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Review

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Latest Comprehensive Knowledge of the Crosstalk between TLR Signaling and Mycobacteria and the Antigens Driving the Process

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Tuberculosis, which is caused by *Mycobacterium tuberculosis* (Mtb), is among the most pressing worldwide problems. Mtb uniquely interacts with innate immune cells through various pattern recognition receptors. These interactions initiate several inflammatory pathways that play essential roles in controlling Mtb pathogenesis. Although the TLR signaling pathways have essential roles in numerous host's immune defense responses, the role of TLR signaling in the response to Mtb infection is still unclear. This review presents discussions on host–Mtb interactions in terms of Mtb-mediated TLR signaling. In addition, we highlight recent discoveries pertaining to these pathways that may help in new immunotherapeutic opportunities.

Keywords: Toll-like receptors, *Mycobacterium tuberculosis*, innate immunity, cytokine, immunomodulatory regulator, immunotherapies

Introduction

Humans are exposed to countless, potentially pathogenic microbes through contact, ingestion, and inhalation. Host defenses against invading pathogens activate the immune system, which comprises acquired and innate immunities. If the host does not properly respond to invasion by these pathogens, serious infectious diseases can develop. Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (Mtb), has been prevalent since a long time and is one of the most common infectious disease. In 2017, TB caused approximately 1.3 million deaths among individuals without HIV infection as well as 300,000 deaths among patients with HIV infection [1, 2]. Mtb is a successful intracellular bacterium that has co-evolved over the years within its hosts. These features of Mtb depend on the immediate activation of innate immunity. Recent studies regarding genetic polymorphisms and related innate immunity factors support the significant roles of these factors in Mtb pathogenesis [3–5]. Host innate immune cells, including dendritic cells (DCs), macrophages, natural killer cells, and neutrophils, interact with various mycobacterial components. These cells express various pattern recognition receptors (PRRs) including C-type lectin receptors, Toll-like receptors (TLRs), RNA helicase retinoic acid-inducible gene I, and Nod-like receptors, all of which play roles in uptake and recognition [6]. Mtb has pathogen-associated molecular patterns (PAMPs) that are identified through PRRs on innate immune cells. However, Mtb can evade immune systems via several intricate mechanisms. In addition, TB-related problems have been identified a recognized in the past, but their severity has been more recently emphasized because of emerging antibiotic resistance in Mtb and the risk of re-infection [7]. There is an urgent need to develop effective treatments for TB considering various aspects such as treatment duration, potential drug toxicity, and drug–drug interactions [8]. To devise a novel strategy against TB, it is necessary to understand the mechanisms by which Mtb is recognized by the host immune system. This review outlines the role of interaction between the TLR pathway and TB pathogenesis in innate immunity and provides an update on TLR signaling during Mtb infection. The findings revealed that the TLR pathway is a new immunotherapeutic target for the development of TB treatments.

Role of the Innate Immune System during Mtb Infection

Mtb can escape antimicrobial immune responses [9] and interrupt the crosstalk between acquired and innate immunities [10]. Mtb has unique interactions with host immune systems, especially with immediate innate immune [11]. The primary innate immune cells participating in Mtb infection are macrophages, neutrophils, DCs, and natural killer cells. PRRs expressed on innate immune cells recognize PAMPs present in Mtb and play a critical role in the induction of innate immune responses [12]. Furthermore, other nonimmune cell types have also been revealed to contribute to host immune responses during Mtb infection. Specifically, macrophages have critical roles in mycobacterial pathogenesis because they are the major hosts for the survival of Mtb during both early and chronic infection [13]. Phagocytosis of Mtb is facilitated through a number of receptors, including complement receptors, mannose receptors, dendritic cell-specific intracellular adhesion molecule-3–grabbing non-integrin, surfactant protein A receptors, class A scavenger receptors, and mannose-binding lectin [14, 15]. After phagocytosis, host defense systems initiate various strategies for eliminating Mtb such as activating pro-inflammatory responses [16, 17], producing reactive intermediates such as ROS and reactive nitrogen species [18], and inducing cell death to inhibit the spread of Mtb infection [19]. Conversely, Mtb also has several strategies to disturb these defenses, such as interference with phagosomal maturation and acidification, resistance to oxidative stresses, escape to the cytosol, formation of granulomas, and modulation of host cell death [9, 20]. Mtb can inhibit host innate immune systems by producing cellular envelope glycolipids and tetra-acylated sulfolipids, which are antagonists of TLR2, thereby inhibiting its role in pathogen recognition [21].

TLR Biology

Human Toll is homologous to *Drosophila* Toll, which exists in 10 types (TLR1–TLR10), whereas in mice, it consists of 12 types (TLR1–TLR9 and TLR11–TLR13). Similar to *Drosophila* Toll, human Toll is also a type I transmembrane protein containing an extracellular domain comprising a leucine-rich repeat domain and a cytoplasmic domain termed the Toll/IL-1R (TIR) domain that exhibits high similarity to the IL-1R family. The extracellular leucine-rich repeat domain is responsible for recognizing and binding PAMPs, which are conserved molecules that are essential for pathogen survival. Dimerization of TLRs results from ligand binding, which triggers the recruitment of adaptor proteins to the intracellular TIR domain. Vertebrate TLRs are classified using sequence homology into six families, namely TLR1 (1, 2, 6, 10), TLR3, TLR4, TLR5, TLR7 (7, 8, 9), and TLR11 (11, 12, 13). Cell surface TLRs include TLR1, TLR2, TLR4, TLR5, TLR6, and TLR10, whereas intracellular TLRs include TLR3, TLR7, TLR8, TLR9, TLR11, TLR12, and TLR13 in endosomes and lysosomes. The cell surface TLRs mainly recognize microbial membrane components, whereas the other TLRs, located on intracellular vesicles, recognize microbial nucleic acids [12, 22, 23].

