



The Role of Innate Immunity against *Mycobacterium Leprae*: A Systematic Literature Review

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A B S T R A C T

Introduction: Innate immunity is the body's defense system that exists from birth and is the body's first defense against infection. This system involves multiple defense mechanisms that work together to recognize, deter, and respond to pathogens such as bacteria, viruses, and fungi. In the context of *Mycobacterium leprae*, the role of the innate immune system is very important because this bacterium has unique pathogenic properties and is capable of infecting human body cells in complex ways. **Methods:** The literature search process was carried out on various databases (PubMed, Web of Sciences, EMBASE, Cochrane Libraries, and Google Scholar) regarding the role of innate immunity against *Mycobacterium leprae*. This study follows the preferred reporting items for systematic reviews and meta-analysis (PRISMA) recommendations. **Results:** One of the main aspects of the role of the innate immune system against *Mycobacterium leprae* is the recognition of this pathogen by phagocytic cells, such as macrophages. *Mycobacterium leprae* evades recognition and destruction by these cells in a number of ways, including cell surface modification of the immune response. **Conclusion:** The innate immunity response plays a significant role in the response to *Mycobacterium leprae* infection. Innate immunity acts as an initial and fast response to mitigate the *Mycobacterium leprae* infection from getting more massive.

1. Introduction

Mycobacterium leprae is a pathogenic bacterium that causes leprosy, also known as leprosy. This disease has existed since ancient times and is still a public health problem in several parts of the world. Although there are effective treatments for leprosy, understanding the role of the immune system, especially innate immunity, in response to *Mycobacterium leprae* remains an important research topic. Innate immunity is the body's defense system that exists from birth and is the body's first defense against infection. This system involves multiple defense mechanisms that work together to recognize, deter, and respond to pathogens such as bacteria, viruses, and fungi. In the context of *Mycobacterium*

leprae, the role of the innate immune system is very important because this bacterium has unique pathogenic properties and is capable of infecting human body cells in complex ways.¹⁻³

One of the main aspects of the role of the innate immune system against *Mycobacterium leprae* is the recognition of this pathogen by phagocytic cells, such as macrophages. *Mycobacterium leprae* evades recognition and destruction by these cells in a number of ways, including cell surface modification of the immune response. Therefore, further understanding how the innate immune system recognizes and responds to *Mycobacterium leprae* is essential in developing new strategies to control leprosy.⁴⁻⁶ This study aimed to explore the role of the innate immune

system in the response to *Mycobacterium leprae*. The study discusses how these bacteria can evade early detection by immune cells, as well as the mechanisms by which the immune system can overcome *Mycobacterium leprae* infection. In addition, it is also important to consider the role of individual genetics in the immune response to leprosy because genetic differences can affect a person's ability to fight the infection.

2. Methods

The literature search process was carried out on various databases (PubMed, Web of Sciences, EMBASE, Cochrane Libraries, and Google Scholar) regarding the role of innate immunity against *Mycobacterium leprae*. The search was performed using the terms: (1) "innate" OR "immunity" OR

"*Mycobacterium leprae*" OR "Leprae" AND (2) "the role of innate immunity". The literature is limited to preclinical studies and published in English. The literature selection criteria are articles published in the form of original articles, an experimental study about the role of innate immunity against *Mycobacterium leprae*, the control group only received liquid without therapeutic effect or no treatment, studies were conducted in a timeframe from 2013-2023, and the main outcome was the role of innate immunity against *Mycobacterium leprae*. Meanwhile, the exclusion criteria were animal models that were not related to the role of innate immunity against *Mycobacterium leprae*, the absence of a control group, and duplication of publications. This study follows the preferred reporting items for systematic reviews and meta-analysis (PRISMA) recommendations.

