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New findings of Toll-like receptors involved in *Mycobacterium tuberculosis* infection

Majid Faridgohar[a] and Hassan Nikoueinejad[b]

[a]Molecular Biology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran; [b]Nephrology and Urology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran

ABSTRACT

Tuberculosis (TB), an important issue in the present age, affects millions of people each year. The infectious agent of TB, *Mycobacterium tuberculosis* (Mtb), interacts with the immune system which prevents the development of this bacterium as much as possible. In fact, the receptors on the surface of immune cells identify the bacteria, one of which is Toll-like receptors (TLRs). Different TLRs including 2, 4, 9 and 8 play critical roles in tuberculosis infection. In this paper, we focused on the role of TLRs which interact with different components of Mtb and, consequently, prevent the entrance and influence of bacteria on the body.

KEYWORDS

Mycobacterium tuberculosis; Toll-like receptors; TLR; immune system; infection

1. Introduction

Mycobacterium tuberculosis (Mtb), the infectious agent of Tuberculosis (TB), causes illness among millions of people each year [1]. Both the emergence of the acquired immune deficiency syndrome and the development of multidrug-resistant (MDR)-TB [2] have increased such estimation to 10.4 million with 1.8 million deaths in 2015 among which 2,50,000 were MDR/rifampicin resistant (RR)-TB [1]. Moreover, about one-third of the world's population has latent TB, but are not yet capable to transmit the disease [3]. Different environmental, genetic, and pathogenic factors influence the progression of active TB [4,5] and also interplay some crucial roles with the immune system during both the early and late phases of infection [6]. Both adaptive [7] and innate [8] immune mechanisms modulate host susceptibility to TB [9]. Innate immune system as early warning part of the system recognizes bacteria through its own receptors such as Toll-like receptors (TLRs). This review summarizes some new aspects of TLR roles in Mtb infection.

2. The role of TLRs against TB

TLRs, a family of single membrane-spanning receptors of which 1 to 10 have been nominated in human beings, are expressed in both immune and non-immune cells [10,11]. TLRs generally play a critical role in both innate immune responses and the initiation of adaptive immunity to Mtb. Actually, polymorphisms of TLRs have been associated with mutated susceptibility to tuberculosis among different populations [12–20]. Innate immune cells initiate subsequent adaptive immune responses after recognizing Mtb by Lucine Rich Repeats of the extracellular domains of the their TLRs [21]. Such interaction among Mtb's ligand and TLRs activates Myeloid Differentiation Primary Response 88 (MyD88) which, as a central role player [22], is used by all TLRs except TLR3 [23]. MyD88, links initial complex to subsequent molecules including Interleukin-1 receptor-associated kinase (IRAK), TNF receptor associated factor (TRAF) 6, transforming growth factor beta-activated kinase 1 (TAK1) and mitogen-activated protein kinases (MAPK). Such signaling pathway mediates the translocation of NF-κ B into the nucleus [24] to induce transcription of inflammatory mediators, expression of adhesion molecules, and further recruitment and activation/apoptosis of macrophages, dendritic cells (DCs) and polymorphonuclear cells (PMNs) in the Mtb infected area [2]. From one side, MyD88-deficient mice are highly susceptible to Mtb infection [25,26] and from the other side, Mtb is able to meddle such signaling as its cell wall proline-proline-glutamic acid (PPE) family protein Rv1808 manipulates the host cytokine profile via MAPK and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathways [27]. To clarify mechanisms underlying such effects, one recent study revealed the critical role of MyD88 and TIR-domain-containing adapter-inducing interferon-β (TRIF) in the activation and maturation of DCs in response to a potent adjuvant activating antigen presenting cells (APCs), named heat

CONTACT Hassan Nikoueinejad hnikuinejad@yahoo.com, hnikuinejad@bums.ac.ir

shock protein (Hsp) 70 derived from Mtb [28]. Another study showed the apoptotic effect of 38-kDa antigen of Mtb on macrophages through TLRs 2 and 4 [29]. Among the TLRs been identified, TLR2, TLR4, TLR9 and possibly TLR8 are the key receptors that are involved in the recognition of Mtb [30–36].

