Mycobacterium tuberculosis and host interactions in the manifestation of tuberculosis☆

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ABSTRACT

The final step of epigenetic processes is changing the gene expression in a new microenvironment in the body, such as neuroendocrine changes, active infections, oncogenes, or chemical agents. The case of tuberculosis (TB) is an outcome of *Mycobacterium tuberculosis* (*M.tb*) and host interaction in the manifestation of active and latent TB or clearance. This comprehensive review explains and interprets the epigenetics findings regarding gene expressions on the host-pathogen interactions in the development and progression of tuberculosis. This review introduces novel insights into the complicated host-pathogen interactions, discusses the challengeable results, and shows the gaps in the clear understanding of *M.tb* behavior. Focusing on the biological phenomena of host-pathogen interactions, the epigenetic changes, and their outcomes provides a promising future for developing effective TB immunotherapies when converting gene expression toward appropriate host immune responses gradually becomes attainable. Overall, this review may shed light on the dark sides of TB pathogenesis as a life-threatening disease. Therefore, it may support effective planning and implementation of epigenetics approaches for introducing proper therapies or effective vaccines.

1. Introduction

Historically, evidence of *Mycobacterium tuberculosis* (*M.tb*) infection was described as early as 5,000 years ago; however, the reason behind the manifestation of tuberculosis (TB) has yet to be understood entirely. To end this fight, the affecting factors in each side of the battle between

M.tb and the host must be identified [1]. Epigenetics, the science of variations, refers to heritable characteristic changes due to different gene expression statuses without any changes in DNA sequence [2].

Under stress, bacteria and their hosts utilize innovative interaction principles to decide whether to compromise or intervene to eliminate threats. Interactions between *M.tb* and humans are often dependent on the strategies of *M.tb* to evade the host responses and replicate in its habitat and persist, unlike the host can clear the infection. Remarkably, this microorganism is adapted to replicate within host phagocytic cells and macrophages that naturally are specialized for killing *M.tb* [3].

Numerous association studies have been performed to identify genetic factors responsible for variation in TB susceptibility, and many relevant single nucleotide polymorphisms (SNPs) in different molecules have been published [4,5]. However, the increase in TB-associated polymorphisms and the heterogeneity of the studied population have led more and more authors to become interested in epigenetic phenomena. Therefore, eradicating dormant or active *M.tb* infections in specific populations is considered an epigenetics phenomenon [6]. The granuloma in TB can be considered a battlefield on which *M.tb* and its host have evolved over millions of years, in which each organism actively tries to fight for the species' survival [7].

In the case of TB, the interactions between bacteria and host are epigenetic events complicated by latency, disease manifestation, or bacterial elimination. [8]. Surprisingly, this microbe is not cytopathic and does not form any particular disorders in the majority of infected subjects (~70 %), but inappropriate host immune response complications damage the lung, and consequently, TB can be manifested as an immunopathologic disease, which reflects epigenetic processes.

Although tremendous studies have been performed on the pathogenesis, protection, and treatment of TB, the mechanisms of *M.tb*-host interaction in this life-threatening re-emerging disease have yet to be fully understood [1,9–11]. To solve this problem, the interactions of *M.tb* and host in each stage of infection should be evaluated prospectively using new advanced molecular techniques. Numerous *M.tb* virulence factors and host inflammatory reactions were discovered using high throughput techniques, which simultaneously evolve in TB pathogenicity [9,10,12,13].

To compile the classic and novel findings in the development and progression of TB, this comprehensive review is conducted to introduce new insights, explain controversial results, and find the biological gaps that can help design new studies in such a complicated disease. Conducting more studies helps understand cellular immunity and find effective immunotherapies when the reversing gene expression toward appropriate host immune responses gradually becomes available.

2. Tuberculosis and the epigenetic alterations

Although the epigenetic changes during *M.tb* colonization to TB manifestations, mild, latent, and acute, have considerable gaps. The epigenetic alterations by *M.tb* on host immune cells, such as inhibition, activation, or switch-off and on, may determine the type of TB disease and its severity. When *M.tb* colonizes in the lung and infection is established, the interactions between pathogen and host responses begin. The leading host effector players, including Th1, Th17, Treg, and macrophage, are involved in eliminating infection [14,15].

Forming granuloma around the bacteria shows a combination of macrophages, NK cells, Th subpopulations, and CTLs. In response to forming a particular immune response, the bacteria also use their virulence factors, such as Ag85, ESAT-6, CFP-10, PPEs, and HSP, to survive in their habitat. In this game, the host can put pressure on *M.tb* by activation of signaling lymphocytic activation molecule (SLAM) in the Th1 subpopulation to induce IFN-γ and IL-2 production. They are the main cytokines in host defense against *M.tb* to potentiate the functions of macrophages, NK cells, and CTLs. This host response powerfully eliminates the *M.tb* and may establish a specific protective immunity [15,16].

However, without an appropriate microenvironment for forming Th1 immunity, the host responses become weak in favor of *M.tb* reactivation in granuloma toward caseous form and, consequently, TB development. Therefore, the severity in such a situation depends on the microenvironments in which the responses form, i.e., the balance between Th1/Th2, Th17/Treg, and the pressure of *M.tb* virulence factors [17,18]. For example, Gallucci *et al.* showed that the increased concentration of LPS in circulation during progressive TB might be implicated in the persistence of the immune-endocrine imbalance toward advanced disease [17].

Many studies have focused on the cytokine's involvement in defense against *M.tb*. For example, medium levels of transforming growth factor beta (TGF-β) and IL-10 limit T-bet for inducing Th1 cells, preventing IFN-γ-associated hypersensitivity (DTH) reactions in TB. This condition results in an equilibrium state between *M.tb* and the host called latency.

Recently, Gallucci *et al.*, using system biology, suggested that GILZ, ANXA1, NFKBIA, and NFKBIB are upregulated in TB patients. Furthermore, concerning disease severity, NFKBIB and ANXA1 increased enormously in moderate and severe TB and GILZ in moderate cases. The pro-inflammatory factors also were higher in severe TB [19]. These differences in TB status have been discussed in the following sections. Fig. 1 shows the central cellular attempts of the immune system in different people to overcome *M.tb* infection. Although resolving status could be a protective extended response, and in latency, *M.tb* is not active in producing TB, the exhaustion or suppression of the immune system causes active TB.

3. Virulence factors of *M.tb*

3.1. *M.tb Antigens involved in the M.tb-host interaction*

In brief, TB is caused by inhaling airborne droplets containing live *M.tb* that transfer to distant areas of the lungs, where the innate host immune system recognizes the pathogen-associated molecular patterns (PAMPs). The first interactions between *M.tb* and host molecules are formed by pattern recognition receptors (PRRs), mostly Toll-like receptors (TLRs), which play essential roles in the production of pro-inflammatory cytokines, such as TNF-α, IL-1, and IL-12 via MyD88 [20].

3.2. *Interactions of M.tb with TLRs*

Previous studies have shown that TLR2 recognition of *M.tb* lipoglycans and lipoproteins and members of the PE-PGRS family develops a bridge that activates adaptive immunity against mycobacterial infection [21–23]. Lipoarabinomannans (LAM) and lipomannans (LM) are integral components of the *M.tb* cell wall and consist of a D-mannan core and a D-arabinan domain. Several previous reports have shown that TLR2-dependent cells are activated by *M.tb* cell wall lipoglycans (mannose-cap lipoarabinomannan (ManLam), phosphatidylinositol mannosides). *M.tb*-induced Man-Lam acts as an anti-inflammatory molecule by inhibiting IL-12 and TNF-α production and increasing IL-10 production by dendritic cells (DCs). Furthermore, LM activates macrophage type 2 (M2), which is dependent on the presence of TLR2 and has a significant inhibitory effect on the production of TNF-α, IL-12p40, and NO by lipopolysaccharide (LPS)-activated macrophages (M1) [24].

Some *M.tb* glycolipoproteins such as LpqH (Rv3763) and LprG (Rv1441c) induce the expression of TNF-α, IL-10, IL-12, and apoptosis in differentiated THP-1 cells, and monocyte-derived macrophages, while this effect is TLR2-mediated. These proteins also inhibit IFN-γ-regulated MHC-II expression on alveolar macrophages in a TLR2-dependent manner [25]. The protein PstS1 (Rv0934) induces activation of the extracellular signal-regulated kinase 1/2 and mitogen-activated protein kinase 1 (MAPK-1) pathways through TLR2 and TLR4, leading to *TNF-α* and *IL-6* expression [26]. Moreover, as a surface-exposed protein, PE_PGRS33 triggers TNF-α release from macrophages in a TLR2-dependent manner and induces macrophage apoptosis [27].
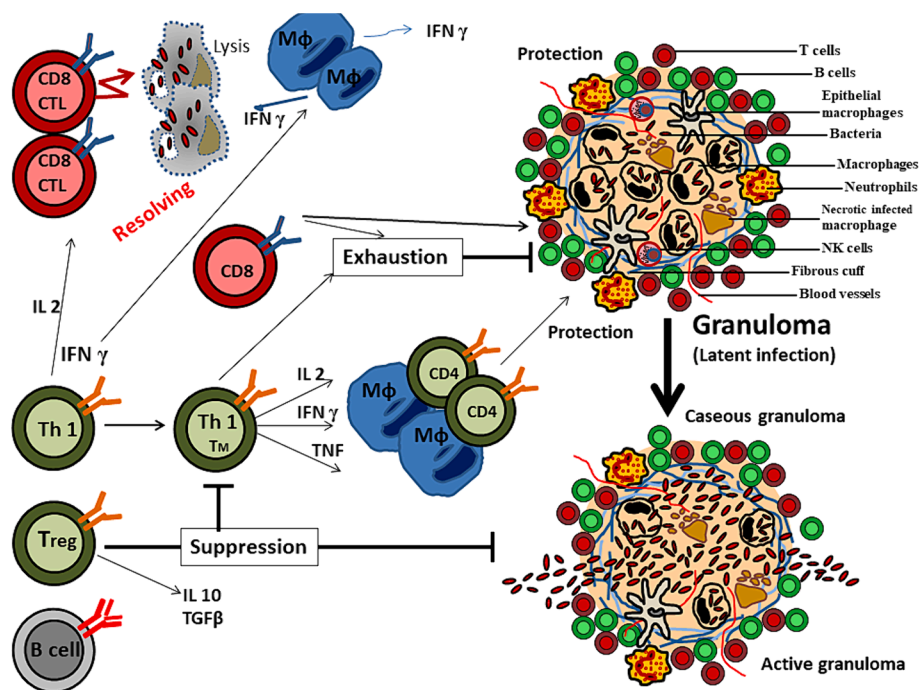
Fig. 1. The main host immune responses against *M.tb* in health and disease. The figure shows that epigenetic phenomena caused by various environmental and physiological mechanisms can change the immune responses toward protection, infection, or disease. Understanding epigenetic alterations in *M.tb*-host interactions can result in discovering effective immunotherapies for TB. Particularly when the reversing immune responses gradually become attainable. The figure illustrates that the main cellular immune system attempts to overcome *M.tb* infection in different people are wildly divergent. Resolving *M.tb* status could be a protective extended anti-*M.tb* response, and in latency, *M.tb* is not so active in creating TB; however, in the exhaustion or suppression conditions of the immune system, *M.tb* can disseminate and cause active TB.

