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Immune System Responses against *Mycobacterium tuberculosis* and its Mechanisms to Escape from the Immune System

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ABSTRACT

Background: *Mycobacterium tuberculosis* (MTB) employs a variety of strategies to evade the host immune response, enabling its persistence and the development of tuberculosis. These evasion tactics involve thwarting lysosome formation, manipulating intracellular pH, and disrupting apoptosis and autophagy processes within host cells. Specifically, MTB interferes with lysosome acidification by modulating calcium ions (Ca2+), iron ions, and hydrogen ions (H^+), creating an optimal environment for its survival within host cells. Furthermore, MTB inhibits host cell apoptosis and autophagy, critical defense mechanisms against intracellular pathogens. Understanding these immunological escape mechanisms is paramount for developing effective tuberculosis therapies. Future research should focus on targeting MTB evasion strategies to pave the way for innovative tuberculosis treatments.

Conclusion: There is still a long road ahead of us to understand the immunological escape mechanism used by MTB. Over the past 50 years, numerous studies have looked into the immune response and the pathogenic processes of MTB.

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Introduction

Mycobacterium tuberculosis (MTB) is the most common reason of tuberculosis(TB) in people, and its infection causes more than 1.5 million deaths internationally yearly (1). Innate immune cells are the first to encounter *M. tuberculosis*, and how they respond controls how the infection develops. DCs initiate the adaptive response and define its characteristics. Macrophages are responsible for both causing and maintaining infection as well as exerting cell-intrinsic antimicrobial regulation (1, 2). This bacterium is an intracellular parasite that often assaults macrophages and inhibits their apoptosis (3).

Innate immune responses are essential for the activation of the adaptive T cell response, granuloma formation, and long-term containment of *M. tuberculosis* intracellular growth. This is why they are necessary to successfully contain the *M. tuberculosis* infection (4). Aerosolized *M. tuberculosis* cough is the main source of tuberculosis transmission. B and T adaptive immune cells are not affected by tuberculosis innate immunity or newly discovered memories. However, adaptive immunity is critical in suppressing this bacteria all through granulomatous latency, which is supported with the aid of the infiltration of innate immune cells. Remain diluted The bovine tuberculosis vaccine *Bacillus* Calmette Guerin (BCG) is used in sports to protect young children from highly disseminated *M. tuberculosis* infection (5). Chemokines and cytokines secreted through innate immune cells, along with macrophages (Mφ) and DCs, play a critical role in host protection in opposition to *M. tuberculosis* (2). DCs and Mφs are expert antigen-presenting cells (APCs) that may effectively phagocytose *M. tuberculosis*, the etiologic agent of tuberculosis (TB) (6). These immune cells apprehend the TB pathogen through numerous pattern recognition receptors (PRRs), such as (yet not anymore limited to) Toll-like receptors (TLRs), Nod-like receptors (NLRs), and C-kind lectin receptors (CLRs) (7). TLR1, TLR2, TLR4, and TLR9, as well as their downstream signaling proteins, are members of the TLR family and play an important role in the start of the immune response throughout the pathogenesis of TB. In the inflammatory pathway, it is also linked to the coordinated release of cytokines like IL-1 and IL-18 (interleukin), which may be involved in the pathogenesis of TB (8).

Furthermore, alveolar macrophages are the primary responders to the inhalation of tubercle bacilli and constitute a crucial aspect of the innate response to *M. tuberculosis* contamination (4). The formation of granuloma is a result of *M. tuberculosis* contamination, which might start with a group of non-infectious cells, and it's widely assumed that granulomas prevent the unfolding of bacteria to locations outside the lungs; however, it can come to be an area for long-term endurance of bacteria (9). The innate immune reaction protects a few people to the extent that they continue to be uninfected. In others, the innate immune system isn't always enough, and an adaptive immune reaction is generated. That is generally protecting but no longer sterilizing, and people continue to be latently inflamed (10).

The emergence of antigen-specific CD4+ T cells that release IFN (interferon) and activate macrophages and other antigen-presenting cells (APC) to destroy intracellular bacteria is a hallmark of adaptive immunity against *M. tuberculosis* infection. To suppress *M. tuberculosis* for the chronic contamination section, CD8+ T-cells are also essential. Also, it was noted that IL-17 and Th17 cells may play a role in *M. tuberculosis* pathogenesis (8).

Immune system responses to M. tuberculosis

Innate immunity

Macrophages are produced by hematopoietic cells in the bone marrow, grow into mature monocytes in the peripheral circulation, and then migrate to the tissue where they maintain homeostasis (low-stage recruitment) or are employed in response to infection or inflammation (recruitment at an excessive stage) (11). M. tuberculosis' primary target is macrophages, and mycobacteria are found in the phagosomes of inflammatory macrophages. The phagocytosis process used by *M. tuberculosis* to enter macrophages is aided by a receptor. This process is controlled by a variety of incredible cell surface molecules, including the complement receptors CR3 (CD11b/CD18) and CR4 (CD11c/CD18), macrophage mannose receptors, and others (MMR) (12). Macrophages may eliminate this bacterium by a variety of processes, including the production of cytokines, oxygen and nitrogen components, acidification of the phagosome, and intracellular *M. tuberculosis* autophagy, among others (7). A homeostatic lysosomal process called autophagy breaks down cellular additives into their parts. It is possible to kill more *M. tuberculosis* by promoting autophagy. Autophagy, lysosomal biogenesis, and host anti-mycobacterial responses depend critically on the increased adjustment of the Lamp2, Rab7, and Feb genes by PPAR- (13).

Research has proven that AMP-activated host protein kinase-PPARγ, pathway coactivator 1α (p.c-1), and membrane occupancy and repeat popularity linker containing 2 (MORN2) is concerned with the induction of autophagy and modifies *M. tuberculosis* contamination (14). This bacteria can modify autophagy with its numerous additives, which include ESAT-6 and the greater intracellular survival (eis) gene. If autophagy is prompted, *M. tuberculosis* colocalizes with the autophagy marker LC3, PL fusion happens, and growth is constrained (15). The feature of activated macrophages relies upon regulation with the aid of distinctive signaling pathways, consisting of pattern recognition receptors (PRRs), leading to unique macrophage polarisation guidelines. In the presence of microbial ligands, the Th1 cytokine (IFN-) helps polarize macrophages and come to be pro-anti-inflammatory M1-kind cells, generating phenotypes usual of classically activated macrophages (CAM) and leading to the multiplied expression of nitric oxide synthase (iNOS). In the evaluation, macrophages activated with the promotes Th2 cytokines (IL-4, IL-13, or IL-10) are polarized to M2, M2a, M2b, and M2c phenotypes, respectively, that are related to alternatively activated macrophages (AAM), which show anti-inflammatory, phagocytosis-promoting, and tissue restore activities (16).

Tuberculosis-inflamed macrophages go through NK-mediated apoptosis via this Fas pathway to restrict *M. tuberculosis* viability. Fas is a membrane loss of life receptor of the tumor necrosis factor (TNF receptor) circle of relatives chargeable for cellular lysis, whose ligand (FasL) is expressed in NK cells. After FasL-Fas binding, a dying-inducing signaling complex (DISC) is formed, including numerous proteins, Fas-related demise area (FADD), and caspase-8. Caspase 8 activations utilizing DISC initiates the extramitochondrial apoptotic pathway. NK cells are granular innate lymphocytes that have a strong cytolytic capability. NK cells act early at some stage in contamination and are not constrained by a major histocompatibility complex (MHC). Fifty-nine diverse additives Tuberculosis cellular wall additives with mycolic acids are direct ligands of the herbal cytotoxicity receptor (NCR) NKp44 on NK cells (7). Several *M. tuberculosis* cell wall additions may instantly attach to NKp44 on NK cells. NK cells may also have molecules that are overexpressed on the surface of inflamed cells from *M. tuberculosis* (9). After exposure to pathogens or cytokines, macrophages, neutrophils, and DCs release IL-12, an efficient NK cell stimulatory substance. Interferon-gamma (IFN-) is

produced and secreted as a result of IL-12 signaling, which also enhances NK cell characteristics. It has been shown that *Mycobacterium avium* and MTB are both inhibited by IL-12-activated NK cells (17).

