

## Review Article

# Pattern Recognition Receptors and Cytokines in *Mycobacterium tuberculosis* Infection—The Double-Edged Sword?

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Tuberculosis, an infectious disease caused by *Mycobacterium tuberculosis* (Mtb), remains a major cause of human death worldwide. Innate immunity provides host defense against Mtb. Phagocytosis, characterized by recognition of Mtb by macrophages and dendritic cells (DCs), is the first step of the innate immune defense mechanism. The recognition of Mtb is mediated by pattern recognition receptors (PRRs), expressed on innate immune cells, including toll-like receptors (TLRs), complement receptors, nucleotide oligomerization domain like receptors, dendritic cell-specific intercellular adhesion molecule grabbing nonintegrin (DC-SIGN), mannose receptors, CD14 receptors, scavenger receptors, and FC $\gamma$  receptors. Interaction of mycobacterial ligands with PRRs leads macrophages and DCs to secrete selected cytokines, which in turn induce interferon- $\gamma$ - (IFN $\gamma$ -) dominated immunity. IFN $\gamma$  and other cytokines like tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) regulate mycobacterial growth, granuloma formation, and initiation of the adaptive immune response to Mtb and finally provide protection to the host. However, Mtb can evade destruction by antimicrobial defense mechanisms of the innate immune system as some components of the system may promote survival of the bacteria in these cells and facilitate pathogenesis. Thus, although innate immunity components generally play a protective role against Mtb, they may also facilitate Mtb survival. The involvement of selected PRRs and cytokines on these seemingly contradictory roles is discussed.

## 1. Introduction

Despite 100 years of research, infection with *Mycobacterium tuberculosis* (Mtb) is still a major health problem worldwide and one of the main causes of human death by a particular infectious agent. Every year, 10 million new cases are diagnosed, and 2 million people die because of tuberculosis (TB) [1]. The incidence of TB is increasing in association with increased numbers of HIV/AIDS patients. The problem was further worsened by the emergence of multidrug resistant (MDR) and extensively drug resistant (XDR) Mtb [2]. Host immunity is usually capable of inhibiting Mtb growth in most individuals and often leads to latent infection, which is characterized by the confinement of live but inactive bacteria in the granuloma. According to the World Health Organization (WHO), one-third of the world's population is infected with latent TB, but only 10% of it develops active TB [3]. The possibility of developing active TB is increased with

the incidence of immune-compromising conditions such as AIDS and diabetes. This indicates that the host immune system is active in most individuals and provides protection against Mtb infection. The host defense mechanisms against mycobacterial infection are largely divided into two phases: innate immunity and adaptive immunity. This review focuses on the natural, innate immunity against Mtb, although the two arms of the host immune response complement each other in defense against Mtb.

TB begins with the engulfment of Mtb through inhalation into the pulmonary alveoli. After inhalation, the first line of host defense starts with the recognition of Mtb by phagocytic cells of the innate immune system such as macrophages and dendritic cells (DCs). Macrophages and DCs express numerous pattern recognition receptors (PRRs) that recognize antigenic molecules expressed on Mtb called pathogen-associated molecular patterns (PAMPs) [4–6]. Among the various PRRs, toll-like receptors (TLRs) seem to play the most

important role in Mtb infection. These receptors interact with pathogen-specific ligands, facilitate uptake of Mtb, and initiate an intracellular signaling cascade in host cells that induces production of cytokines [7] which are essential to elicit the adaptive immune response and arrest bacterial growth. Thus, TLRs serve as a link between innate and adaptive immune defense against infection with mycobacteria. The proinflammatory cytokines produced through mycobacterial recognition of PRRs in turn regulate antimycobacterial mechanisms of macrophages such as generation of reactive nitrogen intermediates (RNI) and reactive oxygen intermediates (ROI) [8]. Interferon- $\gamma$  (IFN $\gamma$ ), in combination with tumor necrosis factor- $\alpha$  (TNF $\alpha$ ), upregulates nitric oxide synthase 2 (NOS2) expression and induces production of RNI within the phagolysosome, thus mediating intracellular Mtb killing [9]. Anti-inflammatory cytokines, however, usually facilitate Mtb infection by opposing proinflammatory immune responses of host cells [9]. An extensive knowledge about host immune responses is essential for understanding the pathophysiology of TB.

