STM JOURNALS

International Journal of
Pathogens

ISSN: 3048-829X
Volume 3, Issue 2, 2026
July–December
DOI (Journal): 10.37591/IJPG

https://journals.stmjournals.com/ijpg

Review IJPG

Decoding the *Mycobacterium Tuberculosis*-Macrophage Interplay: From Immune Defense to Pathogen Persistence

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Abstract

Tuberculosis (TB) is a chronic infectious disease caused by Mycobacterium tuberculosis (Mtb) and has been responsible for over one billion deaths worldwide over the past two centuries, remaining a major global health challenge despite advances in diagnosis and treatment. The barriers that make tuberculosis difficult to treat and eliminate are inextricably tied to its intracellular habitat. However, a research gap lies in understanding the molecular mechanisms of its survival and host cellular defense against the pathogen. Thus, it is relevant to understand the insights related to the interactions between Mtb effectors and macrophages, the first interacting host cells. In the present review, we highlighted the interactions between Mtb effectors and macrophages. We additionally explored and discussed how Mtb manipulates the defense mechanisms of macrophages to survive and the ability of macrophages to govern and destroy Mtb. The biological processes illustrated in the review explain the control and elimination of Mtb through a variety of mechanisms, including autophagy, apoptosis, inflammasome stimulation, ncRNA activity, phagosomal pH imbalances, and the production of antimicrobial chemicals. However, these difficult conditions reveal Mtb's limitations in its capacity to manage and make use of them for survival. The discrepancy in Mtb-macrophage crosstalk, where macrophages fail to successfully manage Mtb infection, supported by the expanding discovery of Mtb egress mechanisms, should be the key problem in TB control. These insights offer important clues related to the pathways and events providing information essential for TB diagnosis, treatment and prevention.

Keywords: Tuberculosis, *mycobacterium tuberculosis*, macrophages, Mtb effectors, Mtb-macrophages interaction

INTRODUCTION

The human mucosal hindrance is made up of macrophages, epithelial lining, inflammatory reactions, and secreted soluble chemicals [1]. Invading pathogen detection, microbicidal mechanism activation, and subsequent immune response coordination are all parts of the programming of macrophages. There are macrophages in every part of the body, and there are two main groups found in the lungs: interstitial macrophages and alveolar macrophages [2].

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Received Date: June 24, 2026
Accepted Date: June 02, 2026
Published Date: July 20, 2026

Citation: Muskan Jain, Reetika Debroy. Decoding the *Mycobacterium Tuberculosis*-Macrophage Interplay: From Immune Defense to Pathogen Persistence. International Journal of Pathogens. 2026; 3(2): 55–70p.

According to the 2021 report on Global Tuberculosis, Mtb is an obligatory intracellular bacterium that infects approximately 10 million people annually. The current coronavirus disease (COVID-19) is a global epidemic, which has overturned gains and losses in the fight against TB by many years, and has killed 1.5 million people because of the disease. This bacterium targets alveolar macrophages when it enters the lungs

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through the respiratory system. Mtb needs to engage with the host macrophage to effectively carry out the infection.

The spread of the Mtb process can randomly resume through the following major steps: Pathogen-associated molecular patterns (PAMPs) are used to attach Mtb, after that, host macrophage pattern recognition receptors (PRRs) are used to identify Mtb, and Macrophages get stimulated, intracellular cascades are activated, and signaling pathways are enhanced [3, 4]. Mtb's intracellular interaction with macrophages is difficult and complex because of the adverse intracellular macrophage environment (ROS and RNS production, acidic pH, food shortage, etc.).

Despite the obstructed hindrance of macrophages, Mtb can successfully establish infection by evading host macrophage defenses via evolving escape methods [4]. This ability to escape has consequences for tuberculosis prevention, including low vaccine potency, multi- and extensively drug-resistant tuberculosis (MDR-XDR), protracted treatment, and high tuberculosis incidence.

Treatment and TB control will be aided by an understanding of the coevolution of Mtb and the host macrophage. The Mtb-macrophage crosstalk has been the topic of extensive investigation, yet it is still not fully understood. Is this because Mtb has the genetic resources necessary to circumstantially adapt to and thrive in the unfavorable environment of macrophages [4]. To clarify crucial mechanisms and identify prospective molecular targets, we examine the key determinants of Mtb and newly discovered molecular processes that characterize various stages of this interaction.

MYCOBACTERIUM TUBERCULOSIS

The bacteria that cause tuberculosis, *Mycobacterium tuberculosis* (Mtb), continue to be of tremendous interest on a global basis. The new coronavirus infection (COVID-19) has made significant gains and advanced the fight against tuberculosis by many years. Mtb is an obligatory intracellular bacterium, first identified by Robert Koch as the causing agent of human tuberculosis (TB) more than a century. Mtb affects about 10 million people annually, of whom 1.5 million die from it. The peculiar, waxy coating on the cell surface of Mtb caused by the presence of a dense layer of mycolic acid within the cell wall makes it resistant to Gram staining, although Mtb is genetically closer to Gram-positive bacteria [5].

Mtb exhibits very high aerobic physiology and needs an abundance of oxygen to exist. It affects the lungs and is primarily a bacterium of the mammalian respiratory system. Around 4,000 genes make up the 4.4 106 Mbp Mtb H37Rv genome. The Mtb genome's annotation reveals that this bacterium has a few distinctive characteristics. More than 200 genes, or appx. 6% of the total are designated as genes encoding for enzymes taking part in the metabolism of fatty acids [6]. Macrophages, epithelial lining, inflammatory responses, and released soluble things form the host mucosal barrier. The programming of macrophages includes the identification of approaching pathogens, activation of microbicidal mechanisms, and coordination of the subsequent immune response. It is considered that Mtb has its initial interaction with resident macrophages when it enters the alveolar passages of exposed humans as an aerosol droplet, but it is also conceivable that the pathogen could be initially ingested by alveolar epithelial type II pneumocytes. In alveoli, this type of cell is more abundant than macrophages, and Mtb can colonize and survive *ex-vivo* in these pneumocytes [6].

Host Cells and Environment for Mtb

TB is spread by airborne droplets generated from the sneeze or cough from a diseased person to an uninfected individual. Upon inhalation by a healthy individual, the pathogen-containing droplets travel via the mouth or nasal passages, upper section of the respiratory system, and the bronchi to reach the lung's alveoli. Although tuberculosis highly affects the lungs, it can also spread to different organs and tissues. Colonization of the host cells/tissues by the pathogen leads to cellular infiltration of inflammation-associated immune cells occurs to these areas thus leading to development of granulomas, which are cellular aggregates composed of macrophages, multinucleated giant cells, epithelioid and foamy cells, granulocytes, and lymphocytes [7].