Due to their critical function in the presentation of *M. tuberculosis* antigen, DCs are crucial for bridging innate and adaptive immunity. Explicit mannose receptors (Mrs) and the non-integrin DC-specific ICAM receptor (DC-sign) on human monocyte-derived DCs can recognize *M. tuberculosis* ligands, such as *M. tuberculosis* lipoprotein lprG and hexamannosylated phosphatidylinositols (PIMs) (7). Research has shown that DCs support the cellular immune response against mycobacterial infection. In areas of *M. tuberculosis* contamination, DCs are significantly expressed with the start of the inflammatory response against M. tuberculosis. Immature DCs with a focus on processing and ingesting antigens may be identified in the lung mucosa. After interacting with pathogens, they develop and move to lymphoid organs, where they produce a large number of T cells by expressing MHC and stimulatory molecules on their cell surfaces as well as secreting immunoregulatory cytokines like IL-12 (18). Throughout tuberculosis contamination in mice and human beings, neutrophils assist DCs to give *M. tuberculosis* Ags to T cells. Especially, neutrophils enhance the ability of DCs to prompt CD4 cells by providing *M. tuberculosis* to DCs in an extra powerful way. Neutrophil-DC crosstalk is predicted to immediately affect the immune reaction to any contamination by eliciting an Ag-specific immune response. Key players in the innate immune response that defends against mycobacterial invasion are neutrophils (19).

Opsonic receptors, in particular CRs and FcRs, as well as non-opsonic receptors, in particular CLRs, are involved in the phagocytosis of *Mycobacterium* by neutrophils. Human neutrophils lack several of the lectins involved in *M. tuberculosis* absorption in macrophages, such as mannose receptors. Nonetheless, it has been proven that a few CLRs are involved in mycobacterial phagocytosis, which employs neutrophils. CR3 regulates mycobacterial phagocytosis in a variety of ways (20). An immediate oxidative burst reveals the crucial neutrophil trait of phagocytosis, which controls the immediate response to *M. tuberculosis* infection. Microbes are absorbed in phagosomes throughout the length of phagocytosis, at which point they suddenly join with intracellular granules to create phagolysosomes. Reactive oxygen species (ROS) that are produced when oxidants and proteolytic enzymes are released from the granules help control infections like M. tuberculosis. Contains nicotinamide adenine dinucleotide phosphate oxidase (NADPH-oxidase) complex in phagolysosomal membranes. Hypochlorous acid and different extra-poisonous intermediates are produced via myeloperoxidase. Consequently, ROS are taken into consideration as critical bactericides of neutrophils (19). Additionally, research has proven that activation of neutrophils with lipopolysaccharide (LPS), interleukin-8, or phorbol myristate acetate (PMA) results in the release of cellular components that form an extracellular fibrillar matrix known as neutrophil extracellular traps (NETs). Those additives are proteins, particularly neutrophil elastase (NE) and myeloperoxidase (MPO), DNA, and fibers derived from chromatin, which kill bacteria extracellularly (21). Neutrophils can experience the dimensions of the pathogen and might generate extra NETs in the presence of larger pathogens like *Mycobacterium bovis*. Within the pathogenesis of tuberculosis, *M. tuberculosis* has been pronounced to induce NETs that trap, however, are not able to kill mycobacteria in vitro (20).

Adaptive immunity

In humans and animals, CD4+ T cells are required for protective immunity against TB; however, adaptive immune responses do not

successfully eradicate *M. tuberculosis* or promote aseptic immunity (22). Contrary to CD4+ T lymphocytes, CD8+ T lymphocytes have long been assumed to have no role in preventing infection and sickness caused by M. tuberculosis. MHC class I molecules enable CD8+ T cells to detect antigens from *M. tuberculosis* and to generate IL-2, IFN-, and TNF-. By interacting with the Fas (CD95)-Fas ligand and using the cytolytic agents perforin, granulysin, and Fas, CD8+ T cells are able to kill M. tuberculosis. This direct cell-to-cell contact causes M. tuberculosis-infected cells, particularly M, to undergo apoptosis. It also deprives *M. tuberculosis* of its normal development environment while decreasing its survival via an unidentified mechanism (23).

Because of the cytokine and chemokine production, epithelioid cells, mononuclear phagocytes, fibroblasts, T and B lymphocytes, and other cellular populations are attracted to the site of macrophages harboring this bacterium. These immune-regulating cells create an organized mass called a granuloma (24). A complex lesion made up of different immune cells, the granuloma effectively surrounds the *M. tuberculosis* infection and restricts its growth and dissemination. On the other hand, it also provides a location for the *Mycobacterium* to live and remain as a latent infection (25). Apoptotic macrophages, squamous cells, dendritic cells, neutrophils, and multinucleated large cells create confluent layers around the necrotic macrophages that are commonly seen in the middle of the granulomatous formation (24). The top layer of the structure is surrounded by T cells, B cells, and NK cells, which are the primary IFN- producers and may identify certain peptides connected to basic histocompatibility complexes (25). According to a recent research, complementary regulatory proteins component H and properdin may also aid in this tactic by boosting the proinflammatory cytokine responses required for granuloma formation and maintenance. Granulomas, which are present in the majority of *M. tuberculosis* infections, provide an immune environment that enables the host to control the infection by carefully balancing the production of pro- and anti-inflammatory cytokines. IL-10 is a key negative regulator, while TNF and IFN are considered to be significant proinflammatory cytokines associated with the formation and characteristics of granulomas (24).

Findings support the hypothesis that B cells may modify anti-inflammatory responses to affect how *M. tuberculosis* contamination manifests. B cell-mediated antibody synthesis may have particular effects. The passive switching of monoclonal antibodies specific for *M. tuberculosis* cellular wall additives may enhance the final infection outcomes in mice, whereas binding of antibodies to inhibitory Fc receptor II B lowers macrophage IL-12 production and adversely impacts Th1 responses. Macrophages infected with *M. tuberculosis* may also be impacted by the cytokine production of B cells. B cells from TB patients' pleural effusions and mouse B cells that express type I IFN changed the polarization of macrophages towards an anti-inflammatory phenotype (9).

Therefore, type I IFNs are the primary cytokines prompted in lung B cells in *M. tuberculosis* infection (26). After experiments in mice, naive antigen-specific T cells migrate upon the antigen in the lung's vacating lymph nodes (LN) that vacate inflamed tissues. Antigen-particular T cells establish chronic contacts, and undergo a chain of coordinated interactions with DCs. CD69 is the first marker of T-cell activation and is first detected within three hours after antigen release (27). The C-type lectin superfamily type II membrane protein CD69 is expressed on activated NK cells, macrophages, and monocytes. It is believed that the expression of CD69 indicates that NK cells are interested in cytotoxicity. Moreover, to indicate T cell activation following mitogen stimulation, the detection of CD69 is more sensitive than the detection of IFN-. As a result, the presence of CD69 is a trustworthy sign of early T-cell

activation (28). After CD69 expression, activated T cells emerge with less motility and lose their capacity to migrate out of LNs because of a lack of sphingosine-1-phosphate-1 (S1P) receptor expression. Over the following 2 days, a programmed collection of events occurs in the activated T cell, mainly CD44 upregulation, CD62L downregulation, and initiation of cell division (27). CD44 is a cell adhesion molecule from the hyaluronate receptor family that has been shown to have a specific role in regulating lymphocyte movement. Hyaluronic acid, collagen, fibronectin, and osteopontin are cytoskeletal components related with CD44, which is expressed on hematopoietic cells. CD44 is also essential for the migration of activated T lymphocytes to inflammatory areas (29).

Activated T cells travel and encounter DCs as they start to multiply. When S1P1 is re-expressed and CD69 is incorrectly expressed at the cell surface, T-cell migration is then possible. Activated T cells re-engage the antigen in the environment, presumably via interactions with macrophages, DCs, and complex effector activities that aid in the pathogen's removal (27).