3.3. Interaction of M.tb with non-TLRs

Recently, studies have shown that some PRRs other than TLRs (non-TLRs), such as complement receptors 3 (CR3), the nucleotide-binding oligomerization domain (NOD)-like receptor 2 (NOD2), and members of C-type lectin receptors can elicit innate immune responses against TB [28]. *M.tb* can bind to several receptors on the surface of mononuclear phagocytes, including complement receptor 3 (CD11b/CD18), enhancing uptake of *M.tb* by macrophages through the binding of C3 and interaction with C3 receptors on mononuclear phagocytes. In addition, it can bind to the CRs through both complement-dependent and independent pathways [29].

NOD-like receptor 2 (NOD2) induces innate immunity in response to peptidoglycan-derived muramyl dipeptide (MDP). Moreover, several recent studies suggest that this protein mediates resistance to mycobacterial infection through innate and adaptive immunity [30].

Furthermore, C-type lectin receptors are a group of the innate immune system components that bind to surfactants and mannose-binding lectin protein (MBL), including the mannose receptor (MR), dendritic cell-specific ICAM-3- grabbing non-integrin (DC-SIGN), DC-associated C-type lectin-1 (Dectin-1), and macrophage inducible C-type lectin (Mincle) [31,32]. Macrophages primarily use MR and CR3 for phagocytosis of *M.tb*. In contrast, ManLam has been proposed as a causative molecule for MR-mediated *M.tb* phagocytosis. It has also been shown that the involvement of ManLam-mediated MR during the phagocytic process induces *M.tb* into the primary phagosomal niche and enhances the survival of human macrophages by limiting phagosome-lysosome fusion. In addition, macrophage MR can interact with mannose residues of *M.tb* lipoglycoprotein LpqH, thus facilitating mycobacterial phagocytosis [33].

Formerly, ManLam or PIM in the *M.tb* cell wall was shown to bind DC-SIGN on immature dendritic cells and macrophage subpopulations. This interaction may impair dendritic cell maturation, modulate

cytokine secretion by phagocytes and dendritic cells, and suppress protective immunity against TB. However, it has recently been shown in experimental *M.tb* infections that DC-SIGN can protect the host by limiting tissue pathology rather than helping mycobacteria evade the immune system [34].

Mincle is expressed on macrophages, recognizes cord factors and *M.tb* cell wall glycolipids, and regulates macrophage activation. Also, *M.tb* umbilical factor activated macrophages to produce inflammatory cytokines and NO, which are entirely suppressed in Mincle-deficient macrophages [35].

Another ligand, MBL, has a collagen-like domain and a CRD that binds high-mannose and *N*-acetylglucosamine oligosaccharides on *M.tb*. This activates MBL-associated serine proteases, which in turn activate the complement pathway in an antibody-independent manner, leading to complement—or collectin-receptor-mediated phagocytosis [31].

3.4. Interaction of M.tb with extracellular matrix proteins (ECM)

Principally, pathogens must attach to the host through various cells to initiate an invasion. Therefore, they have developed several adhesives that bind to selected host molecules. It is known that *M.tb* can adhere and penetrate non-phagocytic cells such as respiratory epithelial cells and epithelial cells. Direct penetration may be significant for reaching and spreading into the blood and lymphatic system. *M.tb* also interacts with lung cells, causing necrosis and disruption of cell barriers, facilitating their passage and preparation for entry into the bloodstream [36,37].

Among the essential proteins are the so-called fibronectin (Fn)-binding proteins (FnBPs), members of the antigen 85 complex (Ag85). This *M.tb* complex comprises three proteins, antigens 85A, B, and C, encoded by three genes (*Rv3804c*, *Rv1886c*, and *Rv0129c*, respectively) [38]. They are mycolic acid transferases, potent immunogens, and significant antigens in the immune response against *M.tb* infection. The

interaction of Ag85B with Fn involves binding various regions of this protein to the Fn collagen-binding domain. Peptide mapping of the 110–84 sequence defined residues 108–98 as minimal inhibitory roles, with six residues (FEWYYQ) representing the most critical interactions of Fn. This pattern forms a helix at the protein level, bears no resemblance to FnBP properties in other prokaryotes and eukaryotes, and appears to be unique to *M.tb* [39].

Malate synthase G (*Rv1837c*) is another *M.tb* FnBP molecule in the glyoxylate pathway. This protein's binding site for Fn is in the C-terminal region, unique to *M.tb*. This protein is secreted and anchored to the cell wall by an undefined mechanism. This protein on the surface of bacteria can bind to laminin. Several studies have suggested that *M.tb* housekeeping enzymes contribute to activating virulence-enhancing factors [40].

PE_PGRs are a large family of proteins from *M.tb*, and only a few, such as the Wag22 antigen (*Rv1759c*), can bind to Fn. Of note, PE_PGRS33 (*Rv1818c*) and PE_PGRS1 (*Rv0109*) were also shown to bind Fn as they are Fn binding sites in the PGRS domain. However, the motives involved are unclear [41].

Heparin-binding hemagglutinin adhesin (HBHA) (Rv0475) is an *M.tb* ECM binding that interacts with sulfated carbohydrates in lysine- and proline-rich regions, enhancing binding to host tissues. Furthermore, HBHA is involved in the extrapulmonary shedding of *M.tb*. These results suggest that HBHA is essential for mycobacterial escape from the lung and the development of extrapulmonary infection. Besides, HBHA regenerates actin filaments at the endothelial cell barrier and mediates mycobacterial binding and localization in a human laryngeal epithelial cell line (HEp-2) and lung cell type II cell line (A549) [42,43].

Many pathogenic bacteria use laminin adhesion protein to form a starting point for tissue entry. Mycobacteria also have laminin-binding proteins called mycobacterial laminin-binding proteins. For example, the histone-like protein (HLP) of *M.tb* (Rv2986c) or the HupB protein can bind to cell surface laminin of mouse sarcoma, epithelial cells, and human lung cells and two heparin sulfate-binding sites on Hlp [44,45]. Another laminin-binding protein is ESAT-6, one of the virulence factors of *M.tb*.

Lung cells express membrane laminin; ESAT-6 exhibits dose-dependent binding to human laminin. These observations suggest that ESAT-6 uses laminin to bind to the bacterial surface [46].

4. An overview of immune responses to *M.tb*

Once droplets enter the lungs and *M.tb* colonizes in this site, resident pulmonary neutrophils, alveolar macrophages, and lung DCs can be infected, releasing inflammatory mediators, antimicrobial peptides, cytokines, and chemokines (CCs). CCs and chemokine receptors (CCR) are the primary mediators of *M.tb* danger signals and are involved in cell recruitment and migration. Macrophages are the main effectors of *M.tb* killing but are also an ecological niche for *M.tb* replication [47,48]. DCs may also engulf bacteria at the infection site but cannot kill them [49–52].

Although *M.tb* evolves many proteins in different life cycles stages, such as Ag85, CFP-10, ESAT-6, and PPEs, to manipulate the host immune responses and survive. Most of these molecules are strong immunogenes that the host can respond to and eliminate the infection. Many other mechanisms have also been involved in the ability of *M.tb* to arrest phagosome maturation, DC1 forming, and Th1 differentiating [16], but our understanding of these mechanisms remains incomplete. The host's main immunological molecules can be considered in four different stages as the host's strategies: (i) inflammatory reactions and leukocyte recruitment by CCRs (CCR1-7, and CXCR1,2) in response to secretion of inflammatory cytokines such as IL-1β, TNF-α, Il-6, IFN-I, IL-10, CCL-1–5, CXCL-1,-2,-3,-5,-6,-7,-8, On the other hand, the host's critical immune molecules which can play pivotal roles in the host responses toward TB manifestation, fulminant disease, latency or exacerbation including [53]. (ii) responses by activation of transcription factor

expression (T-box transcription factor, T-bet), GATA-3, retinoic acid receptor-related orphan nuclear receptor gamma (ROR-γt), or FoxP3 and STAT). (iii) production of cytokines and immunomodulators dependent to the expression of the transcription factor) IL-12, IFN-γ, iNOS, IL-4, IL-13, IL-17, IDO, TGF-β and IL-10 [54]. (iv) elimination of infection or TB development by release of effector molecules in tissue damage. These conditions can be changed depending on host (human) or microbe (*M.tb*) activities under the influence of epigenetic strategies [16,55].

