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From inflammatory mediators to immune response: A comprehensive analysis of immune impairment in patients with polymicrobial forms of leprosy

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Abstract. Leprosy is a chronic infectious disease caused by Mycobacterium leprae that primarily affects the skin and peripheral nervous system. In the polymicrobial form of leprosy, the intertwining of ever-increasing pathogens and overloaded immune responses leads to significant tissue damage. This article analyzes the background of leprosy and the polymicrobial form of the disease, describes the process of activation of the immune system by antigenic exposure to leprosy, the associated mediators produced and the mechanisms of immune injury, and describes the limitations and future directions of research in patients with the polymicrobial form of leprosy, as well as exploring in detail how the cytokines and chemokines produced in the process affect the structure and function of the tissues. The mechanisms of the immune mediators produced that cause tissue injury. In addition, this review discusses the limitations and future directions of current research on immune injury in leprosy, which will provide a reference direction for future research to improve the prevention, diagnosis, treatment and prognosis of leprosy.

Keywords: Leprosy, polymicrobial, immune mediators, immune damage

1. Introduction

Leprosy, also known as Hansen's disease, has a long history, and its earliest records may date back to ancient Egyptian documents from around 2000 B.C. Although there are no explicitly documented cases of leprosy existing in China, many symptoms that may be associated with leprosy have been described [1]. This chronic infectious disease is caused by Mycobacterium leprae, the structure of which consists of a cell wall, a pod membrane and a cytoplasm. One of the critical components of the cell wall is lipoarabinomannan (LAM), which has immunomodulatory properties and is closely associated with bacterial survival [2]. Pods of Mycobacterium leprae may be lipids, including tuberculosis wax lipids (PDIM) and phenolic glycolipid-1 (PGL-1), and the terminal sugar residues of PGL-1 are distinctly antigenic and capable of triggering the production of specific antibodies in the organism [3].

Mycobacterium leprae mainly affects the skin, peripheral nerves, mucous membranes of the upper respiratory tract and the conjunctiva of the eye and can lead to skin lesions and neurological dysfunction. Although most humans have some specific immunity to Mycobacterium leprae, genomic

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studies have revealed that certain specific susceptibility genes may make individuals more susceptible to the disease. A current study by a Chinese team on the genetic susceptibility of Chinese people to leprosy has shown that the relationship between the strength of the immune response to leprosy and the number of Mycobacterium leprae in the body is very complex, and is influenced by a combination of the characteristics of the pathogen, the immune response of the host, as well as other environmental and genetic factors, and is not simply proportional [4-6].

Leprosy is comprehensively classified on the basis of four aspects: clinical manifestations, bacteriology, pathology and immunology [7]. Currently, the Ridley-Jopling classification (five-classification method) is commonly used in China, which is based on the characteristics of the body's cellular immunity from strong to weak, and the number of Mycobacterium leprae from small to large, and so on, and classifies leprosy into five classes: tuberculoid leprosy(TT), tuberculoid borderline(BT), borderline leprosy(BB), lepromatous borderline(BL), and lepromatous leprosy(LL), as well as tinterminate leprosy(I). type of undetermined category (I) leprosy. There is also the implementation of multidrug therapy (MDT), which was used by WHO in 1981 to categorize leprosy into polymicrobial and oligomicrobial types, i.e., the skin smear bacteriological classification. In the skin smear classification, the multibacillary type includes BB, BL and LL, and all patients with positive skin smears, while the oligobacillary type includes TT, BT and patients with negative skin smears.

Patients with the polymicrobial form of leprosy usually present with extensive skin damage, reflecting high levels of Mycobacterium leprae in the patient. The nasal mucosa of these patients is the main route of pathogen expulsion and is highly infectious, spreading mainly through respiratory droplets and other means. Increased numbers of Mycobacterium leprae may lead to sustained exposure of the immune system to a large number of antigens, which in turn triggers a complex series of immune responses. As a result, the immune system produces inflammatory mediators, such as cytokines and chemokines, which promote an inflammatory response leading to skin and nerve damage. However, the weaker immune response in patients with the polymicrobial form of leprosy makes it unable to control the pathogens effectively, which leads to the persistence and exacerbation of the disease.

2. The immune system in leprosy

2.1. Antigen exposure and immune system activation

In patients with the polymicrobial form of leprosy, there is a high number of Mycobacterium leprae in the body, leading to a high level of antigenic exposure, which activates the immune system. However, due to inadequate immune response, this activation is ineffective in clearing the bacteria and instead triggers ongoing inflammation and tissue damage.

Based on current findings in leprosy, the process of antigen exposure in the body can be summarized in the following stages:

2.1.1. Stage of infection. Mycobacterium leprae enters the body through broken skin or mucous membranes of the upper respiratory tract, and spreads bloodstream in the body through phagocytosis by macrophages, among other things. It has now been shown that Mycobacterium leprae can alter the behavior of macrophages and destroy myelin, an alteration caused by phenolic glycolipid-1 (PGL-1), which causes macrophages to produce excess nitric oxide, which is potentially destructive [8].