Upon the recognition of a ligand, the cytoplasmic TIR domain of TLRs interacts with several signaling adaptors such as myeloid differentiation primary response protein 88 (MyD88), TIR domain-containing adaptor inducing IFN-β (TRIF), TIRAP/MAL, and TRAM [24]. Various kinases (Interleukin-1 receptor-associated kinase (IRAK)4, IRAK1, IRAK2, TBK1, and inhibitor of NF-κB kinase ε) and ubiquitin ligases (TNF receptor associated factor (TRAF) 6 and Pellino 1) are recruited and activated. The recognition of PAMPs by TLRs occurs via two signaling pathways: MyD88-dependent and TRIF-dependent pathways. The adaptor protein MyD88 serves as an essential "hub" in TLR signaling, and it associates with most TLRs. Activation of MyD88-dependent pathways triggers the phosphorylation of transforming growth factor (TGF)-β-activated kinase-1, which then activates three distinct pathways involving the inhibitor of NF-κB kinase complex and MAPKs: ERK, JNK, and p38 pathways. Consequently, this activation mediates translocation of the transcription factors activator protein 1 and NF-κB, which then induce the expression of inflammatory cytokines [25, 26]. The TRIF-dependent pathway is specific to only a few TLRs such as TLR3 and TLR4. TRIF interacts with TRAF6 and TRAF3. The TRAF6 downstream pathway activates the transforming growth factor-β-activated kinase (TAK) 1 complex, which induces the activation of NF-κB and MAPKs. In the case of TRAF3, this pathway induces interferon-regulatory factor 3 phosphorylation, and then phosphorylated interferon-regulatory factor 3 forms a dimer that serves as a transcription factor in the nucleus, in which it induces the expression of type I IFN genes [27]. When these pathways are excessively activated and respond to immune stimuli in a dysregulated manner, the host experiences a severe inflammatory condition [28] (Fig. 1).

