# IMMUNOBIOLOGICAL ASPECTS OF MYCOBACTERIUM LEPRAE: A NARRATIVE REVIEW

# ASPECTOS INMUNOBIOLÓGICOS DE MYCOBACTERIUM LEPRAE: UNA REVISIÓN NARRATIVA

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## ABSTRACT

**Indroduction:** Mycobacterium leprae is an obligate intracellular pathogen responsible for leprosy, a neglected tropical disease with challenging diagnostic methods. Understanding the mechanisms underlying M. leprae's interaction with the host, survival, and dissemination is essential for elucidating its pathogenesis, identifying therapeutic targets, and advancing immunization strategies. **Methods:** This narrative review consolidates key findings on the bacterium's structure, molecular interactions with the host, immune evasion strategies, metabolism, replication, and in vivo dissemination. **Results:** Relevant original scientific articles published in indexed international journals were systematically selected, focusing on studies

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addressing the immunobiological aspects of M. leprae. Data extraction followed a standardized approach, capturing study design, variables analyzed, statistical methods employed, key findings, and identified limitations. **Conclusion:** The comprehensive insights provided here enhance our understanding of M. leprae's immunobiology, offering valuable perspectives to drive progress in the diagnosis, treatment, and prevention of leprosy. **Abbreviations:** AFB: acid-fast bacillus; LL: lepromatous-lepromatous; TT: tuberculoid-tuberculoid; BT: borderline-tuberculoid, BB: borderline-borderline, BL: borderline-lepromatous; CLRs: C-type lectin receptors; PG: contains peptidoglycans; AG: arabinogalactans; AM: as well as mycolic acids; LAM: lipoarabinomannan; LM: lipomannan; PIM: phosphatidylinositol mannoside, PDIM: phytocerol dimycocerosate lipids; PGL I: glycolipids such as phenolic glycolipid I; MIP: mannosylphosphatidyl-myo-inositol; ManLAM: mannose-LAM; PRRs: pattern recognition receptors; TLRs: Toll-like receptors; NLRs: NOD-like receptors; ADRP: adipose differentiation-related protein; pSLCs: proliferative Schwann cells; GLS: granulomatous lesions.

**Keywords:** Dissemination. Mechanisms of interaction. Mycobacterium leprae and survival.

## RESUMEN

**Introducción:** *Mycobacterium leprae* es un patógeno intracelular obligado responsable de la lepra, una enfermedad tropical desatendida con métodos de diagnóstico desafiantes. Comprender los mecanismos subyacentes a la interacción de *M. leprae* con el huésped, su supervivencia y diseminación es esencial para elucidar su patogénesis, identificar objetivos terapéuticos y avanzar en estrategias de inmunización.**Métodos:** Esta revisión narrativa consolida hallazgos clave sobre la estructura de la bacteria, sus interacciones moleculares con el huésped, estrategias de evasión inmune, metabolismo, replicación y diseminación in vivo.**Resultados:** Se seleccionaron sistemáticamente artículos científicos originales relevantes publicados en revistas internacionales indexadas, enfocándose en estudios que abordan los aspectos inmunobiológicos de M. leprae. La extracción de datos siguió un enfoque estandarizado, capturando el diseño del estudio, variables analizadas, métodos estadísticos empleados, hallazgos clave y limitaciones identificadas.**Conclusión:** Los conocimientos integrales proporcionados aquí mejoran nuestra comprensión de la inmunobiología de *M. leprae*, ofreciendo perspectivas valiosas para impulsar avances en el diagnóstico, tratamiento y prevención de la lepra. **Abreviaturas:** AFB: bacilo ácido-alcohol resistente; LL: lepromatosa-lepromatosa; TT: tuberculoide-tuberculoide; BT: tuberculoide-borderline; BB: borderline-borderline; BL: borderline-lepromatosa; CLRs: receptores de lectina tipo C; PG: contiene peptidoglicanos; AG: arabinogalactanos; AM: ácidos micólicos; LAM: lipoarabinomanano; LM: lipomanano; PIM: mannoside de fosfatidilinositol; PDIM: lípidos dimicocerosato de fitocerol; PGL I: glicolípidos como el glicolípido fenólico I; MIP: mannosilfosfatidil-mio-inositol; ManLAM: manosa-LAM; PRRs: receptores de reconocimiento de patrones; TLRs: receptores tipo Toll; NLRs: receptores tipo NOD; ADRP: proteína relacionada con la diferenciación adiposa; pSLCs: células de Schwann proliferativas; GLS: lesiones granulomatosas.