For example, in natural immunity, neutrophils have a dual effect; recruitment of moderate amounts favors host responses, and low or higher levels favor inflammatory reactions and, consequently, *M.tb* dissemination. The same outcomes are expected for monokines or natural cytokine productions; for example, the high levels of TNF-α, IL-6, and IL-1β can exacerbate the inflammatory responses and induce hypersensitivities, but the low level of these monokines is necessary for proper protective responses. Furthermore, type I interferons, which are implicated in *M.tb* infection, dependent on the members of this family, may potentiate or inhibit the macrophage responses. *M.tb* infection can induce the production of high levels of IFN-α by macrophages with potentiation of response, particularly when certain virulent strains are causing the infection. On the other hand, IFN-β induces the production of IL-10 by macrophages and inhibits the production of IL-12 and TNF-α by macrophages. Notably, some members of the type I IFNs can also block macrophage activation by Th1 cells, impairing their responsiveness to IFN-γ [56].

Overall, the proper immune response against *M.tb* is compartmentalized. First, *M.tb* infects macrophages or immature DCs at the entry site (lung), which migrate to the regional lymph node's T-cell zone (second compartment), where they mature into DC1 and produce IL-12. Generating an appropriate immune response (Th1) in the lymph node compartment is critical, with specific *M.tb* CD4$^+$ T cells recognizing *M.tb* antigens bound to MHC molecules on mature DCs and secreting IL-12. In the presence of IL-12, certain Th0s are activated and differentiate into Th1 blasts. These specific effector cells are attracted to the *M.tb* replication site via the bloodstream as a third compartment. Specific Th1 cells circulating at sites of lung infection produce IFN-γ and IL-2, activate infected macrophages, specific cytolytic lymphocytes (CTLs), and NK cells to clear *M.tb* infection and protect the host from TB infection. In this microenvironment, the following activated macrophage-killing mechanisms operate O_2-dependent factors, proteases, and autophagy for eliminating *M.tb* infection. Correspondingly, secreted cytokines activate cell-mediated immunity (CMI), and activated macrophages and CTLs eliminate *M.tb* (Fig. 2).

If Th0 cells fail to convert activated Th1 cells, solid granulomas containing active TB or *M.tb* can develop at sites of *M.tb* replication. Under these circumstances, *M.tb* neutralizes the killing activity of infected macrophages by increasing endosomal pH, suppressing apoptosis, altering cytokine secretion patterns, and scavenging toxic superoxide radicals [48,50].

The CMI, which contains DC1 as mature antigen-presenting cells (APCs), CD4$^+$ and CD8$^+$ T lymphocytes, NK cells, and most notably activated macrophages, plays a prominent role in defense against TB [57,58]. Th1 cells activate and promote the antibacterial functions of macrophages by secreting IFN-γ and TNF-α, whereas IL-2-activated CD8$^+$ CTLs kill *M.tb*-infected macrophage via programmed cells mechanism (PCD) that use granulysin, perforins and granzymes [50,57].

Thus, a well-modulated immune response to *M.tb* requires proper regulation, primarily formed by T-reg and Th2 responses. Although less active, these lymphocyte subpopulations can inhibit hypersensitivity reactions and prevent immunopathological damage. The complex immune response required to eliminate *M.tb* is characterized by a Th1-dominant pattern that generates IFN-γ and IL-2 that can recruit and activate macrophages and CD8$^+$ CTLs, and a milder pattern to prevent pathological damage, likely regulatory T-reg and Th2 responses. Such complex mechanisms may provide an immunological basis for the
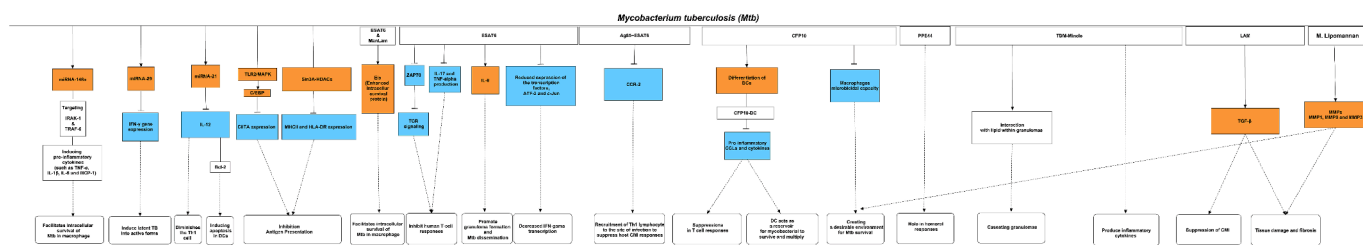
Fig. 2. The host gene expression possibility in *M.tb* infection. The demonstration of host activities in response to *M.tb* strategies and the possible outcomes. Ag85: Antigen85, ATF-2: Activating transcription factor-2, CIITA: Class-II *trans*-activator, CCR2: C-C chemokine receptor 2, C/EBP: CCAAT/enhancer-binding protein, CFP-10: 10-kDa culture filtrate protein, CMI: Cell-mediated immunity, DC: Dendritic cell, Eis: Enhanced intracellular survival, ESAT-6: 6 kDa early secretory antigenic target, HLA-DR: Human leukocyte antigen-DR, IFN-γ: Interferon-gamma, IL-6: Interleukin 6, IRAK-1: Type I interleukin-1 receptor-associated protein kinase, LAM: lipoarabinomannan, MAPK: Mitogen-activated protein kinase, MCP-1: Monocyte chemoattractant protein 1, MHCII: Major Histocompatibility Complex Class II, MMPs: Matrix metalloproteinases, PPE: Pro-Pro-Glu (PPE) motif proteins, Sin3A-HDACs: Sin3A-Histone deacetylases, TB: Tuberculosis, TCR: T-cell receptor, TDM: Trehalose-6,6-dimycolate, TGF-β: Transforming growth factor-beta, TLR-2: Toll-like receptor 2, TRAF6: TNF receptor (TNFR)-associated factor, ZAP70: Zeta-Associated Protein Kinase 70.

prevention and treatment of tuberculosis [54,59–61] (Fig. 2).

DCs can efficiently incorporate antigens into the cytosolic (endogenous) processing pathway using the Fc gamma receptor type 1 (FcγRI), whereas other cell types cannot. In the cytosol, the proteasome cleaves antigenic peptides into epitopes and transports them to the endoplasmic reticulum for loading into class I human leukocyte antigen (HLA) molecules. This cross-presentation phenomenon leads to the presentation of HLA-I-Ag complexes to CTLs [62]. As a result, antigen-specific CTLs can destroy *M.tb*-infected macrophages and augment Th1 immune responses for protection. However, Th1 and IFN-γ production alone do not accurately reflect the protective response to anti-TB.

Like IFN-γ, low levels of IL-17 were thought to be effector cytokines against *M.tb* infection [63,64]. This indicates that IFN-γ and low IL-17 levels may help establish a protective immune response to some anti-TB subunit vaccines used as BCG boosters [63]. On the other hand, Jurado *et al.* suggested that CD4$^+$IFN-γ$^+$IL-17$^+$ lymphocytes were the primary source of IFN-γ and IL-17. They argued that the amount of *M.tb*-specific CD4$^+$IFN-γ$^+$IL-17$^+$ subpopulations in TB patients' bloodstream and pleural fluid is directly related to disease severity. In other words, TB patients with low responders had the highest percentage of CD4$^+$IFN-γ$^+$IL-17$^+$ cells, indicative of severe pulmonary lesions [18].

Low IL-17 production and corresponding amounts of IFN-γ enhance TB prophylaxis, whereas high levels of IL-17 production, even in the presence of IFN-γ, induce pathological delayed-type hypersensitivity (DTH) reactions [64,65]. IL-17 can enhance protective immune responses by enhancing IL-12 secretion [64]. In TB studies, introducing recombinant IL-12 into the liver of neutropenic mice reduced hyperactivation of infection [64,66]. IL-17 is a potent cytokine in neutrophil recruitment and activation; therefore, it can be concluded that early recruitment of neutrophils to the site of infection stimulates IL-12 release to induce Th1 responses [64,65].

As mentioned earlier, the polarity of different types of adaptive immune responses depends on APC functions. If indoleamine 2,3-dioxygenase-1 (IDO) is activated in APC, it catalyzes tryptophan and can induce a T-reg reaction to induce immune regulatory TGF-β pandemic. High levels of TGF-β exacerbate TB manifestations and can reactivate the latent form into the acute form, causing pulmonary fibrosis [51,52,67].

Indeed, despite 100 years of studies on TB and improving our knowledge of cellular immune responses to *M.tb,* the epigenetic condition necessary for reprogramming the inappropriate immune response towards protective immunity is yet to be accessible. However, with more studies on the epigenetic events in *M.tb*-host interactions, reprogramming by immunotherapies is close, as converting gene expression toward appropriate host immune responses gradually becomes attainable [54,68].

5. Genetic polymorphism in TB patients

Genetic polymorphism in TB has been studied widely; however, a large and homogenous cohort was not conducted on a particular population. The studies are heterogeneous due to ethnic variations, different sample sizes, and methodologies; thus, these factors may cause statistical bias in any definite infection/disease [69]. In addition, the gene variation repeatedly reported in TB subjects through linkage does not account for non-familial patients [70]. However, this part of the scientific approach must be considered seriously. Therefore, large sample sizes and advanced techniques such as next-generation sequencing (NGS), exome sequencing, and pyrosequencing should offer more reliable data for finding effective genetic biomarkers for TB theranostics.

Many relevant studies have been performed to identify the genetic factors responsible for variations in susceptibility to TB. However, single nucleotide polymorphisms (SNPs) should be considered a theranostic factor in TB patients. In the case of TB, several SNPs have been reported as possible causes of resistance/infection. Among them polymorphisms of cytokines, TLRs, and HLA genes were further evaluated, such as IFN-γ, TNF-α, IL-1, IL-6, IL-10, IL-12, and IL-17 [69,71–76].

