



IMMUNOLOGICAL ASPECTS OF LEISHMANIASIS: A REVIEW ON THE LATEST DEVELOPMENTS

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ARTICLE HISTORY	ABSTRACT
Received on: 24-05-2026 Revised on: 14-06-2026 Accepted on: 07-08-2026 Keywords: Covering tissues, acute besides chronic wounds, and helical healing *CORRESPONDING AUTHOR Ihsan K. A. Alkardhi	Leishmaniasis is a vector-borne disease of ancient origin caused by protozoan parasites of the genus <i>Leishmania</i> and transmitted by female phlebotomine sand flies, with an estimated 1.7 to 3 million new cases and approximately 20,000 deaths each year, concentrated in poor rural and semirural communities. Unlike many other vector-borne infections, <i>Leishmania</i> does not establish a self-limiting infection in the vertebrate host: it escapes the innate response and persists within a tissue-resident macrophage reservoir, producing a clinical spectrum that extends from asymptomatic carriage to cutaneous, mucosal and visceral disease. This review synthesises current understanding of the immunological basis of that spectrum. It follows the response from the moment of inoculation sand fly saliva, complement deposition, the early neutrophil influx and phagocyte uptake through dendritic-cell priming to the polarisation of CD4⁺ T-helper subsets, and examines how the Th1/Th2 balance, together with Th17 and regulatory T cells, separates control of infection from progressive disease. Macrophage activation states, the tissue-specific immune microenvironments of skin and mucosa, and species- and strain-specific evasion strategies are considered in turn, alongside the genetic and epigenetic determinants that modulate susceptibility. The review then examines the translation of this knowledge into practice through immune-based diagnostic biomarkers, vaccine strategies directed at immune pathways, and immunomodulatory therapies given alongside conventional drugs. Persisting gaps are identified, in particular the absence of a licensed vaccine for visceral leishmaniasis and the lack of a gold-standard laboratory method for diagnosis. Keywords: Leishmaniasis; <i>Leishmania</i>; innate immunity; T-helper polarisation; macrophage activation; immune evasion; immunodiagnostics; vaccine development.

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I. INTRODUCTION

Leishmaniasis is a communicable disease of ancient origin caused by protozoan parasites of the genus *Leishmania* of the family Trypanosomatidae. It is a vector-borne infectious disease transmitted by the female phlebotomine sandflies and is mainly found in poor, rural or semirural communities. The World Health Organization estimated that leishmaniasis causes 1.7 to 3 million new cases worldwide each year and approximately 20,000 deaths. The infection is endemic across the tropics, the subtropics and the Mediterranean basin, and its geographical range continues to widen as the distribution of competent

sand fly vectors shifts [3]. Transmission begins when an infected female sand fly deposits metacyclic promastigotes into the dermis during blood feeding; the parasites are then taken up by resident phagocytes and convert into amastigotes that replicate within the phagolysosome, a compartment that is ordinarily hostile to intracellular microorganisms [9,10]. Because this intracellular niche is also the principal effector cell of the host, the outcome of infection is determined largely by the quality of the immune response that the parasite elicits rather than by parasite burden alone [8,17]. Disease caused by different *Leishmania* species can present with multifocal cutaneous leishmaniasis (MCL), mucosal leishmaniasis (ML), and visceral

leishmaniasis (VL), often leading to substantial disability or disfiguring after primary cutaneous lesions. The clinical spectrum therefore extends from asymptomatic carriage and self-healing lesions to progressive, disfiguring or fatal disease, and the same species may give rise to different syndromes in different hosts [6,14]. Mucosal involvement remains one of the most devastating forms of leishmaniasis that threatens the life of the patient, especially in patients with concurrent HIV infection [1]. The unique combination of immune evasion strategies developed by the *Leishmania* parasites underlies the diversity of clinical manifestations of leishmaniasis [2–4]. Despite decades of investigation, no licensed human vaccine exists for any form of the disease, chemotherapy still depends on a small number of toxic compounds against which resistance is emerging, and no single laboratory method serves as a diagnostic gold standard [44,48,59]. This review therefore brings together current evidence on the immunology of leishmaniasis: it follows the response from the moment of inoculation through innate recognition and macrophage activation to the polarisation of CD4⁺ T-helper subsets, considers the tissue-specific immune microenvironments of skin and mucosa together with the species- and strain-specific evasion strategies operating within them, and then examines how this knowledge is being translated into immune-based diagnostics, vaccines and immunomodulatory therapies.

2. OVERVIEW OF LEISHMANIASIS IMMUNOPATHOLOGY

Unlike other vector-borne diseases such as malaria, leishmaniasis transmission does not establish a self-limiting infection in the vertebrate host. Instead, *Leishmania* escapes the innate response, establishing a persistent and asymptomatic infection in a tissue-resident macrophage reservoir [1]. *Leishmania*-specific CD4Th1 and CD8T cell responses are responsible for effective control of these asymptomatic infections, while the presence of separate leishmania-specific CD4Th2 or CD4Th17 cell responses prevents CD4Th1 induction and leads to pathogen dissemination. This Th2 paradigm-finding has been validated in leishmania-coinfected patients and lesions, showing that parasite transport occurs from infected to naïve macrophages in lesions prior to T-cell help and acting at the same time as a coinfection in the asymptomatic reservoir. It also provides insight into the delayed development of lesions after cutaneous exposure before the first detectable IL-4 response. Thus, the picture of the *Leishmania*-immunity has emerged, where each stage of infection survives specific immunity. At cutaneous stages, a common profile is Th2 and Th1. At visceral stage, a Th2 profile appears. At mucosal lesion, a profile blends both Th1 and Th2 together [5–8].