**Palabras-clave:** Diseminación. Mecanismos de interacción. *Mycobacterium leprae* y supervivencia.

## 1 INTRODUCTION

Leprosy, caused by Mycobacterium leprae, is one of the oldest known infectious diseases affecting humanity. The pathogen is an obligate intracellular mycobacterium with a bacillary morphology that may appear slightly straight or curved and can be found either isolated or in clusters in patient samples. M. leprae exhibits a pronounced affinity for macrophages and Schwann cells, leading to dermatoneurological manifestations, including axon degeneration, demyelination, loss of tactile and thermal sensitivity, and motor disabilities [1]. M. leprae is classified as an acid-fast bacillus (AFB) due to its ability to retain red staining with fuchsin even after decolorization with an acid-alcohol solution. This characteristic is demonstrated using the Ziehl-Neelsen or Kinyoun staining methods [2].

M. leprae is distributed worldwide, with India and Brazil being the most affected countries. According to Job et al. (2005), the transmission dynamics of this bacillus remain poorly understood. It is believed that transmission occurs through prolonged contact between untreated patients and susceptible individuals. Research suggests that the primary portal of entry for M. leprae is the upper respiratory tract. Due to challenges in developing laboratory methods for identifying the bacillus, leprosy diagnosis remains primarily clinical [4, 5, 6]. The genetic degeneration of M. leprae has led to its slow replication rate and prolonged incubation periods. Despite this, studies suggest that the bacillus employs various mechanisms to evade the host's immune system effectively [7]. Most infected individuals mount an effective intracellular immune response against M. leprae. However, a small subset of individuals develops a Th2-dominant response, creating an environment that facilitates the survival and proliferation of the mycobacterium [8].

Leprosy presents several clinical forms, each associated with distinct immunological responses of the host [9]. Based on an assessment of the immune response, along with clinical, immunological, bacteriological, and histological features, Ridley and Jopling proposed a classification in 1966 that includes two major poles and three intermediate forms. At one pole, the lepromatous-lepromatous (LL) clinical form, the disease manifests with severe symptoms,

including widespread lesions. The humoral immune response (Th2 type) is less effective against the pathogen in this form, leading to the presence of foamy macrophages and a high bacterial load. At the opposite pole is the tuberculoid-tuberculoid (TT) clinical form, where the disease is more localized, with fewer granulomatous lesions and a lower bacillary load, resulting from a robust cellular immune response (Th1 type) to the pathogen. Between these two extremes are the intermediate forms—borderline-tuberculoid (BT), borderline-borderline (BB), and borderline-lepromatous (BL)—which are categorized based on their proximity to either pole [10]. To further simplify classifications and guide therapeutic regimens for leprosy, the World Health Organization (WHO) introduced two groups based on the number of lesions and peripheral nerve thickening: the multibacillary (MB) group, which includes individuals with six or more lesions, encompassing LL, BL, and BB patients; and the paucibacillary (PB) group, which includes patients with fewer than five lesions, encompassing TT and BT patients [11].

To achieve better control of the disease, studying the mechanisms of interaction, survival, and dissemination of M. leprae within the host is essential for gaining a deeper understanding of its pathogenesis, identifying potential therapeutic targets, and developing effective immunization strategies. In this context, this review aims to consolidate key findings on the bacterium's structure, molecular interactions, immune evasion strategies, metabolism, replication, and in vivo dissemination.

## 2 METHODS

Original scientific articles published in databases such as PubMed, Scopus, LILACS, and Google Scholar were selected for this review. The search encompassed publications from 1979 to 2024. The keywords and terms used in the searches included: "Mycobacterium leprae," "leprosy," "immune response," "immune evasion," "metabolism," "replication," and "dissemination." The articles were selected based on rigorous criteria, including relevance to the topic, methodological quality, and publication timeframe. Two independent reviewers conducted the selection process, and any disagreements were resolved through consensus or with the assistance of a third reviewer. Data extracted from the selected articles included author(s), title, journal, publication year, methodology, key findings, and conclusions. The

analysis of this data facilitated the construction of a narrative outlining the primary strategies employed by M. leprae to interact with the host, evade the immune response, and establish chronic infection. The review also addressed topics such as bacterial structure, mechanisms of host receptor recognition, immune response modulation, bacillary metabolism, and the processes of replication and dissemination. To ensure the quality and reliability of the review, we assessed the methodological quality of the included studies and considered potential publication bias. Additionally, the review was regularly updated to integrate new scientific evidence.