3. TLR2

3.1. TLR2 and innate immune cells

TLR2 expression on macrophages is important in determining the fate of innate immune responses to Mtb [37,38]. From one side, initial high TLR2 expression on macrophages may worsen the outcomes of infection via different mechanisms such as secretion of anti-inflammatory cytokines [39] as well as conferring to signaling pathways [40,41]. From the other side, it may maintain the dormant state of the Mtb and survive the bacilli in a latent form to avoid its activation [42]. In this regard, different components of Mtb have been shown to elicit the production of a broad range of components by macrophages in a TLR2-dependent manner [43]. For example, a cell-associated lipoglycoprotein of Mtb, called MPT83, acts as a TLR2 agonist which mediates the induction of matrix metalloproteinase 9 (MMP-9) by human THP-1 cells [44] (Figure 1). The other example is a heat-killed Mtb H37Ra called MTBRa which upregulates TNF-α expression through activation of TLR2/ERK signaling, and increases MMP-1 and MMP-9 production in human pleural mesothelial cells [45]. The Rv2660c protein, preferentially expressed during latent infection of Mtb for adaptation to lack of nutrition and hypoxia, stimulates human macrophages by interacting with TLR2 to secrete pro inflammatory cytokines which might maintain latency of Mtb [46]. Early secreted antigen 6 (ESAT-6) of Mtb promotes apoptosis of macrophages via TLR2/NF-κB activation [47], mycolic acid [48] as well as lipoprotein components [31,49,50] of Mtb activate macrophages via TLR2 (Figure 1) to bypass two strategies allowing Mtb to evade host immunity: down regulation of major histocompatibility complex (MHC) class II molecules (which restricts its antigen presentation) [51] and restriction of pro inflammatory responses (which delay the onset of adaptive immune responses) [52]. There is evidence emphasizing the effects of TLR2 on other innate immune cells, some of which are as follows: TLR2/dectin-1 cooperation induces Reactive Oxygen Species (ROS) production to induce the activation and apoptosis of neutrophils [53]; peptidoglycan components of mycobacterial cell wall are able to interact with TLR-2 which promote the activation of resting natural killer cells and Interferon gamma (IFN-γ) production [54]; TLR2-induced epithelial-derived C-X-C motif chemokine ligand 5 (CXCL5)

