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REVIEW

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Phagocytosis: strategies for macrophages to hunt *Mycobacterium tuberculosis*

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Abstract

Macrophages, as crucial innate immune cells, play a fundamental role in combating *Mycobacterium tuberculosis* (Mtb). The most powerful strategy for macrophages to eliminate Mtb is phagocytosis. They identify extracellular pathogens through various receptors and then engulf them, eliminating pathogenic microorganisms through reactive oxygen species, reactive nitrogen species, and a range of enzymes derived from phagosome-lysosome fusion. However, this process may also provide a potential ecological niche for Mtb. This is due to the fact that Mtb is capable of ensuring its survival within macrophages. Mtb infection results in obstructing the usual phagosome maturation and acidification. In addition, Mtb is capable of escaping from phagosomes and entering the cytoplasm of its host cell. This process of escaping phagosomes appears to promote necrosis in infected macrophages, and facilitate the expansion of intracellular bacterial populations. Therefore, enhancing the bactericidal capacity of macrophages or preventing Mtb invasion may prove to be a promising strategy for the adjuvant treatment of tuberculosis. This review highlights the processes and outcomes of macrophage recognition and phagocytosis of Mtb, and describes the mechanisms involved in Mtb resistance to phagocytosis. Moreover, recent advances in the modulation of macrophage phagocytosis to assist in the treatment of tuberculosis will be discussed.

Keywords Phagocytosis, Macrophages, *Mycobacterium tuberculosis*

Introduction

The macrophage is a type of innate immune cell known for its potent phagocytic abilities [1]. They play a crucial role in defending the host against the invasion of pathogenic microorganisms. However, their effectiveness is not always guaranteed, especially when it comes to combating *Mycobacterium tuberculosis* (Mtb), the primary causative agent of tuberculosis — a globally prevalent disease with significant mortality rates. In 2022, the estimated global incidence of tuberculosis was 10.6 million patients, with approximately 1.3 million deaths attributed to the disease globally in that year. While this was down from the best estimates of 1.4 million in both 2020 and 2021, it remains the second leading single infectious cause of death globally after coronavirus disease [2]. Mtb is a successful pathogen that primarily invades the host through the respiratory tract via droplets or aerosols. Once it breaches the immune barrier of the respiratory tract and enters the lungs, it comes into contact with alveolar macrophages [3]. Macrophages capture Mtb by phagocytosis and isolate it in phagosomes, employing various mechanisms to kill the imprisoned Mtb. However, Mtb has evolved mechanisms to evade macrophage killing, leading to a battle between them that greatly influences the course and outcome of Mtb infection [4, 5].

In macrophages, the processes of phagocytosis and phagolysosome biogenesis are fundamental for maintaining tissue homeostasis, facilitating development,

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eliminating invading microorganisms, and processing and presenting antigens. These processes also play a significant role in the interaction between Mtbs and macrophages. When macrophages engulf Mtb, they form phagosomes. Subsequently, several metabolic changes occur in macrophages, including an increase in oxygen uptake known as the respiratory bursts. The generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) during this process are crucial mechanisms employed by macrophages to kill Mtb [6, 7].

Phagosome formation triggers a pre-programmed pathway of phagosome-lysosome fusion, a process regulated by Ca^{2+} as well as by the small GTP-binding proteins Rabs and their downstream effectors involved in organellar trafficking [8]. The acidic environment within the fused phagolysosome facilitates the action of lysosomal enzymes, such as cell wall lysozyme, protease, nuclease, and other hydrolases, which ultimately mediate the killing process [9]. Unfortunately, Mtb can interfere with the Rab-controlled membrane trafficking, leading to the arrest of phagosome maturation. This perturbation significantly weakens the bactericidal capacity of phagosomes against intracellular pathogens. This process, known as Mtb-induced phagosome maturation arrest or inhibition of phagosome-lysosome fusion, is crucial for the successful hiding of Mtb in macrophages [4].

The phagocytosis of macrophages plays a crucial role in resistance to Mtb. Here, we review how macrophages use phagocytosis to hunt and eliminate Mtb. A deeper understanding of phagocytosis may contribute to our comprehension of the dynamic interaction between macrophages and Mtb, providing valuable insights into the complex interplay between macrophages and Mtb.