In the last several years, immunologists have made substantial progress in our understanding of host innate immune response to Mtb and on the specific roles of different immune components and effectors in the process of host protection. However, mycobacteria possess the ability to evade destruction by the innate host defense mechanisms [10]. Thus understanding the nature of the innate response is crucial for us to be able to modulate it to prevent Mtb infection. This review focuses on our current understanding of the recognition of Mtb by the PRRs and subsequent regulation of host innate immune response to Mtb specifically on the cellular response to cytokines secreted as well as their role in protection of the host or promotion of Mtb pathogenesis. More extensive reviews on the subject can also be obtained from previous studies (see, e.g., [2, 3, 6, 8, 10–16]).

## 2. Pathogenesis of *M. tuberculosis*

Mtb usually infects the lungs where the tubercle bacilli are inhaled into the pulmonary alveoli. Here, we discuss the pathogenesis of Mtb mainly on the basis of studies that have been performed in animal models, particularly in mice. After inhalation, the alveolar resident macrophages initially ingest the bacilli. Most bacilli are destroyed at this stage. Mtb that evades the initial destruction will multiply which then results in disruption of the macrophages and may manifest as active TB disease [11, 12]. In most cases however, chemokines are released by the alveolar macrophages, which lead to the recruitment of monocyte-derived DCs and macrophages to the lungs [11, 12]. These newly recruited cells readily ingest but usually do not destroy the bacilli. At this stage, Mtb grows logarithmically with nominal tissue damage [11, 12]. At the same time, blood monocytes accumulate at the infection site. T-cell mediated immunity then develops after two to three weeks of infection [11, 12, 16]. Antigen-specific T lymphocytes that migrate to the infection site will multiply within the early lesions or tubercles and release proinflammatory cytokines such as IFN $\gamma$  which in turn activates macrophages to kill the

intracellular mycobacteria [17]. Eventually, bacillary growth stops, and the central dense necrosis in primary lesions (granuloma) contains the extracellular growth of mycobacteria. This phase of infection is known as the latent phase where the growth of mycobacteria is put in check. Reactivation of latent TB can occur months or years afterwards when the immune system is weakened [9, 18, 19].

## 3. Is Innate Immunity Adequate for Host Protection?

After inhalation, alveolar macrophages engulf the Mtb bacilli and initiate the innate immune response as a first line of host defense. Innate and adaptive immunity are synergistic, and innate immune responses orchestrate the initiation of downstream adaptive immune responses. Figure 1 illustrates the transmission profile of TB in the Mtb-infected host. Upon exposure to Mtb, a major percentage of individuals remain uninfected probably because of the expression of adequate innate immunity. However, we hypothesize that an inadequate innate immunity in some individuals is unable to contain the infection and adaptive immune responses are thus needed to arrest growth of bacteria and to confer host protection. The adaptive immunity provides protection against the development of active TB, and these individuals remain latently infected. Latent infections are susceptible to be reactivated when the hosts' immunity weakens or when they become immunocompromised [9, 18, 19]. In the worst case scenario, a defective adaptive immune response in individuals with inadequate innate immunity leads to early progression of active TB. Thus a high level of host innate immune response itself can effectively protect Mtb infection, while a defective or impaired innate immune response requires the help of adaptive immune response to furnish protection against Mtb infection.

This notion however is rather simplistic since it does not take into consideration the initial bacterial load, the environmental influence, and the host's immunogenetics. These three factors can modulate the effectiveness of the innate immune response. A low-dose mycobacterial load induces a Th1 type immune response while a high-dose challenge with mycobacteria is known to shift cellular responses towards Th2 type response [20, 21]. Mice immunized with low-dose mycobacteria induced Th1 response and showed partial protection against Mtb H37Rv challenge, while mice immunized with high-dose mycobacteria primed a mixed Th1/Th2 response, predominantly Th2 response, that overcomes the initial protection provided by Th1 response and showed massive pneumonia [20, 21]. The nature of immune response is also influenced by environmental factors such as the presence of environmental mycobacteria which prime Th1 type responses, whereas infection with soil transmitted helminths induces Th2 type responses and stimulates T-regulatory cells which secrete anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor- $\beta$  (TGF- $\beta$ ) [22, 23]. Host's genetic factors also influence the nature of immune response and could thereby determine the fate of Mtb infection on whether it will