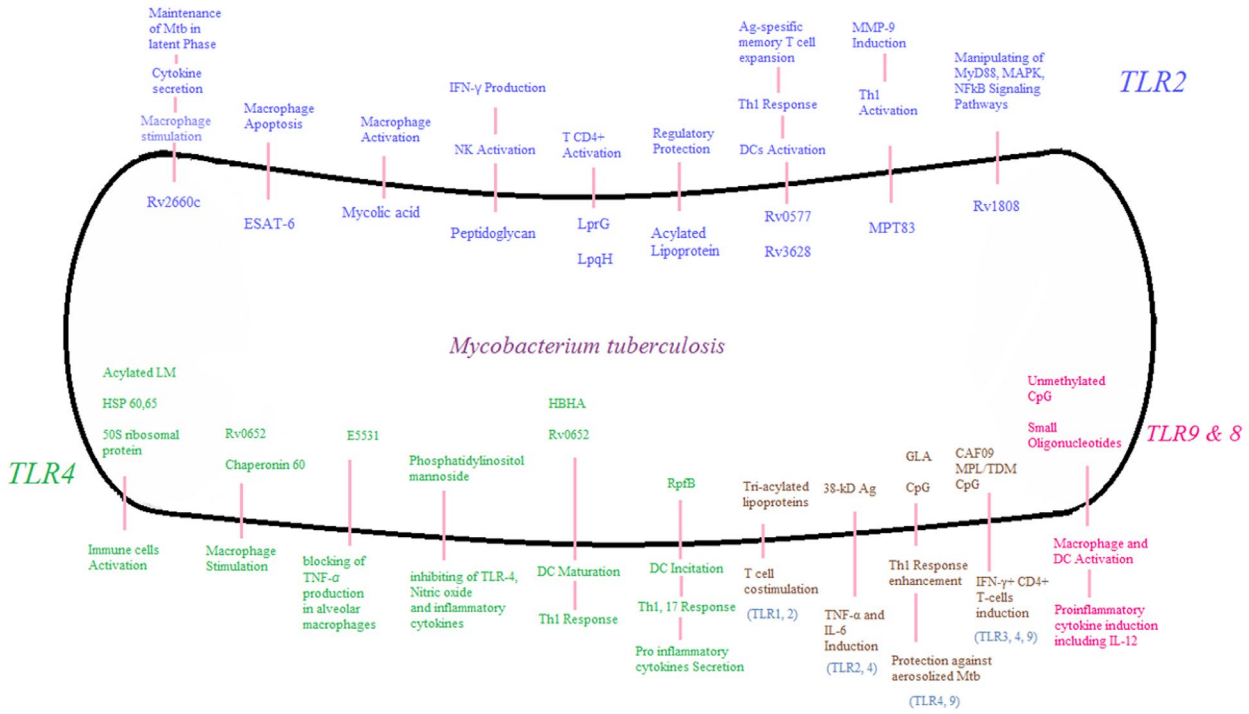

Figure 1. Different Mtb components stimulate the immune system through Toll-like receptors (TLRs). The role of each TLR is depicted in this figure separately. TLRs interact with Mtb components and cause the activation of macrophages, NK cells, dendritic and T cells and also induce cytokine secretion. Such roles of TLRs is crucial in primary identification of Mtb and development of appropriate immune responses to overcome the Mtb infection. LM: Lipomannan, Hsp: Heat Shock Protein, HBHA: Heparin-binding hemagglutinin, Rpf: Resuscitation-promoting factor, CAF: Cationic adjuvant formulation, MPL: Monophosphoryl lipid-A, TDM: Trehalose dimycolate, ESAT: Early secreted antigen, Nk cell: Natural killer cell, IFN-γ: Interferon-Gamma, DC: Dendritic cell, Th: T helper, MMP: Matrix metalloproteinase, MAPK: Mitogen-activated protein kinase, NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells, TNF: Tumor necrosis factor, IL: Interleukin.

is critical for PMN-driven destructive inflammation in pulmonary tuberculosis [55]; TLR2-induced pro-inflammatory cytokines produced by DCs or monocytes may contribute to the pathogenesis of Mtb -associated immune restoration disease [56]. From the point of vitamin D, the effect of TLR2 in macrophages should also be noted. TLR2 enhances the expression of genes of vitamin D receptor and vitamin-D-1-hydroxylase and in this way promotes the production of the antimicrobial peptide cathelicidin by human macrophages [57,58]. Such links between TLR2 and vitamin D-mediated innate immunity suggests the contribution of TLR2 in resistance to Mtb infection.