Macrophages recognize and capture Mtb

Mtb is initially recognized and engulfed by alveolar macrophages upon breaching the immune barrier of the upper respiratory tract [10]. Although other immune cells also aid in mycobacterial phagocytosis, alveolar macrophages are the primary phagocytic site during the initial stages of infection [6, 11]. For this reason, alveolar macrophages are considered sentinels in the process of Mtb infection. The main mechanism by which macrophages recognize and consume microorganisms is receptor-mediated phagocytosis [12]. Several receptors, such as Fcγ receptors (FcγRs) [13], complement receptor [14, 15], mannose receptor [16], surfactant protein A [17], CD14 receptor [18], and scavenger receptor [19, 20], are involved in this process. Receptor-mediated phagocytosis can occur through either opsonic or non-opsonic mechanisms.

Opsonization phagocytosis

Opsonization phagocytosis refers to the uptake of bacteria by macrophages that have been coated with complement factors, antibodies, and surfactants [21]. For example, FcγRs on the surface of macrophages recognize bacteria bound by immunoglobulin G, while the CR3 receptor identifies bacteria coated with complement factor C3bi [13]. Surfactant protein A enhances the interaction between Mtb and macrophages by directly increasing phagocytosis and acting as a bacterial opsonin. On the other hand, surfactant protein D can accumulate Mtb and reduce phagocytosis [17]. In addition, soluble mannose, which is predominantly found in the blood, binds with lectins to enhance Mtb infection by promoting the entry of Mtb into phagocytes, facilitating pathogen transmission, and aiding the establishment of infection [17]. While opsonization-mediated macrophage phagocytosis can occur during mycobacterial infection, it is generally accepted that non-opsonization phagocytosis is the predominant phagocytic mechanism early in the infection process [21].

Non-opsonization phagocytosis

Non-opsonization phagocytosis is primarily based on the recognition of pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRR_S) on macrophages (Fig. 1). Some macrophage PRRs involved in the identification of Mtb include C-type lectin receptors, toll-like receptors (TLRs) [22], Nod-like receptors (NLRs), scavenger receptors, CD14, and cytoplasmic DNA sensors [21]. These receptors allow macrophages to recognize specific molecular patterns on Mtb and initiate phagocytosis without the need for opsonins such as antibodies or complements.

The mannose receptor (MR) is a C-type lectin receptor that can recognize glycolipids, such as Lipoarabinomannan (LAM) and mannose-capped lipoarabinomannan (ManLAM), which are abundantly expressed, on the surface of Mtb [23]. Phagocytosis of Mtb by host macrophages is predominantly mediated by MR. The association between MR and phagocytosis depends on the length and abundance of ManLAMs exposed on the bacterial surface [24]. The involvement of MR in the phagocytosis of ManLAMs is crucial for limiting phagosome-lysosome fusion, enabling the bacteria to establish a unique ecological niche within the host cell, known as the mycobacterial phagosome [25]. In addition, studies suggest that MR-mediated Mtb recognition triggers tyrosine residue phosphorylation and Grb2 recruitment, activating the Rac/Pak/Cdc-42 signaling cascade, which is important for Mtb uptake [26]. Activation of MR mediates Grb2 recruitment thereby initiating the phagocytosis signaling pathway, and MR-dependent restriction of