How does Mycobacterium escape the immune system

The structure of MTB and the development of mycelium prevent the phagolysosome from growing and becoming more acidic. Bacterial proteins that restrict the resupply of vacuolar ATP and guanosine triphosphate (GTP) enzymes, which control phagocyte maturation, include early secretory antigen-6/culture filtrate protein and adenosine 5′-triphosphate (ATP)1/2 (secretion ATPase1/2, secreted secA1/2 protein) (30). Coronin 1, a tryptophan-aspartate-rich coat protein, is drawn to phagosomes containing active bacilli but is promptly released from those containing inactive mycobacteria (31, 32). The quantity and activity of activated MTB in the microsomes are strongly associated with the duration of the recruitment process and the amount of coronin 1. MTB decreases the number of lysosomes by increasing coronin 1 expression on the host phagocyte membrane (33). Furthermore, maturation is prevented by the cytokine interferon (IFN) via the signal transducer and activator of transcription1 (STAT1)-dependent production of interleukin (IL)-10. IL-10 prevents excessive IL-1 from impairing the caspase-1-dependent maturation of pleural fluid mononuclear cells. By inhibiting the lysosomal glycoprotein LAMP-1 from being produced in the phagosome exon, BCG live immunization may halt phagosome maturation (3). Protein kinase G (PKnG) is a protein that resembles protein kinase in eukaryotes. On the other hand, PKnG increases MTB anabolism, catabolism, growth rate, virulence, and drug resistance by downregulating GlpK and adrenoleukodystrophy (ALD) expression, upregulating Ag85A and Ag85C expression, blocking lysosome maturation, and upregulating bacterial infectiousness. However, through improving signal transduction in host cells, PKnG produced by MTB inhibits the union of phagosomes and lysosomes. MTB and PKnG, therefore, interact with each other (34-36).

Another significant technique for preventing the development of phagosomes/lysosomes in macrophages is to prevent the fusion of phagosomes with lysosomes. According to studies, the pro-inflammatory transcription factor NF-B (nuclear factor kappa B) controls how much lysosomal enzyme is released into phagosomes, which in turn controls how infections are killed. Furthermore, by boosting the production of membrane transport molecules during infection, NF-B regulates the fusion of phagolysosomes (37). Phosphatidylinositol 3-phosphate is an essential component of the macrophage cell membrane, which is found on the surface of early endosomes and phagosomes (PI3P) (38). Following MTB infection, calmodulin-dependent PI3P biosynthesis decreases, and the toxin lipoarabinomannan (LAM) is transported in a

manner that blocks the process of joining phagosomes and lysosomes (39, 40). The host cells for MTB are believed to be dendritic cells (DCs), and DC-specific intercellular adhesion molecule-3 grabbing nonintegrin (DC-SIGN) captures and internalizes intact MTB through mannose-capped lipoarabinomannan (ManLAM), a mycobacterial cell wall element that is also produced by MTB-infected macrophages (41, 42). Unexpectedly, combining DC-SIGN and ManLAM inhibits DC maturation. Earlier, it was mentioned that MTB may survive in macrophages by preventing lysosome-phagosome fusion (Figure 1). However, some MTB strains cannot adapt to surviving inside the endocytic vesicles of macrophages (43). By turning on phospholipase A2 in host cells, these bacteria can produce favorable circumstances for survival in the cytoplasm (3, 44).

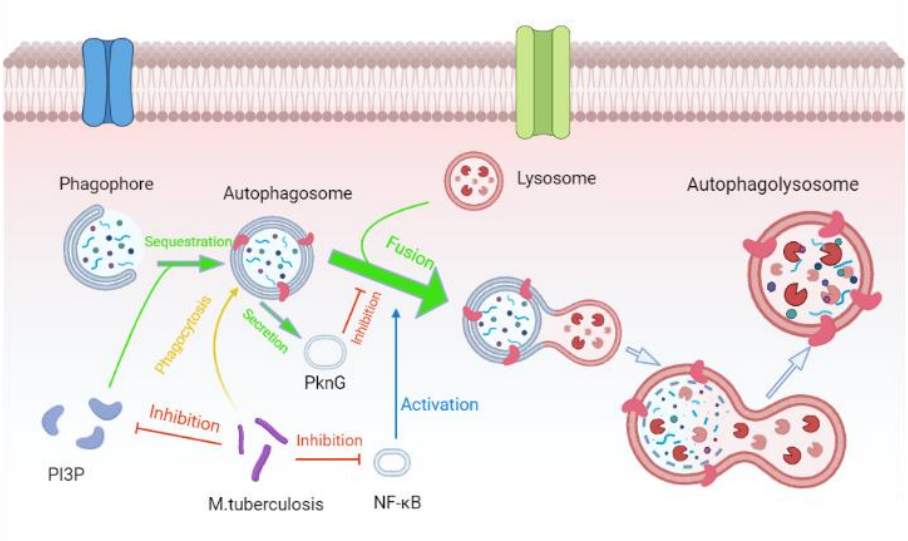

Fig 1. How to prevent lysosome and phagosome fusion. While phagocytic MTB directly suppresses the fusion of phagosomes with lysosomes by secreting PknG, NF-B suppression also lessens this fusion. Lower production and increased hydrolysis of PI3P, a crucial component on the surface of phagosomes, also hinder the fusion, allowing MTB an escape route (3, 44).

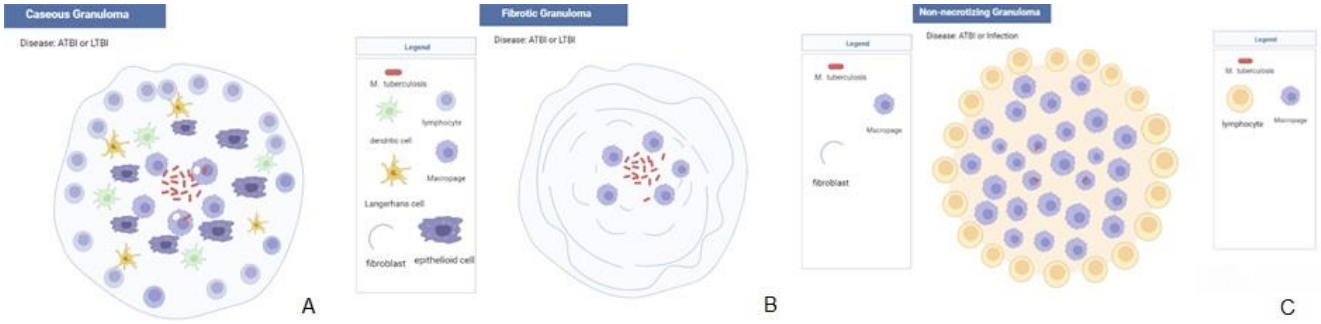

Fig 2. Granulomas of infection that serve as a home for bacteria and are either active tuberculosis infection (ATBI), latent tuberculosis infection (LTBI), or both.

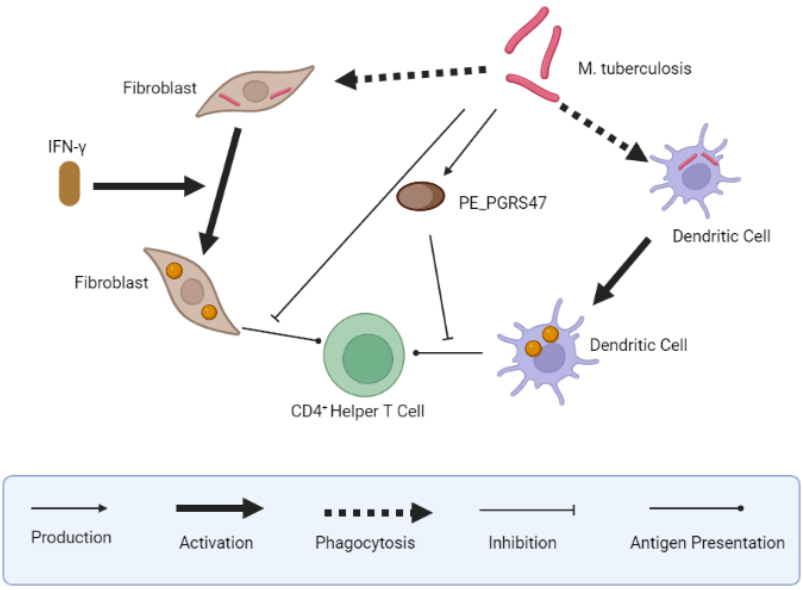

Fig 3. A granuloma composed of macrophages, epithelioid cells, fibroblasts, lymphocytes, and Langhans cells is the characteristic lesion of MTB infection. They are inflamatory by nature, but through time, their structure has become more solid and complex. Although they function as a crucial host-defense mechanism for regulating bacteria, they provide a safe sanctuary for MTB, some of which may stay dormant for a considerable amount of time until the possibility for reactivation and dispersion occurs. Effective TB therapy requires an understanding of the physiopathology and inflammatory state of granulomas.