2.1.2. Intracellular colonization. In the polymicrobial form of leprosy, Mycobacterium leprae proliferates in macrophages and Schwann cells. Single-cell and spatial sequencing studies of leprosy biopsy specimens by Robert L. Modlin in the United States revealed that leprosy granulomas constitute a complex cellular structure in macrophages and lymphocytes that functions to contain and kill invading pathogens [9].

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2.1.3. Antigen presentation. As the bacterial population increases, antigens are recognized by the immune system and antigen-presenting cells, such as dendritic cells, capture and present these antigens, activating T cells. No specific studies have been found that directly address the antigen presentation phase of leprosy. A study by Furen Zhang's team in China has shown [10] that the immune escape mechanism of leprosy bacteria infecting the human body was revealed by single-cell RNA sequencing, in which the depletion of CD8+ T cells caused by the immune checkpoint receptors TIGIT and LAG3 prevented the body from initiating an effective immune response to clear the pathogenic bacteria.

2.1.4. T-cell activation. Antigen presentation activates specific T cells, including helper T cells (CD4+) and cytotoxic T cells (CD8+). May trigger an immune response against Mycobacterium leprae [10].

2.1.5. Release of inflammatory mediators. Activated T cells and other immune cells release cytokines and chemokines that regulate and enhance the immune response [9].

2.1.6. Inflammation production and tissue damage. Sustained antigen exposure leads to extensive skin damage and nerve damage, reflecting the high exposure of the immune system to the antigen [9].

The activation of the immune system induced by the antigen exposure process described above leads to the activation of T-cells appearing as a series of immune responses, including the production of cytokines and chemokines. These immune mediators promote an inflammatory response and may lead to localized tissue damage, resulting in immune injury.

Whether or not Mycobacterium leprae enters the body and the severity of the disease depends mainly on the immune status of the infected organism. When the body's autoimmune system response is insufficient or defective, the Mycobacterium leprae that invades the body multiplies and activates the body's immune response, which is not sufficient to resist the hematogenous dissemination of Mycobacterium leprae, but the presentation of antigens activates specific T-cells and other immune cells, releasing cytokines and chemokines [11].The release of cytokines and chemotaxis of chemokines elicits an associated immune response, which is regulated and augmented by a persistently activated immune system, leading to inflammation production and tissue damage [12].

2.2. Inflammatory mediators

In patients with the polymicrobial form of leprosy, the presence of large numbers of Mycobacterium leprae in the patient's body leads to the release of a variety of inflammatory mediators, including cytokines and chemotactic factors. The release of cytokines and chemotaxis of chemokines elicits an associated immune response, which is regulated and augmented by a persistently activated immune system that may lead to inflammation production and tissue damage. Currently associated with inflammatory mediators may include [13, 14]:

2.2.1. Tumor necrosis factor alpha (TNF-α). A cytokine, mainly produced by macrophages, activates immune cells and enhances the inflammatory response, as well as being involved in the regulation of apoptosis and cell proliferation. The increase of TNF-α in the polymicrobial form of leprosy may lead to an enhanced local immune response, causing persistent inflammation and tissue damage, and it is an important inflammatory cytokine.

2.2.2. Interferon-γ (IFN-γ). A cytokine produced by T cells and NK cells activates macrophages, enhances their bactericidal capacity, promotes Th1-type immune responses, and participates in immune regulation. A sustained increase in IFN-γ in the polymicrobial form of leprosy may lead to neural tissue damage.

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2.2.3. Interleukins (IL-1, IL-6, IL-12, etc.). Cytokines play a key role in regulating the inflammatory response and promoting the activation and differentiation of T cells and B cells. Overproduction of these interleukins may lead to chronic inflammation and tissue damage.

2.2.4. Chemokines (CCL2, CXCL8, etc.). There are mainly small molecule proteins that bind to specific receptors to direct immune cells to the site of infection and promote an immune response. An increase in chemokines may lead to localized inflammation and tissue damage.

2.2.5. Other mediators of inflammation. Include a number of other cytokines and chemotactic factors that may play a role in specific situations or in specific populations.

There are no specific, well-defined studies related to the inflammatory mediators of leprosy, based on the relevant inflammatory mediators produced by the bacteria upon entry into the organism, and these inflammatory mediators may act individually or together in the polymicrobial form of leprosy to form a complex network of immune responses, which on the one hand control the infection, and on the other hand may lead to tissue damage and promote the progression of the disease. The study of the mechanism of action of these inflammatory mediators in leprosy is important for the development of more effective treatments and improvement of patient prognosis.