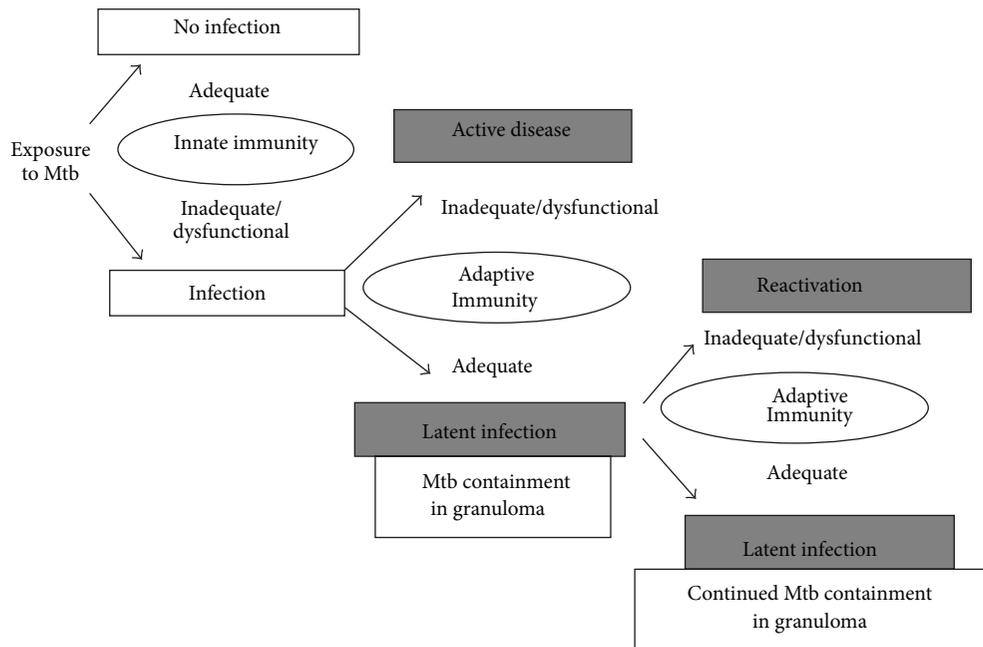


FIGURE 1: Pathogenesis and transmission profile of Mtb. Adequate innate immunity is believed to protect the host from Mtb infection in the majority of people, while inadequate innate immune response leads to Mtb infection. The adaptive immunity then restricts Mtb growth which leads to Mtb containment in granulomas which causes latent TB infection. Defective adaptive immunity causes active TB and promotes reactivation of the latent TB.

manifest as a clinical disease [24]. Genetic factors are shown to contribute to TB incidences, with an estimated heritability ranging from 36 to 80% [25]. Moreover, diverse lineages and different strains of Mtb have been shown to induce highly heterogeneous immune responses upon infection, and the incidence of TB relies upon their ability to alter innate immune responses and the secretion of cytokines by host phagocytic cells [26–30]. Thus there appears to be a complex interaction between the host, pathogen, and the environment which determines the type and efficacy of the immunity induced by the Mtb infection to progress to active disease or to be contained as latent infection or eliminated by the host.

#### 4. Innate Immune Recognition of *M. tuberculosis*

Phagocytosis is the key mechanism of defense against Mtb infection after it is being inhaled. The alveolar resident phagocytic cells, macrophages and DCs, engulf Mtb bacilli and cause initiation of infection. The PAMPs of Mtb are recognized by specific PRRs, expressed on phagocytic cells, and allow entry of the bacilli into the cells which is central in initiation and coordination of the host innate [31] and subsequently adaptive immune response. This PRR-dependent entry is also important as a key determinant of the fate of Mtb. Although phagocytosis is mainly involved in the killing of pathogen, the growth of some Mtb bacilli can also be promoted depending on the route of entry into phagocytic cells. Prior to phagocytosis, Mtb or Mtb components are recognized by a variety of different PRRs that

include TLRs, complement receptors (CRs), scavenger receptors, nucleotide-binding-oligomerization-domain- (NOD-) like receptors (NLRs), dectin-1, surfactant protein A (Sp-A) receptors, mannose receptors (MRs), and the dendritic cell-specific intercellular adhesion molecule grabbing nonintegrin (DC-SIGN) [32–34].