M. tuberculosis inhibits the acidification of phagolysosomes

By delaying phagocytosis and the acidification of phagosomes, MTB may be able to thrive in an environment with a pH of 6.2, which is much less acidic (45). The macrophages can maintain a pH of neutral thanks to specific molecules on the cell wall and its structure (45), which work as a barrier. Next, MTB modifies the makeup of the phagosome to prevent acidification. Second, the protein tyrosine kinase A is also encoded by the same operon that codes for protein tyrosine phosphatase (PtpA). (Protein tyrosine kinase (PtkA)). The ability of a PtkA deletion mutant MTB to thrive in the THP-1 macrophage infection paradigm was demonstrated by Tsui et al. (46), demonstrating that PtkA directly contributes to acid inhibition. The mutant was unable to prevent phagosome acidification (46). Moreover, MTB infection causes macrophages to secrete granulocyte-macrophage colony-stimulating factor, which in turn stimulates the production of cytokine-inducible SH2-containing protein (CISH) via STAT5 (47). Direct activation of the infected macrophages by IFN-inducible nitric oxide synthase 2 then inhibits intracellular MTB multiplication. LRG-47, a member of the 47-kD guanosine triphosphate family, works without the assistance of nitric oxide synthase 2 to safeguard macrophages from illness. LRG-47-deficient macrophages are unable to undergo full acidification, which lessens their immunological response to MTB (3, 48).

M. tuberculosis inhibits oxidative stress and the function of reactive oxygen and reactive nitrogen intermediates

An imbalance of pro- and anti-oxidants, often known as oxidative stress, may be harmful. Oxidative stress may damage DNA bases by causing protein and lipid peroxidation. The prolonged MTB latency in the host is caused by the inhibition of oxidative stress as well as the suppression of lysosome maturation, acidification, and macrophage phagocytosis (49). One of the 12 alternative sigma factors of *M. tuberculosis* is SigH, which is induced by heat, oxidative stress, and nitric oxide stress (49). According to Dutta et al.(49), the innate immune system of the host is controlled by a SigH-dependent regulon, which is required for persistent infections. (50). The division cell wall cluster's FtsZ and FtsQ interact with the MTB gene cluster Rv0014c-Rv0019c, which produces the proteins PknA and FtsZ-interacting protein A (FipA). This connection protects MTB against oxidative harm. During oxidative stress, FipA interacts with FtsZ and FtsQ to cause PknA-dependent phosphorylation of FipA at T77 and FtsZ at T343, which is necessary for cell division (51). An MTB strain has a lower chance of surviving in an oxidizing environment if FipA is disrupted. The main thiol in MTB is mycothiol, also known as acetyl Cys-GlcN-Ins or MSH. It has an antioxidant effect to stop MTB from entering macrophages and detoxifies a variety of toxins. The gene mshD, which is involved in the production of MSH, encodes mycothiol synthase, the last enzyme in MSH biosynthesis (52). An MTB strain with a missing mshD gene develops poorly and is more sensitive to hydrogen peroxide on agar plates devoid of catalase and oleic acid. The divIVA family of proteins includes the MTB protein Wag31. Before wag31 interacts with penicillin-binding proteins, it first binds amino-acid residues in the SET domain through nuclear receptors. Also, it could stop the oxidative stress-related cleavage of MTB (53). It's interesting to notice that virup contains the DivIVA homolog Mup012c, which protects M. ulcerans from oxidative stress (3, 54).
When phagocytosis is initiated, macrophages produce a respiratory burst as well as reactive oxygen and nitrogen intermediates. Similar to this, PMNs play a crucial role in the first MTB response. Reactive oxygen species are produced and pathogens are destroyed by PMNs to offer protection (ROS) (55). Two widespread MTB lineages in Argentina, South America, and the Mediterranean generate considerable PMN mortality by activating signaling pathways that result in ROS production through p38 activation and heightened effector effects, regardless of their capacity to infiltrate PMNs (31, 56). Moreover, MTB's thicker cell wall and its special enzyme, phospholipase D, effectively decrease ROS. As shown, the peroxidase activity of MTB in the presence of Mn+ produces catalase-peroxidase, which imparts resistance to the negative effects of reactive oxygen and nitrogen intermediates (44, 57). While H_2O_2 and NO significantly increase the expression of the genes encoding the KatG and TrxB2 enzymes in MTB, it is suggested that these two enzymes provide the organism with the ability to live in oxidative conditions (58). To control oxygen free radicals, the filtrate protein CFP 10 and the early-secreted antigenic target ESAT-6 of the RD-1 region of the MTB genome regulate NF-B-dependent gene expression and ROS generation, respectively (59, 60). Moreover, CFP-10 and ESAT-6 work better together than they do alone. It has been shown that the histone-like MTB protein Lsr2 is resistant to reactive oxygen intermediates but not reactive nitrogen intermediates. The EIS gene has also been shown to help MTB survive oxidative stress by limiting ROS generation through the c-Jun N-terminal kinase-ROS signaling pathway. Glutathione is not produced by MTB; instead, it produces the important low-molecular-weight thiols MSH and ergothioneine (ERG). GGC serves as a precursor for the creation of ERG and glutathione. ERG is produced by five genes (egtA, egtB, egtC, egtD, and egtE), but the DegtB mutant,

which lacks ERG but accumulates GGC, is more resistant to oxidative and nitrosative stress than the DegtA mutant, which also lacks GGC. This study shows that GGC removes MTB's reactive oxygen and nitrogen species (40, 61).

Granuloma formation: help M. tuberculosis evade immune responses

A key host defensive mechanism for confining germs is the creation of granulomas (62). Immune cell clusters called granulomas comprise lymphocytes surrounding infected and uninfected blood-derived macrophages, foamy macrophages, epithelioid cells, and Langerhans cells (63). (Figure 2). It is noteworthy that various granulomas manifest in various infectious diseases. Non-necrotizing granulomas, necrotic neutrophilic granulomas, and fibrotic lesions are all common manifestations of active illness; the necrotic region in the middle of this form of granuloma is made up of dead macrophages and other cells (64). Researchers have discovered that *M. tuberculosis* lives in a metabolically altered condition in the core hypoxic zone during latent infections, but during active TB, it may multiply in peripheral oxygenated zones (65, 66). The hallmark lesion of MTB infection is a granuloma made up of macrophages, epithelioid cells, fibroblasts, lymphocytes, and Langhans cells. While they are naturally inflammatory, throughout time their structure has become increasingly substantial and intricate. They offer a safe haven for MTB, some of which may remain latent for a long time until the chance for reactivation and dispersion comes, since they perform as an essential host-defense mechanism for controlling bacteria. Understanding the physiopathology and inflammatory state of granulomas is crucial for effective TB treatment (25).