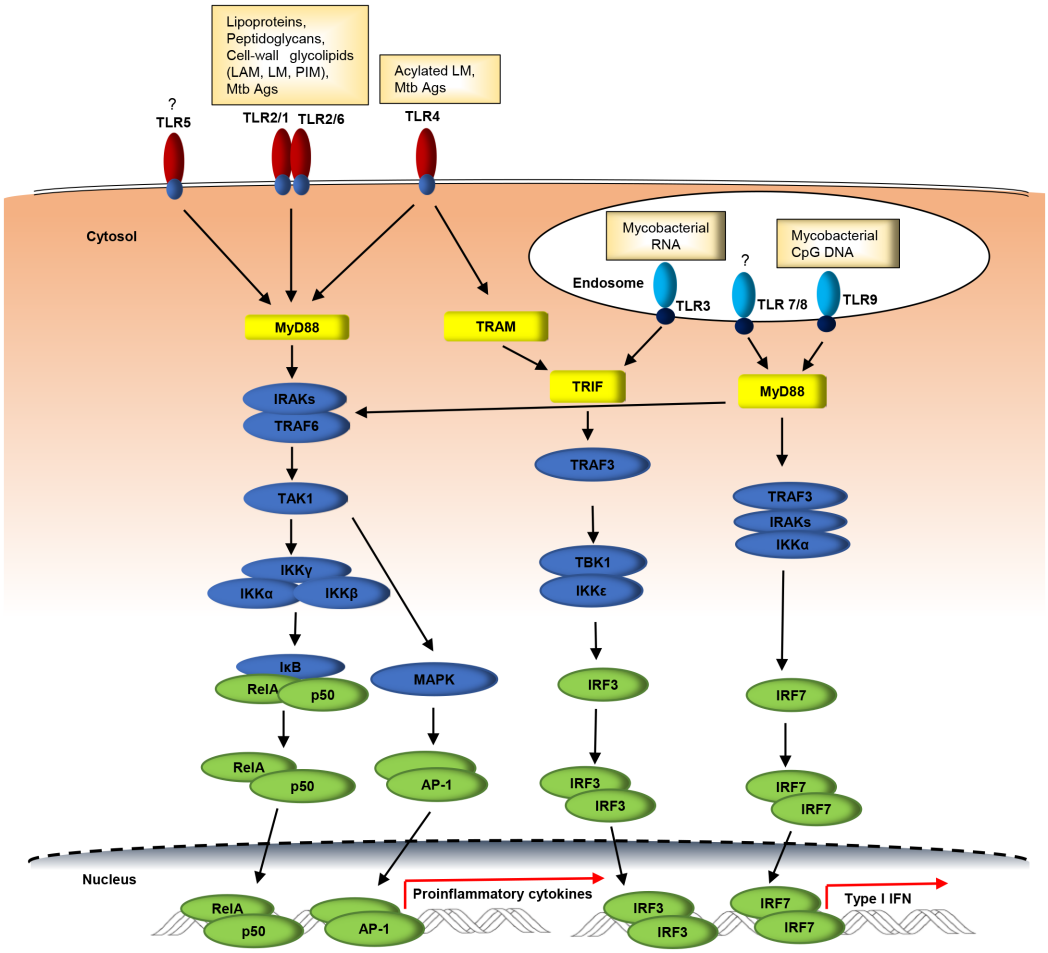

Fig. 1. A scheme of TLR signaling pathways related to mycobacterial recognition.
TLRs are involved in the innate immune response to various mycobacterial ligands (Shown in box). TLR2 and TLR1 or TLR2 and 6 and TLR5 co-localize at the cell surface, at which they sense their respective ligands, whereas TLR3, TLR7, TLR8, and TLR9 are located in endosomes, in which they recognize microbial or host-derived nucleic acids. Only TLR4 is expressed on both the cell surface and in endosomes (not shown in the figure). Stimulation of TLR1/2 by mycobacterial ligands leads to the engagement of Toll/IL-1R (TIR) domain-containing adaptor proteins (either myeloid differentiation primary-response protein 88 [MyD88] or TIR domain-containing adaptor protein inducing IFNβ [TRIF] and TRIF-related adaptor molecular [TRAM]). Engagement of the adaptor molecules activates downstream signaling pathways that involve associations between IL-1R-associated kinases (IRAKs) and the adaptor molecules TNF receptor-associated factors (TRAFs), followed by activation of MAPKs, which in turn activate transcription factors. These major transcription factors are NF-κB (RelA/p50), activator protein 1 (AP1), and interferon-regulatory factors (IRFs). A major result of the activation of extracellular TLRs is the induction of pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β. However, a major consequence is the induction of IRFs, leading to the production of type I IFNα and IFNβ. LAM, Lipoarabinomannan; LM, Lipomannan; PIM, Phosphatidylinositol mannoside; TAK1, TGFβ-activated kinase 1; IKK, Inhibitor of NF-κB kinase; IκB, inhibitor of NF-κB.

Interaction between the TLR Pathway and Mycobacteria

Several studies suggested that TLRs are essential factors for Mtb infection. Despite a number of studies revealing a critical role of TLR signaling in mycobacterium detection in vitro, the in vivo significance of TLRs remains unclear [14, 29]. In particular, TLR1, TLR2, TLR6, TLR9, and possibly TLR4 are the key receptors involved in the recognition of mycobacterial infection. In this part, we introduce studies discussing the role of the TLR pathway against mycobacterial infection (Table 1).

TLR2

TLR2, forming heterodimers with TLR1 or TLR6, is a

Table 1. The roles of TLRs in mycobacterial infection.

TLR	Function	Bacteria	Ref.
TLR2	Induction of pro-inflammatory cytokines	Mtb	[35-37]
	Induction of ROS generation, chemokine production, and MAPK activation	Mtb	[38, 39]
	Reduction of bacterial burden	Mtb	[40-42]
	Reduction of neutrophil-derived inflammation by regulating CXCL5 production	Mtb	[43]
TLR3	Induction of IL-10 via the PI3K/AKT signaling pathway	BCG	[46]
	Progression of infection through activation of TLR3 pathway using poly (I:C)	Mtb	[47, 48]
TLR4	Induction of phagocytosis	Mtb	[53]
	Induction of pro-inflammatory cytokine	Mtb, BCG	[54, 55, 61]
	Control of the balance cell death	Mtb	[63]
TLR7	Induction of killing bacteria through autophagy	Mtb	[64]
TLR9	Induction of pro-inflammatory cytokines	Mtb	[37]
	Induction of Th1 response and Th1-associated cytokine IFN-γ	Mtb	[72]

well-known receptor that is involved in recognition and response by innate immune cells including macrophages and DCs. In particular, TLR2 is the central receptor involved in the recognition of mycobacteria. Stimulation of TLR2 by mycobacterial ligands is important for inducing the intracellular signaling that activates the NF-κB and MAPK pathways. These pathways trigger the production of pro-inflammatory cytokines and chemokines and induce phagocytosis, the killing of Mtb, and antigen presentation. TLR2 mainly recognizes a variety of mycobacterial cell wall antigens such as lipoarabinomannan, lipomannan (LM), 38- and 19-kDa mycobacterial lipoprotein, phosphatidylinositol mannoside, and triacylated (TLR2/TLR1) or diacylated (TLR2/TLR6) lipoproteins [30–34]. In a previous study, TLR2 was demonstrated to be essential for the expression of pro-inflammatory cytokines, as inhibition of TLR2 expression in Raw 264.7 macrophages inhibited TNF-α expression in response to Mtb infection [35]. In addition, an important role for TLR2 and TLR6 was found in the production of IL-1β through the MyD88 pathway during Mtb infection [36]. IL-12 release in macrophages and DCs is also dependent on TLR2 in response to Mtb infection [37]. ROS generation is also induced by TLR2, and it is important for the MAPK pathway-dependent expression of CXCL8 and CCL2 in human primary monocytes [38]. In human DCs, TLR2 also induces ROS production to stimulate DC maturation and lymphocyte proliferation in response to Mtb [39]. The role of TLR2 was also indicated through an in vivo study in which TLR2 KO mice, but not TLR6 KO mice, exhibited reduced Mtb clearance and granuloma formation in the lungs and enhanced susceptibility to Mtb infection. TLR2-deficient mice also display decreased pro-inflammatory cytokine production [40–42]. In TLR2 KO mice, Mtb increases the bacterial burden and disturbs the control of neutrophilic inflammation. TLR2 downregulates CXCL5 production to prevent neutrophil-mediated pathology during Mtb infection [43]. In addition, TLR2 cooperates with other TLR family including TLR4 [44] and TLR9 during Mtb infection. Despite published supports, several murine studies revealed that TLR2 is not essential for host protection against acute Mtb infection [41, 42, 45].