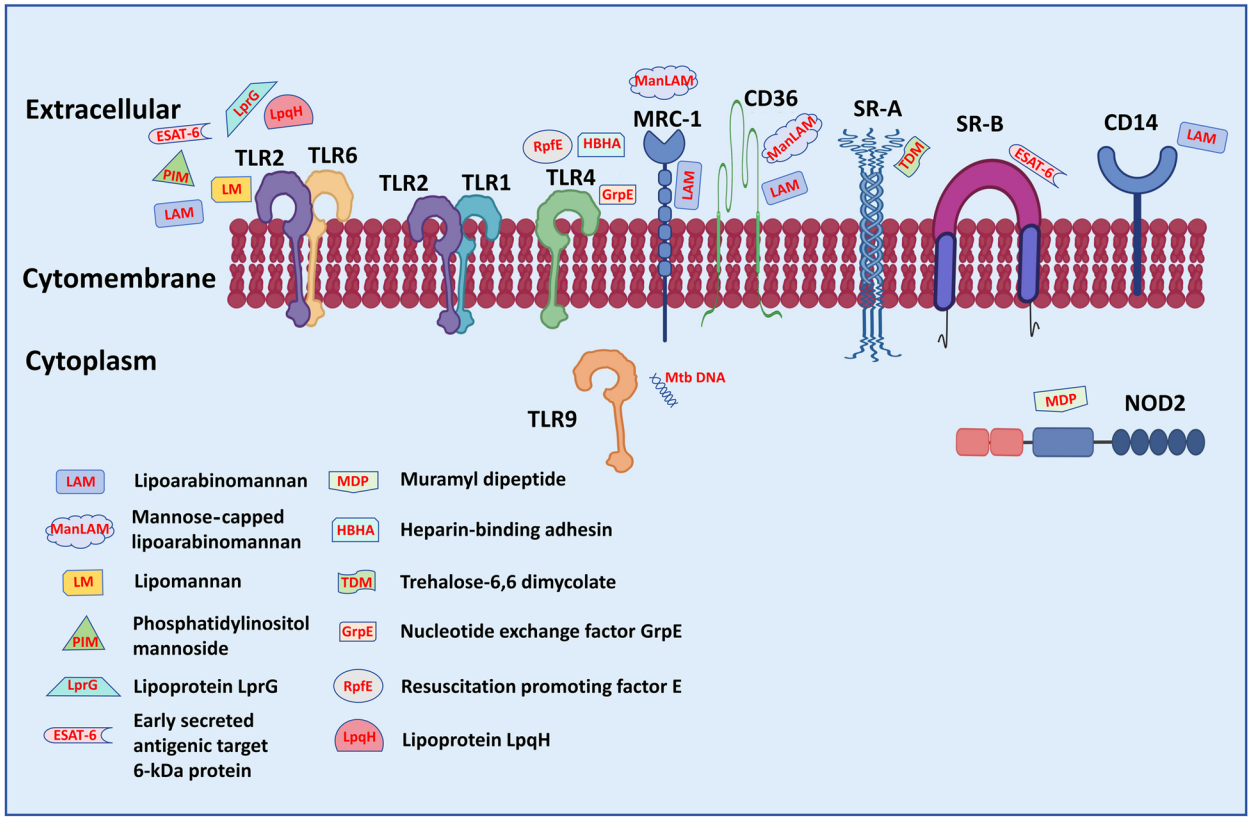

Fig. 1 The pattern recognition receptors (PRRs) involved in Mtb infections. PRRs responsible for recognizing of mycobacterial pathogens and their cellular locations are shown in black. The corresponding ligands for each receptor are represented in red. TLR1: Toll-like receptor 1; TLR2: Toll-like receptor 2; TLR4: Toll-like receptor 4; TLR6: Toll-like receptor 6; TLR9: Toll-like receptor 9; MRC-1: Mannose receptor C type 1; CD14: Cluster of differentiation 14; CD36: Cluster of differentiation 36; SR-A: Scavenger receptor class A; SR-B: Scavenger receptor class B; NOD2: Nucleotide-binding oligomerization domain 2

SHP-1 recruitment limits phosphatidylinositol 3-phosphate (PI3P) generation and phagosome-lysosome fusion.

Many mycobacterial components (such as LAM, ManLAM, Early secreted antigenic target 6-kDa protein (ESAT-6), Phosphatidylinositol mannoside (PIM), etc.) interact with TLR2 and induce cell apoptosis [27, 28]. Mtb enters macrophages via TLR2 and induces apoptosis via the p38 MAPK pathway [29]. Additionally, Mtb targets the TLR2/MyD88 pathway to escape phagocytic restriction, in contrast to the *Mycobacterium bovis* Bacillus Calmette-Guérin (BCG) vaccine [30]. Mtb can activate Toll-like receptor 1 (TLR1) and Toll-like receptor 6 (TLR6), which form heterodimers with TLR2 and are involved in the recognition of *Mycobacterium* antigens [31, 32]. In a model of tuberculous pleurisy, crosstalk between different receptors, including TLR2, TLR4, and MR, effectively induces interferon-γ (IFN- γ) production upon Mtb binding [33].