TLR2 has a protective role against MTB infection, but it also has a detrimental effect. Immune responses, including TLR2, can lengthen the time that MTB can survive in macrophages. TLR2 accumulates immune cells, stimulates the production of inflammatory cytokines in macrophages, and causes granulomas to develop. Latent MTB in granulomas, according to the theories of Ehlers et al. (67), can still control the immune response. TNF-derived signals in the mature granuloma attract highly dynamic effector T cells and preserve the granuloma shape. Peptide-loaded MHC class II molecules work in the plasma membrane to activate T cells from MHC compartments, resulting in an immunological response to MTB (67). Additionally, fibroblasts in an immunological environment express MHC class II after receiving IFN- stimulation to present antigens to CD4+ T cells (68). Additionally, IFN-treated fibroblasts produce isolated proteins, peptides, and antigens (69). The absence of antigen presentation in MTB-infected fibroblasts, however, suggests that MTB can evade T-helper immune monitoring by infecting fibroblasts (3, 70-72). The PE PGRS47 protein of MTB, which is generated by the Rv2741 gene and inhibits MHC class II-restricted antigen presentation by MTB-infected DCs, is an additional factor. By eliminating cells, it inhibits autophagy and supports MTB in avoiding the effects of innate and adaptive immunity (Figure 3) (9, 73).

Ca2+ enhances lysosome formation

Calcium ions (Ca2+) are a common cellular second messenger involved in nearly every aspect of cell life, including cell division, movement, growth, and death. Ca2+ signals almost every part of cell life, from cell division to cell death, in a controlled way(74, 75).

Ca2+ is kept separate in several organelles in the cytoplasm that act as storage for Ca2+ inside the cell, which is a key part of this control. Ca2+ release from lysosomes and other small-capacity individual vesicle stores located throughout the cell, as opposed to large-capacity Ca2+ stores like the endoplasmic reticulum (ER) and Golgi

apparatus, is likely more beneficial for local control (74-76).

These two separate forms of Ca2+ reserves are hypothesized to be created, preserved, or refilled by several methods. In the ER plasma membrane (PM), membrane contact sites (MCS), persistent Ca2+ influx replenishes ER reserves (3, 77).

Macrophages with MTB infection require more Ca2+. Purinergic receptors P2Y2 (purinergic receptor P2Y, G-protein coupled, 2, P2RY2) and P2Y7 on the surface are what predominantly cause changes in Ca2+ concentration (purinergic receptor P2Y, G-protein coupled, 7, P2RY7). P2Y2, a pore-shaped receptor, rapidly increases intracellular Ca2+ concentration, in contrast to P2Y7. Guanosine triphosphate, or GTP, is a P2Y2 activator, but it only works in concert with P2Y7. Enhancing the fusion of phagosomes and lysosomes results in killing (3, 74, 75).

An increase in extracellular Ca2+ concentration improves the ATP-induced fusion of phagosomes and lysosomes while increasing phospholipase D activity (3, 78). It has been proposed that Ca2+ loss in macrophages carrying MTB phagosomes can somewhat inhibit phagosome-lysosome fusion (3).

Iron ions inhibit lysosome formation

With lysosomal dysfunction, iron is both necessary and sufficient for cell growth (79). Surprisingly, iron supplementation rescues cell proliferation in lysosomal dysfunction caused by both pharmacological and genetic factors. Iron is required as a cofactor for the MTB-encoding enzymes to function and is involved in oxidative metabolism and electron transport. It is also one of the components required for the creation of several nutrients, genetic material, pyrimidine nucleotides, and amino acids. Clinical experience has demonstrated a correlation between iron consumption and mortality risk in patients with tuberculosis. Alveolar macrophages that have been inactivated have poor antibacterial activity and can't stop MTB development. MTB is moved to other locations so that it can present antigens and sensitize nearby T cells there. Sensitized lymphocytes release several lymphokines, including IL-2, IL-6, and INF, which can interact with TNF to eradicate MTB in lesions (80, 81). IFN is one of the main lymphokines. The expression of Nramp1, which carries iron(II) across the plasma membrane, is increased by IFN- stimulation (80). Thus, one way that Nramp1 prevents extracellular pathogenic bacterial invasion is by pumping iron out of the phagosome and into the cytosol, which restricts the amount of iron that can enter her Bloodstream (79, 80, 82, 83).

Iron deficiency-induced mitochondrial metabolism and hypoxia-inducible factor (HIF) signaling are significantly changed by lysosomal dysfunction. Together, these findings show that lysosomal acidity plays a crucial role in iron homeostasis, which is essential for cell proliferation (79, 82, 83). In PDHB-null cells (Pyruvate dehydrogenase (lipoamide) beta), we postulated that lysosomal pH dysfunction reduces cellular iron, which may impede aconitase activity and indirectly diminish citrate availability. BafA1 considerably decreases the amount of restored aconitase activity brought on by iron supplementation, which is in line with this theory. Moreover, iron feeding restores PDHB-knockout Jurkat cells' sensitivity to BafA1 (3, 61).

Lysosomal dysfunction causes profound metabolic alterations due to iron deficiency. This includes disturbances in electron transport chains, modification of cerebral carbon metabolism, and activation of hypoxia-like signals (3, 84).

Hydrogen Ions inhibit lysosome formation

To keep their internal pH acidic, lysosomes must actively concentrate H^+ ions (protons). The lysosomal membrane contains a proton pump that actively moves protons from the cytoplasm into the lysosome to achieve this. Vacuolar-type proton transporting ATPases (V-ATPases) is responsible for establishing phagosomal acidification by

transporting protons. Furthermore, the counter transport will be done by CIC-7 CI-/H Different exocytic and endocytic organelles contain the V-ATPase. Although the existence of V-ATPase has been proven since 1990 (Lukacs et al.), it is still unknown how this proton pump enters phagosomes. The V-ATPase a3 subunit was discovered to be more abundant in phagosomes than in late endosomes or lysosomes (85, 86).

Phagosomes, like lysosomes, take up proton pumps from late endocytic organelles. The a3 component is also present on a number of lysosome-related organelles, such as melanocytes, hormone-containing granules, and pancreatic insulin granules (3).

Membrane proton ATPase controls the concentration of H^+ to maintain endosomal acidity. (87) When the lysosomal H^+ content approaches or reaches the required concentration, the proton ATPase activates the lysosomal zymogen, enabling its hydrolytic activity and pathogen-killing role (88). It has been discovered that the phagocytic membrane's proton-ATPase lacks a proton pump, which prevents extracellular H^+ from being pumped into the phagosome and allows MTB to survive there (89). IFN-γ-activated macrophages interfere with nutrient uptake by MTB and maintain a pH of ~5 within phagosomes. The number of infected macrophages is significantly decreased because the pH of macrophages that are not activated by IFN- is >6 (89). Furthermore, since lysosomal V-ATPase is recruited directly to the phagosomes via tubular lysosomes to generate the acidic environment hostile to infections, the loss of proton ATPase may be the primary cause of the absence of acidification of MTB-containing phagosomes (90).

Hydrogen ions and their usage in cells have a variety of different paths. Hydrogen ions (especially H^+) have been known to maintain the acidic internal pH in the process of phagocytosis with the help of V-type H^+ ATPase. The V-type H^+ ATPase is an ATP-driven enzyme that, through the major active transport of H^+ across various biological membranes, converts the energy of ATP hydrolysis into electrochemical potential differences of protons (90-93).

Inhibition of apoptosis and autophagy

Host cell apoptosis upon MTB infection is primarily related to MTB virulence (94). Liendau et al. The mildly virulent MTBH37R and BCG strains of M. bovis were utilized as in vitro infection models to research how MTB affects macrophage apoptosis and how it interacts with THP-1 cells that had undergone phorbol myristate acetate differentiation (95). They are found to induce strong apoptosis. The pathogenic wild-type MTB strains H37Rv and M. bovis, in contrast, are unable to strongly cause macrophage apoptosis. This suggests that miR-30A and other toxic elements of her MTB strain regulate the apoptotic responses of macrophages. Increased autophagy-inhibited intracellular MTB clearance is suppressed by increased miR-30A expression. Autophagy is a maintenance procedure that affects both cell survival and death (3, 61).

