this strategy involves drug repurposing. Anti-inflammatory and immunomodulatory drugs with well-characterized safety profiles are being explored for their potential to reduce disease severity and modulate pathogenic immune responses in

leishmaniasis. The use of such agents may accelerate therapeutic development while minimizing safety uncertainties associated with novel compounds [33]. In addition, network-based approaches have been employed to identify critical host cell targets that are essential for parasite survival. By mapping host–parasite interaction networks, these methodologies facilitate the identification of existing drugs capable of modulating host functions exploited by *Leishmania*, thereby opening new avenues for therapeutic intervention [34].

## Conclusion

The ability of *Leishmania* to establish and maintain a stable intracellular niche represents the central axis of its chronic pathogenicity. Adaptation to the acidic phagolysosomal environment, sensing of lysosomal cues through mechanisms such as protein kinase A activation, and manipulation of host metabolic and cell death pathways allow the parasite not only to survive but also to differentiate and replicate persistently within host cells. These biological adaptations transform an otherwise microbicidal compartment into a permissive environment, laying the foundation for long-term infection.

The immunopathology of leishmaniasis arises from a complex interplay between immune evasion and sustained inflammatory activation. While *Leishmania* suppresses key components of innate and adaptive immunity including reactive oxygen and nitrogen species production, dendritic cell activation, and effective macrophage polarization persistent antigen exposure drives progressive T cell exhaustion and profound cytokine dysregulation. This imbalance results in an immune response that is insufficient to eliminate the parasite yet sufficiently active to promote chronic tissue damage in both cutaneous and visceral disease.

Recognizing leishmaniasis as a model of chronic immunopathology has direct therapeutic implications. The limitations of conventional antiparasitic treatments, together with the

emergence of drug resistance, underscore the need for complementary host-directed strategies. Accumulating evidence on immunometabolism, immune regulation, and host–parasite interaction networks support the development of host-targeted therapies and drug repurposing approaches aimed at restoring immune control, mitigating pathological inflammation, and ultimately limiting parasite persistence.

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