## 3 RESULTS AND DISCUSSION

### 3.1 Bacterial cell wall structure

The cell wall of M. leprae shares similarities with that of other mycobacteria. It is composed of mannosylated macromolecules and glycoproteins, which play a crucial role in the bacterium's interaction with host phagocytes. These components facilitate recognition and binding through C-type lectin receptors (CLRs) present on the surface of dendritic cells [12].

The inner part of the M. leprae cell wall contains peptidoglycans (PG) linked to arabinogalactans (AG), as well as mycolic acids (AM) connected to arabinose, forming a complex (AM-AG-PG) that extends throughout the wall and constitutes the central component of the mycobacterial structure. The outermost layer is composed of lipopolysaccharides, including liporabinomannan (LAM), lipomannan (LM), and phosphatidylinositol mannoside (PIM), along with phytocerol dimycocerosate lipids (DIM and PDIM) and glycolipids such as phenolic glycolipid I (PGL I) [13-15].

Liporabinomannan (LAM) consists of three components: a polysaccharide structure, a mannosylphosphatidyl-myo-inositol (MPI) anchor, and covering portions. Among the three known types of LAM, M. leprae predominantly exhibits the ManLAM (mannose-LAM) type. The immunomodulatory functions of LAM include suppressing T-cell activation, inducing interferon (IFN)-γ-mediated macrophage gene expression, scavenging oxygen radicals, inhibiting protein kinase C activity, and promoting the production of macrophage-associated cytokines, such as tumor necrosis factor-α (TNF-α) [16].

Another crucial molecule is phenolic glycolipids (PGLs), which are produced by several mycobacteria, many of which are pathogenic. Discovered in 1980, PGL-I is particularly significant due to its exclusive presence in M. leprae. The triglycosyl unit of PGL-I consists of phenol-PDIM and a M. leprae-specific trisaccharide, which is composed of 3,6-di-O-methylglucose linked β-1→4 to 2,3-di-O-methylrhamnose, which is then linked α-1→2 to 3-O-methylrhamnose. These components are connected by a glycosidic bond to the phenol group. PGL-I plays an important role in host-pathogen interactions, particularly in modulating the secretion of inflammatory cytokines [15, 17].

The diverse antigenic molecules that make up the bacterial structure of M. leprae are directly linked to its ability to modulate recognition by host cells, thereby facilitating the evasion of the immune response.

### 3.2 Molecular interaction and evasion of the host immune response

The recognition of M. leprae by innate immune cells occurs through pattern recognition receptors (PRRs), including Toll-like receptors (TLRs) [18-20], mannose receptors, and NOD-like receptors (NLRs) [20-22]. Despite the efficient interaction of this pathogen with PRRs, M. leprae employs various mechanisms to evade the immune response, ensuring its persistence and survival within the host.

The lipoproteins of M. leprae serve as ligands for TLR2/1 and TLR2/6 heterodimers [23,24]. Additionally, this microorganism can activate other innate receptors, such as TLR4; however, the interaction of PGL-I with TLR4 reduces the activity of the signaling pathway in macrophages [25]. Peptidoglycan (PG) and LAM, found in the cell wall of M. leprae, are also ligands for TLR2 [26]. Moreover, the interaction of M. leprae with the TLR2 receptor promotes the expression of CORO-1A (tryptophan-aspartate-containing coat protein) on the surface of the phagosome, preventing its fusion with the lysosome. CORO-1A not only inhibits phagolysosome formation but also suppresses signaling in pathways involved in activating innate immunity [27].

The human NOD2 receptor triggers an innate immune response through the release of IL-32, signaling monocytes to differentiate into dendritic cells [22,28]. However, the

peptidoglycans present in the cell wall of M. leprae contain peptide side chains with glycine or diaminopimelic acid (DAP) residues [29,30]. This molecular modification in M. leprae peptidoglycans disrupts their interaction with NOD1 and NOD2 receptors, thereby promoting the evasion of the innate immune response [31].