2.3. Immunological damage

In the polymicrobial form of leprosy, prolonged antigenic stimulation leads to sustained activation of the immune system and the release of large amounts of inflammatory mediators. These mediators cause an inflammatory response at the site of infection, which is manifested by tissue edema, vasodilatation and infiltration of immune cells. The main mechanisms by which the immune system damages tissues include:

2.3.1. Self-attack. Attacks by immune cells on normal tissues result in damage, especially in skin and nerve tissues. One study showed similarities between Mycobacterium leprae and the body's B- and T-cell epitopes, especially in the type I response to leprosy [15].There have also been studies exploring the potential mechanisms of molecular mimicry in leprosy nerve injury, with similarities between specific proteins of Mycobacterium leprae (50S ribosomal protein L2 and lysine tRNA synthetase) and myelin basic proteins of the host, and that this similarity may lead to an autoaggressive response by the immune system [16].This phenomenon may occur due to misdirection of the immune response.

2.3.2. Immune mediators. Inflammatory mediators cause direct damage to tissue cells [17],possibly by inducing apoptosis or destroying cellular structures. For example, it is currently indicated that Mycobacterium leprae and cytokines may induce apoptosis in human Schwann cells [18].

2.3.3. Chronic inflammation. Prolonged immune activation and inflammatory response may lead to tissue fibrosis and loss of function, with long-term consequences for the health of the organism [19].

2.3.4. Immune tolerance. Due to prolonged exposure to high concentrations of antigens, the immune system may partially develop tolerance, weakening the effective response to pathogens and thus reducing the ability of the immune system to clear them [20].

These mechanisms are characterized in the polymicrobial form of leprosy by a sustained high load of antigenic exposure, and this sustained immune response and inflammatory state leads to typical clinical manifestations such as extensive skin damage and neurological dysfunction. Therefore, the ability to control these mechanisms of immune damage is critical to the treatment and prognosis of leprosy.

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2.4. Limitations of current research and future directions for patients with polymicrobial forms of leprosy

There is a paucity of literature related to the study of inflammatory mediators in leprosy, and no definitive experimental studies have been able to demonstrate which inflammatory mediators play a dominant role in the polymicrobial form of leprosy. Research on these aspects can be intensified in the future, while focusing on a comprehensive understanding of the entire network of inflammatory mediators in leprosy. To search for and characterize new inflammatory mediators and their roles in the polymicrobial form of leprosy to provide a more comprehensive understanding of the disease. To assess the impact of specific inflammatory mediators on the disease process in leprosy to provide a basis for new therapeutic approaches.

Mechanisms of immune injury regarding leprosy are extremely complex, and current research has failed to comprehensively analyze all of its components. To explore in depth the mechanisms of immune injury in leprosy, including changes at the cellular and molecular levels. To comprehensively analyze the immune response network and inflammatory pathways in leprosy using technologies such as transcriptomics, proteomics and metabolomics. To study how to effectively control immune tolerance and develop therapeutic approaches to modulate the immune system.

On the public health side, research should be conducted on how to control and prevent the spread of leprosy more effectively, especially among high-risk groups.

On the social front, mental health and social support systems for persons affected by leprosy should be strengthened and misconceptions and stigmas about leprosy should be eliminated in order to improve the social acceptance of persons affected.

In addition, the impact of factors such as geographical and genetic background, individual differences, long-term follow-up and chronic effects had not yet been sufficiently studied.

3. Conclusions

The mechanisms of production of inflammatory mediators and immune damage caused by massive antigenic exposure in patients with polymicrobial forms of leprosy have not yet been clearly characterized. An in-depth study of the associated inflammatory mediators and immune damage would provide a more complete understanding of the organism's knowledge of the cellular immune function of Mycobacterium leprae. The study of developmental mechanisms is crucial for improving diagnostic methods, treatments, and disease prevention.

The relationship between antigen exposure and immune damage in leprosy research is a very complex interaction process. The presence of Mycobacterium leprae in large numbers leads to sustained antigenic exposure, which triggers a strong immune response that may cause the immune system to activate the release of a large number of inflammatory mediators, e.g., TNF-α, IFN-γ, IL-1, IL-6, and others. These inflammatory mediators not only help to control the infection, but may also attack normal tissues, leading to tissue damage and chronic inflammation, especially in the skin and nerve tissues. Therefore, the treatment of polymicrobial leprosy should not only consider the elimination or reduction of pathogens, but also the control of the overactivation of the immune system and inflammatory damage.

It is crucial to study the direction of this area in the future, and in-depth research into the specific mechanisms of immune damage, particularly the role of inflammatory mediators in disease development, could help to develop better treatment protocols, potentially including immunomodulatory therapies and interventions targeting specific inflammatory pathways. In addition, such research could help to improve the prognosis of persons affected by leprosy and reduce health problems resulting from chronic inflammation caused by the disease.

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