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Macrophages present in the lungs are the first cells of the immune system that Mtb interacts within the host. Mtb may infect many different types of cells, including neutrophils, macrophages, and endothelial cells. Once within the cell, Mtb can live in various cellular compartments, such as phagosomes and autophagosomes, and if these organelles are disrupted, Mtb can also spread to the cytosol. To manage the infection, the host will employ many cellular and immunological responses that will compete with a wide range of Mtb evasion and virulence tactics that, if successful, will allow bacterial survival and multiplication [8].

ACTIVATION OF HOST INNATE IMMUNE DEFENSES

Autophagy

Autophagy is a pivotal cellular process important for maintaining cellular homeostasis by removing defective organelles, misfolded proteins, and intracellular pathogens, which are engulfed by lysosomes for deterioration. Lysosomes decompose these substrates and either reutilize or create new sources of energy with the basic components. Autophagy is stimulated under stress conditions, likely in caloric restriction, and as a defense against intracellular pathogens.

In relation to *Mtb* infection, autophagy plays a multilayered role in innate and adaptive immune responses against the pathogen, encompassing modulating proinflammatory cytokine production. Autophagic activation in macrophages is an efficient way to improve the intracellular death of Mtb [9]. ATG polymorphisms, especially those in the autophagy gene IRGM, are linked to TB vulnerability. Proteins are activated by antibacterial autophagy to transport intracellular pathogens to the lysosome for ubiquitination-mediated destruction.

LC3-associated phagocytosis (LAP) is a unique macrophage pathway that removes microbes via engagement of NADPH oxidase to the phagosome, accompanied by LC3 conjugation and thereafter fusion with lysosomes for bacterial degradation. It is documented that *Mycobacterium tuberculosis* expresses a conserved protein A (CpsA). This protein facilitates the pathogen to resist LAP, thus preventing effective macrophage-mediated clearance of *M. tuberculosis*, as illustrated in Figure 1 [10, 11].

Sirtuin-3 (SIRT3) plays a crucial role in maintaining respiratory processes. SIRT3 coordinates mitochondrial and autophagic activities to support anti-mycobacterial responses through coordinated activation of AMPK and mTOR, autophagy and immunometabolism promote anti-TB immunity [12]. This axis controls the transcription factor TFEB, which is essential for lysosomal biogenesis and autophagy. Immunometabolism and autophagy are TFEB's antimicrobial actions (Figure 1) [13].

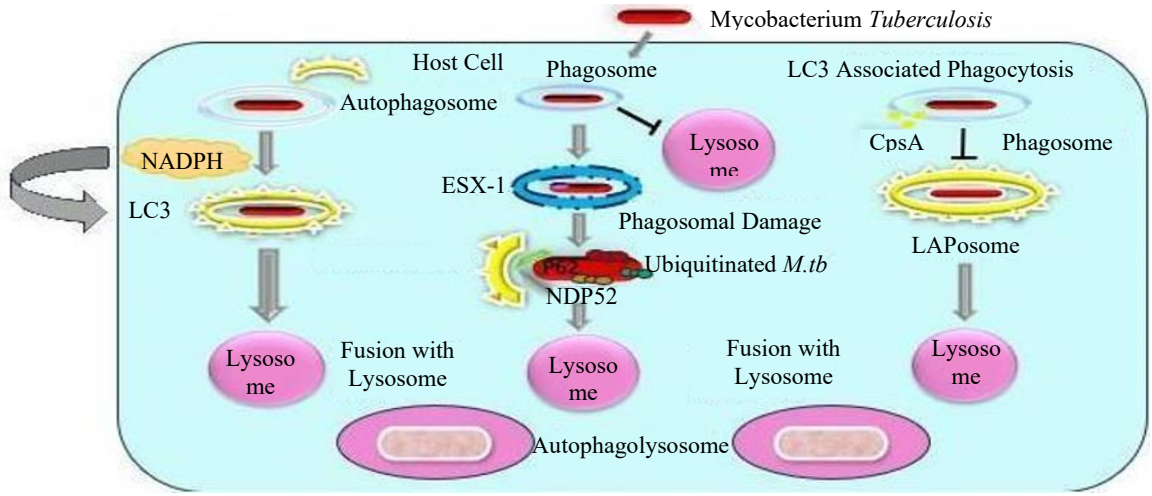


Figure 1. After phagocytosis, Mtb can elude phagosomal acidification, but autophagy activators can limit its intracellular growth. Mtb's ESX-1 system causes ubiquitination to attract autophagic adaptors, while CpsA inhibits LC3-associated phagocytosis (LAP).

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Apoptosis

The direct antimicrobial effects of macrophage apoptosis or encapsulation in apoptotic bodies, which attracts other macrophages and dendritic cells, can both inhibit Mtb growth. Death receptors (Fas and TNFR), triggering of caspase, the development of apoptotic bodies, efferocytosis (recognition and swallowing of apoptotic bodies by competent phagocytes through multiple cell-surface receptors), and anti-inflammatory cytokines (TGF, IL-10, IL-32) can all interfere with intrinsic and extrinsic apoptosis to control infection to some degree, as shown in Figure 2 [14–16].