Another key pattern recognition receptor (PRR) is the mannose receptor (CD206), which plays a significant role in promoting mycobacterial infection. This receptor is highly expressed on M2 macrophages, which produce anti-inflammatory cytokines and exhibit a reduced oxidative response. In M. leprae, the LAM molecule is coated with mannose residues, facilitating its interaction with CD206. Additionally, phosphatidyl-myo-inositol mannosides, abundant in the mycobacterial cell wall, bind to CD206 during phagocytosis [32]. As a result, entry via the mannose receptor prevents the fusion of the phagosome with the lysosome, thereby enhancing the survival of M. leprae. Furthermore, the microorganism negatively regulates the production of reactive oxygen intermediates, such as hydrogen peroxide, hydroxyl radicals, and superoxide anions, produced after phagocytosis, which helps it survive within the macrophage [33,34]. M2 macrophages also promote the production of immunosuppressive molecules such as TGF-β, IL-10, fibroblast growth factor (FGF)-β, CD163, CD209, arginase 1, and indoleamine 2,3-dioxygenase (IDO), all of which are involved in tissue repair and immune suppression [35-37]. IL-10-programmed macrophages are particularly characterized by strong expression of the mannose receptor, CD206 [38].

On the other hand, Hashimoto et al. (2002) demonstrated that M. leprae downregulates the expression of MHC class I, MHC class II, and costimulatory molecules on antigen-presenting cells (APCs). This downregulation reduces the interaction between APCs and T lymphocytes, impairing the presentation of M. leprae-derived antigens and hindering the formation of an effective adaptive immune response.

### 3.3 Metabolism of M. leprae

Despite having a high number of pseudogenes and a slow metabolism, M. leprae employs sophisticated strategies to utilize energy sources and supplies from host cells. Additionally, it

can induce gene reprogramming within the host, ensuring its survival, replication, and persistence.

M. leprae modulates glucose metabolism in host cells, enhancing the production of reducing energy and promoting the regeneration of glutathione, which in turn helps control free radicals [40]. Schwann cells infected with M. leprae exhibit increased glucose uptake, alongside a significant rise in the activity of glucose-6-phosphate dehydrogenase (G6PDH), a crucial enzyme in the pentose phosphate pathway [41]. Moreover, M. leprae infection reduces lactate generation and release, while simultaneously inducing cellular protection against hydrogen peroxide through the pentose phosphate pathway in a glutathione-dependent manner [40].

The accumulation of lipids in the cytoplasm of phagocytic cells, resulting in a foamy appearance, is a hallmark of M. leprae infection. Leprosy dermal granulomas are characterized by foamy macrophages containing lipid droplets coated with adipose differentiation-related protein (ADRP) and perilipin, molecules that regulate lipid metabolism [20]. In vitro studies have shown that M. leprae infection strongly induces the expression of these molecules, which are localized within phagosomes. Tanigawa et al. (2012) demonstrated that M. leprae reduces the degradation of lipid droplets, thereby modulating lipid metabolism and enhancing its survival within host cells. Additionally, M. leprae regulates glucose metabolism in the host cell, increasing the availability of reducing energy, promoting glutathione regeneration, and controlling free radicals [40]. Schwann cells infected with M. leprae show increased glucose uptake and enhanced activity of glucose-6-phosphate dehydrogenase (G6PDH), a key enzyme in the pentose phosphate pathway [41]. Furthermore, M. leprae infection minimizes lactate generation and release, while inducing cellular protection against hydrogen peroxide via the pentose phosphate pathway in a glutathione-dependent manner [42-46].

### 3.4 Replication and in vivo dissemination of M. leprae

M. leprae, like other intracellular pathogens, targets cells that either promote its development or are susceptible to the subversion of their protective functions, facilitating its replication and dissemination within the host (Falkow, 1991).

Although M. leprae infection in humans initially presents with sensorimotor loss [48-50]

mediated by inflammation, the earliest events of peripheral nervous system (PNS) infection remain poorly understood. Tapinos et al. (2006) suggested that M. leprae exploits the regenerative properties of the PNS to expand its niche within Schwann cells. This strategy may reflect the bacterium's efforts to protect and propagate within the Schwann cell environment during human infection. Once inside Schwann cells, M. leprae employs mechanisms that promote cell resistance or rejuvenation, keeping infected cells in an active state to acquire essential factors for bacterial survival. Moreover, Schwann cells serve as a safe haven for M. leprae, as the blood-nerve barrier of the PNS shields the bacterium from the host's immune response [3,50]. These favorable conditions enable long-term bacterial persistence within host cells, supported by the non-toxic, non-cytopathic, non-apoptotic, and non-tumorigenic nature of M. leprae [51,52].