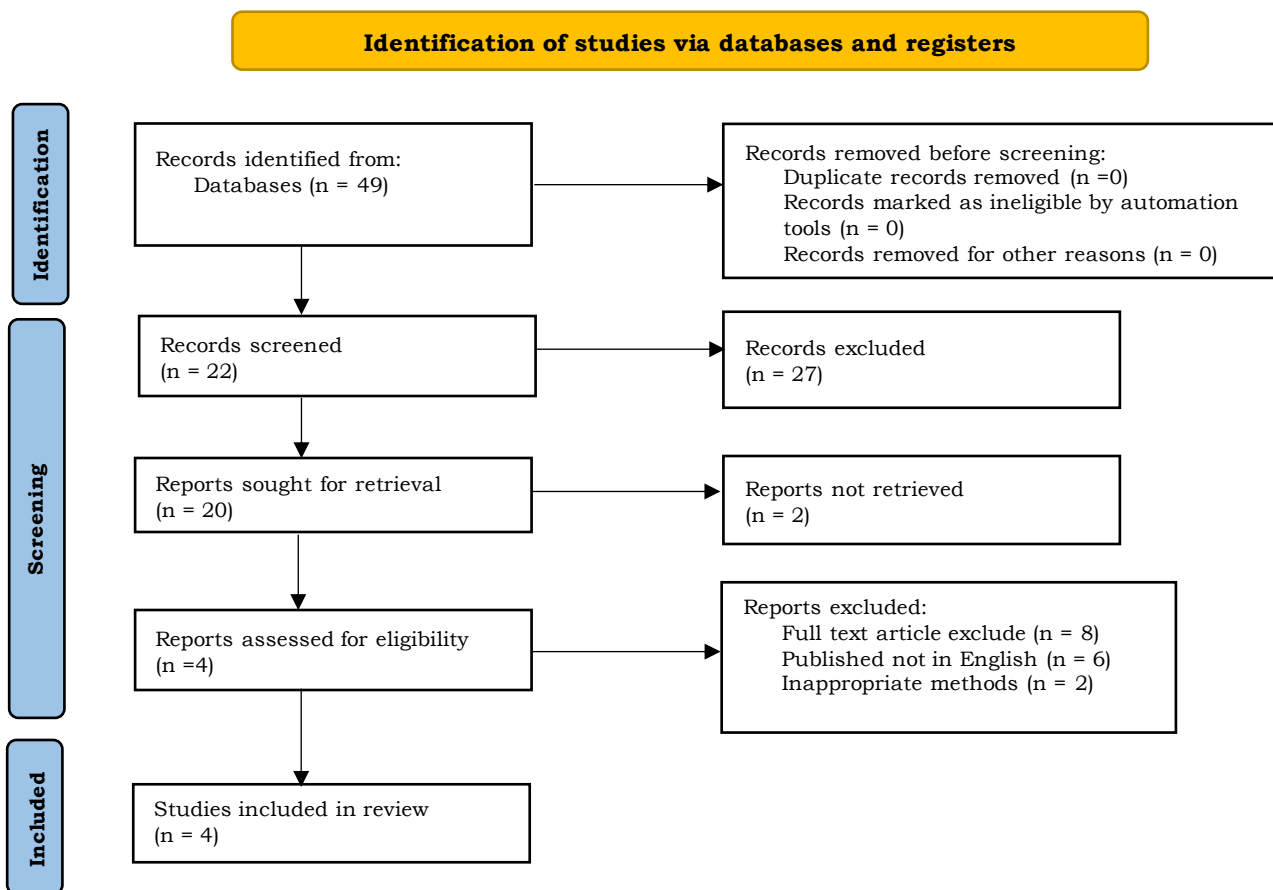


Figure 1. Research PRISMA diagram.

3. Results and Discussion

The role of the innate immune system in the response to *Mycobacterium leprae*

The innate immune system has an important role in the response to *Mycobacterium leprae*, the bacteria that causes leprosy. This is the body's defense system that first interacts with pathogens that enter the human body. One important aspect of the innate immune system is its ability to recognize common patterns in pathogens known as "polypathogens" (pathogen-associated molecular patterns or PAMPs). *Mycobacterium leprae* possess various PAMPs, such as lipopolysaccharide (LPS) in their cell walls, which can be recognized by receptors on innate immune cells, such as toll-like receptors (TLRs) and NOD-like receptors (NLRs). This recognition triggers an initial immune response. When PAMPs such as LPS are identified by TLR and NLR receptors on innate immune cells, this triggers a cascade of biological responses. Some of these responses include the activation of macrophages and other phagocytic cells to engulf and destroy *Mycobacterium leprae*, as well as stimulating the production of cytokines and other inflammatory mediators that play a role in inflammation and the coordination of the immune response. Recognition of PAMPs by the innate immune system is an important first step in the fight against *Mycobacterium leprae* infection. However, as previously mentioned, these bacteria have the ability to evade detection and immune response by various mechanisms of immune invasion, including cell surface modification and the ability to live in human cells where immune cells cannot reach. Therefore, although the innate immune system plays an important role, a more specific adaptive immune response is also often required to combat *Mycobacterium leprae* effectively.^{7,8}