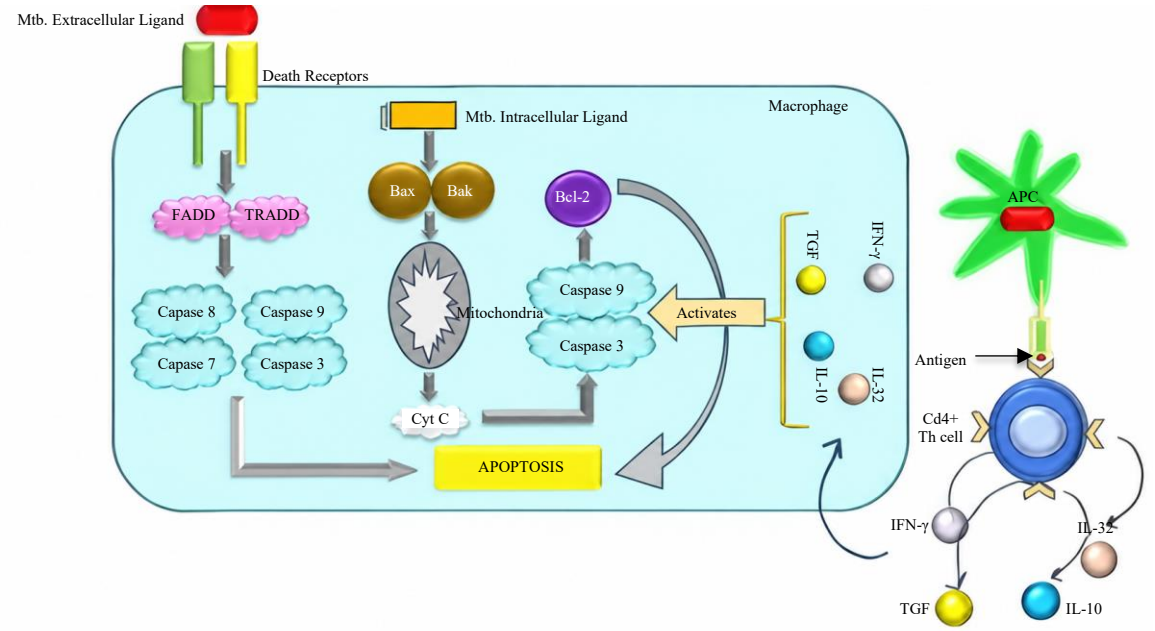


Figure 2. Macrophages undergo various mechanisms to stimulate apoptosis, and it involves activation of caspases via intracellular and extracellular ligands. Antigen-presenting cells (APC), such as macrophages and dendritic cell, present antigen to T-Helper cell which in turn secrets cytokines, like TGF, IFN-γ, and IL-32, thereby promoting apoptotic signaling pathway.

Secretion of the Cytotoxic Molecule

Macrophages respond to Mtb capture in a variety of forms by producing bactericidal substances that is cytotoxic signals which results in cell organelles swelling, rupture of plasma membrane and, thereby lysis of cell, leading to the secretion of proteins that are responsible for activation of inflammasome and release of proinflammatory cytokines. This process is known as Necrosis [16].

Activation of necrosis can occur via various pathways that includes, pyrotopsis, necrotopsis, and ferrotopsis. The production of ROS and RNS in macrophages, cofactor-dependent enzymes triggers ferrotopsis. The formation of ROS by acid sphingomyelinases through NADPH oxidase and cathepsins improved infection and BCG breakdown in macrophages. NADPH oxidase and cathepsins improved infection and BCG breakdown in macrophages [15, 17, 18].

Necrotopsis is triggered by Nicotinamide adenine dinucleotide (NAD+) is a deacetylase that activates the Sirtuin (SIRT7) enzyme. After Mtb infection, it loses expression in macrophages. A recent study described how the SIRT7-mediated defensive pathway drives Mtb clearance in macrophages using NO generation and apoptotic control [15, 18].

Activation of Inflammasome and Pyrotopsis During Tuberculosis

Inflammasomes are the main component of the innate immunity, and they work by sensing the intracellular pathogen and cellular stress signals. These are cytosolic multiprotein complexes which get

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activated via inflammatory reactions activated by caspases 1, which ultimately upregulates the differentiation and secretion of pro-inflammatory cytokines involving IL-1β and IL-18. These cytokines play crucial role in host defense mechanisms by accelerating recruitment of immune cells and increasing antimicrobial activity [19].

Amongst contemporary inflammasomes, the NLRP3 is widely documented in Mtb infection. Following the recognition of PAMPs and DAMPs, activation of NLRP3 occurs which results in the recruitment apoptotic assembly. This apoptotic assembly induces the activation of caspases which ultimately triggers and activates IL-1β and IL-18. Many studies have shown that NLPR3 takes significant risk in controlling the infection in early phases by elevating the antibacterial reaction in macrophages [20].

Furthermore, AIM2 inflammasomes also participates in defense mechanism against Mtb. Double stranded DNA released from damaged bacteria is identified by AIM2 that triggers the equivalent signaling to that of NLRP3, which ultimately results in activation of caspase cascade and, thereby cytokines secretion. Current findings reveal that AIM2 mediated reaction plays a role in inhibiting the replication of bacteria and increasing the immune response towards it [21].

A significant outcome of inflammasome activation is pyroptosis, an extensive form of program cell death. Unlike apoptosis, pyroptosis is defined by swelling of cells, formation of fenestrated membrane and release of intracellular constituents. Triggered caspases 1 degrades gasdermin D, forming a N-terminal fragments that create pores in the plasma membrane. These pores promote the secretion of IL-1β and IL-18 which finally results in lysis of cell [22, 23].

Expression of Non-Coding RNA

Long non-coding RNAs (lncRNAs), as well as microRNAs (miRNAs) play roles in gene regulation and Mtb infection, although they cannot produce proteins. These elements manage macrophage apoptosis as well as autophagy in dynamic TB contamination to target key host proteins for microbe control and freedom. In active TB, the circular RNA CircAGFG1 elevated autophagy and declined apoptosis [24]. Human macrophages may be protected from Mtb infection by persuading apoptosis and reducing inflammation by silencing miR-125b-5p. In the fight against MTB, this indicates a particular focus area [25]. In active TB, lncRNAs PCED1B-AS1 and MIAT effect macrophage apoptosis and autophagy, despite the lack of a clear molecular link between lncRNAs and macrophages [26, 27]. Apoptosis was reduced and autophagy was increased in RAW264.7 macrophages infected with BCG. ncRNAs' mechanism of action may provide new targets for TB. However, due to the constant discovery of novel host ncRNAs, these mechanisms are far from comprehensive [28, 29].

Polarization of Macrophages During Mtb Infection

Macrophages possess substantial plasticity and can take up various activation states to respond to environmental cues. During Mtb infection, polarization of macrophage plays a pivotal role in estimating the result of host–pathogen interaction. Mainly, macrophages are divided into M1 macrophages (classically activated), and M2 macrophages (alternatively activated) [30, 31].

M1 macrophages are triggered by IFN-γ, TNF-α and stimulus produced by microbes. These are characterized by increased production of RNS, ROS, NO and cytokines that are pro inflammatory such as IL-6, IL-β, and IL-10. These antimicrobial effectors generate an adverse intracellular environment that restricts the replication of Mtb and enhances the clearance of bacteria [32, 33].