Davis and Ramakrishnan (2009) emphasize that infected and reprogrammed cells play a key role in the formation of granulomas, which are pathological hallmarks of mycobacterial infections in both murine models and patients with leprosy and tuberculosis [54,55]. While mycobacterial granulomas are traditionally regarded as crucial for containing infection, recent studies in zebrafish have suggested that granulomas may also facilitate mycobacterial dissemination during the early stages of infection.

Once colonized, M. leprae fully exploits the plasticity of Schwann cells, converting infected cells into proliferative Schwann cells (pSLCs) with the ability to produce chemoattractants and trophic factors. These molecules promote macrophage recruitment, bacterial transfer, and the survival of infected macrophages. Interestingly, some of the immunological factors and chemokines released by pSLCs are also known to promote granuloma formation [56]. Collectively, these events facilitate macrophage recruitment by pSLCs, contributing to the formation of granulomatous lesions (GLS). In vitro and in vivo studies by Wang et al. (2013) further support the notion that M. leprae-laden M1 and M2 macrophages within granulomas play a crucial role in the spread of infection.

## 4 CONCLUSIONS

Leprosy is a disease studied globally, with the primary goals of reducing new cases and ultimately eradicating it. However, despite these efforts, the number of infections has

unexpectedly increased over time. This rise can be attributed to insufficient knowledge of the pathogenic mechanisms of M. leprae and ongoing challenges in accessing medical treatment, particularly in endemic regions such as East Africa, Southeast Asia, and Brazil, which continue to account for a large proportion of new cases. This review highlights the unique biological properties of M. leprae, focusing on its survival within host cells like macrophages and Schwann cells. It does so by modulating the innate immune response and lipid metabolism. M. leprae has a limited number of gene-coding regions and numerous pseudogenes, with non-coding regions comprising nearly half of its genome. As a result, these bacteria are highly reliant on host cells for the production of lipids and cell wall components. Alterations in lipid metabolism are crucial for bacterial survival and proliferation. A comprehensive understanding of M. leprae's bacterial structure, immune evasion mechanisms, and metabolic and dissemination strategies is critical for advancing the diagnosis, treatment, and prevention of leprosy. Continued research in this field will not only deepen our understanding of the disease but also aid in the development of more effective approaches to combat this persistent infection.

## 5 EXPERT OPINION

A deep understanding of the interaction between *Mycobacterium leprae* and the host has the potential to significantly impact the diagnosis, treatment, and prevention of leprosy. Advances in molecular biology and immunology techniques may lead to the identification of new biomarkers, improving early detection and enabling intervention before disease progression. However, integrating these discoveries into clinical practice presents challenges, including costs and the need for specialized training of healthcare professionals. Additionally, the stigma associated with leprosy remains a barrier to active case detection and treatment adherence.

The research field still faces technological and methodological limitations, particularly due to the inability to culture *M. leprae* in artificial media. The reliance on animal models, such as armadillos and mice, restricts the scalability and broader application of studies. Novel approaches, including three-dimensional cell culture models and advances in organoid technology, may facilitate a more detailed investigation of the bacterium’s interaction with different human cell types.

The search for an effective vaccine and the development of new therapies, including targeted drugs that disrupt *M. leprae* immune evasion mechanisms, remain priorities in leprosy research.

Over the next five to ten years, advancements in the field are expected to result in faster

and more accurate diagnostics, more individualized therapeutic approaches, and more effective strategies to interrupt transmission. The use of gene-editing technologies, such as CRISPR, could allow a deeper analysis of the genetic mechanisms underlying *M. leprae* pathogenicity and potentially pave the way for novel targeted therapies.

From a speculative perspective, within the next five to ten years, leprosy may be closer to elimination as a public health issue due to early diagnosis and advanced preventive strategies. The development of new vaccines and therapies, combined with increased awareness and stigma reduction, could significantly transform the disease landscape.

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## 7 CONFLICTS OF INTEREST

The authors declare that they have no conflict of interst.

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