TLR3

The role of TLR3, a sensor of extracellular viral or host RNA derived from infected or damaged cells, in TB pathogenesis has not been elucidated. A recent study revealed that mycobacterial RNA-induced IL-10 production is regulated by TLR3 through PI3K/AKT. Upon *Mycobacterium bovis* bacillus Calmette-Guérin (BCG) infection, $TLR3^{-/-}$ mice exhibited reduced IL-10 production but elevated IL-12 production compared with the findings in controls as well as inhibited AKT phosphorylation. In addition, BCG-infected $TLR3^{-/-}$ mice exhibited reduced pulmonary bacterial burden and tissue damage [46]. However, the evidence supporting the link between TLR3 and TB outcome remains controversial. TLR3 pathway stimulation using agonist poly (I:C) led to increased bacterial load and mycobacterial growth. Intranasal poly (I:C) treatment aggravates lung pathology and increases bacterial growth in H37Rv-infected mice through type I IFN [47, 48]. Nevertheless, poly (I:C) is being studied as a candidate for a vaccine against TB. TLR3 stimulation

through poly (I:C)-encapsulating nanoparticles enhances the pro-inflammatory immune response to BCG-infected macrophages in a synergistic manner [49]. A novel liposome adjuvant, dimethyl dioctadecyl ammonium bromide combined with poly (I:C) and cholesterol (DPC), can play a role in Mtb subunit vaccine development. In this case, poly (I:C) could attenuate disease severity following Mtb infection in mice [50].

TLR4

TLR4 is well known for recognizing endotoxins produced by gram-negative bacteria such as LPS [51]. Although some earlier studies focused on the TLR2 pathway, recent investigations uncovered evidence of the critical role of the TLR4 pathway in mycobacterial infection [52]. The TLR4 signaling pathway plays various essential roles in Mtb infection. LPS, a TLR4 ligand, upregulates TLR4/NADPH oxidase complex 2 expression and increases ROS levels. Blockade of TLR4 using anti-TLR4 receptor antibody and the endotoxin antagonist E5531 inhibits the killing of Mtb by macrophages and TLR4-dependent Mtb-induced pro-inflammatory responses [53, 54]. TLR4 recognizes cell wall lipids, glycoproteins, and antigens in Mtb. Acylated forms of *M. bovis* BCG LM modulate inflammatory activities via the TLR4 signaling pathway in macrophages [55]. Upregulation of TLR4 in response to Mtb infection has also been noted, with the surface of expression of both TLR4 and TLR2 on lymphocytes in patients with TB being significantly higher than that in healthy control individuals [56, 57]. These results confirmed that the expression of TLR4 on CD14+ monocytes, but not TLR2, is upregulated in individuals who received BCG vaccines compared with the findings in unvaccinated individuals [58]. In the case of neutrophils, Mtb stimulation also induces the expression of TLR4, TNF-α, and scavenger receptors [59, 60]. Another study demonstrated that TLR4 expression is required to protect mice against chronic Mtb infection. TLR4-mutant C3H/HeJ mice have higher susceptibility to H37Rv infection than wild-type mice. TLR4-mutant mice cannot induce inflammatory responses properly upon exposure to endotoxins or Mtb [57, 61], but other results found no significant difference in susceptibility between wild-type and TLR4-mutant mice [43, 62]. TLR4-dependent signals play an essential role in the maintenance of the balance between apoptotic and necrotic cell death upon H37Rv infection [63]. Despite accumulating evidence from the aforementioned studies, several investigations have questioned the importance of TLR4 in mycobacterial infection in vivo [41, 62]. Further studies are necessary to identify the role of TLR4 in mycobacterial infection.

TLR7 and TLR8

TLR7 and TLR8 mainly recognize ssRNA. In many studies, they were found to be related to intracellular infection such as viral infection. The ligands of TLR7 and TLR8 in Mtb are unclear. However, some studies found that TLR7 is also involved in Mtb infection. In macrophages, TLR7 expression is upregulated by Mtb. TLR7 is important for cell viability and the induction of autophagy [64]. In addition, TLR8 expression is increased in THP-1 macrophages after BCG infection [65]. In a clinical study, TLR7 and TLR8 genetic polymorphisms were linked to increased susceptibility to Mtb infection with high phagocytosis [65, 66]. TLR8 agonists play roles in protecting against Mtb challenge in TLR8 transgenic mice. Regarding immunization, ESAT-6 antigen has a better effect in combination with a TLR8 agonist [67].