Cellular factors, signaling proteins, TNF-, IFN-, transforming growth factors, IL-6, IL-12, IL-4, and IL-10 are involved in MTB entrance and host cell death. needs controlling signaling pathways, among other things. IFN- may be produced and released by natural killer T (NKT) cells to stop the growth of MTB in macrophages (96, 97).

Major players in the first line of defense against MTB are DCs and macrophages, which can also maintain complementary roles in the eradication of pathogenic microorganisms. Interestingly, cell-mediated immunity plays a major role in MTB infection, while the function of humoral immunity is still debatable (98). T cells are crucial to the defensive response and are fundamentally activated by MTB exposure. Th1 cells protect against intracellular infection by secreting IL-2 and IFN-. Immune responses are negatively impacted by the IL-4, IL-5, and IL-10 that Th2 cells release (96, 99).

Comparatively, it was shown that the fraction of T cells expressing the T cell receptor was comparable in tuberculosis patients and controls, indicating that cells are involved in the early immune response (96, 100). Macrophages infected with MTB often undergo one of three processes: necrosis, apoptosis, or survival. Apoptosis is a critical defense mechanism of macrophages against MTB in the early stages of infection. DCs receive antigens from apoptotic cells, which improves adaptive immunity. Bacterial growth is regulated by apoptosis, which also lowers intracellular viability. Autophagy is regulated by related genes (101). It is a homeostatic process involving removing unwanted substances and degrading non-functional cytoplasmic components (proteins, lipids, organelles) via lysosomes. As an important immune defense mechanism, autophagy is also involved in innate and adaptive immune responses. TNF-induced macrophage apoptosis mimics MTB-induced apoptosis, whereas non-apoptotic complement-induced cell death does not affect bacterial activity. Hence, immunological escape and/or latent infection could result from highly toxic MTB's suppression of apoptosis and autophagy (96, 99).

In general, those macrophages that are infected with MTB have 3 outcomes: necrosis, apoptosis, or survival. Apoptosis is a key defense mechanism against MTB in the initial stages because it regulates bacterial reproduction and lowers their survival in cells. On the other side, autophagy regulates the homeostatic process that uses the lysosome to remove extraneous material and dysfunctional cytoplasm. It also takes part in the adaptive immune system and innate immunity. The action of the bacteria is unaffected by the cell death brought on by the nonapoptotic complement. Consequently, strongly virulent MTB can cause immunological escape and/or latent infection by inhibiting apoptosis and autophagy (11,17).

Conclusion

There is still a long road ahead of us to understand the immunological escape mechanism used by MTB. Over the past 50 years, numerous studies have looked into the immune response and the pathogenic processes of MTB. However, MTB-caused tuberculosis continues to pose a threat to health globally. Its immunological escape capabilities, which significantly improve its survival inside the host, are mostly to blame for this. Future tuberculosis therapies will be focused on MTB infection characteristics and immune evasion mechanisms. MTB can stay dormant in the host by blocking lysosomal acidification, oxidative stress, apoptosis, and autophagy, as well as limiting macrophage development. Iron, Ca^{2+}, and H^{+} also contribute to MTB's immunological escape. Several proteins and genes work together to carry out this activity. As a consequence, this work opens up a brand-new area for the investigation of innovative medications to treat TB.

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Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Ravesloot-Chávez MM, Van Dis E, Stanley SA. The innate immune response to *Mycobacterium tuberculosis* infection. *Annu Rev Immunol* 2021; **39**:611-37.
2. Wang C, Peyron P, Mestre O, et al. Innate immune response to *Mycobacterium*

tuberculosis Beijing and other genotypes. *PLoS One* 2010; **5**(10):e13594.
3. Zhai W, Wu F, Zhang Y, et al. The immune escape mechanisms of *Mycobacterium tuberculosis*. *Int J Mol Sci* 2019; **20**(2):340.
4. Nahid P, Jarlsberg L, Kato-Maeda M, et al. Interplay of strain and race/ethnicity in the innate immune response to M. tuberculosis. *PLoS One* 2018; **13**(5):e0195392.
5. Ferluga J, Yasmin H, Al-Ahdal MN, et al. Natural and trained innate immunity against *Mycobacterium tuberculosis*. *Immunobiology* 2020; **225**(3):151951.
6. Khan N, Vidyarthi A, Pahari S, et al. Distinct strategies employed by dendritic cells and macrophages in restricting *Mycobacterium tuberculosis* infection: different philosophies but same desire. *Int Rev Immunol* 2016; **35**(5):386-98.
7. Liu CH, Liu H, Ge B. Innate immunity in tuberculosis: host defense vs pathogen evasion. *Cell Mol Immunol* 2017; **14**(12):963-75.
8. Mortaz E, Adcock IM, Tabarsi P, et al. Interaction of pattern recognition receptors with *Mycobacterium tuberculosis*. *J Clin Immunol* 2015; **35**(1):1-10.
9. Sia JK, Rengarajan J. Immunology of *Mycobacterium tuberculosis* infections. *Microbiology spectrum* 2019; **7**(4):7.4. 6.
10. Natarajan K, Kundu M, Sharma P, et al. Innate immune responses to *M. tuberculosis* infection. *Tuberculosis* 2011; **91**(5):427-31.
11. Guirado E, Schlesinger LS, Kaplan G, editors. Macrophages in tuberculosis: friend or foe. Semin Immunopathol; 2013: Springer.
12. Yoshikai Y. Immunological protection against *Mycobacterium tuberculosis* infection. *Tanpakushitsu Kakusan Koso* 2009; **54**(8 Suppl):1014-9.
13. Lam A, Prabhu R, Gross CM, et al. Role of apoptosis and autophagy in tuberculosis. *American Journal of Physiology-Lung Cellular and Molecular Physiology* 2017; **313**(2):L218-L29.
14. Silwal P, Kim JK, Yuk JM, et al. AMP-activated protein kinase and host defense against infection. *Int J Mol Sci* 2018; **19**(11):3495.
15. Schorey JS, Schlesinger LS. Innate immune responses to tuberculosis. *Microbiology Spectrum* 2016; **4**(6):4.6. 31.
16. Shen P, Li Q, Ma J, et al. IRAK-M alters the polarity of macrophages to facilitate the survival of *Mycobacterium tuberculosis*. *BMC Microbiol* 2017; **17**(1):1-11.
17. Allen M, Bailey C, Cahatol I, et al. Mechanisms of control of *Mycobacterium tuberculosis* by NK cells: role of glutathione. *Front Immunol* 2015; **6**:508.
18. Mihret A. The role of dendritic cells in *Mycobacterium tuberculosis* infection. *Virulence* 2012; **3**(7):654-9.
19. Hilda JN, Das S, Tripathy SP, et al. Role of neutrophils in tuberculosis: a bird's eye view. *Innate Immun* 2020; **26**(4):240-7.
20. Borkute RR, Woelke S, Pei G, et al. Neutrophils in tuberculosis: Cell biology, cellular networking and multitasking in host defense. *Int J Mol Sci* 2021; **22**(9):4801.
21. Muefong CN, Sutherland JS. Neutrophils in tuberculosis-associated inflammation and lung pathology. *Front Immunol* 2020; **11**:962.
22. Wolf AJ, Desvignes L, Linas B, et al. Initiation of the adaptive immune response to *Mycobacterium tuberculosis* depends on antigen production in the local lymph node, not the lungs. *J Exp Med* 2008; **205**(1):105-15.
23. De Martino M, Lodi L, Galli L, et al. Immune response to *Mycobacterium tuberculosis*: a narrative review. *Frontiers in pediatrics* 2019; **7**:350.
24. Bekale RB, Du Plessis SM, Hsu NJ, et al. *Mycobacterium tuberculosis* and interactions with the host immune system: Opportunities for nanoparticle based immunotherapeutics and vaccines. *Pharm Res* 2019; **36**(1):1-15.
25. Jagatia H, Tsolaki AG. The role of complement system and the immune response to tuberculosis infection. *Medicina* 2021; **57**(2):84.