Leishmania differentiates its stage and tissue tropism restraining the host's large repertoire of immune responses employing sophisticated immune-evasion

strategies once entered at each specific tissue. Upon delivery to the dermis by infected sandflies, *Leishmania* introduces a quiescent setup with infection spreading from cell to cell. Many of the existing known immunobiology of *Leishmania* applies across species and most of them reside on early stage of infection, taking the pathogen as undifferentiated *L. major* amastigote [5–10].

3. INNATE IMMUNE RESPONSES TO LEISHMANIA

An essential step in leishmaniasis pathogenesis is the entry of the parasite, which can occur through different routes, depending on the species and strain involved. In the case of *L. major* and *L. braziliensis*, which cause cutaneous and mucosal leishmaniasis, transmission typically occurs through the skin. Other species capable of inducing visceral leishmaniasis, such as *L. infantum* and *L. donovani*, can also enter through the skin, but the disease can develop following oral ingestion via the gut or through the conjunctiva. Furthermore, trypanosomatids can be transmitted via transfusion in cases where they are present in the blood [1,2,6,10,11].

Leishmania is inoculated alongside sand fly saliva, which promotes inflammation and increases leukocyte recruitment to the site of infection. The parasite is rapidly taken up by professional phagocytes, including macrophages, dendritic cells, and neutrophils. Upon internalisation, it undergoes morphological differentiation from promastigotes to amastigotes and survives intracellularly within phagolysosomal compartments by modulating innate and adaptive immune responses. The complement system plays a key role in phagocyte recruitment to the site of entry and in parasite uptake. The lipophosphoglycan-rich coat of *Leishmania* protects against complement-mediated lysis; nevertheless, complement component 3 is rapidly deposited on the surface, and opsonisation promotes phagocytosis through C3 receptors on macrophages, neutrophils, and dendritic cells. Other mechanisms implicated in parasite dissemination and entry into phagocytic cells include the production of metalloproteases and sphingomyelinases by *Leishmania*, modification of the actin cytoskeleton by salivary proteins and parasites, and parasite-induced extrusion of the infected cell [9,12–15]. These early events, and the factors that modify them, are summarised in Figure 1.

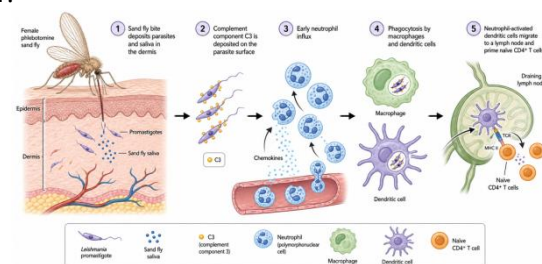


Figure 01: Route of infection and the early innate response to *Leishmania*. Parasites deposited during the

sand fly bite meet complement and an early neutrophil influx before uptake by macrophages and dendritic cells, after which neutrophil-activated dendritic cells prime the CD4⁺ T-cell response [9,26–28].

3.1. Pattern Recognition and Phagocyte Activation

Mammalian innate immune responses constitute the 1st line of defence against *Leishmania* transmission from the sand fly bite site to target organs [16]. Rapid phagocytic cell recruitment is directed by sand fly saliva, which augments inflammation and Th2 immune responses [1], while parasite-induced macrophage activation modulates leishmanial replication. Early influx of neutrophils and subsequent monocyte recruitment at the bite site is orchestrated by parasite-induced, neutrophil-attracting chemokines such as CCL3 and/or the complement fragment C5a. Arrival of neutrophils precedes that of macrophages by several hours, yet *Leishmania* rapidly localize to macrophages. Despite resistance, mice lacking macrophage chemokine receptor 2 (CCR2) or granulocyte-monocyte progenitors over-recruit neutrophils and display similar disease progression compared with wild-type mice; additional monocyte recruitment contributes to an enhanced inflammatory response and neutrophil clearance [14,17].

3.2. Macrophage Activation States and Microbicidal Mechanisms

Leishmania species replicate strictly within professional phagocytes, mainly dermal macrophages, enabling them to exploit the host's immune detection and clearance machinery. These parasites are able to evade immunoediting and exploit the immunogenic potential of specific antigens, thus producing a disease spectrum from asymptomatic to generalized skin lesions to tissue-disseminated visceral leishmaniasis. Macrophages are exposed continuously to environmental cues, which condition differential activation states in line with immunological experience. Macrophage function during *Leishmania* infection ranges from pro- to anti-inflammatory, directly influencing disease outcome [18]. Although classically activated macrophages (M1) generated by exposure to Th1 cytokines produce superior microbicidal effector mechanisms, Th2-conditioned macrophages (M2) are also able to restrict *Leishmania* proliferation in human and murine species. Immunoregulation during *L. braziliensis* and *L. infantum* infection is mediated by alternatively activated M2 macrophages that favor parasite development and overt pathology [19]. Such polarization is not limited to macrophages and extends to the wider inflammatory milieu, involving the orchestrated interplay of distinct cell types and mediators and leading to a spectrum of clinical manifestations [6,9,12].