TLR9

TLR9 recognizes bacterial DNA [68, 69], possibly including Mtb DNA, activates macrophages to induce pro-inflammatory responses [70], and induces T-cell differentiation [71]. TLR9 has a protective role against Mtb infection in combination with TLR2. TLR2/TLR9$^{-/-}$ mice displayed markedly high susceptibility to Mtb infection in associated with defective IL-12 p40 and IFNγ production, but in the presence of TLR2, TLR9$^{-/-}$ mice exhibited only minor reductions in resistance compared with the findings in double gene-deficient mice [72]. Several recent investigations demonstrated that TLR9 is associated with Mtb infection. One study identified the immunomodulatory mechanism of vitamin D using heliotherapy in TB via the upregulation of TLR9 [73]. Accumulating genetic evidence indicates that particular TLR9 polymorphisms might portend a higher risk for TB [74–76].

Diverse Functions of TLRs in Response to Mtb Antigens

Antigens from pathogens are of considerable interest for use in vaccine development and the diagnosis of infectious diseases including TB [77]. In particular, Mtb has a variety of antigens because it has unique cell walls and it secretes

Table 2. Mycobacterial antigens that regulate TLRs signaling pathway.

TLR	Antigen	Characteristic	Function	Cell Type	Ref.
TLR2	Rv1737c	DosR	Induction of TLR2 expression and macrophages activation	Macrophage	[122]
	LpqT	Lipoproteins	Suppression of activation of MAPK pathway, MHC II antigen processing. Induction of apoptosis	Macrophage	[84, 85]
	LprG	Lipoproteins	Suppression of MHC II antigen processing, Induction of pro-inflammatory cytokines	Macrophage	[85, 86]
	LprA	Lipoproteins	Suppression of MHC II antigen processing, Induction of pro-inflammatory cytokines	Macrophage	[87]
	19-kDa Antigens (LpqH)	Lipoproteins	Suppression of MHC II antigen processing Induction of pro-inflammatory cytokines, activation of MAPK pathway, apoptosis	Macrophage	[91, 92]
	MPT83	Secreted lipoproteins	Induction of activation of MAPK and NF-κB pathway, pro-inflammatory cytokines, apoptosis. Enhancement of APC function	Macrophage	[93, 94]
	Lipomannan	Cell wall component	Induction of activation of MAPK and NF-κB pathway, pro-inflammatory cytokines, granuloma macrophage fusion	Macrophage	[95-97]
	Lipoarabinomannan	Cell wall component	Induction of activation of MAPK and NF-κB pathway, pro-inflammatory cytokines, granuloma macrophage fusion	Macrophage	[98]
	PE_PGRS11	PE family protein	Induction of activation of MAPK and NF-κB pathway. Suppression of ROS generation	Endothelial cell	[100]
	PE_PGRS33	PE family protein	Induction of activation of MAPK and NF-κB pathway, apoptosis	Macrophage	[101, 102]
	PE_PGRS62	PE family protein	Induction of activation of MAPK and NF-κB pathway Suppression of pro-inflammatory cytokines	Dendritic Cell, Macrophage	[103, 104]
	PPE17	PPE family protein	Induction of activation of MAPK and NF-κB pathway, pro-inflammatory cytokines	Macrophage	[105]
	PPE18	PPE family protein	Induction of activation of MAPK and NF-κB pathway, anti-inflammatory cytokines. Suppresion of pro-inflammatory cytokines	Macrophage	[106, 107]
	PPE26	PPE family protein	Induction of activation of MAPK and NF-κB pathway, pro-inflammatory cytokines, cell surface markers, T cell immunity	Macrophage	[109]
	PPE32	PPE family protein	Induction of activation of MAPK and NF-κB pathway, pro- and anti-inflammatory cytokines,	Macrophage	[110]
	PPE60	PPE family protein	Induction of activation of MAPK and NF-κB pathway, pro-inflammatory cytokines, Th1/Th17 immunity	Dendritic Cell	[111]
	PPE68	PPE family protein	Induction of activation of MAPK, anti-inflammatory cytokines. Suppression of pro-inflammatory cytokines	Macrophage	[108]
	Hsp60	Heat shock protein	Induction of activation of MAPK, anti-inflammatory cytokines. Suppression of pro-inflammatory cytokines	Macrophage T cell	[112, 113]
	ChoD	Cholesterol oxidase	Induction of activation of MAPK, anti-inflammatory cytokines, ROS generation	Macrophage	[115]
	Rv0577	Potential glyoxylase	Induction of activation of MAPK, pro-inflammatory cytokines, DC maturation, Th1 immunity	Dendritic Cell	[116]

Table 2. Continued.