Additionally, CD14 can bind to LAM, a major structural surface component of Mtb, leading to macrophage secretion of interleukin-8 [34]. Other receptors such as CD40, CD43, and CD44 have also been implicated in mycobacterial recognition [35–37]. Nucleotide-binding oligomerization domain 2 (NOD2) plays an important role in the recognition and control of mycobacterial infection [38]. The activation of NOD2 by muramyl dipeptide (MDP) in Mtb-infected human alveolar macrophages has been shown to increase bacterial growth control and recruit autophagy-related proteins to phagosomes/autophagosomes containing bacteria [39].

While in vitro studies have provided insights into the role of specific receptor(s) in mycobacterial infection, in vivo studies using receptor-deficient animals have often shown little or no effect on Mtb infection. It is likely that Mtb infection does not occur solely through a single receptor-mediated pathway [40, 41]. Receptors vary in function and expression in different cells [12]. Substitution or supplementation of different receptors is more important in the complex environment of multiple cells in vivo. In addition, the type and expression of receptors may vary between different environments

for a given cell in vivo. This implies that multiple factors must be taken into account when studying receptor effects.

Formation and maturation of the phagosome

The formation of the phagosome

After encountering macrophages and other phagocytes, Mtb interacts with extracellular receptors. This interaction triggers the activation of cytoskeletal regulatory molecules within the phagocyte, leading to the reorganization of the actin cytoskeleton and the extension of membrane processes around the mycobacteria. This process results in the formation of a structure called the phagocytic cup [8, 42]. Once the phagocytic cup is sealed, it matures into a phagosome. Shortly after sealing, the phagosome then matures through processes such as acidification and fusion with lysosomes. These steps are important for the degradation of engulfed material, including mycobacteria, within the phagosome [42]. Overall, the interaction between Mtb and phagocytes triggers a series of events involving the activation of cytoskeletal regulatory molecules, membrane reorganization, and phagosome maturation, which are essential for the engulfment and subsequent degradation of the bacteria.

The acidification of the phagosome

Acidification of the phagosome is primarily achieved by the recruitment of the V-ATPase pump, a protein complex responsible for transporting protons across the phagosome membrane [43]. Upon recruitment of the V-ATPase pump, the phagosome pH decreases from approximately 6.5 to approximately 4.5 [44]. The acidification process begins immediately after the sealing of the phagocytic cup is sealed and progresses gradually, reaching pH values as low as 4.5–5.0 in certain cell types. However, it is important to note that the rate and extent of phagosome acidification can vary significantly among different types of phagocytes. For example, neutrophils tend to maintain a slightly alkaline phagosome pH for prolonged periods [45]. M2 macrophages, which are induced by the cytokine interleukin-4, rapidly reach high acidic pH levels within minutes of phagosome sealing [46]. These differences in phagosome pH reflect the specific functions of different phagocytes. M2 macrophages are typically involved in the clearance and recycling of cellular fragments at a steady state. Accordingly, the hydrolytic enzymes derived from lysosomes, exhibit optimal activity at acidic pH, making acidification essential for efficient degradation of phagocytosed material. In contrast, phagosomes of human M1 macrophages, like those in neutrophils, maintain a pH close to neutral [45, 46]. This neutral pH is advantageous for preserving certain antigens for presentation to immune cells. The acidification in M1 macrophages may result from increased ROS production and decreased proton pump activity [46]. The function of M1 cells during Mtb infection remains unclear. Further research is needed to determine the balance between ROS production and phagosome maturation.