Conversely, M2 macrophages are activated by cytokines, such as IL-4, IL-10, and IL-10, and are linked with anti-inflammatory responses, remodeling of tissues, and healing of wounds. These macrophages synthesize the enhanced level of CD206 and anti-inflammatory proteins such as IL-10 and TGF-β. However, M2 macrophages are crucial for constraining damage of tissues, they may unintentionally support the Mtb perseverance by limiting antimicrobial responses and declining the formation of bactericidal molecules [30, 32].

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Mounting evidence depicts that Mtb activity alters polarization of macrophage to form an optimal intracellular niche. Many Mtb virulent proteins enhance the transition from M1 to M2, hence suppressing the immune response. Out of virulent proteins, ManLAM is an important part of Mtb cell wall that alters macrophages signaling and elevates anti-inflammatory reactions. Moreover, IL-10 formation inhibits secretion of pro-inflammatory cytokines, thus enhancing expressing M2 associated gene expression [30, 34].

Emerging data have shown the close relationship between metabolism of macrophage and polarization during infection. M1 macrophages primarily depend on aerobic glycolysis to satisfy the energetic demands. Concurrently, M2 depends on oxidative phosphorylation and oxidation of fatty acid. Mtb can modulate cellular metabolism of host via pathways including AMPK, HIF-1α and mTOR, therefore, altering polarization of macrophage and immune responses. Such modulations in metabolic pathways heavily affect formation of cytokine, antigen presentation and ultimately leads to survival of bacteria [31, 33].

Critically, polarization of macrophages resides as dynamic range instead of to rigidly defined states. During early phases of infection, M1 linked responses are foremost and contribute to controlling bacteria. In contrast, chronic infection mostly drives macrophages towards an M2, specifically within granulomatous lesions, accelerating long term infection. Hence, understanding molecular mechanisms behind polarization of macrophage may provide novel insights towards therapeutics against Mtb. Nowadays, therapeutic approaches are mainly focusing on alteration of macrophages polarization. Pharmacological agents that accelerate M1 polarization and inhibit M2 polarization have shown efficacious results in experimental models of tuberculosis [31, 32].

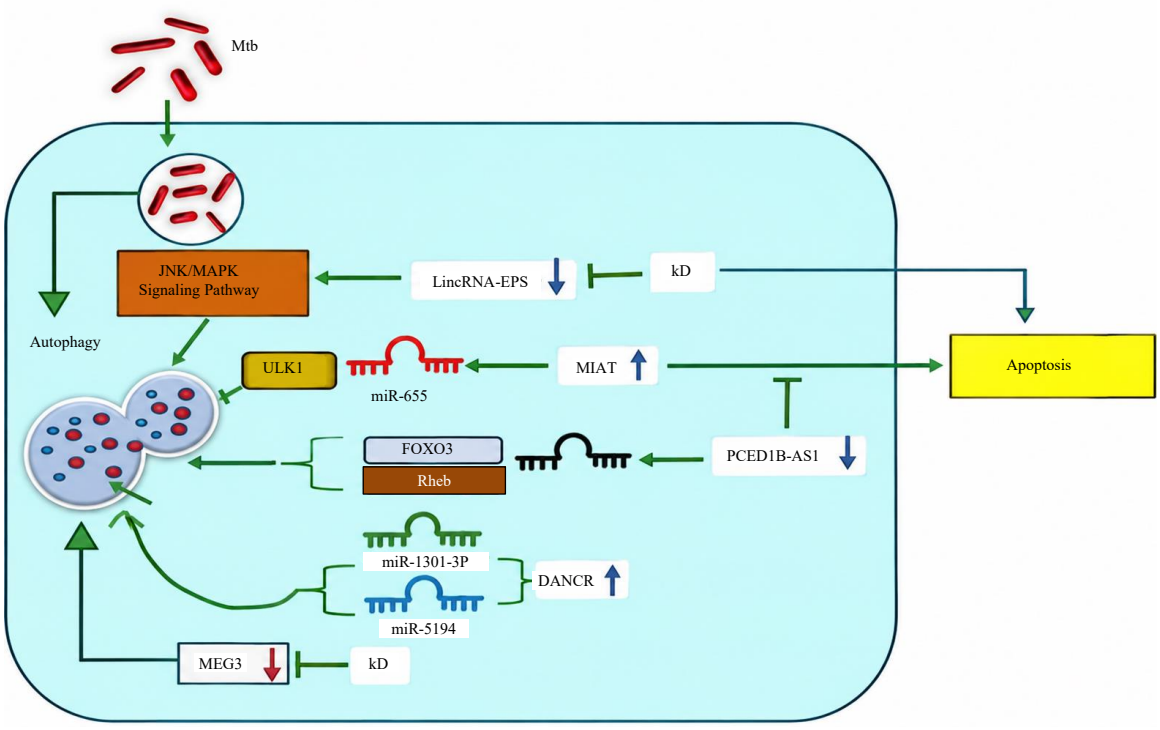


Figure 3. lncRNA expression in Mtb-infected macrophage.

Caloric Restraint

Mtb infection initiates immunometabolism modifications. Modifications in the host's nutritional condition have no effect on effector cell capacities. Disease-resistance reactions are expensive in terms of energy use, metabolic shift, and food intake. In sensitive to Mtb infection DBA/2 mice, regulated caloric restriction (CR) results in no malnutrition. According to Palma et al., CR switched immune cells'

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metabolism from FAO to glycolysis and decreased the mTOR activity linked with activation of Autophagy [35].

CR is not an unforeseen technique of further developing insusceptibility to Mtb, however, it might likewise give a clever strategy of treating Mtb disease where TB is rapidly expanding close with overnutrition and heftiness. However, only mouse models have been used to investigate this strategy. Nevertheless, additional research is required to govern even if it applies to human TB [35].

EMERGING MECHANISMS OF Mtb TO EVADE THE IMMUNE SYSTEM

Inhibiting Phagosome/Lysosome Fusion

Mtb is highly efficient in overcoming host defense. Two things are prevented by it: first, it inhibits the phagosome from developing normally into an acidic, hydrolytically active region, and second, it limits the development of a focused, effective immune response that may elicit an immunological response from the host cell [36].