3.2. TLR2 and T cells

According to some studies [59], TLR2 signaling may not influence the memory as well as the induction of T cell immunity to Mtb. Its engagement on T cells may affect T-cell trafficking [60] in some ways such as inducing the production of C-C motif chemokine ligand 8 (CCL8) chemokines to recruit $CD4^+$ cells to pleural effusion of Mtb infected patients [61] or mediating the recruitment of forkhead box P3 ($Foxp3^+$) T regulatory cells (Tregs) to the lungs to control inflammation [62]. Some other studies reveal that TLR2 engagement on $CD4^+$ T cells may increase Mtb Ag-specific responses and contribute to protection against Mtb infection [63]. The role of such an engagement in the contribution of $CD4^+$ cells against Mtb is supported by the study in which pretreatment with TLR2-antagonistic antibody significantly inhibits the cytokine production caused by a major membrane protein II of Mtb [64]. Furthermore, Mtb lipoproteins LprG and LpqH induce the activation of memory CD4+ T lymphocytes via the existence of TLR2 on their surface [65]. (Figure 1) From one side, TLR2 serves as a co-stimulatory receptor for mycobacterium-specific T cell development and participates in the maintenance of T cell memory [66]. From the other side, it plays some protective regulatory roles [22,67–69] especially when it is engaged on $CD4^+$ T cells [63] by related ligands such as acylated lipoproteins of Mtb [65]. An evidence emphasizing the stimulatory function of TLR2 is about Rv0577 [70] and Rv3628 [71] proteins, 2 TLR2 agonists, which have critical roles in the activation of DCs in a TLR2-dependent manner and the initiation of the adaptive immune response by polarizing the development of T cells to a type 1 T helper (Th1) response and the expansion of Ag-specific memory CD4+ T cells. (Figure 1) Also, an evidence emphasizing the regulatory activity of TLR2 is related to a recent study which has shown that TLR2 activates extracellular-signal-regulated Kinase (ERK) signaling in macrophages to promote anti-inflammatory macrophage responses and blunts Th1 responses against the Mtb [72]. Furthermore, Wnt-β-catenin, a critical regulator of pathogen-specific TLR2 responses, accompanied by Notch1, controls the expression of genes that could foster the generation of Treg cells [73].

In the case of $CD4^+$ subtypes, type 17 T helper (Th17) cells play a critical role in conferring optimal protection against Mtb. In this regard, TLR2 may be an important upstream molecule in mediating Th17 responses to Mtb via mediating the induction of p19 (a subunit of IL-23), Interleukin 1 (IL-1) β [74], Interleukin 6 (IL-6), and transforming the beta growth factor (TGF-β) in DCs [75]. In this way the Th17 cells show their protective effect by speeding up the Th1 cells to populate in the site of infection [76]. This condition results in the sustainability of Th1 responses mediated by TLR2 and now could be an attractive target for effective vaccination [74]. Actually, deficiencies in TLRs may fail some responses to Mtb. For example, such deficiency inhibits Th17 differentiation (following complete Freund's adjuvant immunization) [77]. Protection induced by novel vaccines may be achieved by TLR2 engagement. For example, S-[2,3-bis(palmitoyloxy)propyl]cysteine (Pam2Cys) [78], PPE57 [79], Rv3628 [71] and Rv3203 Mtb proteins [80], as TLR agonists, are potential candidate antigens to be used in future prophylactic vaccines against Mtb strains. Although a TLR2 agonist such as recombinant MPT83 (rMPT83) may induce the macrophage function [81], the inclusion of such agonists into new vaccines may not be fully effective in some situations such as when they are used in the elderly population [82].

Findings about TLR2-Mtb interaction may yield some clinical applications regarding treatment considerations. For example, TLR2 rescues Th1 cells from exhaustion and therefore can be considered as an important target in the treatment of patients with chronic infections [83]. Also, Mtb promotes arthritis development through TLR2, and TLR2 could represent a therapeutic target for this form of arthritis [84]. However, some limitation should be considered in the case of such clinical applications. For example, CD36-TLR2 cooperation may lead to a decreased macrophage response [85], and some mycobacterium antigens expressed inside infected macrophage may suppress protective immune responses such as TLR2-induced IL-12 production [86]. TLR2 gene polymorphisms may increase the risk of susceptibility to Mtb [87–89].