In addition, macrophages also play a role in stimulating local inflammation in response to *Mycobacterium leprae* infection. This includes the release of pro-inflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF- α), which help activate other immune cells and mobilize the overall immune response. Macrophages are phagocytic cells that play an important role in fighting *Mycobacterium leprae* infection. When

macrophages detect *Mycobacterium leprae*, they can take up the bacterium by phagocytosis. In addition, macrophages can produce various effector molecules, such as oxygen radicals and nitric oxide, which can kill these bacteria. Macrophages are phagocytic cells that have the ability to ingest and internalize *Mycobacterium leprae*. This is the first step in trying to eliminate bacteria from the body. After phagocytosis occurs, these bacteria become trapped inside vesicles called phagolysosomes, where they can potentially be destroyed by various enzymes and effector molecules. Macrophages can produce reactive oxygen radicals (ROS) as part of the response to *Mycobacterium leprae*. ROS are highly reactive molecules and can damage the cellular components of *Mycobacterium leprae*, aiding in killing the bacteria. Besides ROS, macrophages can also produce nitric oxide (NO), which has antimicrobial properties. NO can interfere with the function of *Mycobacterium leprae* cells and contribute to the elimination of bacteria.⁹

The innate immune system response often causes inflammation, which is the body's attempt to isolate and destroy pathogens. In the context of leprosy, inflammation can activate other immune cells, such as neutrophils and dendritic cells, to assist in fighting *Mycobacterium leprae* infection. Inflammation triggers the release of proinflammatory cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF- α). These cytokines can activate other immune cells, including neutrophils and dendritic cells, which also play a role in fighting *Mycobacterium leprae* infection. Neutrophils are other phagocytic cells that can engulf bacteria and other pathogenic particles, while dendritic cells play a role in recognizing and presenting antigens to T cells, which are part of the adaptive immune response. During inflammation, blood vessels can experience increased permeability, which allows immune cells and effector molecules to more easily reach the site of infection. This helps increase the body's ability to respond to *Mycobacterium leprae* infection in the infected area. Inflammation can also trigger increased blood flow to the infected area. This brings more immune cells and immune factors to the infection site, which helps in intensifying the immune response. However,

inflammation can also have a negative impact if it is excessive or prolonged. Chronic inflammation can cause tissue damage and severe disease symptoms. In leprosy, excessive inflammation can contribute to nerve damage and to clinical manifestations of the disease, such as skin discoloration and deformity.¹⁰

Innate immune cells can also produce various types of cytokines, including interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF- α), which play a role in coordinating the immune response and stimulating the inflammatory process. These cytokines can affect the activity of other immune cells and affect more specific adaptive immune responses. IL-1 and TNF- α play a role in activating other immune cells, including T cells and B cells. This activation is important for initiating and maintaining a more specific adaptive immune response against *Mycobacterium leprae*. IL-1 and TNF- α can affect blood vessels in the infected area to increase permeability, allowing immune cells and effector factors to move more freely to the site of infection. These cytokines also assist in the mobilization and recruitment of immune cells to areas infected with *Mycobacterium leprae*, such as neutrophils and macrophages. This is an important step in the treatment of this bacterial infection. IL-1 and TNF- α contribute to the inflammatory process and stimulate the production of other pro-inflammatory cytokines. This can produce localized inflammation that aids in the isolation and destruction of pathogens but can also be a source of symptoms and tissue damage if excessive. In addition, IL-1 and TNF- α may also play a role in further modulating the adaptive immune response by influencing the activation and differentiation of T cells and B cells. This means that in addition to stimulating the initial immune response, these two cytokines also assist in directing the body's immune response to more effectively combat *Mycobacterium leprae*. Although the innate immune system plays an important role in the initial response to *Mycobacterium leprae*, it is important to remember that this bacterium also has unique self-protection mechanisms that allow it to persist for a long time in human cells without being detected or destroyed by the immune system. Therefore, although the innate immune system can initiate an initial response, it is

often necessary to activate more specific adaptive immune systems, such as T cells and B cells, to effectively combat *Mycobacterium leprae* infection.^{11,12}