When alveolar macrophages engulf Mtb, it is determined for degradation within the phagosome. Nevertheless, Mtb has evolved various mechanisms to evade these defense processes, which allow Mtb to survive and divide within macrophages. Out of many, some key virulence factors that promote evasion are protein kinase G(PknG), protein tyrosine phosphatase (ptpA), and secreted acid phosphatase (SapM) [37].

PknG plays a vital role in Mtb pathogenesis and metabolic adaptation. It helps in inhibiting both phagosome-lysosome fusion and autophagosome maturation, thus obstructing bacterial clearance. Regarding its mechanism of action, PknG disrupts host vesicular trafficking by phosphorylating specific host proteins, especially small Rab GTPases, namely RAB7.

This phosphorylation phenomenon inhibits the hydrolysis of RAB-7-bound GTP, hence impeding the transition essential for autophagosome maturation and finally its degradation. As a result, Mtb potently protects itself and ensures its survival within host macrophages as shown in Figure 4 [38, 39].

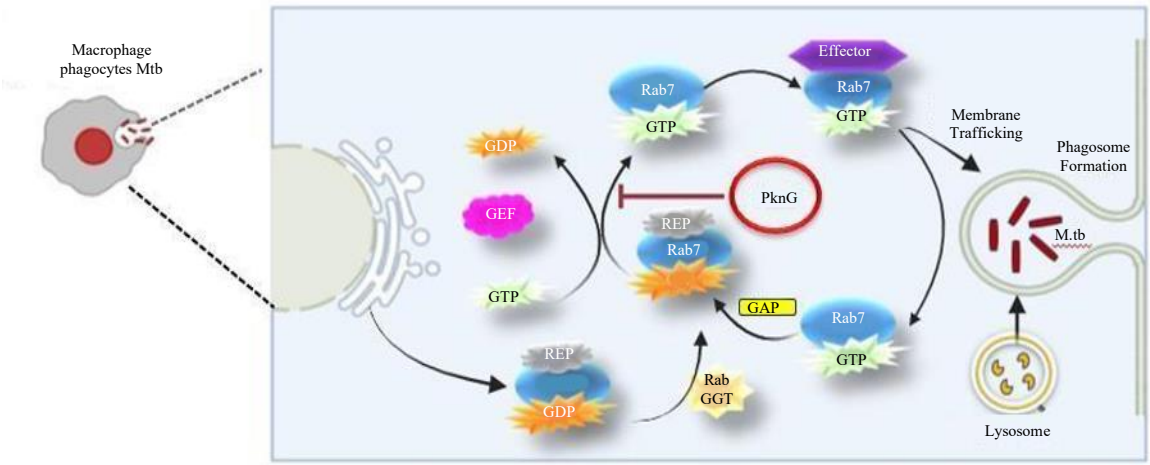


Figure 4. PknG inhibits phagosome-lysosome fusion by acting upon host Rab7 GTPase. PknG binds with Rab7 and hampers its activation inhibiting the conversion of Rab7-GDP to its active GTP-bound form. This phenomenon inhibits the recruitment of active Rab7-GTP to the phagosomal membrane, therefore, hindering phagosome maturation and lysosomal fusion.

Beyond these virulence factors, there are other mechanisms that inhibit phagosome-lysosome fusion. For example, cell wall lipids of Mtb, specifically phthiocerol dimycocerosates (PDIMs), play a pivotal role in enhancing bacterial survival with host macrophages [40].

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Inhibition of Autophagy

After successful evasion from the phagosomal degradation mechanisms or even while inhabiting within the phagosome, Mtb persists to downregulate host autophagic processes. Recent investigations have revealed that a lipid present in the cell wall, PDIM, inhibits autophagy. It suppresses LC3-associated phagocytosis (LAP) by blocking the mobilization of NADPH oxidase to the phagosomal membrane, which in turn hinders the formation of ROS crucial for the degradation of bacteria, as shown in Figure 1 [10, 11, 38].

Furthermore, Mtb secretes the effector protein EsxH, which particularly targets the host Endosomal Sorting Complex Required for Transport. EsxH form a complex with the VPS4 subunit, disrupting ESCRT-mediated membrane trafficking and, therefore, inhibiting autophagosome-lysosome fusion. This perturbation successfully hampers autophagic degradation, which allows Mtb to evade the host immune system and maintain a replicative niche within macrophages [41].

An alternative essential strategy used by Mtb encompasses the modification of the host target of rapamycin complex 1(mTORC1), a key determinant of autophagy. Additionally, PtpA also plays a major role in inhibiting autophagy. PtpA triggers this phenomenon by dephosphorylating the host protein tuberous sclerosis complex 2 (TSC2), a principal inhibitor of mTORC1. The phosphorylation of TSC2 results in prolonged activation of mTORC1 signaling, which leads to autophagic inhibition as shown in Figure 5 [42].