TLR	Antigen	Characteristic	Function	Cell Type	Ref.
TLR2	Hip1	Serine hydrolase	Suppression of pro-inflammatory cytokines, DC maturation and Th1/Th17 immunity	Dendritic Cell Macrophage	[117, 118]
	Rv3529c	Sulfotransferase	Suppression of MAPK, NF-κB pathway pro-inflammatory cytokines, ROS generation, phagosome-lysosome fusion	Macrophage	[119]
	Rv0774c	Extracellular esterase	Suppression of MAPK, pro- and anti-inflammatory cytokines, NO production	Macrophage	[120]
	Lrp	Leucine-responsive regulatory protein	Suppression of NF-κB pathway, pro-inflammatory cytokines, APC function	Macrophage	[121]
	Rv3131	FMN binding nitroreductase domain-containing protein	Induction of activation of NF-κB pathway, pro-inflammatory cytokines	Macrophage	[123]
	Rv2660c	Hypothetical protein	Induction of activation of pro-inflammatory cytokines Increasing the intracellular survival of bacteria	Macrophage	[124]
	Rv3628	Soluble inorganic pyrophosphatase	Induction of activation of MAPK and NF-κB pathway, pro-inflammatory cytokines, Th1 immunity	Dendritic Cell	[125]
	DATIN	Dormancy Associated Translation Inhibitor	Induction of activation of pro-inflammatory cytokines	Macrophage	[126]
	MymA	55-kDa Mtb flavin-containing monooxygenase	Induction of activation of NF-κB pathway, pro-inflammatory cytokines, Th1 immunity	Macrophage	[127]
TLR4	Rv2882c	Secreted culture filtrate	Induction of activation of MAPK and NF-κB pathway, Induction of expansion of the T-cell, Improvement of protective efficacy with BCG	Macrophage	[132]
	Rv0652	Secreted culture filtrate	Induction of activation of MAPK pathway and the expression of surface molecules on cell, DC maturation, and proinflammatory cytokine production, Enhancement of the polarization of T effector cells to Th1 immunity	Macrophage, Dendritic cell	[133, 134]
	GrpE	Heat shock protein	Induction of activation of MAPK and NF-κB pathway, Induction of T cell proliferation	Dendritic Cell	[138]
	RpfB (Rv1009)	Resuscitation-promoting factor	Induction of activation of MAPK and NF-κB pathway, Induction of T cell proliferation	Dendritic Cell	[139]
	Rv3841	Secreted culture filtrate	Induction of activation of MAPK and NF-κB pathway, Induction of T cell proliferation	Dendritic Cell	[140]
	HSP65	Heat shock protein	Induction of activation of NF-κB pathway	Endothelial cell	[137]
TLR2/4	ESAT-6	Secreted culture filtrate	Induction of activation of MAPK, pro-inflammatory cytokines, type I IFN, T cell immunity	Macrophage	[141-143]
	38-kDa Antigens (PstS-1)	Secreted culture filtrate	Induction of activation of MAPK pathway, ER stress	Monocyte	[44, 144]
	HSP70	Heat shock protein	Induction of activation of NF-κB pathway	Endothelial cell	[137]
	Rv3463	Secreted culture filtrate	Induction of expression of surface molecules and pro-inflammatory cytokines, Induction of bactericidal effects via phagosome maturation	Macrophages	[145]

antigens following infection. Mtb antigen discovery efforts have continued for several decades, and several studies already revealed their immunogenicity for improving the design of TB vaccines [78]. Although these studies mainly focused on T-cell immune responses [79–82], the correlation between Mtb antigens and TLR has recently been actively studied (Table 2). Mtb antigens mainly interact with TLR2 and TLR4, with TLR2 having a dominant role.

TLR2-Associated Mtb Antigens

TLR2 is an important receptor for recognizing Mtb. Several Mtb antigens interact with TLR2. They include both cell wall components of Mtb such as lipoprotein, LM, and 38- or 19-kDa antigens and specific proteins or enzymes found only in Mtb.

TLR2-Associated Mtb Lipoprotein Antigens

LpqT is a ligand of TLR2 that suppresses MAPK and NF-κB signaling. The ligand can boost mycobacterial survival by inhibiting TLR2-dependent effects on inflammatory cytokine expression and cell apoptosis in macrophages. This lipoprotein is also involved in inhibiting major histocompatibility complex II (MHC II) antigen processing in CD4+ T cells to evade immune surveillance [83, 84]. LprG and LprA are also agonists that bind directly to TLR2. In macrophages, these antigens induce inflammatory cytokine expression and negatively control MHC II antigen processing to modulate inflammation [85–87].

LpqH, a 19-kDa lipoprotein, also triggers TLR2 activation, leading to upregulation of the expression of death receptors and ligands that induce apoptosis. LpqH is also associated with the induction of autophagy-dependent TLR2/TLR1/CD14 and vitamin D3 signaling for anti-mycobacterial activity. LpqH participates in the manipulation of adaptive immunity by inducing cytokine secretion and directly regulating the activation of memory in $CD4^+$ T cells [88–90]. In addition, 19-kDa lipoproteins are also well-known TLR2 ligands. These antigens induce apoptosis via the TLR2 pathway in macrophages. In addition, TLR2-mediated PPARγ expression is induced by 19-kDa lipoproteins, thereby promoting inflammatory responses by activating the MAPK pathway [91, 92]. Additionally, 19-kDa lipoproteins are involved in IFN-γ signaling. IFN-γ signaling is associated with the expression of class II transactivator, which regulates chromatin remodeling. 19-kDa lipoproteins inhibit IFN-γ signaling and class II transactivator expression through the TLR2 pathway.

The secreted mycobacterial protein MPT83 is involved in immune responses via the TLR2 pathway. This protein induces pro-inflammatory cytokine production and apoptosis by activating the MAPK and NF-κB pathways. However, MHC II antigen processing is inhibited by MPT83 [93, 94]. Both of these components are recognized by TLR2, and they activate the immune responses of innate immune cells.