The heterogeneous nature of macrophage responses has required the definition of those cellular and microenvironmental signals that establish and sustain specific activation states. CD40 and IL-4 have emerged as essential mediators conditioning M2 macrophage activation during *L. braziliensis* infection and

independently of IL-10 production. IL-4 signals recruit specialized epigenetic modifiers, such as the homeodomain protein Meis1, which cooperate with the transcription factor STAT6 to promote the transition from a stable to a more labile M1-like state even in unexposed macrophages. This plasticity is further supported by microRNA let-7 and concomitant loss of miR-155. Ruddiness–dark pigmentation of *L. braziliensis* skin lesions (associated with remodelling of the epidermal–dermal junction) correlates with enhanced IL-10 production along with increased macrophage expression of an apical Ca²⁺-activated K⁺ channel TSEN4. This channel is expressed in parasitized *L. braziliensis* skin lesions, facilitating IL-10 secretion, whereas THH-forward *L. major* isolates do not generate these late lesions when injected in BALB/c mice, underscoring how simple reinfection events can accelerate and aggravate the disease [12,20–22].

In strong CD8⁺ T cell-responder mouse strains, the tissue-specific ability of *L. mexicana* to drive the establishment of heterogeneous pockets including macrophage–neutrophil co-infiltrates stimulates recruitment of regulatory T cells. Counterintuitively, these nested lesions remain uncontrolled and can sustain transmission as lesions expand. A distinctive advantage of *L. tropica* is its ability to elicit M1 amplification following phagocytosis. Co-expression of inflammatory responses shielding *L. longifloccum* and *M. tarentolae* still maintains sufficient virulence to foster skin hyperplasia. The full advantage of relative latency in *L. donovani*—wherein IL-10 CD8 permeation takes centre stage—is further amplified through transient co-existence alongside *Leishmania* phylloform, which additionally interferes with *L. amazonensis*-migration [23]. Figure 2 contrasts the two activation states and their consequences for the parasite.

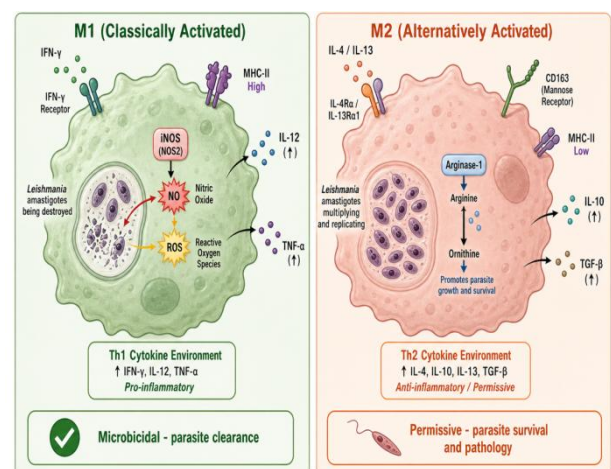


Figure 02: Macrophage activation states during *Leishmania* infection. Classically activated (M1) and alternatively activated (M2) macrophages differ in microbicidal capacity and in their consequences for parasite survival and pathology [18–22].

3.4. Neutrophils and Early Host Defense

Upon sand fly bite, *Leishmania* parasites are deposited cutaneously within saliva-enriched pools. In the mammalian host, resident tissue macrophages or dendritic cells (DCs) are the first cells to ideally capture *Leishmania* following the sand fly bite, which resembles the natural transmission route [24]. Within hours, neutrophils infiltrate and abrogate capture by tissue macrophages or DCs. Consequently, they become a predominant cell population to encounter parasites [25]. Neutrophils, as first responders, are therefore crucial in initial defense against *Leishmania*. They contribute actively to innate immunity through distinct mechanisms. Cytokines like IL-10 and TNF, released to the microenvironment, also promote Th2 (anti-inflammatory) and Th17 (inflammatory) responses that shape long-term adaptive immunity, suggesting a regulatory role beyond classical immune response. *Leishmania* parasites induce neutrophils to release chemokines and monocyte-attracting factors such as CCL2, CCL3, and CCL4 further modulating the innate response. Thus, neutrophil-activated DCs engage in cross-presentation, a defined process occurring at the early stage of *Leishmania* infection. Neutrophils also enhance parasite killing via NETs, the formation of which increases in infected tissues and correlates with protective immunity [9,26–28].