5.1. The role of CCs and CCRs in leukocyte recruitment

In TB, CCRs such as CCR1 and CCR2 play an essential role in recruiting immune cells to the site of infection (lungs). Although under some specific conditions, CCLs can also lead to excessive inflammation, leading to DTH, damage to local tissues, and cavitation or active TB [77]. These molecules mostly play essential roles in the first line of defense, which is immune cells' recruitment to the site of infection, which is the most crucial part of *M.tb*-host combat in an epigenetic manner.

For example, it can be noted that down-regulation of the *CCR2* expression after introducing PPD and ManLam on APCs, particularly monocytes and DCs, might be an *M.tb* hamper for preventing the emigration of mature DCs and monocytes to and within local lymph nodes. This mechanism inhibits APC-T cell interactions and establishes an effective immune response [78–80]. Moreover, *M.tb* downregulates CCR2 as a chemoattractant for the recruitment of Th1 lymphocytes to the site of infection by exploiting the expression of its virulence factors, mainly Ag85 and ESAT-6. Suppressing CMI responses for elevated levels of CCR1 (driven by MIP-1a) and CCR2 (ligand for MCP-1) on T cells in TB implicates early cellular responses that determine Th1/Th2 polarisation [81]. In addition to monocytes and B cells, immune cells express significantly higher amounts of *CCR1* and *CCR2* [82]. Therefore, the amount of *CCLs* and *CCRs* in the recruitment of immune cells at the site of infection may contribute to healing or disease development. Chemokines and chemokine receptors are essential for future medicine [83,84].

The tryptophan metabolite indoleamine 2,3-dioxygenase-1 (IDO-1) has dual actions in *M.tb* infection and host factors, regulating tryptophan availability and downstream metabolite formation [51]. Increased IDO-1 activity during bacterial infection may limit tryptophan availability to T cells, thereby regulating proliferation [85]. IDO-1 activity in APCs inhibited the proliferation of mycobacterial antigen-specific T cells. A recent study by Li *et al.* has suggested that pleuritic fluid from a TB patient contains inhibitory components that interfere with T-cell responses, and these can be partially blocked with the IDO inhibitor and 1-methyl-DL-tryptophan [86,87].

5.2. Monocytes and macrophages, the main effectors

Many sections of this review explain and discuss monocyte/macrophage activities as the leading players in *M.tb* infection. However, some effector mechanisms, which less fit those explanations, are discussed here in detail.

Human alveolar macrophages are the frontline cells controlling TB's subsequent replication and spread of infection. Therefore, understanding the alveolar macrophage biology as an immune response and their interactions with *M.tb* is essential for understanding how to address TB control at various stages of the disease and developing better future vaccination and drug strategies [88].

Human macrophages produce nitric oxide (NO) through increased activity of inducible nitric oxide synthase (iNOS) [89]. *INOS* and *NO* are expressed by cytokines and inflammatory mediators such as TNF-α, IFN-γ, LPS, IL-1, hypoxia, and picolinic acid [90]. High-level expression of *NO* in response to cytokines or pathogen-derived molecules is essential for host defense against intracellular microorganisms such as *M.tb* [91–94]. NO and other reactive nitrogen intermediates (RNIs) can modify bacterial DNA, proteins, and lipids at both the microbial surface and intracellular levels and induce apoptosis in mycobacterial-bearing macrophages [89,95]. Certain studies suggest inhibiting *iNOS* expression and NO production is a possible release mechanism for infectious agents such as *M.tb* [96,97]. In the latent state, a medium level of iNOS, which induces NO production, balances the pressure of the Th1 response and suppresses the intensity of virulence factors [98,99]. Besides, many studies on the mechanisms by which NO may affect antimicrobial activities are not yet clearly understood [89,95].

Another mechanism that eliminates *M.tb* and acts as the host's last line of defense is matrix metalloproteinases (MMPs), which disrupt the ECM. *M.tb* infection of monocytes and macrophages induces MMP-9 secretion [100–103]. MMPs have specific inhibitors called tissue metalloproteinase inhibitors (TIMPs). Pro-inflammatory chemokines and cytokines increase MMP activity and are tightly regulated by complex signaling pathways, leading to matrix disruption and high MMP concentrations in TB cases [104]. Thereby, MMPs may alter CCL and cytokine activity and alter inflammatory cell recruitment [104,105]. The catalytic activity of MMPs is controlled by four main points: gene expression, compartmentalization (*e.g.*, in the immediate *peri*-cellular environment), proenzyme activation, and enzyme inactivation. Excessive MMP activities have been implicated in TB pathogenesis, but suppression of MMPs can also impair host responses by inhibiting cell recruitment [106].

MMP-9 and MMP-3 are MMPs that play essential roles in TB. In this study, authors found that pleural MMP-9 concentrations correlated with granuloma formation and that cells expressed high levels of MMP-9 in addition to caseous necrosis of granulomas, suggesting that MMP-9 is a component of the caseation process [107]. Neutralisation of TNF-α and, to a lesser extent, IL-18 significantly reduced MMP production in response to *M.tb*. Exogenous addition of TNF-α or IL-18 induced *MMP* expression by macrophages even in the absence of bacteria. Immunomodulatory cytokines such as IFN-γ, IL-4, and IL-10 suppressed BCG-induced MMP production, albeit through different mechanisms. IFN-γ treatment increased macrophage TNF-α secretion but decreased MMP activity. Conversely, IL-4 and IL-10 appear to act by decreasing the amount of TNF-α available to macrophages [100].

Epigenetic changes in histone acetylation regulate the expression of *MMP-1* and *MMP-3* in response to *M.tb* and is one of the epigenetic mechanisms affecting MMPs [108]. In addition, NO has been suggested to decrease MMP secretion from macrophages [109] and IFN-γ-induced NO production might be one of the mechanisms, resulting in decreased MMP-9 activity [110].

5.3. T Cell activation and circulation

Ideally, the main suitable immune response against *M.tb* is CMI, orchestrated by Th1, effector lymphocyte to activate monocyte/macrophages, NK cells, and CTLs to eradicate the infection and induce an adequate protective response. The specific transcription factor for the differentiation of Th0 to Th1 is T-bet. The secretion of IL-12 from mature DCs in the immunological synapse of DC-1-Th0 contact in the local lymph node can induce this factor. Then, the Th1 cells recirculate to the site of infection to produce IFN-γ. Another host factor that contributes to the immune system against *M.tb* is TGF-β.

After infection, mycobacterial products such as LAM induce the production of TGF-β by monocytes and DCs at disease sites [111]. TGF-β suppresses CMI in T cells and inhibits proliferation and IFN-γ production; in macrophages, it antagonizes antigen presentation, pro-inflammatory cytokine production, and cellular activation [112]. In addition, TGF-β promotes the production and deposition of macrophage collagenase [112] and a collagen matrix [113]; thus, it may be involved in tissue damage and fibrosis in TB.

Of note, TGF-β and IL-10 appear synergistically with the anti-inflammatory response. TGF-β selectively induces IL-10 production; both cytokines show synergy in inhibiting IFN-γ production [114]. TGF-β may also interact with IL-4. Th17 cell abundance in patients with pulmonary TB has been significantly lower than in healthy controls and patients with latent TB [115]. Furthermore, it has been suggested that reduced Th17 responses, a Th subpopulation with TGF inflammatory and antagonistic activities, may be associated with clinical manifestations of pulmonary TB. Therefore, low activation of this Th subtype may be involved in defense rather than immunopathogenesis [97].

5.4. Effector cytokines in the lung microenvironment

The spread of *M.tb* depends on the activity of innate and adaptive immune responses, leading to the influence of cytokine network activity and immune cell factors. IL-18 is a pleiotropic cytokine that regulates innate and adaptive immune responses and is produced by various hematopoietic and non-hematopoietic cells, including DCs and macrophages [116]. In an IL-12 or IL-15 microenvironment, IL-18 is a potent inducer of IFN-γ in NK cells, and Th1 lymphocytes and IL-18 synergize with IL-2 and IL-23 to increase IFN-γ production [116–119]. It also regulates Th2 and Th17 cell responses and CD8^{+}CTLs and neutrophil activity, depending on the host microenvironment. Without IL-12 and IL-18, foreign antigens can trigger Th2 responses [116].

IL-12, IL-23, and IL-27 play specific roles in initiating, amplifying, and controlling cellular responses to TB. In particular, IL-12 and, to a lesser extent, IL-23 generate cellular defense responses and promote survival, whereas IL-27 attenuates the inflammatory response and is required for long-term survival. Inconsistently, IL-27 also limits bacterial regulation, suggesting that a balance between bacterial killing and tissue damage is necessary for survival. Understanding the balance of IL-12, IL-23, and IL-27 is vital for designing immune interventions in TB [120].

IL-6, like IL-12, is produced by APCs and may contribute to the early events of Th1/Th2 development. However, IL-6, in contrast to IL-12, has been reported to polarise naïve CD4^{+}T cells into IL-4-producing Th2 effector cells [121,122]. It also suggests that IL-6 affects Th1 differentiation and may inhibit IFN-γ signaling via specific induction of suppressor of cytokine signaling 1 (SOCS1) in activated CD4^{+} T cells

[122,123].

Notably, the cytokine's bioactivity was determined by the intensity of IL-18 production, the amount of natural inhibitory IL-18 binding protein (IL-18BP), and the level of IL-18 receptor (IL-18R) on the responding cells [116]. Without IL-18, *M.tb* could not potently induce downstream effector molecules such as IFN-γ, NOS-2, NO, and IDO, suggesting that the tissue environment is less favorable for classical activation (Table 1) [124].