The formation of phagolysosomes

Fusion of the phagosome with the lysosome is responsible for phagosome maturation, leading to the formation of phagolysosomes. The Rab family of small GTPases plays a critical role in this process, regulating vesicular trafficking between organelles by controlling the recruitment of binding partners and interactions with the cytoskeleton [47]. Phagosomes first fuse with early endosomes and acquire the small GTPase Rab5. The Rab5 effector, rabaptin-5, recruits the class III phosphoinositide 3-kinase vacuolar protein sorting 34 (vps34) [48]. The activity of molecules such as vps34 leads to the cyclic accumulation of PI3P on phagosomes [49]. PI3P mediates the recruitment of early endosome antigen 1 (EEA1) and class C core vacuole/endosome tethering (CORVET) complexes to the phagosome membrane [50]. This recombination and fusion process is critical for the progression of phagosome maturation. The subsequent removal of Rab5 from the phagosome surface and the recruitment of the Rab7 GTPase indicate the transition from early to late phagosomes, which then undergo fusion with late endosomes and/or lysosomes [51, 52]. The MON1-CCZ1 complex plays a key role in this process known as Rab conversion [53]. However the process is still not fully understood. The complete maturation of phagosomes requires the emission of tubular extensions, which are generated by the activation of Rab7, the recruitment of Rab-interacting lysosomal protein (RILP), and the subsequent association of phagosomes with microtubule-associated motors [52]. The fusion of phagosomes with lysosomes requires the presence of N-ethylmaleimide sensitive factor (NSF), soluble NSF attachment proteins (SNAPs) and Rab7. In addition, the SNAP receptors vesicle-associated membrane protein 7 (VAMP7), vesicle-associated membrane protein 8 (VAMP8), syntaxin 7, and syntaxin8 have been identified as important components of the lysosomal fusion machinery [54]. During this process, the phagocytosis of small bodies leads to the incorporation of lysosomal-associated membrane proteins 1 (LAMP1) and 2 (LAMP2), which are essential for the later stages of maturation and the elimination of microorganisms [55].

Although phagosome maturation is a conserved process, the outcome can vary among different cell types