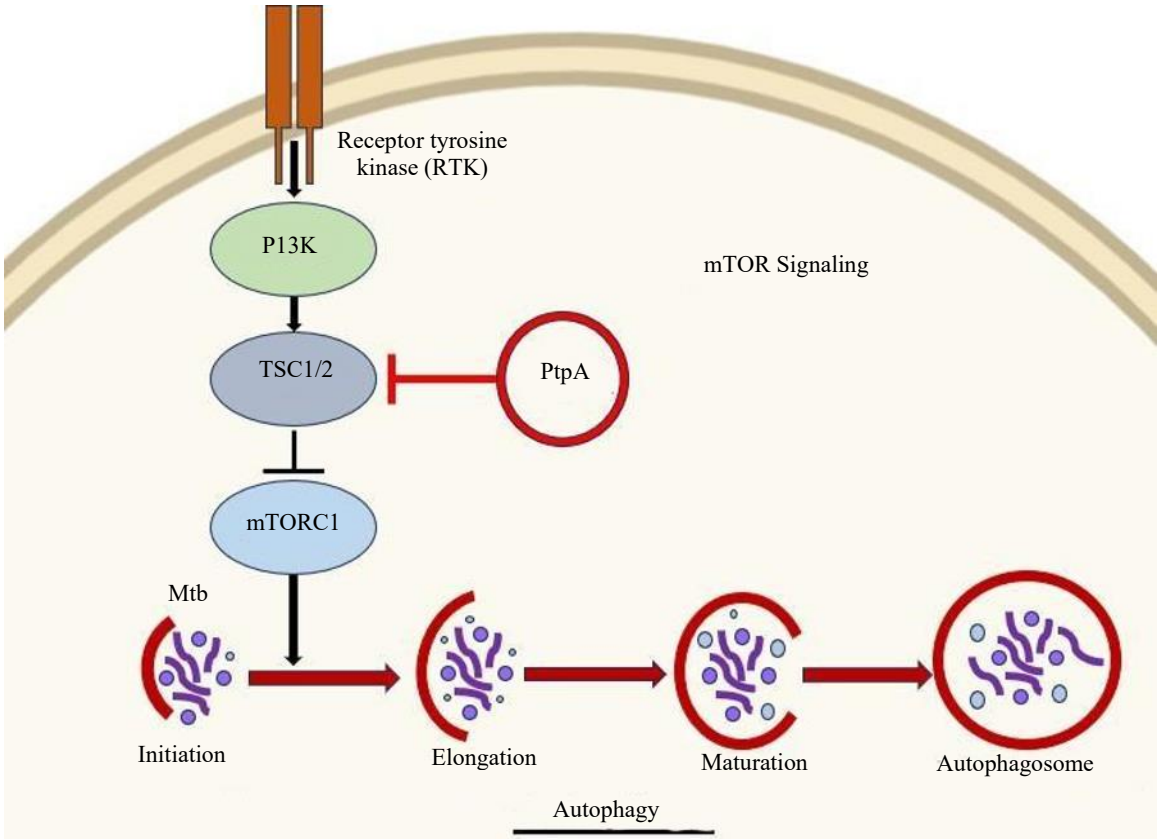


Figure 5. Mtb inhibits autophagy by modifying the mTORC1 signaling pathway – the bacterial effector PtpA removes the phosphate group from TSC2, which is a regulatory protein that restricts mTORC1 activity. Thus, mTORC1 remains constantly active, hampering the initiation of autophagy.

Inhibition of Apoptosis

Mtb exhibits the potential to differentially modify cytokine secretion to control macrophage apoptosis, thereby facilitating its intracellular survival. Several studies have shown that Mtb can hamper

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macrophage apoptosis via powerful induction of interleukin 10 (IL-10) production. Increased levels of IL-10 result in the elevation of anti-apoptotic protein Bcl-2 and the concurrent reduction of pro-apoptotic factor, namely, cleaved caspases-1. P53, NO and TNF. Furthermore, IL-10 upregulates the expression of B-cell lymphoma (Bcl-3), which counteracts TNF synthesis by suppressing NF-κB nuclear translocation and signaling, as shown in Figure 6 [43, 44].

Additionally, IL-17A, a cytokine primarily secreted by T helper 17 (Th17) cells during Mtb infection, plays a major role in tuberculosis pathogenesis. Experimental data validates that exogenous IL-17A upregulates the intracellular survival of both BCG and Mtb strains in murine-derived macrophages (BMDMs) as compared to untreated controls. IL-17A targets nuclear translocation of p53, leading to enhanced Bcl-2 expression and decreased Bax expression. This phenomenon leads to diminished cytochrome c release and inhibition of caspase-3 activation, hence blocking apoptosis, as shown in Figure 6 [43].

Another important phenomenon employed by Mtb is the involvement of Epstein-Barr virus-induced gene 3 (EB13), which is a subunit of 1L-27 and IL-35. Increased expression of EBI3 has been observed in CD14+ macrophages from infectious patients as compared to healthy ones. Similarly, Mtb induces the production of EBI3 protein in murine peritoneal macrophages. EBI3 inhibits the extrinsic apoptotic pathway by hampering the cleavage and activation of caspase-3 and caspase-8, which in turn helps Mtb to evade the host immune system, as shown in Figure 6 [43].

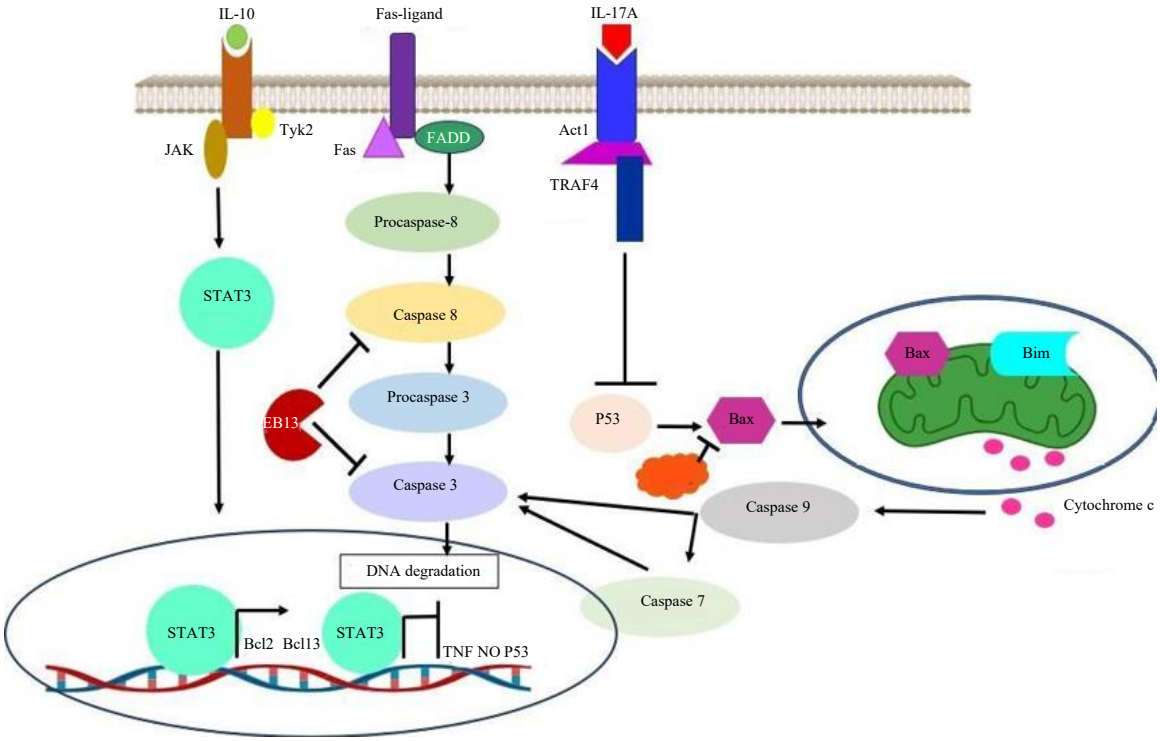


Figure 6. Mtb evades macrophages apoptosis by inducing anti-apoptosis cytokines. Three cytokines-IL-10, IL-17A, and EBI3 play a key role in this process. IL-10 promotes the expression of anti-apoptotic proteins Bcl-2 and 3 while inhibiting pro-apoptotic mediators like TNF-α, NO, and p53. IL-17A hampers p53-dependent Bax translocation to mitochondria, therefore, preventing apoptosis. EBI3 inhibits caspase 8 and caspase 3 activation.

