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ROLE OF M1 MACROPHAGES IN TUBERCULOSIS: KEY PLAYERS IN IMMUNITY AND PATHOGENESIS

Annotation. This article explores the role of M1 macrophages in the immune response to tuberculosis (TB), focusing on their contributions to the pathogenesis of the disease. M1 macrophages, characterized by their pro-inflammatory properties, play a critical role in the initial immune defense against *Mycobacterium tuberculosis* (Mtb). These macrophages activate the immune system by producing pro-inflammatory cytokines such as TNF-α, IL-12, and IL-1β, as well as engaging in antimicrobial mechanisms through the generation of reactive oxygen species (ROS) and nitric oxide (NO). The formation of

granulomas, which contain the infection, is also influenced by M1 macrophages. The article discusses the balance between M1 and M2 macrophage activation, as dysregulation can lead to chronic inflammation or failure to eliminate the pathogen effectively. Additionally, therapeutic implications, including cytokine modulation and vaccine development strategies to enhance M1 macrophage function, are discussed as potential avenues for improving TB treatment and prevention.

Keywords: M1 macrophages, Tuberculosis. Mycobacterium tuberculosis, Immune response

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РОЛЬ МАКРОФАГОВ М1 ПРИ ТУБЕРКУЛЕЗЕ: КЛЮЧЕВЫЕ ФАКТОРЫ ИММУНИТЕТА И ПАТОГЕНЕЗА

Аннотация. В этой статье исследуется роль макрофагов M1 в иммунном ответе на туберкулез (ТБ), особое внимание уделяется их вкладу в патогенез заболевания. Макрофаги M1, характеризующиеся своими провоспалительными свойствами, играют важнейшую роль в начальной иммунной защите от микобактерий туберкулеза (Мтб). Эти макрофаги активируют иммунную систему, продуцируя провоспалительные цитокины, такие как TNF-α, IL-12 и IL-1β, а также задействуя антимикробные механизмы посредством образования активных форм кислорода (АФК) и оксида азота (NO). На образование гранулем, которые содержат инфекцию, также влияют макрофаги M1. В статье обсуждается баланс между активацией макрофагов M1 и M2, поскольку нарушение регуляции может привести к хроническому воспалению или неспособности эффективно устранить патоген. Кроме того, в качестве потенциальных путей улучшения лечения и профилактики туберкулеза обсуждаются терапевтические возможности, включая модуляцию цитокинов и стратегии разработки вакцин для усиления функции макрофагов M1.

Ключевые слова: макрофаги M1, туберкулез. Микобактерии туберкулеза, иммунный ответ.

Introduction. Macrophages are central players in the immune system's defense against infections, including tuberculosis (TB). *Mycobacterium tuberculosis* (Mtb), the causative agent of TB, primarily infects macrophages, and the outcome of the infection largely depends on the macrophages' ability to mount an effective immune response. Macrophages can differentiate into various phenotypic states, with the most relevant being **M1** and **M2** macrophages. The M1 phenotype is classically associated with a pro-inflammatory response, whereas M2 macrophages typically promote tissue repair and resolution of inflammation. In the context of TB, **M1 macrophages** play a pivotal role in initiating and sustaining immune responses that are critical for containing *Mtb* infection. This article delves

into the role of M1 macrophages in TB, their immune mechanisms, and their therapeutic potential in controlling TB infection.

Macrophage Polarization: M1 vs. M2. Macrophage polarization refers to the process by which macrophages adopt distinct functional phenotypes in response to specific environmental signals. This polarization is influenced by cytokines, microbial patterns, and the microenvironment.

1. **M1 Macrophages**:

- **Activation**: M1 macrophages are typically induced by **interferon-gamma (IFN-γ)** and **lipopolysaccharide (LPS)**, which activate the **Toll-like receptors (TLRs)**. The key features of M1 macrophages include the production of pro-inflammatory cytokines such as **tumor necrosis factor-alpha (TNF-α)**, **interleukin-1 beta (IL-1β)**, **IL-6**, and **IL-12**. These cytokines help to recruit other immune cells to the site of infection and promote the formation of **Th1 immune responses**, which are crucial for controlling intracellular pathogens like *Mtb* (Gautam & Schlesinger, 2016).

- **Effector Functions**: M1 macrophages are highly microbicidal due to the production of reactive oxygen species (ROS), **nitric oxide (NO)**, and **pro-inflammatory cytokines**. These molecules directly kill or inhibit the growth of pathogens, including *Mtb* (Harvie & Iyer, 2017). M1 macrophages also express high levels of **major histocompatibility complex (MHC) class II molecules**, facilitating antigen presentation to CD4+ T cells.

2. **M2 Macrophages**:

- M2 macrophages, in contrast, are induced by cytokines such as **IL-4**, **IL-13**, and **IL-10**. These cells are involved in immune regulation, tissue repair, and anti-inflammatory responses. While M2 macrophages are essential for resolving inflammation and promoting tissue healing, they are less efficient at killing pathogens like *Mtb* and may contribute to the persistence of infection by suppressing strong immune responses (Gautam & Schlesinger, 2016).