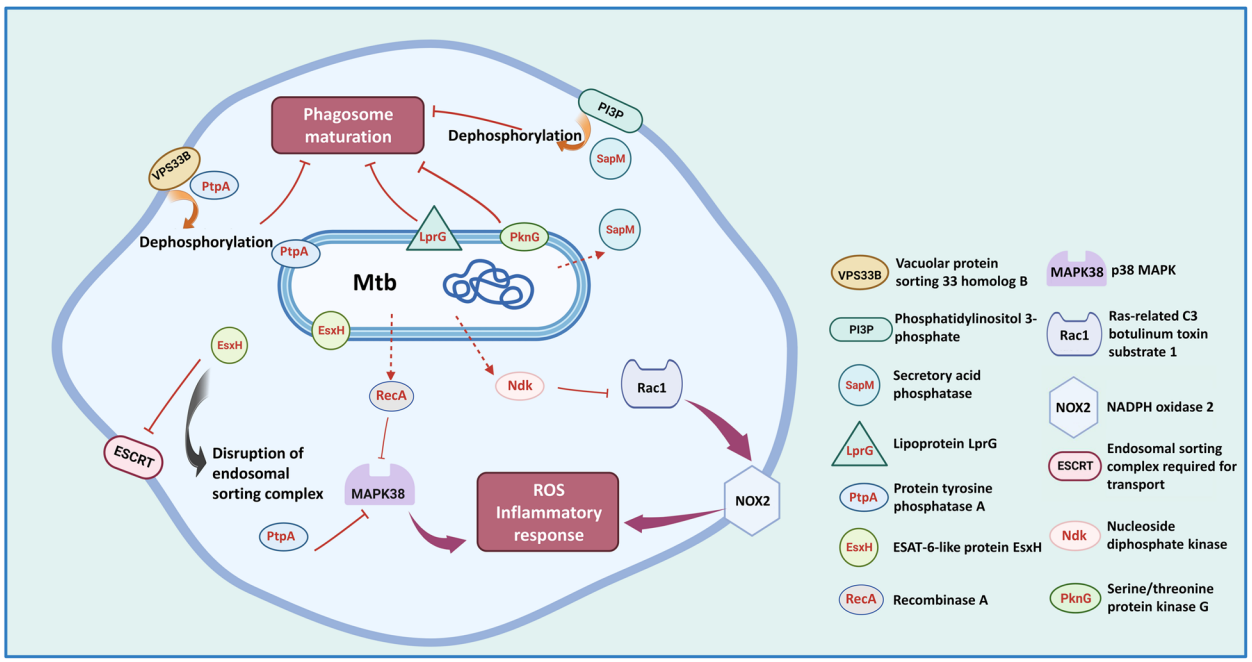

Fig. 2 The factors of *Mycobacterium tuberculosis* interfering with macrophage functions. Schematic representation of different levels of interference by mycobacterial factors in host phagosome maturation and ROS inflammatory response. Mycobacterial factors are depicted in red and host factors in black

[56]. Consistent with the characteristics of phagosome acidification, neutrophils and most macrophage populations exhibit rapid destruction of phagocytosed material through efficient phagosome maturation. In these cells, the phagosomes completely degrade their cargo contents, ensuring efficient clearance of pathogens or cellular debris. However, to preserve antigenic peptides for presentation, Phagosomes of dendritic cells often undergo partial degradation rather than complete degradation of phagocytosed material. This allows the preservation of intact antigens within the phagosome, which can then be processed and presented on the cell surface to activate T cells [57]. In macrophages, M1 macrophage polarization induced by long-term stimulation with IFN-γ and lipopolysaccharide reduces not only phagosome fusion but also phagosomal acidification. Conversely, M2 macrophage polarization accelerates the kinetics of phagosome maturation [46]. This results in faster phagosomal acidification and an enhanced proteolytic capacity of their phagosomes.

Resistance of Mtb to phagocytosis

Macrophages eliminate pathogens in various ways

Activated macrophages use different mechanisms to eliminate Mtb, including the generation of ROS and RNS [6]. The process of generating ROS and RNS is known as the respiratory burst, which encompasses a series of metabolic changes following macrophage activation upon phagocytosis. Several enzymes are involved in generating ROS free radicals, including NADPH oxidase located on the phagosomal membrane. This enzyme reduces O_2 to superoxide anion, which is subsequently transformed into hydrogen peroxide by the action of superoxide dismutase [58]. Nitric oxide (NO) is produced by nitric oxide synthase in M1 macrophages, and NO can easily react with superoxide to form peroxynitrite, anions, and nitrogen dioxide [59]. These oxygen-dependent killing mechanisms have crucial functions in macrophage-mediated defense against Mtb. Furthermore, phagosomes within macrophages fuse with lysosomes, creating an acidic environment that facilitates the function of hydrolytic enzymes, namely cell wall lytic enzymes, proteases, and nucleases present in the lysosome. These enzymes contribute to the destruction of Mtb by degrading its cellular components [59, 60]. Moreover, antimicrobial peptides known as defensins play vital roles in killing pathogens within macrophages.

Mtb is capable of surviving within macrophages

Although phagocytosis by macrophages can eliminate pathogens in various ways, Mtb specifically targets alveolar macrophages as the main host owing to its ability to ensure its survival within macrophages. Several studies have shown that alveolar macrophages contribute to the