*4.1. Immune Recognition of M. tuberculosis: Role of Toll-Like Receptors in Phagocytosis and M. tuberculosis Killing.* TLRs are phylogenetically conserved receptors expressed, among other cells, on macrophages and DCs which recognize PAMPs of pathogens [35]. Interaction of specific mycobacterial ligands with TLRs leads to macrophage activation which triggers signaling pathways (Figure 2) in which the adaptor molecule, myeloid differentiation primary response protein 88 (MyD88), plays a central role [36]. MyD88 links mycobacterial ligand bound TLRs to the interleukin-1 receptor-associated kinase (IRAK) which subsequently recruits TNF receptor-associated factor 6 (TRAF6), TGF- $\beta$ -activated protein kinase 1 (TAK1), and mitogen-activated protein kinase (MAPK) in a signaling pathway that mediates translocation of the nuclear transcription factor NF- $\kappa$ B into the nucleus. NF- $\kappa$ B promotes transcription of the genes of host innate immune defense and subsequent expression of proinflammatory cytokines and chemokines (Figure 2) [37–41]. IL-12 and IL-18 induce IFN $\gamma$ -dominated immunity, which involves natural killer (NK), Th1, and CD8+ T cells, activates macrophages, and leads to bacterial growth inhibition. Activation of macrophages initiates phagosome maturation and promotes antimycobacterial effector mechanisms