4.1. T helper Cell Subsets in Leishmaniasis

T helper cell subsets are an important part of the adaptive immune response to *Leishmania* infection, and they can determine whether host immune responses will lead to resistance or reactivation of latent infection [29]. To govern a robust T-helper-respon, *Leishmania*-specific antigen presentation by activated dendritic cells to naive CD4⁺ T cells is required. Once differentiated, helper T cells may drive distinct immune responses, modulating their phenotype according to the antigenic stimulation. Th1 cells play a crucial role in the control of the local *Leishmania* infection, based on the production of IFN- γ , which activates macrophages to eliminate intracellular parasites. Acquired resistance to further challenges is sustained in the presence of *Leishmania*-specific T helper-dependent CD8⁺ T cell responses. In addition, parasites induce Th1 and Th2 responses in different models of human cutaneous leishmaniasis. An increase in Th17 cells is also observed in some individuals, with IL-17 involved in tissue damage and immune-regulatory activity. Because of the importance of the balance between Th1/Th2 and Th17 responses, the characterization of the T helper subset involved in other forms of leishmaniasis visceral leishmaniasis, mucosal and general cutaneous leishmaniasis, the atypical manifestation of cutaneous leishmaniasis would provide relevant information useful for the development of therapeutics and vaccines. A very similar review shows that the distinction between susceptibility and resistance hinges on the relative contribution of Th1 and Th2 responses [30]. In susceptible hosts, *Leishmania* promotes cytokine profiles associated with Th2 responses. Such profiles

obscure Th1 polarization by limiting the availability of APC-derived IL-12 and by acting on the strength of the Th1 response after the establishment of the infection. In resistant hosts, the capacity of *Leishmania* to steer the immune response towards the Th2 pathway is diminished. These somewhat contradicting views sharpen the focus on Th1 and Th2 responses and their cross-talk rather than on protective effector T-cell subsets per se. Mice are viewed as resistant when they activate *Leishmania*-specific effector T cells strong enough to localize the infection. At the heart of this multilineage view of leishmaniasis immunobiology, several unanswered questions arise regarding the nature of *Leishmania* antigens, the spatiotemporal sequence of antigen presentation, and the determinants of Th1 or Th2 preferential commitment [14,17,31]. Figure 3 summarises the four subsets, their signature cytokines and the outcome associated with each.

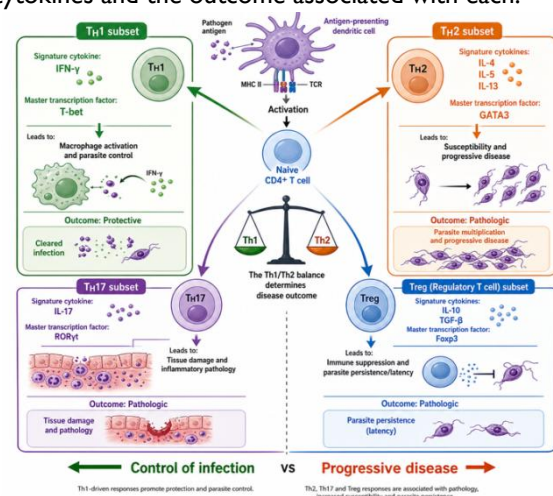


Figure 03: CD4⁺ T-helper polarisation and its consequences. The Th1/Th2 balance, together with Th17 and regulatory T cells, separates control of infection from progressive disease and determines whether latent infection is reactivated [29,30].

4.2. Cytokine Networks and Their Effects on Disease Outcome

Leishmania parasites possess remarkable capacity to evade host immune responses, leading to diverse clinical manifestations in humans. Cytokines are vital determinants of the outcome of infection, influencing the balance between pro- and anti-inflammatory immune responses. Different haematogenous or lymphatic tissue, where *Leishmania* parasites persist in different clinical cases, might also improve understanding of the very early immune responses and their effects on different outcomes. Immature dendritic cells (DC) and DC subsets exhibit differential capacity to interact with and respond to different *Leishmania* species. Time-course studies show that, in non-susceptible mice, infection of peripheral dendritic cells (pDC) by the infective metacyclic form of *Leishmania* major transiently stimulates several innate immune pathways, including Interferon-regulatory factor (IRF)/Interferon- α (IFN- α) and NF- κ B, that peak at the first day post-infection. The pro-inflammatory milieu of

tolerised lesions, pro-IL-1 β in particular, may provide the impetus for the subsequent dissemination of secondary Leishmania major infection to the systemic compartment in the susceptible host. Myeloid/epithelial mixture-activated dendritic cells fail to appropriately regulate the transition of a primary Leishmania major effector T-cell response to a memory state in a systematic manner; secondary flow-restoration analysis reveals evident differences between cutaneous leishmaniasis and Visceral Leishmaniasis (VL). Leishmania parasites, constantly prepare population genetic markers, such as gross rearrangement in the role of genomic or mitochondrial mutator along the population centre traversal distance well beyond the detection level [5,7,17,26,32]. Table I lists the principal cytokines and chemokines and their reported association with outcome.

Table 01: Cytokines and chemokines shaping the outcome of *Leishmania* infection, as discussed in sections 3 and 4 of this review.