26. Bénard A, Sakwa I, Schierloh P, et al. B cells producing type I IFN modulate macrophage polarization in tuberculosis. *American journal of respiratory and critical care medicine* 2018; **197**(6):801-13.
27. Winslow GM, Cooper A, Reiley W, et al. Early T-cell responses in tuberculosis immunity. *Immunol Rev* 2008; **225**(1):284-99.
28. Tian Y, Hao Y, Dong M, et al. Development of a monoclonal antibody to pig CD69 reveals early activation of T Cells in pig after PRRSV and ASFV infection. *Viruses* 2022; **14**(6):1343.
29. Leemans JC, Florquin S, Heikens M, et al. CD44 is a macrophage binding site for *Mycobacterium tuberculosis* that mediates macrophage recruitment and protective immunity against tuberculosis. *J Clin Invest* 2003; **111**(5):681-9.
30. Rohde K, Yates RM, Purdy GE, et al. *Mycobacterium tuberculosis* and the environment within the phagosome. *Immunol Rev* 2007; **219**(1):37-54.
31. Schüller S, Neefjes J, Ottenhoff T, et al. Coronin is involved in uptake of *Mycobacterium bovis* BCG in human macrophages but not in phagosome maintenance. *Cell Microbiol* 2001; **3**(12):785-93.
32. Flynn JL, Chan J. Immune evasion by *Mycobacterium tuberculosis*: living with the enemy. *Curr Opin Immunol* 2003; **15**(4):450-5.
33. Ma J, Yang B, Yu S, et al. Tuberculosis antigen-induced expression of IFN-α in tuberculosis patients inhibits production of IL-1β. *The FASEB Journal* 2014; **28**(7):3238-48.
34. Wong D, Chao JD, Av-Gay Y. *Mycobacterium tuberculosis*-secreted phosphatases: from pathogenesis to targets for TB drug development. *Trends Microbiol* 2013; **21**(2):100-9.
35. Sajid A, Arora G, Singhal A, et al. Protein phosphatases of pathogenic bacteria: role in physiology and virulence. *Annu Rev Microbiol* 2015; **69**(527):47.
36. Walburger A, Koul A, Ferrari G, et al. Protein kinase G from pathogenic mycobacteria promotes survival within macrophages. *Science* 2004; **304**(5678):1800-4.
37. Gutierrez MG, Mishra BB, Jordao L, et al. NF-κB activation controls phagolysosome fusion-mediated killing of mycobacteria by macrophages. *J Immunol* 2008;181(4):2651-63.
38. Pandey AK, Sassetti CM. Mycobacterial persistence requires the utilization of host cholesterol. *PNAS* 2008; **105**(11):4376-80.
39. Vergne I, Chua J, Deretic V. Tuberculosis toxin blocking phagosome maturation inhibits a novel Ca2+/calmodulin-PI3K hVPS34 cascade. *J Exp Med* 2003; **198**(4):653-9.
40. Naeem MA, Ahmad W, Tyagi R, et al. Stealth strategies of *Mycobacterium tuberculosis* for immune evasion. *Curr Issues Mol Biol* 2021; **41**(1):597-616.
41. Tailleux L, Schwartz O, Herrmann JL, et al. DC-SIGN is the major *Mycobacterium tuberculosis* receptor on human dendritic cells. *J Exp Med* 2003; **197**(1):121-7.
42. Geijtenbeek TB, Van Vliet SJ, Koppel EA, et al. Mycobacteria target DC-SIGN to suppress dendritic cell function. *J Exp Med* 2003; **197**(1):7-17.
43. Jamwal SV, Mehrotra P, Singh A, et al. Mycobacterial escape from macrophage phagosomes to the cytoplasm represents an alternate adaptation mechanism. *Sci Rep* 2016; **6**(1):1-9.
44. Chai Q, Wang L, Liu CH, et al. New insights into the evasion of host innate immunity by *Mycobacterium tuberculosis*. *Cell Mol Immunol* 2020; **17**(9):901-13.
45. Chen Z, Wang T, Liu Z, et al. Inhibition of autophagy by MiR-30A induced by mycobacteria tuberculosis as a possible mechanism of immune escape in human macrophages. *Jpn J Infect Dis* 2015; **68**(5):420-4.
46. Wong D, Li W, Chao JD, et al. Protein tyrosine kinase, PtkA, is required for *Mycobacterium tuberculosis* growth in macrophages. *Sci Rep* 2018; **8**(1):1-12.

47. Queval CJ, Song OR, Carralot JP, et al. *Mycobacterium tuberculosis* controls phagosomal acidification by targeting CISH-mediated signaling. *Cell Rep* 2017; **20**(13):3188-98.
48. MacMicking JD, Taylor GA, McKinney JD. Immune control of tuberculosis by IFN-γ-inducible LRG-47. *Science* 2003; **302**(5645):654-9.
49. Sharp JD, Singh AK, Park ST, et al. Comprehensive definition of the SigH regulon of *Mycobacterium tuberculosis* reveals transcriptional control of diverse stress responses. *PLoS One* 2016; **11**(3):e0152145.
50. Dutta NK, Mehra S, Martinez AN, et al. The stress-response factor SigH modulates the interaction between *Mycobacterium tuberculosis* and host phagocytes. *PLoS One* 2012; **7**(1):e28958.
51. Sureka K, Hossain T, Mukherjee P, et al. Novel role of phosphorylation-dependent interaction between FtsZ and FipA in mycobacterial cell division. *PLoS One* 2010; **5**(1):e8590.
52. Buchmeier NA, Newton GL, Fahey RC. A mycothiol synthase mutant of *Mycobacterium tuberculosis* has an altered thiol-disulfide content and limited tolerance to stress. *J Bacteriol* 2006; **188**(17):6245-52.
53. Mukherjee P, Sureka K, Datta P, et al. Novel role of Wag31 in protection of mycobacteria under oxidative stress. *Mol Microbiol* 2009; **73**(1):103-19.
54. Arora G, Sajid A, Singhal A, et al. Identification of Ser/Thr kinase and forkhead associated domains in *Mycobacterium* ulcerans: characterization of novel association between protein kinase Q and MupFHA. *PLoS Negl Trop Dis* 2014; **8**(11):e3315.
55. Romero MM, Balboa L, Basile JI, et al. Clinical isolates of *Mycobacterium tuberculosis* differ in their ability to induce respiratory burst and apoptosis in neutrophils as a possible mechanism of immune escape. *Clin Dev Immunol* 2012; 2012.
56. Imai K, Kurita-Ochiai T, Ochiai K. *Mycobacterium* bovis bacillus Calmette-Gueérin infection promotes SOCS induction and inhibits IFN-γ-stimulated JAK/STAT signaling in J774 macrophages. *FEMS Immunol Med Microbiol* 2003; **39**(2):173-80.
57. Lamichhane G. *Mycobacterium tuberculosis* response to stress from reactive oxygen and nitrogen species. *Front Microbiol* 2011; **2**:176.
58. Ganguly N, Giang PH, Gupta C, et al. *Mycobacterium tuberculosis* secretory proteins CFP-10, ESAT-6 and the CFP10: ESAT6 complex inhibit lipopolysaccharide-induced NF-κB transactivation by downregulation of reactive oxidative species (ROS) production. *Immunol Cell Biol* 2008; **86**(1):98-106.
59. Colangeli R, Haq A, Arcus VL, et al. The multifunctional histone-like protein Lsr2 protects mycobacteria against reactive oxygen intermediates. *PNAS* 2009; **106**(11):4414-8.
60. Shin D-M, Jeon B-Y, Lee H-M, et al. *Mycobacterium tuberculosis* eis regulates autophagy, inflammation, and cell death through redox-dependent signaling. *PLoS pathogens* 2010; **6**(12):e1001230.
61. Sao Emani C, Williams M, Van Helden P, et al. Gamma-glutamylcysteine protects ergothioneine-deficient *Mycobacterium tuberculosis* mutants against oxidative and nitrosative stress. *Biochem Biophys Res Comm* 2018; **495**(1):174-8.
62. Silva Miranda M, Breiman A, Allain S, et al. The tuberculous granuloma: an unsuccessful host defence mechanism providing a safety shelter for the bacteria? *Clin Dev Immunol* 2012; 2012.
63. Guirado E, Schlesinger LS. Modeling the *Mycobacterium tuberculosis* granuloma–the critical battlefield in host immunity and disease. *Front Immunol* 2013; 4:98.
64. Barry CE, Boshoff HI, Dartois V, et al. The spectrum of latent tuberculosis: rethinking the biology and intervention strategies. *Nature Reviews Microbiology* 2009; **7**(12):845-55.