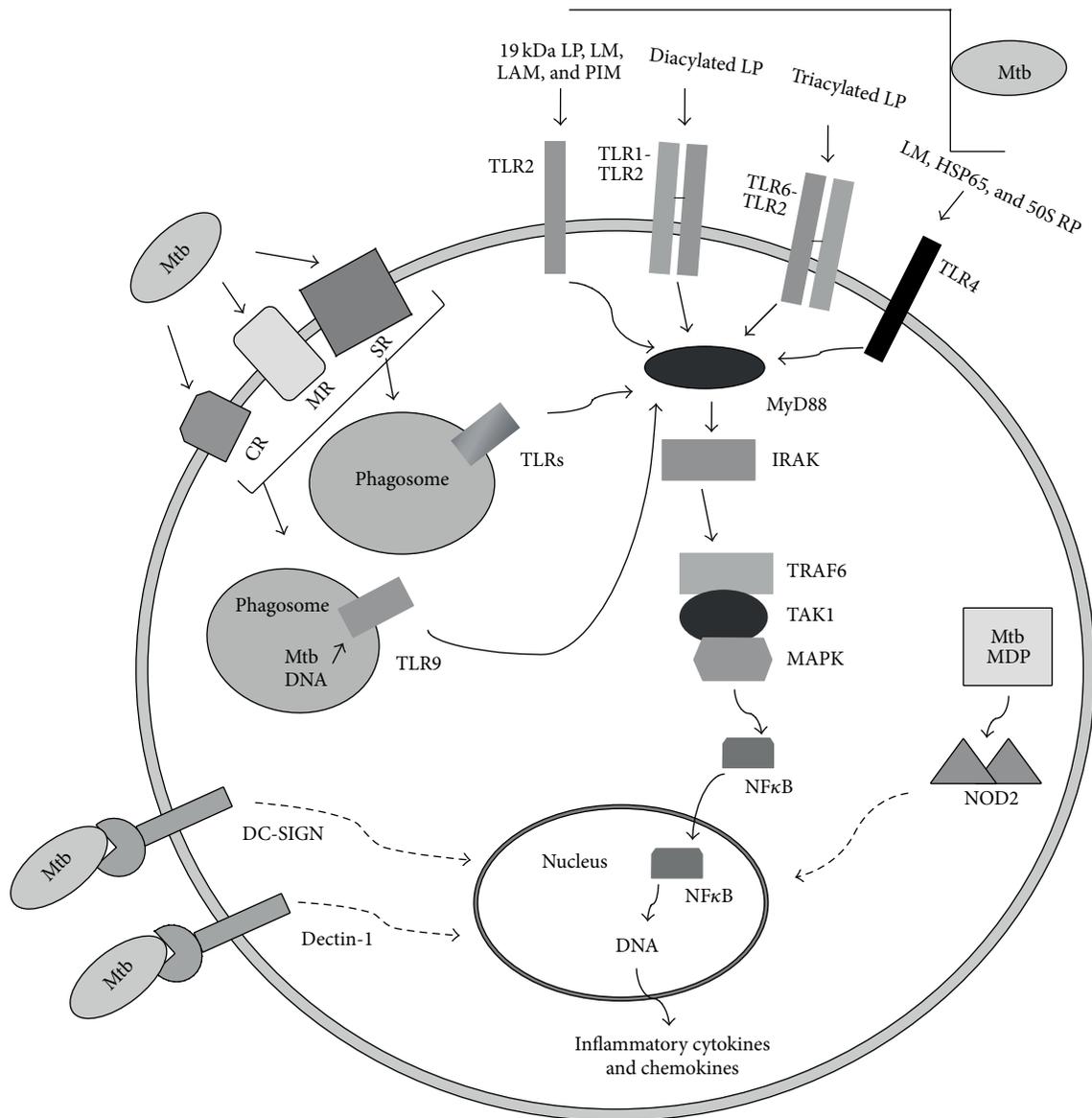


FIGURE 2: Immune recognition of *M. tuberculosis* during phagocytosis. Several pattern recognition receptors (PRRs) on phagocytic cells have been identified for the recognition of conserved pathogen associated molecular patterns (PAMPs) of mycobacteria. TLR2 recognizes the 19 kDa lipoprotein (LP), lipomannan (LM), and lipoarabinomannan (LAM). TLR1-TLR2 and TLR6-TLR2 heterodimers bind diacylated and triacylated LP, respectively. TLR4 binds tri- and tetra-acylated LM, heat shock protein 65 (HSP65), and 50S ribosomal protein (50S RP), whereas mycobacterial DNA is recognized by phagosomal TLR9. Complement receptors (CRs) are mainly responsible for uptake of opsonized *M. tuberculosis*, while mannose receptors (MRs) and scavenger receptors (SR) are for uptake of nonopsonized *M. tuberculosis*. Cytosolic receptor NOD2 interacts with Mtb derived peptidoglycan component muramyl dipeptide (Mtb-MDP). MyD88 is the key component in TLR-mediated defense mechanism whose downstream signaling cascade leads to the activation of NF- $\kappa$ B transcription factor and to the production of inflammatory molecules. TLRs are expressed on phagocytic cell surface and in phagosomes. Dashed arrow represents the presence of numerous signaling molecules in between.

such as autophagy, interferon inducible GTPase such as Irgm-1/LRG47 and induces production of nitric oxide and other RNIs [8, 12, 15, 42].

Among the TLRs identified, TLR2, TLR4, and TLR9 are the key receptors that are involved in recognition of Mtb. Mtb expresses various antigenic ligands that interact with TLR2 and subsequently activate MyD88 mediated signaling pathway. Among these, LpqH, a 19-kDa secreted lipoprotein

of Mtb, interacts with TLR2 and induces production of TNF $\alpha$  and nitric oxide from both murine and human macrophages [43]. LpqH also induces IL-12 production from human monocytes [43]. TLR2 is shown to recognize other mycobacterial lipoproteins such as LprA (Rv1270) [44] and LprG (Rv1411c) [45]. TLR2 also interacts with lipomannan [46] and phosphatidyl-*myo*-inositol mannoside (PIM) [47, 48] to induce immune response [48]. TLR2 forms heterodimers