Role of M1 Macrophages in Tuberculosis

The M1 macrophage response plays a crucial role in the early stages of **Mtb** infection, as well as in the control and clearance of the pathogen. Here's how M1 macrophages contribute to the immune defense against TB:

1. **Recognition of *Mtb* and Inflammatory Response**:

- Upon infection, *Mtb* is recognized by **pattern recognition receptors (PRRs)**, such as **Toll-like receptors (TLRs)**, **NOD-like receptors (NLRs)**, and **C-type lectin receptors (CLRs)**, expressed on the surface of macrophages. Activation of these receptors leads to the production of pro-inflammatory cytokines that initiate the immune response. M1 macrophages respond to **IFN-γ** and **LPS**, both of which are present in the TB microenvironment, promoting the **Th1 immune response** (Cooper & Khader, 2008).

- M1 macrophages are essential for activating **CD4+ T cells** and **CD8+ cytotoxic T cells**, which are critical for controlling the infection. They also contribute to the formation of **granulomas**, which are organized aggregates of immune cells that attempt to contain the infection by restricting the spread of *Mtb* (Harvie & Iyer, 2017).

2. **Effector Mechanisms for Controlling *Mtb***:

- M1 macrophages play a critical role in controlling **intracellular pathogens**. Upon **phagocytosis** of *Mtb*, macrophages produce **reactive oxygen species (ROS)** and **nitric oxide (NO)**, both of which are toxic to the bacterium. The combination of ROS and NO, along with other antimicrobial peptides and proteins, contributes to the **intracellular killing** of *Mtb* within the phagosome (Zhao & Zhang, 2018).

- The antimicrobial activity of M1 macrophages is also associated with the activation of **autophagy**, a process that enables the degradation of intracellular pathogens within macrophages. Autophagy has been shown to play a role in the control of *Mtb* replication in macrophages (Cooper & Khader, 2008).

3. **Granuloma Formation and Immune Surveillance**:

- Granulomas are hallmark structures in TB that form in response to persistent infection. M1 macrophages contribute to the formation of granulomas,

which are essential for containing **Mtb** and preventing its dissemination. In the granuloma, M1 macrophages are surrounded by a variety of immune cells, including T cells, dendritic cells, and other macrophages, forming a microenvironment that limits bacterial spread (Harvie & Iyer, 2017).

- The granulomatous response is a double-edged sword: while it contains the infection, it can also lead to tissue damage if inflammation becomes uncontrolled. The role of M1 macrophages in granuloma formation is essential for controlling the infection but can also contribute to the pathology of TB if over-activated (Gautam & Schlesinger, 2016).

4. **Cytokine Production and Immunoregulation**:

- M1 macrophages are the main producers of key cytokines that influence the course of the immune response during TB. **TNF-α** is one of the most important cytokines produced by M1 macrophages in TB. TNF-α is essential for maintaining the granulomatous structure and for **macrophage activation**, which is necessary for *Mtb* control. However, excessive production of TNF-α can lead to tissue necrosis and damage, a hallmark of advanced TB pathology (Gautam & Schlesinger, 2016).

- Other cytokines produced by M1 macrophages, such as **IL-12**, help promote **Th1 polarization** and are critical for the **adaptive immune response** against *Mtb* (Cooper & Khader, 2008).

Challenges and Potential Therapeutic Implications. While M1 macrophages are essential for controlling *Mtb*, the immune response during TB is often suboptimal, leading to either **persistent infection** or **chronic inflammation**. In some cases, M1 macrophages may fail to effectively eliminate the pathogen, and the immune system may become dysregulated.

1. **Excessive Inflammation**:

- In some patients with **active TB**, **overactivation** of M1 macrophages can lead to tissue damage and necrosis. The **overproduction of cytokines** like **TNF-α** can result in **lung damage**, contributing to the characteristic **cavitary lesions** seen

in TB. Targeting the excessive activation of M1 macrophages could be a potential therapeutic approach to reduce tissue damage (Harvie & Iyer, 2017).

2. **M1/M2 Balance**:

- An effective immune response against *Mtb* requires a balance between M1 and M2 macrophages. The resolution of inflammation after initial infection is critical for preventing tissue damage while maintaining effective immunity. Therapeutic strategies that modulate the balance between M1 and M2 macrophages could potentially help in reducing inflammation without compromising the immune response to *Mtb* (Zhao & Zhang, 2018).

3. **Therapeutic Approaches**:

- Modulating the activation of M1 macrophages through **cytokine therapy** or **small molecules** could enhance the immune response against TB. **TNF-α inhibitors**, while useful in some contexts, must be carefully managed in TB patients, as they can exacerbate infection. On the other hand, **IFN-γ** therapy may enhance M1 macrophage function and promote better control of the infection (Gautam & Schlesinger, 2016).
- **Vaccine development**: Understanding the role of M1 macrophages in the immune response to *Mtb* can inform the design of vaccines that enhance **macrophage-mediated immunity**, potentially improving protection against TB (Cooper & Khader, 2008).

Conclusion. M1 macrophages are central to the immune defense against tuberculosis. Their ability to produce pro-inflammatory cytokines, engage in antimicrobial activity, and contribute to granuloma formation makes them crucial players in the control of *Mtb* infection. However, the balance between pro-inflammatory and anti-inflammatory responses is delicate, and dysregulation of this balance can result in tissue damage or persistent infection. Targeting M1 macrophages and their signaling pathways holds potential for novel therapeutic strategies to enhance the immune response against TB, reduce tissue damage, and improve treatment outcomes, especially in patients with latent or active TB.

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