65. Huynh KK, Joshi SA, Brown EJ. A delicate dance: host response to mycobacteria. *Curr Opin Immunol* 2011; **23**(4):464-72.
66. Flynn JL, Chan J, Lin P. Macrophages and control of granulomatous inflammation in tuberculosis. *Mucosal Immunol* 2011; **4**(3):271-8.
67. Yoshida A, Inagawa H, Kohchi C, et al. The role of toll-like receptor 2 in survival strategies of *Mycobacterium tuberculosis* in macrophage phagosomes. *Anticancer Res* 2009; **29**(3):907-10.
68. Ehlers S, Schaible UE. The granuloma in tuberculosis: dynamics of a host–pathogen collusion. *Front Immunol* 2013; **3**:411.
69. Egen JG, Rothfuchs AG, Feng CG, et al. Macrophage and T cell dynamics during the development and disintegration of mycobacterial granulomas. *Immunity* 2008; **28**(2):271-84.
70. Pieters J. *Mycobacterium tuberculosis* and the macrophage: maintaining a balance. *Cell Host Microbe* 2008; **3**(6):399-407.
71. Jafari A, Nagheli A, Foumani AA, et al. The role of metallic nanoparticles in inhibition of *Mycobacterium tuberculosis* and enhances phagosome maturation into the infected macrophage. Oman Med J. 2020;35(6):e194.
72. Mariotti S, Sargentini V, Pardini M, et al. *Mycobacterium tuberculosis* may escape helper T cell recognition by infecting human fibroblasts. *Hum Immunol* 2013; **74**(6):722-9.
73. Saini NK, Baena A, Ng TW, et al. Suppression of autophagy and antigen presentation by *Mycobacterium tuberculosis* PE_PGRS47. *Nature microbiology* 2016; **1**(9):1-12.
74. Yang J, Zhao Z, Gu M, et al. Release and uptake mechanisms of vesicular Ca2+ stores. *Protein Cell* 2019; **10**(1):8-19.
75. Zhong XZ, Zou Y, Sun X, et al. Inhibition of transient receptor potential channel mucolipin-1 (TRPML1) by lysosomal adenosine involved in severe combined immunodeficiency diseases. *J Biol Chem* 2017; **292**(8):3445-55.
76. Saheki Y, De Camilli P. Endoplasmic reticulum–plasma membrane contact sites. *Annu Rev Biochem* 2017; **86**:659-84.
77. Cruz A, Fraga AG, Fountain JJ, et al. Pathological role of interleukin 17 in mice subjected to repeated BCG vaccination after infection with *Mycobacterium tuberculosis*. *J Exp Med* 2010; **207**(8):1609-16.
78. Kusner DJ, Barton JA. ATP stimulates human macrophages to kill intracellular virulent *Mycobacterium tuberculosis* via calcium-dependent phagosome-lysosome fusion. *J Immunol* 2001; **167**(6):3308-15.
79. Weber RA, Yen FS, Nicholson SP, et al. Maintaining iron homeostasis is the key role of lysosomal acidity for cell proliferation. *Mol Cell* 2020; **77**(3):645-55. e7.
80. Garcia-Bermudez J, Baudrier L, Bayraktar EC, et al. Squalene accumulation in cholesterol auxotrophic lymphomas prevents oxidative cell death. *Nature* 2019; **567**(7746):118-22.
81. Sensi SL, Granzotto A, Siotto M, et al. Copper and zinc dysregulation in Alzheimer's disease. *Trends Pharmacol Sci* 2018; **39**(12):1049-63.
82. Koh J-Y, Kim HN, Hwang JJ, et al. Lysosomal dysfunction in proteinopathic neurodegenerative disorders: possible therapeutic roles of cAMP and zinc. *Mol Brain* 2019; **12**(1):1-11.
83. Zhu XG, Puthenveedu SN, Shen Y, et al. CHP1 regulates compartmentalized glycerolipid synthesis by activating GPAT4. *Mol Cell* 2019; **74**(1):45-58.e7.
84. Sha S, Shi X, Deng G, et al. *Mycobacterium tuberculosis* Rv1987 induces Th2 immune responses and enhances *Mycobacterium* smegmatis survival in mice. *Microbiol Res* 2017; **197**:74-80.
85. Mindell JA. Lysosomal acidification mechanisms. Annu Rev Physiol. 2012;74:69-86.
86. Sun-Wada G-H, Tabata H, Kawamura N, et al. Direct recruitment of H+-ATPase from lysosomes for phagosomal acidification. *J Cell Sci* 2009; **122**(14):2504-13.
87. Iwabuchi K. Lactosylceramide-enriched lipid

raft-mediated infection immunity. *Med Mycol J* 2018; **59**(3):J51-J61.
88. Stewart M. Molecular mechanism of the nuclear protein import cycle. *Nature Rev Mol Cell Bio* 2007; **8**(3):195-208.
89. Choi H-H, Shin D-M, Kang G, et al. Endoplasmic reticulum stress response is involved in *Mycobacterium tuberculosis* protein ESAT-6-mediated apoptosis. *FEBS Lett* 2010; **584**(11):2445-54.
90. Toyomura T, Murata Y, Yamamoto A, et al. From lysosomes to the plasma membrane: localization of vacuolar type H+-ATPase with the a3 isoform during osteoclast differentiation. *J Biol Chem* 2003; **278**(24):22023-30.
91. Kusner DJ, Adams J. ATP-induced killing of virulent *Mycobacterium tuberculosis* within human macrophages requires phospholipase D. *J Immunol* 2000; **164**(1):379-88.
92. Macklaim JM, Fernandes AD, Di Bella JM, et al. Comparative meta-RNA-seq of the vaginal microbiota and differential expression by Lactobacillus iners in health and dysbiosis. *Microbiome* 2013; **1**(1):1-11.
93. Macklaim JM, Clemente JC, Knight R, et al. Changes in vaginal microbiota following antimicrobial and probiotic therapy. *Microbial Ecol Health Dis* 2015; 26(1):27799.
94. Ahmed M, Smith DM, Hamouda T, et al. A novel nanoemulsion vaccine induces mucosal Interleukin-17 responses and confers protection upon *Mycobacterium tuberculosis* challenge in mice. *Vaccine* 2017; **35**(37):4983-9.
95. Gajer P, Brotman RM, Bai G, et al. Temporal dynamics of the human vaginal microbiota. *Sci Transl Med* 2012; **4**(132):132ra52-ra52.
96. Dong Y, Chen H, Gao J, et al. Molecular machinery and interplay of apoptosis and autophagy in coronary heart disease. *J Mol Cell Cardiol* 2019; **136**:27-41.
97. Kaplan O, Demircan G. Relationship of autophagy and apoptosis with total occlusion of coronary arteries. Medical Science Monitor: *International Med J Exp Clin Res* 2018; **24**:6984.
98. Deretic V. Autophagy in immunity and cell-autonomous defense against intracellular microbes. *Immunol Rev* 2011; **240**(1):92-104.
99. Li D, Chen A, Lan T, et al. SCAP knockdown in vascular smooth muscle cells alleviates atherosclerosis plaque formation via up-regulating autophagy in ApoE−/− mice. The *FASEB Journal* 2019; **33**(3):3437-50.
100. D'Acquisto F, Crompton T. CD3+ CD4− CD8−(double negative) T cells: saviours or villains of the immune response? *Biochem Pharmacol* 2011; **82**(4):333-40.
101. Deretic V. Multiple regulatory and effector roles of autophagy in immunity. *Curr Opin Immunol* 2009; **21**(1):53-62.