4. TLR4

Binding TLR4 to different components of Mtb such as 3- and 4-acylated lipomannan (LM), 60- and 65-HSPs, and 50S ribosomal protein [24] activates immune cells in different ways. In this regard, macrophages from TLR4−/− mice do not respond to Mtb HSP65 [33] and show less, yet not completely abolished, tumor necrosis factor alpha (TNF-α) production [90,91]. TLR4 agonists substantially increase the pool of effector memory CD4 and CD8 T cells and reduce the dose and Mtb burden in the lungs [92].

For example, both Mtb protein of Rv0652, a potent TLR4 agonist [93], and Mtb heparin-binding hemagglutinin (HBHA), a Novel TLR4 agonist [94], enhance the polarization of T effector cells toward a Th1 phenotype through dendritic cell maturation. However, TLR4 antagonist E5531 blocks Mtb induced TNF-α production in primary human alveolar macrophages [35] (Figure 1).

The immune-stimulatory impact of TLR4 may be controversial concerning some studies stating that TLR4-deficient mice do not show high susceptibility to Mtb infection; otherwise, non-functional TLR4 and TLR4-deficient mice develop a chronic lung infection when exposed to aerosolized Mtb [90,91,95,96]. Actually, similar to TLR2, TLR4 plays some dual beneficial and pathologic effects on the host immune responses against Mtb. For instance, lipopolysaccharide (LPS), a major mediator of TLR4-mediated inflammatory responses, might negatively be down-regulated by Phosphatidylinositol mannosides of Mtb in such a way that it may inhibit TLR4 and MyD88-dependent production of nitric oxide as well as inflammatory cytokines [97]. Such a strategy, developed by Mtb, may repress host immune responses. Mutually, Mtb proteins such as Rv0652 [98] and chaperonin 60 [99] stimulate macrophages and Resuscitation-promoting factor (Rpf)B [100] and (Rpf)E [101] proteins incite DCs toward Th1/Th17 cell expansion in a TLR4-dependent pathway to secrete pro inflammatory cytokines and hereon have the potential to be effective Mtb vaccines. (Figure 1) If vaccines can succeed in inducing Th1 memory cells for a long time, they can ensure the high efficacy of tuberculosis vaccines [100]. Unexpectedly, the deficiency of Toll-interacting protein (TOLLIP), as a negative regulator of TLR signaling, which has some anti-inflammatory responses in humans by suppressing pro inflammatory cytokines via TLR2 and TLR4 and also by inducing IL-10 through a TLR4-specific mechanism, is associated with a risk of Mtb pathogenesis [102]. In the case of $CD4^+$ subtypes, Th17 cells may secrete IL-17A by the engagement of TLR4 as the main receptor mediating responses to Mtb via the induction of IL-1 [103]. Like TLR2, TLR4 genetic polymorphisms may influence the risk of developing Mtb infection [104].

5. TLR9 and TLR8

TLR9 interacts with mycobacterial DNA and activates macrophages to induce pro inflammatory cytokines [105]. Such activation is ascribed to unmethylated CpG motif [34,106] as well as small oligonucleotides that mimic bacterial CpG motifs [107] which interact with both TLR9 and TLR8. DCs are activated in such a way that their Mtb-induced IL-12 release is TLR9-dependent [108]. (Figure 1) One subtype of DCs, called plasmacytoid DCs, play an important role in the initiation of innate responses and inflammation after the induction of TLR9 stimulation with mycobacterial infection [109]. Such pivotal roles of TLR9 make those findings reasonable stating that TLR9-deficient mice are susceptible to Mtb infection rather than wild-type animals [38,110]. The other confirming idea is that Single Nucleotide Polymorphisms (SNPs) in the TLR9 gene region are associated with susceptibility to pulmonary and meningeal Mtb [111]. A tuberculosis (TB) vaccine consisting of a recombinant fusion protein (H4) and a novel TLR9 adjuvant (IC31) is in clinical development [112].

TLR8 expression can be up-regulated in macrophages after exposure to Bacillus Calmette–Guérin (BCG). Such a finding reveals a role for TLR8 in susceptibility to pulmonary tuberculosis in different populations [36]. The association of TLR8 to such susceptibility depends on its polymorphism [113].