Mediator	Principal source	Immunological effect	Reported association with outcome	Ref.
IL-12	Antigen-presenting cells	Drives commitment of naive CD4 ⁺ T cells to the Th1 lineage	Reduced availability obscures Th1 polarisation in susceptible hosts	[30]
IFN- γ	Th1 cells	Activates macrophages to eliminate intracellular parasites	Control of local infection; acquired resistance to re-challenge	[29]
TNF	Neutrophils, activated macrophages	Pro-inflammatory conditioning of the lesion milieu	Released together with IL-10 into the early microenvironment	[26–28]
IL-4	Th2 cells	With CD40, conditions M2 activation independently of IL-10; recruits STAT6 and Meis1	Susceptibility and progressive disease	[20–22,30]
IL-10	Th2 and	Suppresses	Parasite	[12,

	regulatory T cells, M2 macrophages	effector function; secretion enhanced within <i>L. braziliensis</i> lesions	persistence, latency and tissue repair	20–23]
IL-17	Th17 cells	Tissue damage combined with immune-regulatory activity	Increased in a subset of infected individuals	[29]
pro-IL-1 β	Tolerised lesions	Sustains the pro-inflammatory drive	Dissemination of secondary <i>L. major</i> infection in susceptible hosts	[32]
IFN- α / IRF, NF- κ B	Plasmacytoid dendritic cells	Transient early innate activation peaking one day post-infection	Observed in non-susceptible mice	[32]
CCL2, CCL3, CCL4	Neutrophils	Recruit monocytes to the site of infection	Modulates the innate response and later adaptive priming	[26–28]

5. TISSUE-SPECIFIC IMMUNOLOGY AND RESERVOIRS

An important and largely neglected aspect of leishmaniasis is the influence of the immune microenvironment on disease progression and pathogenesis. Several *Leishmania* species are able to establish infection and cause disease in diverse tissues and organs, including the skin, lungs, liver, and bone marrow. Different tissues exert preferential influence on the distribution and activity of a variety of receptors, proteins, and cytokines that regulate the immune response [1]. Consequently, significant differences in immune parameters and regulators also exist between subclinical skin and other cutaneous leishmaniasis (CL) lesions, such as mucosal leishmaniasis or kinetic disorders in visceral leishmaniasis and post-kala-azar dermal leishmaniasis [8,17,33,34].

In cutaneous leishmaniasis, the skin immune system shapes the immune response at the site of infection, and a distinct skin immune signature is associated with CL lesions. Similarly, visceral leishmaniasis, the most severe form of leishmaniasis, is CCL2-dependent in

humans, rabbits, and mice, and this tissue-specific regulation is affected by *Leishmania* infection. Following systemic *L. donovani* infection, CCL2 knockout mice have decreased *Leishmania* loads in the liver, whereas bone marrow-derived macrophages retain CCL2 expression and are important for *L. donovani* dissemination and drug toxicity. In mice, *L. donovani* pre-infection of the skin induces a different T cell signature in visceral tissues compared with systemic infection, and T cell clustering before systemic *L. donovani* infection leads to increased *Leishmania* loads in visceral tissues [10,11,28].

5.1. Skin Immune Microenvironment in Cutaneous Leishmaniasis

Leishmania parasites are transmitted by the bite of infected female phlebotomine sandflies. Within the vector, the parasites replicate as flagellated promastigotes. Transmission occurs when the insect feeds, injecting saliva that inhibits hemostasis and facilitates the entry of parasites. Thus, *L. major* infection begins with this initial dermal inoculation during the blood-meal process. The development of leishmaniasis depends on the immune response elicited and the subsequent balance of pro-inflammatory and anti-inflammatory responses. Innate and adaptive immune responses are closely linked during leishmaniasis, with early cytokine production by innate immune cells influencing the development and polarization of CD4⁺ T-cell and B-cell responses. A better understanding of local immune responses to *L. major* in human cutaneous leishmaniasis (CL) may facilitate the identification of hitherto unknown mechanisms, cell types, or mediators that could serve as new targets for treatment. Discovery of such factors would be timely, as current treatments are expensive, frequently fail, do not target the host response, and can induce drug toxicity. Immunotherapies intentionally aimed at generating a less pathogenic immune response to *L. major* have been proposed to enhance the efficacy of standard treatments or reduce the required duration of drug administration. Early findings suggest that additional drugs designed to neutralize cytokines such as IL-4, IL-13, or IL-17 (e.g. Dupilumab, an IL-4R α blocker; secukinumab, an anti-IL-17 monoclonal antibody) may constitute promising candidates for adjunctive therapy. The skin immune microenvironment represents a fundamental aspect for the development of better therapeutics for leishmaniasis [26,35,36].

5.2. Mucosal Immunology in Visceral Leishmaniasis

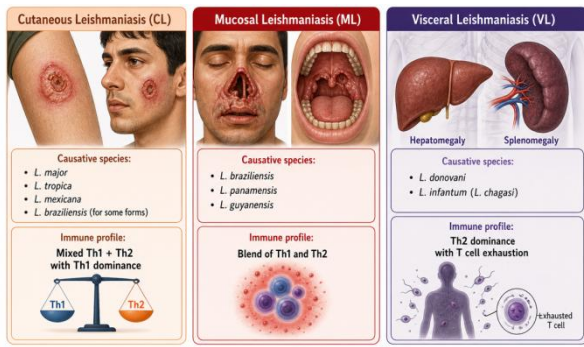
In humans and mice, the mucosal sites critically regulate *Leishmania* infection and the pathogenesis of visceral leishmaniasis (VL) is modulated by the immune responses at these sites [37]. Infection occurs through skin bites from infected sandflies; transmigration to the nasal epithelium and mucus-associated tissues ensures establishment of *Leishmania* in the host and influence dissect host immunity [5,13,38].