Nonetheless, IL-12, IL-15, IFN-γ, and TNF-α stimulate protective immune responses, and IL-10, IL-13, IL-4, and TGF- β suppress protective immune responses against TB. However, low levels of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-17 are required to induce protective immunity. Similarly, hypersecretion of these cytokines may be involved in the spread of M.tb and lung injury in active TB. Therefore, interacting infected DCs and macrophages with T cells in the lung and regional lymph nodes is a central means of establishing protective immunity against M.tb due to cytokines produced by DCs and NK cells, i.e., protection depends on the microenvironment formation by DCs, NK cells, and Th lymphocytes [125,126].

Many authors have suggested an essential role for IL-17A in participating with IFN-γ inducing protective immunity [127,128]. The increased IFN-γ and IL-17 promote autophagy in *M.tb* and develop protective immunity against *M.tb* [129]. In such a situation, *M.tb* might overexpose Ag85 and ESAT-6 to decline T cell immune responses. Furthermore, this state usually induces host immune exhaustion, and the *M.tb*-specific T-lymphocytes show reduced proliferation and functions [130]. Although ESAT-6 is a potent immunogen, it can suppress TCD4$^+$ and TCD8$^+$ lymphocytes [131,132].

6. Autophagy as a host defense strategy

Ubiquitin (Ub) is pivotal in autophagy, one of the essential natural immunity activities against intracellular pathogens. The associated protein ubiquitination plays an important regulatory role in orchestrating the appropriate duration of cell responses to the microenvironmental stimuli, from cell survival to death by protein degradation and autophagy. Therefore, it is a strategic point for *M.tb* to manipulate the cell activities in favor of its dissemination. Ubiquitinated proteins have three destinations: entering the aggresome (autophagy) or driving to the proteasome for degradation, or the immune-proteasome for preparing antigenic determinants for immune responses against intracellular microbes, such as *M.tb*. Many studies demonstrated that several ubiquitin-ligating (E3) enzymes, including Parkin, Smurf1, RNF166, and LRSAM1, can transfer the Ub-coated intracellular bacteria to autophagosomes. However, the ubiquitination mechanism in such a process is yet to be fully understood. For example, in the case of *M.tb*, the studies reported that ubiquitination of *M.tb* is observed even in the absence of Smurf1 and Parkin. This means that more effective molecules should be present in the ubiquitination process of *M.tb* toward autophagy. Thus, any selective/specific receptors or surface *M.tb* factors that can be identified in

such a process selectively facilitate bacterial clearance. Chai *et al.* reported a eukaryotic-like Ub-associated (UBA) domain-containing *M.tb* surface protein Rv1468c. In the presence of this molecule, *M.tb* Rv1468c was directly targeted by host Ub chains instead of ubiquitination by E3 Ub ligases. *M.tb* transfers into microtubule-associated protein 1A/1B-light chain 3 (LC3)-associated autophagosomes in such conditions for autophagic clearance [133]. During autophagy, antigens are transported into autophagic vacuoles and degraded for peptide presentation, thereby promoting protective CMI responses (Fig. 3).

Autophagy, especially macroautophagy, is a eukaryotic catabolic process that plays a central role in the immune response against intracellular pathogens. For *M.tb*, this mechanism helps eliminate *M.tb* within macrophages. This mechanism can be exploited to ensure the presentation of *M.tb* antigens and can be used to design potent vaccines that stimulate appropriate Th1 responses and induce CMI protection. TB vaccines based on macroautophagy may improve anti-TB vaccine candidates [134,135]. Macrophage apoptosis and autophagy have been shown to play essential roles in pathogenesis and host defense against *M. tb* [136].

Nowadays, autophagy is a hot topic in cell death, and many other candidates for inducing autophagy were introduced, such as (TNF)-like weak inducer of apoptosis (TWEAK) through activation of AMP-activated protein kinase (AMPK). However, the *M.tb* produces many different molecules to prevent cell death, for example, inducing high expression of microRNA-889 (miR-889) as a potent autophagy inhibitor via post-transcriptional suppression of the TWEAK expression to maintain mycobacterial survival in granulomas [137]. Furthermore, many other *M.tb* molecules can suppress cell death due to autophagy activation; for example, *M.tb*-Eis inhibits macrophage autophagy and cell death oxygen-dependent pathways. Furthermore, *M.tb* can also escape from the LC3-associated phagocytosis (LAP) pathway by inhibiting the recruitment of NADPH oxidase 2 (NOX2) to the mycobacterial phagosome, and CpsA protein also participates in this process [138].

Generally, increasing ubiquitination inhibitors is another *M.tb* strategy, while increasing ubiquitin complex components is the host strategy in response to this suppression [55]. The ubiquitin ligase Smurf1 is involved in selective *M.tb* autophagy and host defense against TB [139]. Among the factors involved in autophagy, LC3, LAMP1, and Smurf1 are upregulated. On the other hand, proteasomes are converted to immunoproteasomes by large amounts of IFN-γ and TNF-α induced by *M.tb*. However, without ubiquitination, Ag presentation becomes inefficient [66,99,140,141].

Another way of host-*M.tb* interaction is the manipulation of autophagy to win the game of survival; however, the host, by the potentiation of this process in infected cells, increases the chance for *M.tb* killing, while *M.tb* puts pressure on this mechanism to suppress it in favor of bacterial survival in macrophages. Moreover, in response to bacterial infection, the host induces autophagy by recognizing PAMPs, such as TLRs and NODs. However, TLR signaling induced by microbial ligands leads to cell death, mainly through TRAF6 by stabilization/activation of

Table 1

The main subpopulations of the helper cells induce different immune responses against *M.tb* infections. For example, a Th1/Th2 balance favors the Th1 response, inducing host protection and eliminating *M.tb*. On the other hand, the converse balance can exacerbate *M.tb* dissemination, and active TB occurs. T-reg activities are necessary to modulate exacerbated cellular immunity toward type IV hypersensitivity and TB manifestation. Most of the authors suggested that the best protective immune response against *M.tb* infection is a very low Th17, high Th1, moderate T-reg, and low Th2 responses, as each subpopulation in such a situation assembles an appropriate microenvironment for monocyte/macrophages, NK cell, and CTLs to eliminate the *M.tb* infection.

T-cell subpopulations	Cell phenotypes	Selective transcription factors	Cytokine production	Functions
Th1	CD3$^+$CD4$^+$-IFN-γ$^+$	T-bet	IL-2, IFN-γ	Inducing cellular immunity is an appropriate response against intracellular microbes, cancer, and allograft rejection.
Th2	CD3$^+$CD4$^+$IL4$^+$	GATA-3	IL-5, IL-4- IL-13	Response against helminths helps B cells produce IgE.
Th17	CD3$^+$CD4$^+$IL-17$^+$	ROR-γt	IL-17, IL-22	Inducing inflammatory reactions, responses toward extracellular bacteria and fungi, and recruiting neutrophils.
T-reg	CD3$^+$CD4$^+$CD25$^+$Foxp3$^+$	SMAD-Foxp3	IL-10, TGF-β	Modulating all aspects of immune responses, inducing immunological ignorance, with IL-6 inducing IgA production from B cells.
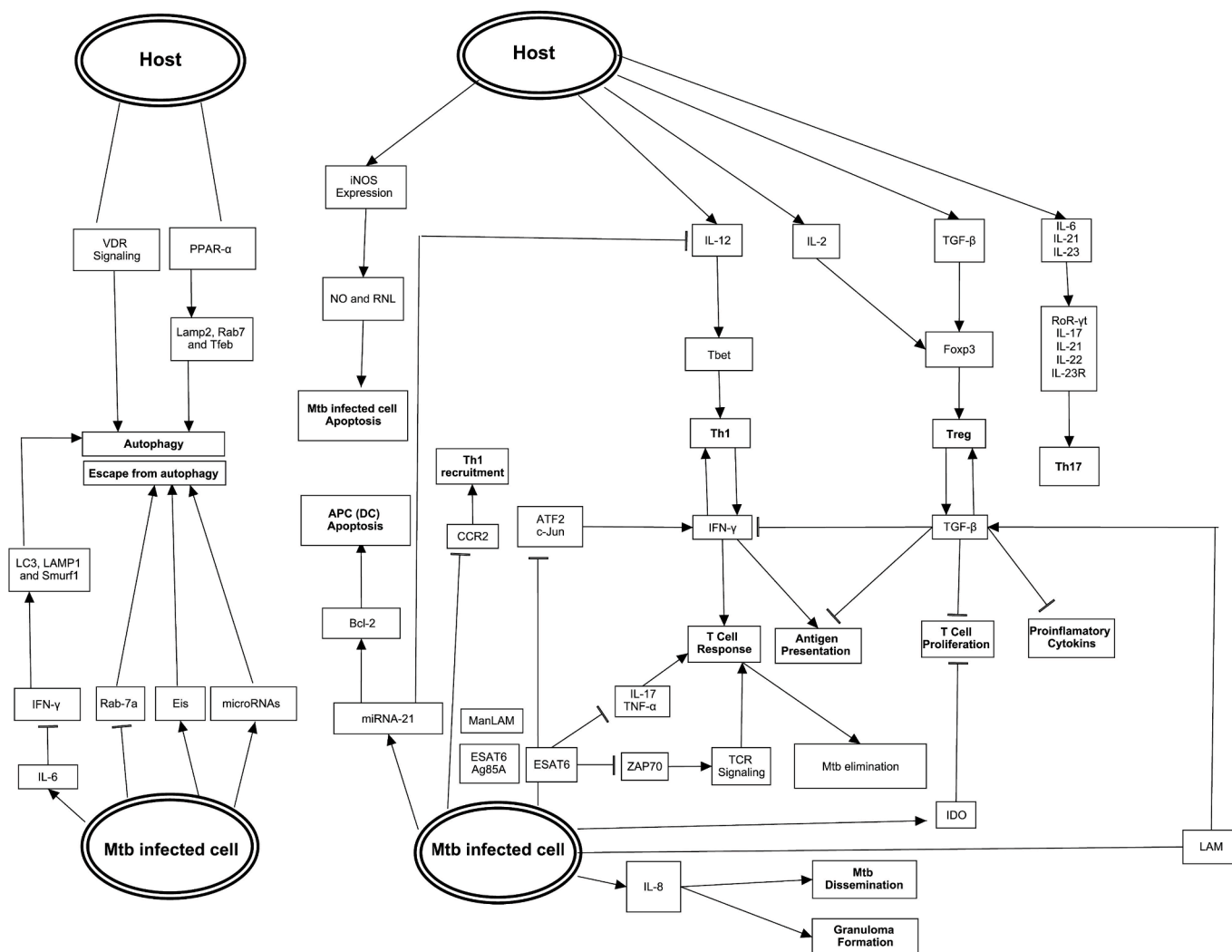
Fig. 3. The *M.tb* and host interactions in terms of gene expression. The illustration of *M.tb* molecules and their possible impacts on host immune responses. APC: Antigen-presenting cells, ATF2: Activating transcription factor-2, Bcl: B-cell CLL/lymphoma 2, CCR2: C-C chemokine receptor 2, DC: Dendritic cell, ESAT-6: 6 kDa early secretory antigenic target, Eis: Enhanced intracellular survival, FoxP3: Forkhead box P3, IDO: Indoleamine 2,3-dioxygenase-1, IL-6: Interleukin 6, iNOS: Inducible nitric oxide synthase, LAM: lipoarabinomannan, Lamp2: lysosomal associated membrane protein 2, LC3: Microtubule-associated protein light chain-3, ManLam: Mannose-capped lipoarabinomannan, NO: Nitric oxide, PPAR-α: Peroxisome proliferator-activated receptor- α, Rab7: Ras-related protein, ROR-γt: Retinoic-acid-receptor-related orphan nuclear receptor gamma, Smurfs: E3 ubiquitin-protein ligase, T-bet: T-box transcription factor, TCR: T cell receptor, Tfeb: Transcription factor EB, TGF-β: Transforming growth factor-beta, VDR: Vitamin D receptor, ZAP70: Zeta-associated protein kinase 70.