with either TLR1 or TLR6. The heterodimers TLR2-TLR1 and TLR2-TLR6 interact with diacylated and triacylated lipoproteins, respectively [48, 49]. TLR2<sup>-/-</sup> mice show defects in formation of granuloma [50]. When challenged with high dose Mtb, TLR2<sup>-/-</sup> mice show greater susceptibility to infection than wild type mice [50, 51]. Furthermore, TLR2<sup>-/-</sup> mice show defect in protection of chronic infection with Mtb [50]. TLR2-mediated activation of macrophages enhanced the expression of genes of vitamin D receptor and vitamin-D-1-hydroxylase which in turn promotes the production of the antimicrobial peptide, cathelicidin, and provides resistance to Mtb [52]. TLR2 is essential for production of TNF $\alpha$ , as inhibitory TLR2 (TLR2-P681H) expression in mouse RAW TT10 macrophage cells absolutely inhibits TNF $\alpha$  production induced by whole Mtb [36]. Consistent with the deduced role of TLR2 in studies using TLR2 knockout mice/macrophages, host genetics that causes even a single mutation in TLR2 gene has been shown to significantly affect the incidence of TB. For example, individuals with TLR2 Arg753Gln single nucleotide polymorphisms (SNPs) are found to be more susceptible to TB compared to healthy controls of a Turkish cohort [53]. Several other SNPs such as TLR2 Arg677Trp, TLR2 597CC, and TLR2 T597C also show an association with susceptibility to TB in different cohorts [54–56] indicating that the TLR2 polymorphisms influence the susceptibility to Mtb infection.

Like TLR2, TLR4 also induces MyD88-mediated signaling pathway upon recognition of selected PAMPs and regulates the production of proinflammatory cytokines [51] (Figure 2). In addition to MyD88 pathway, stimulation of TLR4 also activates MyD88 independent TIR-domain containing adapter-inducing interferon- $\beta$  (TRIF) pathway where TRIF links to interferon regulatory factor-3 (IRF3) which induces interferon- $\beta$  secretion, and this cytokine subsequently activates a series of genes that regulate host protection [37, 57]. A recent study showed that certain strains of Mtb preferentially activate TLR4, whereas others stimulate TLR2 and induce distinct immune responses depending on the TLR that recognizes Mtb [30]. Mtb heat shock protein 65 (HSP65) was shown to signal exclusively through TLR4 as macrophages from TLR4<sup>-/-</sup> mice showed no response to Mtb HSP65, whereas Mtb HSP70 was shown to signal through both TLR4 and TLR2 [58]. Another *in vitro* study showed that Mtb chaperonin 60.1 (Cpn60.1) protein predominantly stimulates TLR4 to induce subsequent immune signaling, whereas Mtb Cpn60.2 can use both TLR2 and TLR4 for its signaling for cytokine production [59]. Recombinant Mtb 50S ribosomal protein Rv0652 stimulates macrophages in a TLR4-dependent and MyD88-dependent signalling pathway to induce secretion of proinflammatory cytokines, predominantly TNF and chemokine such as monocyte chemoattractant protein 1 [60]. The 38-kDa glycolipoprotein of Mtb H37Rv signals through both TLR2 and TLR4 and activates MAPKs, which then induces expression of TNF $\alpha$  and IL-6 in human monocytes during mycobacterial infection [61]. TLR4 antagonist E5531 substantially blocked Mtb induced TNF $\alpha$  production in RAW 264.7 macrophages and primary human alveolar macrophages [62]. Although several molecules are shown to activate TLR4 *in vitro*, the actual

ligands that TLR4 recognizes during mycobacterial infection still remain unknown. Moreover, *in vivo* study showed that TNF $\alpha$  production was greatly reduced in TLR4-deficient mice [63]. TLR4 defective mice (C3H/HeJ) showed greater susceptibility to Mtb infection in comparison to wild type mice [63], but these mice have been shown to display greater resistance than wild type models upon exposure to low dose Mtb [51]. Further studies are thus needed to elucidate the role of TLR4 in Mtb infection.

The role of TLR9 in Mtb infection has recently been revealed. TLR9 interacting with mycobacterial DNA activates macrophages and induces proinflammatory cytokine synthesis [64]. TLR9 in combination with TLR2 was studied to detect both their combined and individual roles [65]. TLR9<sup>-/-</sup> mice infected with Mtb exhibited defective production of IL-12p40 and IFN $\gamma$ . However, in the presence of TLR2, TLR9<sup>-/-</sup> mice showed some extent of resistance to low dose Mtb aerosol challenge indicating that TLR2 may compensate for TLR9 deficiency [65]. Expectedly TLR2/9 double knockout mice showed extensive susceptibility to Mtb infection. The DCs and macrophages of mice deficient either in TLR2 or TLR9 also showed significantly greater defects in response to IL-12. TLR9 in combination with TLR2 seems to cooperate with each other in defence against Mtb infection [65].