Leishmania donovani in experimental models enters through the nasal route and develops in the nasal-associated lymphoid tissues (NALT) and the draining cervical lymphnodes [1]. During early infection, macrophages are rapidly infected, although CD4⁺ and CD8⁺ lipid antigen T cells and CD4⁺/CD8⁺ non-MHC restricted T cells are a major source of protective IFN- γ to control parasite burden. The infection establishes URTI, resulting in extensive damage to the epithelial layer and DIF with a global decrease of total nasal RNA and dysregulation of >4,500 genes. The immunomodulation are different from cutaneous leishmaniasis, while they rely on the NALT as reservoir during skin-bite infection. Mucosal immunity configuration might play a crucial role in the transition from a non-fatal URTI to fatal VL [22,38].

6. IMMUNOPATHOGENESIS ACROSS LEISHMANIA SPECIES

Immunopathogenic mechanisms elicited by *Leishmania* encompass temporally and spatially distinct host immune responses modulated by infecting parasite species and strains. Ongoing genetic and epigenetic investigations continue to characterize biological traits defining distinct lineages, promoting perspective on parasite-driven immune control. Considerable variability, including species-specific differences and strain-dependent changes in pathogenicity within *L. infantum*, influences disease severity and clinical presentation. The relevance of species- and strain-specific immune-evasion strategies in *L. braziliensis*, *L. guyanensis*, and *L. panamensis* underlines the necessity for simultaneous investigations of immune-control mechanisms applied by different *Leishmania* species [13,14,33,39–41].

Delayed-type hypersensitivity, generally recognized as a polarized T cell-dependent immune response pathway, does not entirely comprehend the predominant associations between cutaneous leishmaniasis (CL) and individual *Leishmania* species. Culmination of protective immunity to the infecting parasite *L. braziliensis* demands a CD4⁺ T cell-dependent immune pathway in hosts unable to control the disease during the acute phase of infection, despite rapid peripheral containment of the infecting organism. Mucosal leishmaniasis relates directly to leukocyte immune control and to both the *L. braziliensis* and *L. panamensis* parasites, operating through at least a CD4⁺ T cell-independent route. Diverse immune-monitoring systems, including CD4⁺ and CD8⁺ T cells, natural killer (NK) cells, and innate lymphoid cells, adapt to the nature of the infecting organism to govern protective and pathological immunity within skin, other tissues, and the draining lymph nodes. Regulatory T cell augmentation emerges as a critical factor directly counteracting immune resistance while promoting tissue repair during the infection process [1,21,42,43]. Figure 4 maps the clinical forms to their causative species and reported T-helper profiles.



Th1: T helper 1; Th2: T helper 2; CL: Cutaneous Leishmaniasis; ML: Mucosal Leishmaniasis; VL: Visceral Leishmaniasis.

Figure 04: Clinical forms of leishmaniasis and their immune correlates. Causative species and the T-helper profile reported at each site of disease; a common profile of Th2 with Th1 is described at cutaneous stages, a Th2 profile at the visceral stage, and a blend of both at mucosal lesions [5–8,21].

6.1. Species- and Strain-Specific Immune Evasion Strategies

Various *Leishmania* species display unique strategies to evade host immunity [1]. These strategies may differ not only across species but also within strains of a same species. For instance, *Leishmania major* impairs dendritic cell (DC) maturation primarily through the induction of IL-10, whereas *Leishmania braziliensis* induces an IL-10-independent signalling cascade involving cytosolic phospholipase A2 activation and PGE2 production. Moreover, *Leishmania donovani* resilience to reactive oxygen species produced by activated macrophages is dictated by a single-nucleotide polymorphism in the gene encoding the histone H3 variant H3A. These species- and strain-specific differences present a challenge for the development of an effective vaccine against leishmaniasis, especially in view of the recent demonstration that leishmaniasis is a multi-species disease [44,45].

6.2. Genetic and Epigenetic Factors Modulating Immunity

Some *Leishmania* species are associated with more severe forms of leishmaniasis. Genetic and epigenetic factors such as the presence of mitochondrial DNA have been shown to affect susceptibility. Other factors, such as socioeconomic status or exposure to anti-inflammatory cells in early life, promote the development of the more severe Visceral Leishmaniasis rather than the mild Cutaneous Leishmaniasis. Together with parasites-encoded evolutionary adaptations, these genetic and epigenetic determinants have fuelled the current interest in the genetic predisposition to leishmaniasis and the significant role played by epigenetic mechanisms [1,2,46,47].

7. IMMUNODIAGNOSTICS AND IMMUNE-BASED THERAPEUTICS

Leishmaniasis diagnosis currently relies on clinical, epidemiological, and laboratory data, with the lack of a gold-standard lab method being a major limitation. False negatives can delay treatment and maintain

reservoirs, perpetuating the cycle. Rapid diagnostic methods, effective, safe, affordable, and easy to administer, are urgently needed. Immunological tools are widely used for screening and definitive diagnosis but can have limitations such as cross-reactions and reduced accuracy in immunosuppressed patients. Combining techniques like immunochromatographic tests and recombinant antigen assays improves specificity and sensitivity. Molecular biology approaches are also employed, especially in reference centres, to enhance differential diagnosis accuracy [2,48].