Beclin 1 and Unc-51, like autophagy activating kinase 1 (ULK1). Fig. 5..

6.1. Induction of autophagy by host

Upregulation of lysosome-associated membrane protein 2 (Lamp2), Ras-associated protein (Rab7), and transcription factor EB (TFEB) by peroxisome proliferator-activated receptor-α (PPAR-α) is associated with autophagy and lysosomal biogenesis that plays an essential role in the anti-mycobacterial host defense. Increased production of IFN-γ by *M. tb* activates macrophages to induce autophagy and directs *M.tb* to lysosomes for degradation. This process requires a family of proteins, including microtubule-associated protein light chain 3 (LC3), LAMP1, and the E3 ubiquitin-protein ligase (Smurf1). Furthermore, IL-1β activates autophagy. This is crucial for eliminating *M.tb* infected cells, and the critical signaling pathway is MyD88 [142].

Regarding adaptive immunity, Th1 cytokines (mainly IFN-γ and IL-2) and cell-to-cell contacts between specific T cells and *M.tb*-infected macrophages can induce autophagy [143]. Orphan NR and estrogen-related receptor α (ERRα; NR3B1, ERR1, ESRRA) promote macrophage autophagy [144]. The vitamin D receptor (VDR), a nuclear receptor that

mediates various biological functions of 1,25(OH)2D3 (1,25D3), is involved in anti-mycobacterial responses by activating autophagy, playing an essential role in the autophagy mechanism [145–148]. Activating functional VDR signaling in macrophages represents a mechanism for inducing autophagy and antimicrobial responses against mycobacterial infection. [148].

6.2. M.tb and autophagy

The strategies incorporated by *M.tb* to evade autophagy include (i) up-regulation of the enhanced intracellular survival, (ii) inhibition of IFN-γ by IL-6 produced by *M.tb*, (iii) inhibition of Rab-7a dependent maturation of *M.tb*-containing autophagosomes into autolysosomes and (iv) up-regulation of specific microRNAs that attenuate TLR signaling and autophagy. [136] and suppression of TLR2-dependent autophagy by *M.tb* lipoprotein LprE.

In autophagy, antigenic peptides are transported to the autophagic compartment and degraded for peptide presentation, thereby enhancing the protective CMI response [136]. For degradation, CDC5L, the so-called E3 ligase, is the only splicing factor that plays a vital role.

Therefore, its downregulation leads to decreased ubiquitination, microtubule dysregulation, and mitotic arrest and may contribute to giant cell formation in *M.tb* infection, which can be seen in granuloma formation [149].

As a result of the inhibition of ubiquitination, the misfolded proteins are increased, and its reflection is the expression of HSPs, which prepare the eukaryotic cells for apoptosis. To conclude, three consequences of protein ubiquitination, including aggresome and autophagy, proteasome and protein degradation, and immune-proteasome and Ag presentation, are down-regulated due to suppressing the ubiquitin complex [36]. The *M.tb* antigen release induces inflammatory reactions, but the Ag presentation is suppressed through the down-regulation of XPO1 and suppression of ubiquitination. Furthermore, *M.tb* lipid virulence factors, sulfoglycolipids (SLs), and dimycocerosates (DIMs) manipulate autophagy at several levels of infected macrophages by (a) DIMs, which prevented to some extent phagosomal damage-independent autophagy while activating xenophagy by favoring Esx-1-dependent phagosomal damage; (b) SLs as a TLR2 antagonist limited TLR/MyD88-dependent and phagosomal damage-independent autophagy; (c) DIMs restricted the acidification of LC3-positive compartments containing *M.tb,* preventing intracellular killing [150].

Protective immunity to *M.tb* depends on IFN-γ production, which induces autophagy and, consequently, *M.tb* elimination. Stimulation of autophagy by IFN-γ or some medications such as rapamycin induces co-localization of LC3 with phagosome in *M.tb* infected macrophage toward bacterial killing. [151]. Rovetta *et al.* also reported an association between MAP1LC3B-II/LC3-II levels and autophagy induction by IFN-γ, which arrests mycobacterial phagosome and then *M.tb* dissemination [152]. However, IFN-γ alone is inadequate for bacterial elimination *in vivo*; other host factors might be necessary for a normal effective immune response to *M.tb*, such as IL-12, IL-23, and IL-17 [11,120].

Of course, in TB patients, *M.tb* also interacts with the host, developing responses and activating its virulence factors to escape such responses. Furthermore, ESAT-6 has a novel role in suppressing late-stage autophagy in human DCs [131]. Live *M.tb* and the ESAT-6 protein have been shown to induce transcription of IL-1b and the nucleotide-binding oligomerization domain (NLRP3) to activate the NLRP3/ASC inflammasome in human macrophages [153]. Activation of the NLRP3 inflammasome may play a silencing role in promoting autophagy and vice versa [154]. Describing the relationship between autophagy and the inflammasome is beyond the scope of this review. Specific mycobacterial components may induce inflammasome activation, facilitating exit from the autophagic signaling pathway [148]. Autophagy negatively regulates the activation of transcription, processing, and secretion of several pro-inflammatory cytokines such as IL-1α, IL-1β, and IL-18 [148,155–158].

6.3. Autophagy in lung and lymph node

M.tb obliges to evade these appropriate responses to prevent elimination. In the granuloma, there are two ways in which host and *M.tb* employ to change the responses toward their benefits by overexpressing activation or inhibition of ubiquitination pathways, respectively: (i) Host overexpresses components of ubiquitin complex such as CUL1, CUL3, FBXO6, HUWE1, Smurf1, and UBC. (ii) Conversely, *M.tb* inhibits the ubiquitin complexes COPS5, CAND1, OBSL1, and SIRT7. The host attempts to potentiate ubiquitination in the lymph node compartment by overexpressing ubiquitin complex components such as CUL1, FBXO6, and UBC to induce appropriate protective immune responses. *M.tb* attempts to prevent the host from degrading its proteins at the sites of infection; this is the most critical activity in suppressing the Ag presentation to establish an appropriate response. This step of the immune response to *M.tb* is a strategic point in the lung, particularly in regional lymph nodes, for manipulation [99]. Ubiquitination inhibited by COPS5, CAND1, and SIRT7 overexpression contributes to the down-regulation of Ag presentation and autophagy [159].

M.tb manipulated this process via the expression of two gene sets: (i) Suppression of ubiquitin-activating complexes such as CUL1, FBXO6, and UBC, and (ii) increasing host inhibitor of ubiquitin complexes such as COPS5, CAND1, and SIRT7. The increase of inhibitors probably is the *M.tb* strategy. At the same time, the elevation of ubiquitin complex components is the host strategy in response to this suppression, which has consequences depending on the strength of each organism's pressure in survival [36]. Therefore, in the lymph node, autophagy immediately impacts antigen presentation activities of APCs because the upstream antigen processing depends on proper ubiquitination of the Ag toward the immuno-proteasome complex. Hence, if *M.tb* escapes from ubiquitination, both abovementioned mechanisms have the same direction, i.e., inhibition of *M.tb* antigen presentation in favor of microbe dissemination [160].

7. Epigenetic phenomena and *M.tb* infection

Bacteria influence epigenetic gene expression changes through chromatin structure and host cell transcriptional factors by influencing histone modifications, DNA methylation, chromatin-associated complexes, non-coding RNAs, RNA splicing, and miRNA expression. Thus, *M.tb* can reprogram host gene expression during TB infection [161] and reshape the epigenome in favor of bacteria dissemination. In addition, epigenetic mechanisms coupled with signaling networks regulate gene expression during differentiation, proliferation, and host immune system function [162].