invasion of Mtb, especially in the early stages of infection [61, 62]. One distinctive trait of Mtb is its capability to obstruct the usual phagosome maturation and acidification [63]. To achieve this, Mtb utilizes multiple methods to hinder phagosome maturation, such as the secretion of various macromolecules that interrupt this process (Fig. 2). For instance, early research indicated that the Mtb protein tyrosine phosphatase A (PtpA) targets the V-ATPase machinery, impeding phagosomal acidification [64]. Another phosphatase, secretory acid phosphatase (SapM), also plays a role in blocking phagosome maturation [65, 66]. Additionally, Mtb serine-threonine-protein kinase G (PknG) decreases the expression of host protein kinase C-α (PKC-α), hindering phagolysosome biogenesis [67, 68]. Lipoamide dehydrogenase (LPDC) facilitates the retention of coronin 1 on BCG vacuoles, thus preventing phagosome fusion [69]. The other "weapons" of macrophages, including ROS and inflammatory responses, are also impeded by Mtb. Sun et al. reported that nucleoside diphosphate kinase (Ndk) of Mtb drastically contributes to its virulence by attenuating the host innate immunity mediated by NADPH oxidase [70]. Moreover, the PPE2 (Rv0256c) protein that belongs to the proline–proline–glutamic acid protein (PPE) family directly interacts with p67phox, which is a cytosolic subunit of the host NADPH oxidase, through an SH3-like domain to hinder ROS production and promote the intracellular survival of Mtb in macrophages [71]. Mtb is captured and engulfed by macrophages as prey. However, it only tears off its camouflage once it has entered the phagosome. Subsequently, Mtb employs its abundant means to nullify the bactericidal mechanisms of macrophages, thereby allowing it to survive in the cell for an extended period. Furthermore, Mtb manipulates macrophages, inducing the differentiation of subtypes that favor the survival of the bacteria. Mily et al. discovered that Mtb infection lasting 24 h can encourage the transition of macrophages toward the M1 polarization direction [72]. The limited acidification of M1 cells weakens the protease effect and may inhibit other important bactericidal mechanisms. For these virulence factors, the construction of attenuated strains via gene deletion to prevent the manipulation of macrophages by MTB is important for the ongoing development of TB vaccines.

Mtb is capable of escaping from phagosomes

Mtb can escape from phagosomes and enter the cytoplasm of its host cell [73]. This process of escaping phagosomes seems to promote necrosis in infected macrophages and, as a result, increases the expansion of intracellular bacterial populations [74]. The escape of Mtb from phagosomes is facilitated by damage to the phagosome membrane, which is caused mainly by virulence factors such as ESAT-6 [75]. ESAT-6 is secreted by one of the several type VII secretion systems (T7SSs), Esx-1. ESAT-6 is known to form membrane pores that facilitate the escape of Mtb to the cytosol [76]. The ESAT-like protein EsxP inhibits phagosome maturation, leading to the escape of Mtb from phagosomes into the cytoplasm, which further triggers the host's cytoplasmic sensing pathway, STING/TBK1, to up-regulate the transcription of interferon-β (IFN-β) [77]. Once Mtb escapes from the phagosomes, its DNA also enters the cytoplasm and interacts with cyclic GMP-AMP synthase (cGAS) [78]. Subsequently, IFN-β production is induced, which is harmful to the host in the context of Mtb infection [79].

While macrophages are capable of entrapping and destroying Mtb via xenophagy when it breaks into the cytoplasm, Mtb has developed avenues to thwart, tune, or manipulate the host autophagic reaction [6]. A study has shown that macrophages infected with Mtb can increase the expression of interleukin-6 and hinder IFN-γ by reducing the autophagosome biogenesis induced by the Atg12-Atg5 complex [80]. Shin et al. discovered that when macrophages were infected with a deletion mutant of Mtb known as enhanced intracellular survival (EIS) protein there was a noteworthy increase in autophagosome formation [81]. Additionally, mTOR, a negative regulator of autophagy, could be activated by highly virulent strains of Mtb [82]. Duan et al. showed that EIS restrains autophagy in macrophages by increasing the activity of the Akt/mTOR/p70S6K pathway and upregulating the expression of interleukin-10 [83].

These results reveal that Mtb has developed methods to enable the bacterium to evade elimination and sustain its survival inside host cells. The evasion strategies employed by Mtb allow the bacterium to surmount the host's macrophage-killing mechanisms, ultimately resulting in persistent infection. Comprehension of these mechanisms is indispensable for devising tactics to nullify Mtb evasion strategies, increase the host immune response, and develop more efficacious treatments for tuberculosis.

Macrophage-targeted therapy for tuberculosis

The targeting of host cells for modulation represents a significant adjuvant therapy in the treatment of tuberculosis, known as host-directed therapy (HDT). It is anticipated that HDT will reduce the duration of treatment and the toxicity of host-responsive inflammation, thereby enhancing the efficacy of therapeutic intervention [84]. Furthermore, HDT may facilitate the treatment of drug-resistant tuberculosis with minimal exposure to tuberculosis drugs, which could contribute to slowing the development and spread of drug-resistant Mtb [84].