Modulation of Inflammasome Signaling

Even though inflammasome has protective function against Mtb infection, Mtb also has evolved to alter the inflammasome pathways. The ESX-1 secretion system, specifically, ESAT-6, triggers the damage of membrane and modulates the activation strategy of inflammasomes. Although small amount

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of inflammasome activation may fight the infection, but high levels can lead to damage of tissues. Subsequently, Mtb alters signaling of inflammasomes to create a balance that allows the growth of bacteria [45].

Current evidence has further highlighted the interconnected nodes between inflammasomes, autophagy, and metabolism. Autophagic responses can unfavorably control the activation of inflammasome by clearing damaged mitochondria and depleting the formation of ROS. On the other hand, cytokines derived from inflammasome can modulate the polarization of macrophages. Therefore, understanding these altered signaling can provide some insights so that therapeutic agents can be developed, targeting these pathways while managing aberrant inflammation [44, 45].

Utilization of Nutrients of Granuloma

During Mtb infection, lipid metabolism influences host–pathogen interactions. Caseous granulomas are developed in human TB, which suggests that the host's lipid metabolism has been disrupted by the infection. The caseum's lipid and protein species were identified using immunohistological and biochemical studies. Inhibition of FAO prevents intracellular Mtb development in murine macrophages [46, 47].

Other Evasion Strategies of Mtb

It is also possible to alter (upregulate) transmembrane surface receptors (TREM2 or HRH1) to get past macrophages. Increased expression of these receptors stimulates STING and p38MAPK-NOX2, which inhibits pro-inflammatory cytokines (TNF-a, IL-1b, and ROS) and promotes anti-inflammatory cytokines (IFN-band IL-10). Mtb effectors, like the preliminary secreted protein target 12 (EST12), the methyltransferase (Rv1515c) encoded by the RD 6, or the dormancy regulator DosS minimize macrophage immune responses (ROS, RNS, phagolysosomal maturation, proinflammatory reaction, inflammasome, and antigen presentation) [48].

Mtb can also disrupt the sphingolipid balance of the host or mimic sphingolipid enzymatic activity, which entails activating surface 1-integrin and Rac1 as well as p38K-and JNK-dependent signaling pathways. Rv0081 encourages using cholesterol as the granuloma's only carbon source. Fe2+ shortage is a limiting Mtb growth factor in necroptotic granulomas. By increasing the synthesis of the proteins KatG and AhpC that are involved in DNA repair and antioxidant activity, Mtb carefully regulates the endogenous Fe2+ utilization to avert this challenging condition [43, 49].

MEDICINAL APPROACHES TARGETING MACROPHAGES IN TUBERCULOSIS

Regardless the availability of anti-TB drugs in the market, tuberculosis is still a major concern as the treatment of TB is long and occurrence of MDR and XDR strains is the key limitation to most of the therapeutics available. Standard therapies mainly target the components of bacteria, despite the intracellular living mechanism of Mtb which it allows to evade the host immune system. Subsequently, to overcome this limitation host-directed therapies have emerged to increase host immune response and reestablish antimicrobial signaling [50, 51].

Since macrophages are the key regulators of immune system and are main and primary host cells infected by Mtb, these cells are an attractive target for Host-Directed Therapies. One of the most studied HDT drug is metformin, a frequently used anti-diabetic drug. Metformin triggers the AMPK, a key driver for cellular energy metabolism, which in turn enhances the autophagic and phagosome responses. Elevated autophagic responses stimulate the transport of Mtb to lysosomes, hence ameliorating bacterial clearance. Moreover, metformin has demonstrated to decrease the enhanced inflammation while elevating the host immune response, contributing to improved control of bacterial burden in both experimental and clinical studies [52, 53].

Another significant HDT includes alteration of vitamin D pathway. Vitamin D plays a pivotal role in innate response by triggering the antibacterial peptides which includes cathelicidin (LL-37) and β-

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defensins in macrophages [54]. These peptides exhibit explicit anti-microbial activity and aid the maturation of phagosomes. Activated receptor of vitamin D also enhances autophagic signaling. Many investigations have revealed that vitamin D deficiency is linked with enhanced sensitivity to infection, emphasizing its relevance in defense mechanism of host [55].

Statins, conventionally recommended lipid-based drugs, have also gained prominence as potential HDT against Mtb infection. Along with decreasing cholesterol formation, statins module host immune cells to function and alter intracellular trafficking signaling pathways [56]. Cholesterol acts as a significant source of nutrients for Mtb throughout chronic infection, specifically, within granulomas. By impeding host cholesterol availability and elevating autophagy, statins downregulate survival of Mtb in the macrophages. Experimental studies have highlighted cooperative effects between statins and standard anti-TB drugs, depicting their ability as supportive therapy [57].

Besides small-molecular therapies for tuberculosis, modern strategies involve therapies based on cytokines and modulation of immune checkpoints. Administration of cytokines, such as IFN-γ, has shown advantageous effects in elevating activation pathways in macrophages and killing of bacteria intracellularly. Parallelly, aiming at molecules of immune checkpoint molecules that take part in exhaustion of T-cell may enhance immune response of host against bacterial infection. Even though these therapies are currently under research, they serve as potential treatment for battling Mtb infection [50].

Breakthrough, therapies based on RNA have emerged as promising HDT for eliminating Mtb infection. Various lnRNAs and microRNAs have shown to elevate macrophage autophagic pathways, apoptotic cascades, and inflammatory responses during tuberculosis. Antimicrobial pathways can be improved by targeting these molecules, thereby improving host defense mechanism [58].

Taken together, these Host directed therapies offer a promising strategy to battle tuberculosis infection by elevating host antibacterial function, autophagic signaling, balancing host immune homeostasis and constraining damage of tissues. When used with standard therapies available in the market these above approaches may decrease the duration of treatment, optimize therapeutic outcomes and limit the occurrence of MDR and XDR strains. Progressive studies and investigations into macrophage-centered treatment modalities are thus important for advancement of next generation tuberculosis therapeutic strategies.