Mechanisms that the immune system can use to overcome *Mycobacterium leprae* infection

Mycobacterium leprae has several unique mechanisms that allow it to evade early detection by immune cells and the innate immune system. *Mycobacterium leprae* has a thick lipid layer on its cell wall called the lipid outer layer. This layer contains lipids such as phenolic glycolipids, which allow these bacteria to avoid phagocytosis by macrophages and inhibit the immune response. This lipid outer layer also makes *Mycobacterium leprae* more resistant to the acidic environmental conditions within the phagolysosome, where pathogenic bacteria are usually destroyed. The lipid outer layer makes *Mycobacterium leprae* more difficult for macrophages and other phagocytic cells to recognize and ingest. This is because this layer can inhibit the process of phagocytosis, which will normally occur when macrophages detect pathogens. Phagocytosis by macrophages is usually followed by bacterial digestion in vesicles containing hydrolytic enzymes in the acidic environment of the phagolysosome. However, the lipid outer layer of *Mycobacterium leprae* helps protect the bacterium from these acidic conditions, allowing the bacterium to survive in the phagolysosome and avoid being killed. The lipid outer layer may also contribute to the evasion of the immune response by inhibiting recognition of *Mycobacterium leprae* by innate immune cells. By evading recognition by receptors such as toll-like receptors (TLRs), these bacteria can trick the immune system and evade a strong immune response. Although the lipid outer layer of *Mycobacterium leprae* gave the bacterium an evolutionary advantage in infecting humans and evading the body's immune response, research continues to unravel the mechanisms by which the immune system can overcome this bacterium.¹³

Mycobacterium leprae has a defense mechanism against oxidative stress, which allows it to survive in a macrophage environment that produces oxygen radicals. This makes these bacteria more resistant to

assassination attempts by macrophages. *Mycobacterium leprae* produces antioxidant enzymes such as superoxide dismutase (SOD) and catalase peroxidase (KatG). SOD enzyme converts superoxide anion to hydrogen peroxide, while catalase peroxidase decomposes hydrogen peroxide. These two enzymes play a role in reducing ROS levels in bacterial cells, helping to protect *Mycobacterium leprae* from oxidative damage. *Mycobacterium leprae* also has a mechanism to inhibit excessive oxidative reactions. This involves a number of compounds, such as mannose-6-phosphate, which inhibit macrophage enzymes that play a role in ROS production. Macrophage cells produce ROS in an acidic environment within the phagolysosome. *Mycobacterium leprae* has the ability to survive in this acidic environment and avoid damage by ROS. This ability is largely related to the lipid outer layer, which reduces its permeability to acids.¹⁴

The innate immune system responds to *Mycobacterium leprae* infection by activating macrophages. Macrophages are phagocytic cells that try to ingest and destroy these bacteria. Although *Mycobacterium leprae* has the ability to evade phagocytosis, some bacteria can remain engulfed by macrophages and be transported into phagolysosomes. Immune cells, such as macrophages, can produce reactive oxygen radicals (ROS) and nitric oxide (NO) as part of efforts to kill *Mycobacterium leprae*. ROS and NO have antimicrobial properties and can damage the cellular components of these bacteria. T cells, especially CD4+ (T-helper) T cells, play an important role in fighting *Mycobacterium leprae*. They can respond to antigens presented by macrophages and dendritic cells and mobilize a more specific immune response.¹⁵