6. Cooperation of TLRs

By cooperating with other TLRs, TLR2 forms heterodimers with TLR1 [114], TLR6 [115] and TLR4 [116] to activate the macrophages in response to tri-acylated lipoproteins, soluble tuberculosis factor, and mycobacterial 38-kDa glycolipoprotein antigen of Mtb, respectively. The primary $CD4^+$ T cells use TLR2/TLR1 heterodimers to interact with Mtb lipoproteins, and this interaction results in direct T cell costimulation [65]. (Figure 1) The gene expression of TLR1 and 2 increases in intestinal Mtb infection through the induction of innate immune activation and Th1 polarization [117] from the first months of life and afterwards even after vaccination [118].

In line with this idea, a decrease in TLR1 and TLR6 genes modulate adaptive immunity from the point of the production of BCG-induced cytokines by T cells [119].

The different aspects of the cooperation of both TLR2 and TLR4 have been introduced. A study reported that the mycobacterial 38-kDa glycolipid antigen uses both TLR2 and TLR4 to induce pro inflammatory cytokines such as TNF-α and IL-6 in monocytes during Mtb infection [116]. Another study revealed that the invasion of Mtb to DCs might enhance their maturation [120] and antigen-presenting function [121] through activation of TLR2/4 signaling pathway. In regards to emphasizing the paradoxical effects of TLRs, two studies showed that TLR2 and TLR4 expression causes the Mtb infected cells more susceptible to death and drug resistance [122,123], whereas, two others associated the anti-Mtb activity of macrophages to the expression of such TLRs [124,125].

It seems that TLR2 also has some cooperation to TLR9. Double knockout TLR2/TLR9 mice display greater defects of IL-12 and IFN-γ production in comparison with both single TLR knockout mice [34]. Moreover, mice lacking TLR2/TLR4/TLR9 show a milder phenotype MyD88 deficient mice [126]. However, one recent study stated that signaling through TLR2 and through TLR2 and TLR9 is not required to generate immunity against Mtb growth [127].

Recently, the cooperation of other TLRs has been introduced. For example, Rv2034, a protein that is expressed during pulmonary infection which is strongly recognized by human T-cells, can be used as a new vaccine if introduced in the presence of TLR3, 4 and 9-adjuvants including cationic adjuvant formulation (CAF) 09, monophosphoryl lipid-A (MPL)/trehalose dimycolate (TDM), and CpG, respectively (Figure 1). Such combinations would be able to induce IFN-$\gamma^{+}CD4^{+}$T-cells [128]. Combining glucopyranosyl lipid adjuvant (GLA) and CpG, as TLR4 and TLR9 agonists, in order to enhance the Th1 response against ID93 antigen which is a fusion of four Mtb proteins and leads to an increased protection against aerosolized Mtb challenge is another example in this field [129] (Figure 1).

7. Conclusion

TLRs play a significant role against the invasion of TB in the body. Actually, each one alone can activate different components of the immune system and reinforce anti-TB responses. Therefore, defects and polymorphisms in TLRs may increase the risk of infection and vulnerability to TB. Moreover, TLR agonists may be used in the development of vaccines against Mtb. In the attempt to properly understand the interactions between the host and pathogen receptors, including the TLRs, we greatly hope to achieve an optimal combination for targeting various pathogen components to vaccinate the infection.

Likewise; TLRs can be used as important targets in the treatment of chronic mycobacterial infections. Although various studies have been conducted in the past decade to develop new findings in mechanism of TLRs function, more serious efforts would be needed to prevent the increasing risk of the tuberculosis infection. Such efforts should better clarify signal transduction pathways employed by the immune system to overwhelm Mtb and escape mechanisms employed by Mtb to resist the immune system.

Disclosure statement

No potential conflict of interest was reported by the authors.

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