CONCLUSION

It is predicted that the advances in our understanding of *M. tuberculosis* virulence and relationship to the host macrophage highlighted in this overview will lead to numerous novel treatments that should help minimize or halt the transmission of TB around the world. The journey of TB investigation, which commenced almost a century ago and ultimately culminated in the development of the BCG vaccine and the finding of antibiotics more than 50 years later, must nevertheless be remembered.

Current advancement in molecular biology, transcriptomics, proteomics and single-cell sequencing has substantially broadened our knowledge in understanding the multilayer relationship between immune cells specifically macrophages and *M. tuberculosis.* These findings have shown that the effect of Mtb infection is not entirely evaluated by virulent proteins but also depends upon the macrophage's responses, which involves apoptosis, autophagy, phagosome maturation and polarization of macrophages. The alteration in these immune responses illustrates its exemplary evolutionary adaptation to survive almost all immune reactions. A detailed understanding of these interconnected nodes may enhance the characterization of novel protein and other molecules for early onset of infection, indicators of disease progression and new treatment targets. The fight against tuberculosis (TB) must continue, and new vaccines and drugs should be more effective than older ones like *M. bovis* BCG, streptomycin, and INH. But until worldwide poverty and disparate progress are removed, TB will never be completely eradicated.

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Future Perspective

Given that Mtb is constantly evolving and adapting, we feel compelled to argue that the WHO's aimed to eradicate TB by 2030 may not be accomplished. However, the capacity of Mtb to simultaneously regulate numerous host cell death pathways may present fresh opportunities for the advancement of treatments with multitarget activity. Further screening and operational definition of putative Mtb virulence factors ss well as the disclosure of new approaches that could be employed to create effective treatments and identify fresh pharmaceutical targets are urgently needed.

Future investigation should focus on how we can implement advanced techniques, such as multi-omics techniques, involving metagenomics, transcriptomics, proteomics and metabolomics to design an exemplary treatment that can shorten the span of therapy and overcome the elevating MDR and XDR strains. Moreover, CRISPER-Cas oriented techniques can be used in editing the genome to enhance the identification of new genes of host and *Mycobacterium tuberculosis* which are associated in evading the host immune response and survival of bacteria in host's body.

Host-Directed therapies focusing on signaling pathway of macrophages, autophagy, apoptosis and inflammation reactions are expected to become important treatment to combat the infection. Novel treatment based on RNA may also deliver cutting edge approach to control immune responses of host against Mtb.

Additionally, drug delivery system based on nanoparticle may optimize the delivery of anti-tuberculosis drugs intracellularly enhancing immune response, hence decreasing drug toxicity as well. Finally, it could be a good idea to emphasis the research by bolstering host defensive mechanisms and concentrating on critical axes of Mtb' s egress pathways.

Conflict of Interest

No potential conflict of interest was reported by the authors.

Authorship Contribution

Muskan Jain: Literature review, Writing Original draft preparation.

Reetika Debroy: Supervision, Writing Review and editing.

Acknowledgment

The authors would like to thank the staff and management of Department of Biotechnology, Jaypee Institute of Information Technology, Sector-62, Noida, for providing necessary facilities to carry out the work.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Abbreviations

Mtb	*Mycobacterium tuberculosis.*
ncRNA	Non-Coding RNA.
PAMPs	Pathogen-Associated Molecular Patterns.
PRRs	Pattern Recognition Receptors.
ROS	Reactive Oxygen Species.
RNS	Reactive Nitrogen Species.
MDR-XDR	Multi- and Extensively Drug-Resistant.
IRGM	Immunity-Related GTPase Family M.
LAP	LC3-Associated Phagocytosis.

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NADPH	Nicotinamide Adenine Dinucleotide Phosphate.
LC3	Microtubule-Associated Protein 1 Light Chain 3.
CpsA	Conserved Protein A.
SIRT3	Sirtuin 3.
AMPK	AMP-Activated Protein Kinase.
mTOR	Mechanistic Target of Rapamycin.
TFEB	Transcription Factor EB.
ESX-1	ESAT-6 Secretion System.
Fas	Fas Cell Surface Death Receptor.
TNFR	Tumor Necrosis Factor Receptor.
TGF	Transforming Growth Factor.
IL	Interleukin.
APC	Antigen-Presenting Cell.
IFN	Interferon.
BCG	Bacillus Calmette–Guérin.
NO	Nitric Oxide.
lncRNA	Long Non-Coding RNA.
miRNA	MicroRNA.
MIAT	Myocardial Infarction-Associated Transcript.
DBA/2	Dilute Brown Agouti 2.
CR	Calorie Restriction.
FAO	Fatty Acid Oxidation.
PknG	Protein Kinase G.
PtpA	Protein Tyrosine Phosphatase A.
SapM	Secreted Acid Phosphatase M.
Rab GTPases	Ras-Associated Binding Guanosine Triphosphatases.
PDIM	Phthiocerol Dimycocerosates.
VPS4	Vacuolar Protein Sorting-Associated Protein 4.
ESCRT	Endosomal Sorting Complex Required for Transport.
PtpA	Protein Phosphatase A.
TSC2	Tuberous Sclerosis Complex 2.
Bcl	B-Cell Lymphoma.
BMDM	Bone Marrow-Derived Macrophages.
Bax	Bcl-2-Associated X Protein.
EB13	Epstein-Barr Virus-Induced Gene 3.
CD	Cluster of Differentiation.
JNK	c-Jun N-Terminal Kinase.
KatG	Catalase-Peroxidase.
AhpC	Alkyl Hydroperoxide Reductase Subunit C.
HRH1	Histamine H1 Receptor.
TREM2	Triggering Receptor Expressed on Myeloid Cells 2.
MAPK	Mitogen-Activated Protein Kinase.
NOX2	NADPH Oxidase 2.
RD6	Region of Difference 6.
DosS	Dormancy Survival Sensor.
EST	Early Secreted Target.
NLRP3	NOD-, LRR-, and Pyrin Domain-Containing Protein 3.
DAMPs	Damage-Associated Molecular Patterns.

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AIM2	Absent in Melanoma 2.
CD26	Cluster of Differentiation 26.
ManLAM	Mannose-Capped Lipoarabinomannan.
HIF-1	Hypoxia-Inducible Factor 1-Alpha.
HDT	Host-Directed Therapeutics.

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