TLR2-Associated Mtb Lipomannan Antigens

LM has been reported to induce the expression and secretion of matrix metalloproteinase 9 in macrophages through a TLR1/TLR2- and CD14-mediated pathway [95, 96]. Furthermore, LM is associated with granuloma–macrophage fusion via a TLR2-dependent pathway that is mediated by β_1 integrin/ADAM9[97]. Lipoarabinomannan also interacts with TLR1 and TLR2 signaling pathways and induces signals that activate inflammation [98].

The proline-glutamic acid (PE) and proline-proline-glutamic acid (PPE) gene family members are only found in Mtb. Many studies indicated that PE or PPE proteins are related to various immune responses.

PE family proteins feature a particular PE region. Some PE family protein has multiple copies of polymorphic guanine-cytosine-rich sequences (PGRSs), and they are referred to as PE_PGRS family proteins. Many PE_PGRS proteins are related to the cell wall, and they can be recognized by TLR2. In addition, PE_PGRS proteins can induce the maturation and activation of immune cells by upregulating MAPK and NF-κB signaling [99]. PE_PGRS11 plays a role in regulating resistance to oxidative stress. PE_PGRS11 downregulates H_2O_2-mediated p38 MAPK signaling and increases the survival of bacteria [100]. PE_PGRS33, a surface-exposed protein, interacts with TLR2 and induces the release of TNF-α by activating MAPK signaling in macrophages. This causes the release of cytochrome c, leading to the activation of apoptosis [101, 102]. PE_PGRS62 binds to TLR2 and attenuates the expression of IL-1β, IL-6, and iNOS in macrophages [103, 104].

PPE family proteins have common regions that include a PPE motif near the N-terminal region. PPE17 interacts with TLR2 and activates NF-κB signaling. In a clinical study, an Mtb-infected patient was easily infected by HIV-1 because PPE17 augments transcription, leading to HIV-1 LTR transactivation [105]. PPE18 and PPE68 can induce the activation of MAPK via TLR2, and they are important for

the induction of IL-10 expression in macrophages. Interestingly, recombinant PPE18 proteins can attenuate inflammation and enhance survival in sepsis [106–108]. PPE26 and PPE32 trigger inflammatory responses, leading to activation of the MAPK and NF-κB pathways. Meanwhile, PPE26 $CD4^+$ and Th1-type T cells are polarized by the immune response [109, 110]. PPE60 drives Th1/Th17 responses through the TLR2-mediated maturation of DCs by activating MAPK and NF-κB pathways [111].

Heat shock proteins (HSPs), which are molecular chaperones, are also recognized by TLR2. Hsp60 is a ligand of TLR2, and it upregulates IL-10 production to modulate the immune response. Additionally, HSP60 controls T-cell responses by regulating the surface expression of TLR2 [112, 113].

TLR2-Associated Mtb Proteins or Enzymes Antigens

Other enzymes or factors in Mtb can act as TLR2 ligands. The 30-kDa antigen of Mtb is known as a good inducer of immune responses. It generates ROS production via TLR2. In addition, the 30-kDa antigen upregulates the expression of CXCL8 and CCL2 [114]. ChoD, a cholesterol oxidase, also binds TLR2 and participates in immune responses. ChoD activates the MAPK pathway and stimulates the production of IL-10 [115]. Rv0577 can drive DC maturation and pro-inflammatory cytokine expression by activating MAPK and NF-κB pathways in a TLR2-dependent manner. In addition, Rv0577 has an important role in $CD4^+$ and $CD8^+$ T-cell polarization [116]. Hip1, a serine hydrolase, attenuates pro-inflammatory responses by inhibiting TLR2 activation. This antigen interferes with DC maturation, cytokine secretion, and antigen presentation [117, 118]. Rv3529c and Rv0774c negatively regulate TLR2-mediated pro-inflammatory responses. They suppress the production of pro-inflammatory cytokines and enhance the production of anti-inflammatory cytokines [119, 120].

Leucine-responsive regulatory protein also inhibits pro-inflammatory responses by disrupting NF-κB signaling. Leucine-responsive regulatory protein activates the PI3K/Akt pathway, which has an inhibitory effect on TLR2 [121]. Rv1737c, one of the dormancy survival regulator antigens, is mainly expressed in the latent phase of Mtb infection. Rv1737c upregulates TLR2 expression and induces NF-κB activation on macrophages in a non-TLR4–dependent manner [122]. Rv3131, an uncharacterized member of the dormancy survival regulator regulon, encodes an FMN-binding nitroreductase domain-containing protein, and it induces pro-inflammatory cytokines through the TLR2 signaling pathway. Rv3131 interacts with TLR2 and contributes to the phosphorylation of NF-κB [123]. Rv2660c and Rv3628 augment the expression of pro-inflammatory cytokines by interacting with TLR2. They enhance pro-inflammatory cytokines expression, leading to the activation of MAPK and NF-κB signaling. Rv3628 also polarizes DCs and $CD4^+$ T cells [124, 125].

Dormancy-associated translation inhibitor also interacts with TLR2 and elevates the levels of pro-inflammatory cytokines [126]. MymA, a cell wall-associated protein, also increases pro-inflammatory cytokine expression, leading to the activation of MAPK and NF-κB pathways, which are dependent on TLR2 signaling [127].