Many diverse epigenetic mechanisms were demonstrated in response to pathogenic bacteria, such as *Helicobacter pylori* [163,164], *Salmonella typhimurium* [165], *Listeria monocytogenes*, and *Mycobacterium bovis* BCG [158,166], and even normal microbiota [167]. Fig. 3 shows the main *M.tb*-host interaction in an epigenetic manner by changes in the gene expression, which will be discussed in the following sections.

When droplets containing *M.tb* are inhaled, infection is established in around one-third (~70 %) of subjects, and among infected individuals, only 10 percent ever become symptomatic [168]. The main effectors of *M.tb* clearance are macrophages, the habitat of *M.tb*, which are highly activated by IFN-γ and *M.tb* and transformed into activated macrophages to eradicate the infection. In immunological equilibrium or latent TB (approximately 25 %), the main immune response against *M.tb* (CMI) can only control bacterial replication and consequent dissemination. Solid granulomas arise around bacteria and are composed of mononuclear immune cells such as macrophages at different stages of maturation and T cells of different phenotypes.

In reactivation or active TB infection (2 %), the weakening of the immune system or inappropriate immune responses causes the granuloma to become caseous and liquefy. *M.tb* starts to replicate; then, they leave their host cells and spread to other areas of the lung, other organs, and the environment. That is called active TB. In reactivated or active TB infection (2 %), a weakened immune system or an inappropriate immune response causes granulomas to become cheesy and later liquefy. *M.tb* starts replication, then leaves the host cell and spreads to other lung areas, organs, and the environment. This phase of infection is called active TB [50].

The establishment of these states depends on the immunomodulation of the host immune response through changes in the host epigenome [14]. For example, one mechanism to alter the host epigenome in bacterial infection is to change the levels of chromatin-modifying components. *M.tb* infection upregulates *Sin3A* expression, which encodes a co-repressor that works with HDACs (histone deacetylases) to repress multiple genes, including MHC class II gene expression [169]. In addition, *M.tb* controls the chromatin remodeling of interferon-stimulated genes (ISGs) downstream of IFN-γ. [169,170].

In addition, class-II *trans*-activator (CIITA) is another gene affected by *M.tb* and is thought to be a main regulator of some of the MHC class II genes and their targets. Activation of the TLR2/MAPK-dependent signaling pathway during *M.tb* infection stimulates the recruitment of

the transcriptional repressor C/EBP (CCAAT/enhancer binding protein) and histone deacetylation in the promoter region of CIITA, which SWItch nucleosome remodeling activity/sucrose non-fermentable (SWI/SNF) complex and downregulation of CIITA expression [171,172].

Therefore, to counteract IFN-γ-induced signaling pathways, *M.tb* silences CIITA and CIITA-associated genes such as HLA-DR by recruiting Sin3A-histone deacetylase (Sin3A HDAC) to their promoters [8]. On the other hand, some *M.tb* virulence factors influence the host genome, such as the mycobacterial 19-kDa lipoprotein [170], ESAT-6, ManLam [173], and Eis protein [14,174]. These factors were discussed in detail in other parts of the review.

Histone modifications induced by *M.tb* have been shown to alter innate and adaptive immune response functions [175,176]. In contrast, DNA methylation, especially at promoters and enhancers' sites, is mainly coupled with transcriptional silencing [177–179].

The role of DNA methylation in TB is to permanently shut down gene expression by methylating CpG open sites and CpG islands in gene promoter sites [14].

Another epigenetic mechanism is miRNAs, an essential regulator of gene expression at the post-transcriptional level for regulating the host RNA. The miRNAs are non-coding RNAs that affect the host gene expression at the post-transcriptional level [180]. MiRNAs target host mRNA, which regulates many cytokines and modulates host immune response [181]. *M.tb* can upregulate miRNA-29 to suppress the IFN-γ gene expression, which can induce latent TB into active TB [182]. Furthermore, induction of miRNA-146a production targets and inhibits IRAK-1 (interleukin-1 receptor-associated protein kinase type I) and TRAF-6 (TNF receptor (TNFR)-associated factor), promotes intracellular survival of *M.tb* in macrophages and impairing pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6 and monocyte chemoattractant protein 1 (MCP-1) [183].

Another activity of *M.tb* is the induction of miRNA-21, which suppresses the production of IL-12 by macrophages during BCG infection both *in vitro* and *in vivo,* and also diminishes the Th1 cell responses and activates B-cell CLL/lymphoma 2 (Bcl-2), inducing apoptosis in DCs [184].

Recently, findings demonstrated that miRNA and lincRNA profile variations in TB patients indicated that non-coding RNA and crucial epigenetic effector molecules regulate immune response-associated molecules [185]. Table 2 shows the critical functions of miRNAs in TB pathogenesis.

Furthermore, the sensitive nature of DNA methylation in DCs during *M.tb* infection has been demonstrated [186]. Therefore, *M.tb* modulates the epigenetic mechanisms by which it changes the host gene expression, leading to progression to pulmonary TB or conversion of the latent phase to the active form. Conversely, in *M.tb* infection, suitable epigenetic changes in effector and regulatory T cells induce an appropriate immune activity, which can eradicate the infection by inducing protection against *M.tb* [50,187]. However, results have not yet documented effective epigenetic alterations in DCs, T lymphocytes, macrophages, and B lymphocytes that determine the fate of *M.tb* infection [188].

M.tb is a facultative intracellular bacteria, having robust several virulence factors, such as the 6-kD (ESAT-6, *EsxA*) and the 10-kD culture filtrate protein (CFP-10, *EsxB*), PPE (Pro-Pro-Glu (PPE) motif protein) and Ag85 (Antigen 85) that actively interfere with host innate and adaptive immune responses. On the other hand, an appropriate immune response against *M.tb* can protect the host from *M.tb* invasion. This protective immune response consists of strong Th1 (CMI), weak Th17, weak Th2, and modulated T-reg activity. Overall, the interplay between bacterial virulence factors and host immune responses determines the pathogenesis and severity of TB infection (Fig. 4).

8. Conclusions

Regarding *M.tb* pathogenesis, producing an effective vaccine or

Table 2

The summary of significant host microRNAs (miRNAs) involved in host defense mechanisms against TB pathogenesis.

miRNAs	Target of miRNA	Function(s)	References
miR-17-5p	MiR-17/PKC δ/STAT3 axis	Autophagy	[189]
miR-20a-5p	JNK2	Inhibition of macrophage apoptosis	[190]
miR-21	Phosphofructokinase muscle (PFK-M) isoform	**a.** Suppression of IL-1β, IL-12. **b.** Suppression of phagosome maturation. **c.** Weakening of macrophages and Th1-activities. **d.** Effective *M.tb* strategy to escape the host immune responses toward chronic TB.	[180,191]
miR-23a-5p	TLR2/MyD88/NF-κB pathway	Inhibiting the activation of autophagy	[192]
miR-26a	KLF-4	Induction of suppressor M2 macrophage phenotype (M2 polarization) and suppression of Th1 response	[193]
miR-27a-5p	CACNA2D3, a component of a voltage-dependent calcium transporter	Inhibition of phagosome maturation and autophagy. Down-regulation of calcium signaling and autophagosome formation	[194]
miR-27b-3p	The Bcl-2–associated athanogene 2 BAG2)	Suppression of inflammation and apoptosis	[195]
miR-29	Inhibiting *T-bet* and *EOMES*	Inhibition of IFN-γ, negative regulators for macrophage activities, the high level may change the latency to active TB.	[196]
miR-33	ATG5, ATG12, LC3B, and transcription factors, such as FOXO3 and TFEB	Suppression of autophagy	[197]
miR-99b	Target of TNF-α	Suppression of TNF & IL-6. Directly targets the inflammatory cytokine, particularly TNF-α	[198]
miR-124	MyD88	Activation of NF-kB inflammatory pathway	[199]
miR-125b-5p	DRAM2, UVRAG	Inhibition of macrophage apoptosis and autophagy	[200]
miR-140	TRAF6	Suppression of IL-1β, IL-6, TNF-α, and IFN-γ	[191]
miR-144	Janus / kinase (JAK) signal transducer genes, MAPK, and TLR signaling pathways	IFN-γ and TNF-α suppression and autophagy inhibition	[199]
miR-146a	TRAF6 & IRAK1	Activation of NF-kB inflammatory pathway	[201]
miR-155	Suppression SHIP1 & SOCS1	Inhibition of macrophage: **a.** Apoptosis. **b.** Autophagy. **c.** Production of pro-inflammatory cytokines	[202]
miR-223	IKK-α is a subunit in the NF-kB pathway	Inhibition of IL-6, CCL3, and CXCL2 production. Modulation of inflammatory responses	[203]

(continued on next page)

Table 2 (*continued*)

miRNAs	Target of miRNA	Function(s)	References
		in phagocytic monocytes	
miR-325-3p	LNX1, which encodes an E3 ubiquitin ligase of the serine/threonine protein kinase NEK6	Apoptosis inhibition through activation of STAT3 signaling in macrophages	[204]
miR-378d	NF-kB, Rab10	Suppression of IL-1β, TNF-α, IL-6, Rab10, and IL1β	[205]

immunotherapy method to control the infection is difficult. This is due to the size of the *M.tb* genome and the bacterial behavior established in the latent stage by hiding from the host immune system and immuno-pathological responses in disease presentation. Fig. 5 shows the major consequences of *M.tb* and host responses related to an appropriate immune response and mycobacterium clearance and, in the case of an inappropriate response, disease manifestation and dissemination of bacteria. Furthermore, some *M.tb* virulent factors are multifunctional and sometimes have opposite effects; for example, the Ag85 complex and CFP-10 are highly virulent and immunogenic, but ESAT-6, despite its antigenicity, exerts an immunosuppressive effect on the host immune system; particularly, on IFN-γ-producing Th1 lymphocytes. On the other hand, the genome of *M.tb* contains a unique and abundant family of proline-glutamic acid (PE)/proline-proline-glutamic acid (PPE) proteins, which play central roles in bacterial activities; however, the mechanisms of actions in *M.tb* virulence and immunogenicity are still poorly understood.