Immunotherapy could be crucial for developing new treatments or improving current ones for leishmaniasis, which is an immune-mediated disease. TLRs play a central role in initiating the anti-leishmanial immune response; using TLR agonists or antagonists may enhance treatment efficacy. For example, combination treatment with a TLR2 ligand improved miltefosine efficacy, promoting a Th1 immune response. Topical Imiquimod (a TLR7 ligand) combined with antimony reduced healing time and improved wound repair. Paradoxically, a TLR4 pathway inhibitor, pentoxifylline, combined with antimony, also improved healing and reduced relapse rates. TLR stimulation is also important in vaccine development, with TLR4 and TLR9 ligands used as adjuvants showing promising results in animal models. TLR4 agonist ONO-4007 boosted parasite clearance, and CpG (a TLR9 agonist) improved vaccine efficacy by promoting IL-12 production. Combining TLR4 and TLR9 agonists demonstrated synergistic effects, enhancing vaccine responses. Mice immunized with recombinant LRV capsid and CpG showed protection against increased pathology [1,17,49,50].

7.1. Diagnostic Biomarkers Linked to Immune Responses

Diagnostic Biomarkers Linked to Immune Responses
An indirect biomarker of cutaneous leishmaniasis (CL) is the host's biological reaction induced by leishmanial infection, whereas the most direct biomarker is parasite detection in tissues, for which molecular diagnostic methods with high rapidity, sensitivity, and species discrimination are available [51]. Delayed-type hypersensitivity, evaluated with the Leishmanin skin test, indicates prior exposure to the parasite and allows differentiation of asymptomatic cases. Disease outcome hinges on the immune response, particularly cell-mediated immunity. Accordingly, cytokine profiles and T-cell subpopulations constitute additional immune-based candidate biomarkers of CL [14]. In the context of visceral leishmaniasis (VL), elevated plasma monocyte chemotactic protein 1 (MCP-1) production in response to stimulation with soluble *Leishmania* antigen from infected hosts correlates with a cellular immune response against *L. infantum*. Thus, MCP-1 constitutes a potential surrogate, complementary to the Leishmanin skin test, for assessing cellular immunity to *Leishmania* in canine and human asymptomatic VL [52]. Moreover, the quantity of MCP-1 released serves as a potential basis for simple field tools to guide

control efforts [48,52]. Table 2 summarises the immune-based diagnostic markers and assays discussed above.

Table 02: Immune-based diagnostic biomarkers and assays for leishmaniasis, with their reported value and principal limitations.

Biomarker or assay	Immunological basis	Clinical form	Reported value and limitation	Ref.
Parasite detection in tissue	Direct detection of the organism by molecular methods	CL	The most direct biomarker; rapid, sensitive and able to discriminate species	[51]
Leishmanin skin test	Delayed-type hypersensitivity to parasite antigen	CL, VL	Indicates prior exposure and allows asymptomatic cases to be differentiated	[48,51]
Cytokine profiles and T-cell subpopulations	Cell-mediated immune response	CL	Candidate immune-based biomarkers, since outcome hinges on cellular immunity	[14]
Plasma MCP-1 (CCL2) after stimulation with soluble <i>Leishmania</i> antigen	Cellular immune response against <i>L. infantum</i>	VL, asymptomatic	In canine and human hosts, a surrogate complementary to the leishmanin skin test; the quantity released offers a basis for simple field tools	[52]
Rapid tests: immunochromatographic and recombinant antigen assays	Humoral response to defined antigens	CL, VL	Used for screening and definitive diagnosis; combining techniques improves specificity and sensitivity, but cross-reactivity and reduced accuracy in immunosuppressed patients persist	[2,48]

7.2. Vaccine Strategies Targeting Immune Pathways

Parasitic infections, including those caused by *Leishmania* species, affect millions of people worldwide. The lack of effective vaccines against most parasitic diseases, including leishmaniasis, with the notable exception of the crude vaccine against *C. parvum*, represents a major challenge in public health [1]. Among the various strategies currently in development to tackle leishmaniasis, considering one of the most pragmatic ideas existing strategies to augment the host immune response, which could complement conventional drug treatment could greatly facilitate broad investment. As mentioned earlier, the host immune response to leishmaniasis is extensively modulated by these parasites, and specific vaccines have been designed to exploit pre-existing immune responses instead of inducing new ones. Resistance to *C. parvum* occurs, by definition, in the presence of pre-existing immunity. The host response can therefore favour either a new immune response or the potentiation of an existing one [53–55].

Current vaccine development relies on the use of avirulent *Leishmania* strains, non-viable (killed or inactivated) forms of the parasite, defined components of *Leishmania*, various *Leishmania* DNA (multicistronic RNA and various plasmids) and several immune-modulatory co-adjuvants, including that favour Th2 responses which dominate active leishmaniasis. Furthermore, as highlighted throughout this review, the *Leishmania* parasite uses a variety of strategies to inhibit immune effector cells at a very early stage; perturbing these mechanisms without altering normal immunological pathways provides a formidable obstacle [56]. Moreover, live-attenuated pathogens rarely represent the best vaccine strategy against persisting or replicating pathogens, and the same is true for non-replicating particles. Furthermore, combinations of the naturally occurring adjuvants in *Leishmania* and the anti-inflammatory activities of the parasite create conditions highly unfavourable to any safe induction of the humoral and cellular T H1 and T H17 responses needed to clear these infections. Permitting the parasite to replicate allows the development of these vital immune effectors. Table 3 sets out these strategies alongside their principal obstacles.