Inhibition of Mtb entry into macrophages

A common therapeutic strategy for limiting disease pathogenesis is the direct inhibition of pathogen entry into target host cells. However, this strategy is particularly challenging during Mtb infection because a major target cell, the alveolar macrophage, is also key to host initiation of the immune response [4, 5]. Macrophages are capable of actively recognizing and phagocytizing Mtb through a variety of mechanisms, with their internalization pathway greatly influencing the microbial killing efficiency. Moreover, the extent to which different receptors contribute to this process and their role in the disease process remains unclear [21]. Nevertheless, some progress has been made. A tyrosine kinase inhibitor (Imatinib) employed in cancer therapy has been demonstrated to regulate the uptake of Mtb and facilitate the eradication of the bacteria both within and beyond the host [85]. It has been demonstrated to be high efficacious when administered in conjunction with anti-mycobacterial agents [85]. A decrease in macrophage internalization of Mtb may increase the targeting of antibiotics to the bacteria. Alternatively, the inhibition of a specific internalization pathway may lead to the activation or enhancement of a different uptake mechanism in macrophages, thereby increasing their ability to eliminate bacteria.

Enhancement of the bactericidal capacity of macrophages

Antimicrobial peptides (AMPs) are produced by Mtb ligands following the activation of TLRs in the cytoplasm. These AMPs are responsible for the killing of bacteria by targeting the cell wall of Mtb. Thereby, modulating the activity or production of antimicrobial peptides represents an attractive option for HDT [86]. The active form of vitamin D, 1,25-dihydroxyvitamin D3, induces the production of AMPs and ROS. It is currently being developed as an HDT for the treatment of tuberculosis. Moreover, phenylbutyrate and vitamin D have been reported to exert a synergistic effect [87, 88]. Furthermore, the use of autophagy inducer, such as IFN-γ, increases the delivery of Mtb to autophagosomes and activates these autophagosomes via lysosomal fusion, thereby increasing the clearance of Mtb [89]. The restoration of histone deacetylase sirtuin 1 (SIRT1) activity by an activator of SIRT1 (SRT17200) has been demonstrated to contribute to autophagy and lysosome mediated killing of Mtb [90].

Conclusions

Macrophages are commonly regarded as beneficial for eliminating mycobacteria. They capture and eliminate mycobacteria through phagocytosis [3]. The elimination of Mtb by macrophages has implications for adaptive immunity. By sequestering and eliminating bacteria within phagosomes, macrophages acquire antigen peptides that are presented to T cells, facilitating an adaptive immune response against Mtb [56, 91]. Phagocytosis is an essential component of an organism's resistance to mycobacteria. However, it is also crucial for Mtb to establish early infection [3]. Mtb has developed several mechanisms to evade macrophage killing and establish long-term infection. These mechanisms hinder phagosome maturation, modulate autophagy, and manipulate host immune responses.

Despite the current understanding of the interaction between macrophages and Mtb, the development of effective clinical treatments remains a challenge [4]. The design of immune-enhancing regimens against macrophage phagocytosis or potential therapeutic targets may prove promising for the treatment of disease. The appropriate attenuation of phagocytosis in the early stages of infection may prove a method of avoiding the establishment of infection by Mtb. Furthermore, bacteria that are exposed to the extracellular may be more sensitive to antibodies or antibiotics [3]. The functions of M1 and M2 may have disparate implications for bactericidal and assisted immunity [46]. This may represent a potential strategy for host-directed therapies, whereby the differentiation of macrophages at varying stages of infection could be directed to enhance antigen presentation and phagosomal bactericidal capacity. In summary, to develop clinical adjuvant therapies and explore novel approaches for the prevention and treatment of active tuberculosis, it is crucial to gain a deeper understanding of the complex interactions between macrophages and Mtb.

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Authors' contributions

X.C. and X.J. conceived the idea and laid out the outline of this review. D.L., J.W. generated the figures. Z.X. edited the figures. All authors participated in the interpretation of initial ideas and writing the manuscript. All authors read and approved the final manuscript.

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Data availability

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication
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Competing interests
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