Mtb also releases membrane vesicles (MVs) into the environment. MVs carry virulence factors of Mtb such as phospholipids, proteins, and cell wall components. Lipoproteins are also delivered to the cell by MVs. Carried lipoproteins stimulate the TLR2 signaling pathway and then trigger an inflammatory response [128]. Another study uncovered that exosomes from Mtb-infected cells can inhibit IFN-γ signaling after Mtb infection. These exosomes contain Mtb virulence factors that are delivered to macrophages [129, 130]. The virulence factors of Mtb may modulate the immune system [114, 131].

TLR4 Signaling Pathway-Associated Antigens

Several studies demonstrated that Mtb-derived antigens regulate the TLR4 signaling pathway, including HSPs and culture filtrate proteins, suggesting their potential use in the development of novel vaccines [33]. Rv2882c, an Mtb culture filtrate, induces the activation of macrophages to express pro-inflammatory cytokines, co-stimulatory, and MHC via the TLR4 pathway [132]. Rv0652, another culture-filtrated antigen derived from Mtb, also activates macrophages through the TLR4 pathway and then induces pro-inflammatory responses such as the production of TNF-α and monocyte chemoattractant protein-1 [133]. In addition, Rv0652 is recognized via the TLR4 receptor, thereby inducing DC maturation and the production of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, through MyD88- and TRIF-dependent signaling pathways [134].

Mycobacterial HSPs have been revealed to exert several immunologic effects following Mtb infection [135, 136]. Mtb HSP65 and HSP70 induce the activation of NF-κB signaling and the expression of TLR4, but not functional TLR2, in human endothelial cells. In particular, HSP65 was demonstrated to signal exclusively through TLR4 [137]. Mtb GrpE, a cofactor of HSP70, induces the activation and

maturation of DCs upon binding to TLR4 and promotes Th1-biased T-cell immune responses, as DCs from TLR4$^{-/-}$ mice exhibited no response to Mtb GrpE [138]. Similarly, RpfB is another Mtb antigen that binds to TLR4, followed by MyD88/TRIF-dependent signaling and subsequent MAPK and NF-κB activation in DCs [139]. Activation of DCs by Rv3841 (also known as Mtb ferritin B) is mediated by TLR4, followed by the induction of MAPK and NF-κB signaling pathways and Th1 immune responses [140].

TLR2 and TLR4 Signaling-Associated Mtb Antigens

Several studies identified Mtb antigens that require both the TLR2 and TLR4 pathways to modulate immune responses. ESAT-6, a 6-kDa secreted antigen, can bind to both TLR2 and TLR4. This antigen induces apoptosis by elevating cleaved caspase-9 and caspase-3 expression. ROS generation and MAPK phosphorylation also contribute to the induction of apoptosis. In addition, ESAT-6 stimulates the expression of type 1 IFN. IFN-β is upregulated by ESAT-6 in a TLR2 and TLR4 pathway-dependent manner. By contrast, ESAT-6 inhibits T-cell immune responses by suppressing antigen-presenting cell function [141–143].

The 38-kDa antigen (*e.g.*, PstS-1) from culture filtrates of Mtb H37Rv activates MAPK signaling in human monocytes via TLR2 and TLR4. PstS-1 also plays important roles in the induction of endoplasmic reticulum stress-mediated apoptosis via TLR2 and TLR4. MCP-1, a pro-inflammatory cytokine, is upregulated by 38-kDa antigen, and ROS and endoplasmic reticulum stress levels are consequently elevated [44, 144].

Recombinant Rv3463 induces the expression of surface molecules and pro-inflammatory cytokine production through TLR2 and TLR4 pathways in macrophages. It induces MAPK, PI3K, and NF-κB signaling in macrophages. Also, Rv3463 sustains the active state of Mtb-infected cells and inhibits bacterial growth by enhancing phagosomal fusion [145].

Conclusions and Perspectives

TB remains a severe infectious disorder that can lead to death. The innate immune system, which plays a crucial role in the establishment of appropriate host defense mechanisms, is involved in the early phases of Mtb infection [146]. In this review, we comprehensively summarized recent findings about innate immune recognition by mycobacteria, particularly focusing on TLRs. Several investigations about the Mtb-host relationship have been conducted, but the involvement of various Mtb-derived PAMPs in TB-mediated immunity remains unclear. Based on several preceding investigations [147–149], we suggest that countless Mtb antigens can be potential modulators that can regulate the host immune responses including those of TLRs to regulate uncontrolled inflammatory responses. In particular, Mtb-secreted culture filtrate antigens exhibit serologic reactivity. The ability to activate inflammatory signaling cascades through the TLR pathway means that the modulation of TLR signaling could be targeted as a new treatment strategy against TB[150]. Several factors from Mtb can regulate host innate immunity by dictating a sophisticated system that relates multiple host signaling pathways such as the TLR pathway. However, activating the immune system may induce adverse events in the host, such as the development of autoimmune diseases and breakdown of host immune homeostasis. It is critical to further identify the mechanisms associated with TLR signaling in TB pathogenesis and use these results to overcome the expected effects on TLR signaling to develop promising immunotherapies for TB.

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Conflicts of Interest

The authors have no financial conflicts of interest to declare.

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