Table 03: Vaccine strategies and immunomodulatory approaches directed at immune pathways in leishmaniasis.

Approach	Basis	Reported status or principal obstacle	Ref.
Live avirulent <i>Leishmania</i> strains	Attenuated organism retains the natural antigen repertoire	Live-attenuated agents are rarely the best strategy against persisting, replicating pathogens	[56]
Killed or inactivated whole parasite	Non-viable organism presented to the immune system	Non-replicating particles share the same limitation; replication appears necessary for the required effectors	[56]

Defined <i>Leishmania</i> components	Selected subunit antigens	Must overcome inhibition of immune effector cells at a very early stage of infection	[56]
DNA and RNA constructs	Multicistronic RNA and plasmid vectors driving endogenous antigen expression	Among the strategies currently in development	[56]
Immune-modulatory co-adjuvants	Redirects the response away from the Th2 profile that dominates active disease	Adjuvants naturally present in the parasite and its anti-inflammatory activity oppose the safe induction of Th1 and Th17 responses	[56]
Immunomodulatory therapy with standard drugs	Ranges from immune amplifiers to inhibitors	Protective in animal models when combined with standard drugs; particularly attractive for VL, for which no vaccine is available	[1,17,57,58]
Adjunct immunosuppressive therapy	Dampens pathological inflammation	Early clinical studies in VL reported increased relapse and the appearance of another form of disease; careful adjuvant selection is critical	[22,43,50]

7.3. Immunomodulatory Therapies and Adjunctive Treatments

The immune response during leishmaniasis is characterized by a strong Th1-type response associated with protection against *Leishmania* infections. Despite the evidence supporting the protective role played by Th1-type cells and pro-inflammatory cytokines against cutaneous (CL) or visceral leishmaniasis (VL), the treatment of leishmaniasis remains focused on killing the parasites for the most part. Different immunomodulatory therapies, ranging from immune amplifiers to inhibitors, have demonstrated protection in animal models when administered with standard drugs and could ensure a better control of leishmaniasis in combination with other therapies [1]. This approach appears particularly attractive for VL, the most severe form of the disease for which no vaccines are available yet [17,57,58].

Although systemic immunosuppression is observed in infected patients, it remains debatable whether adjunct therapies suppress the immune system or restore an immune response able to eliminate parasites. Early clinical studies in VL showed an increased incidence of relapses or the appearance of another form of leishmaniasis following treatment with concomitant immunosuppressors. In this context, a careful selection of adjuvants is crucial for desensitizing or re-programming the immune response involved in leishmaniasis and therefore limiting the probability of reactivation of the disease or cross-reactivity against other pathogens [22,43,50]. The immunomodulatory approaches are listed in the lower rows of Table 03.

8. CHALLENGES, GAPS, AND FUTURE DIRECTIONS

The same organism can trigger both visceral and cutaneous leishmaniasis in humans and animal reservoirs; different *Leishmania* species can also cause similar leishmaniasis forms in humans with different severity. Non-canonical Th1/Th2 T helper cells and other T effector cells, together with IL-10 regulatory cells of macrophages, dendritic cells, and T regulatory cells (Tr1 cells), are involved in leishmaniasis outcome

according to the *Leishmania* species, mouse strains/reactive, and genetic background. In addition to the biased Th subset the cytokine milieu and persistence of parasites predispose humans and hosts to autoimmunity, lymphoid sparsity, bacterial co-infections, tumours, and even COVID-19 aggravation [1]. Despite marked progress in understanding host immune response to *Leishmania* and parasite immune evasion strategies, existing therapies are outdated and no human vaccine is available [59]. There is no consensus on the best immunological correlates of protection that vaccine strategies against leishmaniasis should aim to induce [26,36,37,60].

9. CONCLUSION

Leishmaniasis remains a substantial public health concern worldwide, and the study of innate and adaptive immune responses to *Leishmania* parasites has been greatly intensified over the past decades, leading to significant advances in understanding the immunology of leishmaniasis. Immune evasion strategies of *Leishmania* parasites continue to be elucidated, and discoveries of additional immune-relevant biomarkers and mechanisms that influence leishmaniasis pathogenesis and immunology have greatly increased knowledge. Ongoing explorations of the profound influence of immune responses on parasite virulence, which complement detailed studies of immune response evolution, highlight the impact of parasite–host interactions on leishmaniasis pathogenesis. Immune responses triggered by leishmaniasis causative agents remain an active area of investigation with important implications for the design of more effective immunodiagnostic tests and therapeutic vaccines against this neglected disease. An integrated perspective on the current state of knowledge of the immunology of leishmaniasis, along with commentary on its diverse and evolving nature, can provide a comprehensive overview of changes in understanding over the past two decades and their implications for disease control.

10. FINANCIAL SUPPORT

None

11. DECLARATION COMPETING INTEREST

The authors have no conflicts of interest to declare.

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