It is well known that established *M.tb* infection depends on the evasion strategies from the host immune responses. One of the most

effective strategies is latency; in such a situation, the immunogenic molecules reduce under the threshold of host immune responses. However, when *M.tb* flares to the activation phase, it expresses immuno-modulatory factors such as Ag85, ESAT-6, CFP-10, and PPEs to escape host defense activities.

Because *Mtb* has the most complex evasion strategies, a large genomic pool, and a long co-evolution time with humans, more than one hundred years of serious attempts to introduce effective vaccines or therapies have failed [11].

Using *M.tb* immunogenic peptide in the replicating phase may prevent early active TB; however, the remaining latent *M.tb*-infected people will be the source of infection. Furthermore, with the expansion of iatrogenic and acquired immunodeficiency, more latent *M.tb*-infected subjects are progressing toward reactivation. Therefore, strategies for using nucleic acids vaccines, particularly mRNAs and multi-stage vaccines for both active and dormant phases, might be necessary to combat *M.tb* infection. According to epigenetics studies, such vaccines must produce proper immune responses, with strong Th1, moderate T-reg, weak Th2, and very weak Th17 (in the early injection phase).

However, protective attempts for an early activated stage and for latent *M. tb* infection must also be taken into account because the problems of more than two billion people with latent TB remain unresolved. Overall, still revealing the factors that run each condition in such a complex conflict is very difficult, as both are intelligent organisms responsible for surviving the genus [206,207].

Therefore, well-designed studies are essential to understand each player's activities in pathogen-host interactions accurately.
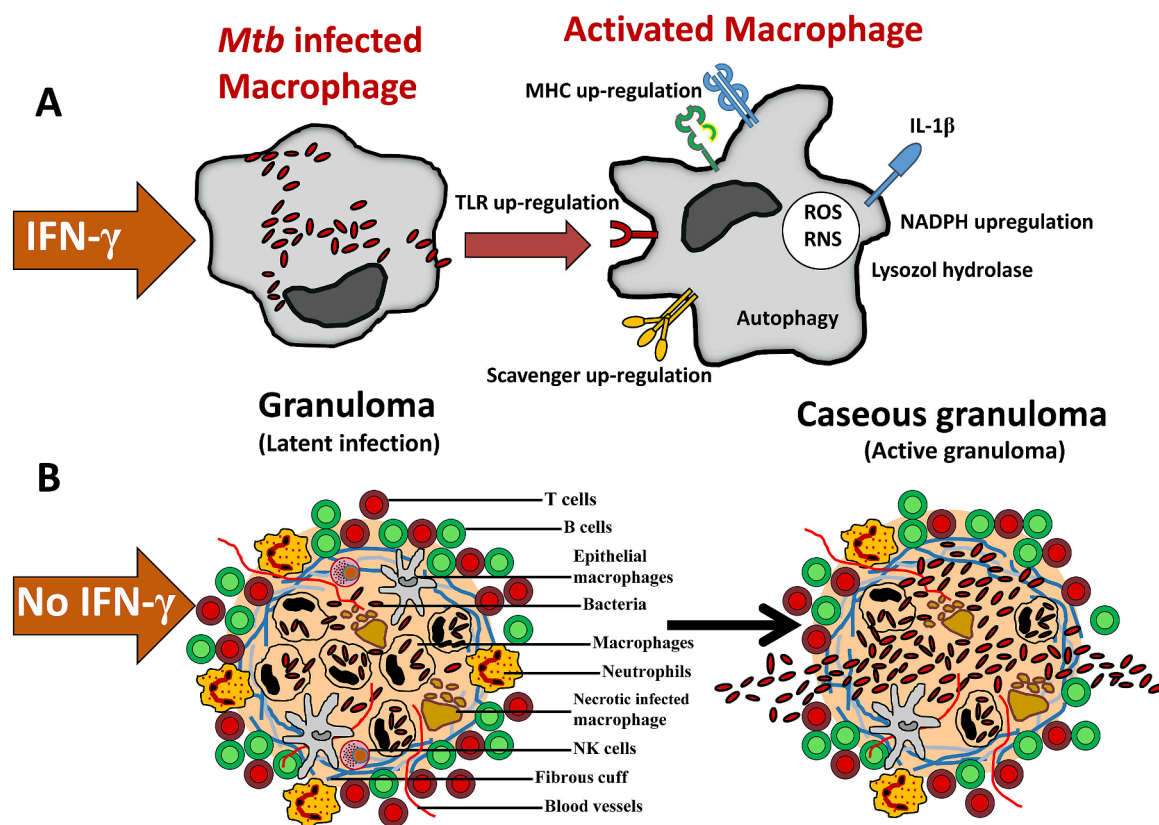
Fig. 4. Th subpopulations' activities determine the infection outcome from *M.tb* elimination (A) to disease manifestation (B). The Th1 subpopulation is the protective immune response to the *M.tb* infection. This subset produces IFN-γ to activate the killing functions of infected macrophages. Then, activated macrophages by up-regulation of respiratory burst, hydrolytic enzymes, autophagy, and MHC-class-II can clear the *M.tb*. The Th1 cytokines, such as IFN-γ and IL-2, activate CTLs and NK-cells to potentiate protective immunity against *M.tb* infection by eliminating *M.tb*-infected macrophages (not shown).

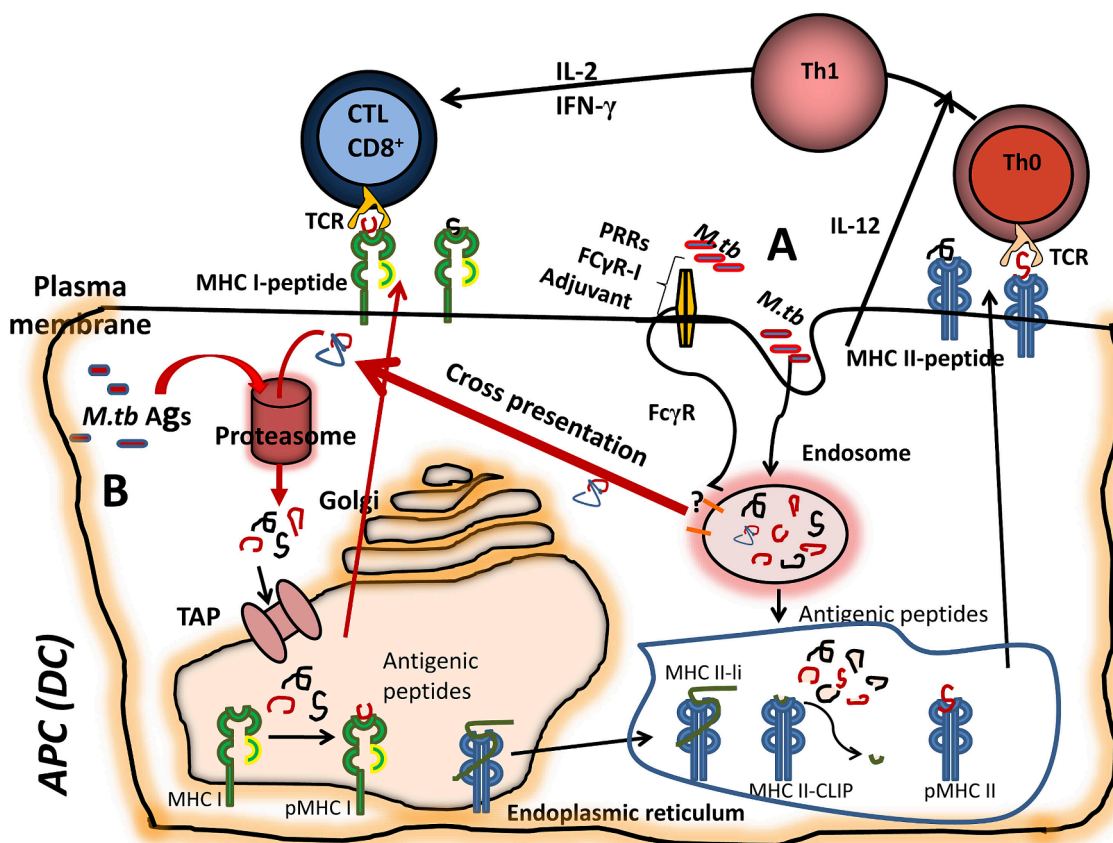**Fig. 5.** Antigen processing, presentation, and possible cross-presentation in M.tb infection. With permission and profound modification from the article authors, Soleimanpour et al. [208]. In an appropriate immune response, M.tb antigens can be processed in exogenous and endogenous pathways. In exogenous pathway (A), M.tb peptides-MHC class II complex presented to Th0 cells by mature DC1. The recognition of the complex in the surface of DC1 with IL-12 creates a microenvironment favoring Th1 and secretion of IFN-γ and IL-2. In contrast, cytoplasmic M.tb antigens and some endosomal antigens in the endogenous pathway are active (B) cleaved by proteasome and load on MHC-I, which is presented to CTLs. In the cross-presentation, IL-2 secretion from Th1 can activate CD8$^+$CTLs to kill M.tb infected cells; in parallel, IFN-γ activates infected macrophages, inducing their killing activities such as O_2 dependent, O_2 independent, autophagy, and even apoptosis to clear the infection. Therefore, activation of CMI can promote anti-intracellular pathogen responses.

CRediT authorship contribution statement

Shadi Abbasnia: Writing – original draft, Investigation. **Amir Mohammad Hashem Asnaashari:** Supervision, Investigation. **Hiva Sharebiani:** Writing – original draft, Methodology. **Saman Soleimanpour:** Supervision, Methodology. **Arman Mosavat:** Writing – review & editing, Validation, Supervision, Methodology, Investigation. **Seyed Abdolrahim Rezaee:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethics approval.
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