The role of genetic innate immunity in the immune response against leprosy

Individuals have unique genetic variations in the genes involved in the innate immune response. Some of these variations, known as genetic polymorphisms, can affect the body's ability to detect and respond to *Mycobacterium leprae*. An important example is the genetic polymorphism in the toll-like receptor (TLR)

gene that can affect the response to *Mycobacterium leprae* PAMPs. Genetic polymorphisms are variations in the DNA sequence between individuals that can influence how the body responds to pathogens such as *Mycobacterium leprae* via the innate immune system. An important example of the response to *Mycobacterium leprae* is the genetic polymorphism in the toll-like receptor (TLR) gene, which plays a role in the detection of PAMPs (pathogen-associated molecular patterns) of this bacterium. The best-known examples are the genetic polymorphisms in TLR2 and TLR1. TLR2 is known as a receptor that is important in recognizing PAMPs present in *Mycobacterium leprae*, including lipoproteins and glycolipids present in the bacterial cell wall. Polymorphisms in the TLR2 and TLR1 genes can affect an individual's sensitivity to *Mycobacterium leprae* infection and the body's ability to respond appropriately. For example, certain genetic polymorphisms in TLR2 and TLR1 have been associated with different levels of risk for leprosy infection and development. Several genetic variants of TLR2 and TLR1 can affect the immune response to this bacterium, thus influencing the severity of the disease and the level of susceptibility.^{16,17}

The ability of phagocytic cells, such as macrophages, to engulf and destroy *Mycobacterium leprae* can also be influenced by genetic factors. Genetic variations in the cellular components involved in the phagocytosis process can influence how effective these cells are at fighting infection. Variations in the genes that encode receptors on the surface of phagocytic cells, such as the phagocytic receptors that recognize *Mycobacterium leprae* PAMPs, can affect the ability of cells to detect and ingest bacteria. Changes in these receptors can affect the availability of targets for phagocytosis. The cytoskeleton of phagocytic cells, such as actin and myosin, plays an important role in the process of phagocytosis. Genetic variations in these components of the cytoskeleton can affect the ability of cells to manipulate cell membranes and ingest pathogens. The production of phagocytic molecules, such as hydrolytic enzymes and other antimicrobial molecules, can be affected by genetic polymorphisms. The ability of cells to produce these enzymes is an important part of the process of

destroying ingested bacteria. Intracellular signals involved in the regulation of phagocytosis can be affected by genetic polymorphisms in the genes involved in these signaling pathways.¹⁸

Individual genetics can also affect the ability of immune cells to produce reactive oxygen radicals (ROS) and nitric oxide (NO) in response to *Mycobacterium leprae*. Differences in the production or activity of antioxidant enzymes can affect cellular resistance to oxidative stress. ROS are highly reactive oxygen molecules that can kill pathogens such as *Mycobacterium leprae*. Production of ROS by immune cells, especially macrophages, is an important mechanism in killing these bacteria. Genetic polymorphisms in the genes that regulate ROS production or the activity of enzymes involved in ROS formation can affect how effectively the body destroys bacteria. Nitric oxide is a gas molecule that has antimicrobial properties and can inhibit bacterial growth. NO production by immune cells can also be influenced by genetic factors. Variations in the genes that regulate the synthesis and activity of enzymes involved in NO production may affect the response to *Mycobacterium leprae*. In addition to the production of ROS and NO, individual genetics can also affect the activity of antioxidant enzymes. These enzymes help protect cells from damage caused by excessive oxidative stress. Genetic polymorphisms in the genes of antioxidant enzymes such as superoxide dismutase (SOD) or catalase peroxidase (KatG) can influence the level of protection against oxidative damage.¹⁹

Genetics may also play a role in regulating the inflammatory response, which is an important component of the innate immune system. Several genetic polymorphisms can affect levels of proinflammatory cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF- α). Genetic polymorphisms in genes involved in the production of pro-inflammatory cytokines may affect the levels of cytokines produced by innate immune cells in response to *Mycobacterium leprae*. For example, variations in the interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF- α) genes have been associated with levels of cytokine production that vary between individuals. In addition to cytokine

production, the regulation of the inflammatory response can also be influenced by genetic factors. Variations in the genes that regulate expression and activity of cytokines and cytokine receptors on target cells can influence how intense and how long inflammation lasts. Some genetic polymorphisms can make individuals more susceptible to excessive inflammation or uncontrolled inflammatory responses, which in turn can contribute to the development of more severe forms of the disease. Conversely, genetic variations can also affect the body's ability to regulate inflammatory responses and stop inflammation where it is no longer needed. Some individuals may be more susceptible to excessive immunosuppression.²⁰

4. Conclusion

The innate immunity response plays a significant role in the response to *Mycobacterium leprae* infection. Innate immunity acts as an initial and fast response to mitigate the *Mycobacterium leprae* infection from getting more massive.

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