While the role of TLRs in Mtb recognition and subsequent induction of immune responses were mostly performed in mouse models and in macrophages, very little is known on their role in DC maturation and cytokine production by DCs. TLRs mediated interaction (phagocytosis) of Mtb causes activation and maturation of DCs which then transport the pathogen to draining lymph nodes and present Mtb antigens to naive T cells, thus initiating adaptive immune responses to Mtb [10]. DCs induce production of numerous cytokines including TNF $\alpha$ , IL-6, IL-10, and IL-12 upon infection with Mtb *in vitro* [66, 67]. Another study showed that secretion of IL-6 and IL-10 by DCs largely depends on TLR2-mediated recognition of Mtb and the production of IL-6 and IL-10 was significantly reduced in the absence of TLR2 signaling in TLR2<sup>-/-</sup> DCs [67]. Both TLR2 and TLR4 on human DCs were found to be activated by muramyl dipeptide derivatives with a single octanoyl or stearoyl fatty acid chain [68].

**4.2. Non-TLR Receptor-Mediated Phagocytosis of *M. tuberculosis*.** Phagocytosis of Mtb can occur via a variety of different receptors other than TLRs, expressed on the phagocytic cellular surface (Figure 2). Host cellular response may be influenced by the type of receptor utilized for internalization of Mtb. Thus, there is no specific route of Mtb entry into phagocytic cells. However, the fate of Mtb survival can be influenced by the route of entry as some of these receptors favor host protection, while some others promote mycobacterial infection.

**Complement Receptors.** Complement receptors (CRs) are membrane proteins expressed on the surface of phagocytic cells. They interact specifically with complement components, some of which are essential for opsonization of

mycobacteria prior to phagocytosis. Complement receptors, namely, CR1, CR3, and CR4, on the phagocytic cell surface are involved in promoting Mtb ingestion [69]. In fact Mtb utilizes such cell surface molecules to gain access into macrophages. Complement component C3 binds to the surface of Mtb and enhances phagocytosis by macrophages through binding with CR1, CR3, and CR4 [69–71]. CR3 is relatively more important among the CRs. In the absence of CR3, human monocytes and macrophages showed about 70 to 80% reduced ability in phagocytosis of Mtb [70, 71]. CRs can mediate uptake of virulent as well as avirulent strains of Mtb, and blocking of CRs inhibits the phagocytosis of Mtb [70]. Furthermore, CR3-Mtb interaction can prevent formation of respiratory bursts which causes phagosomal arrest of early endosomes and produces no inflammatory response [72]. The entry of Mtb through binding with CRs thus appears as a beneficial route for Mtb survival and pathogenesis.

**Mannose Receptors.** Mannose receptors (MRs) are transmembrane C-type (calcium dependent) lectins that bind certain sugars, specifically mannose, present on the surface of pathogens. Both monocyte-derived and tissue macrophages express MRs that are mainly associated with Mtb phagocytosis without prior opsonization. MRs interact with the terminal mannose residues of lipoarabinomannan (LAM) expressed on the cell surface of virulent strains of Mtb (Erdman strain) [73]. Interaction of Mtb derived mannose-sylated lipoarabinomannan (ManLAM) with MR promotes inhibition or delay in phagosome-lysosome fusion [74]. Thus MRs mediate entry of Mtb into macrophages and facilitate the survival and expansion of Mtb due to inhibition of phagosome-lysosome fusion [74, 75]. While CRs recognize both avirulent and virulent strains of Mtb, MRs are reported to recognize only virulent strains [70], indicating that this path of entry is particularly useful for pathogenesis of virulent Mtb.

**NOD-Like Receptors.** The NOD (nucleotide oligomerization domain) like receptors (NLRs) are a class of cytoplasmic protein containing a series of leucine-rich repeats in the C-terminal region, similar to other PRRs of the innate immune system, which interact with the PAMPs of the pathogen. NOD2, a member of NLRs, interacts with bacterial peptidoglycan component muramyl dipeptide (MDP). Mice deficient in NOD2 showed defective cytokine production upon infection with Mtb [76]. Mutation of the *NOD2* gene has been reported to cause defects in cytokine production by mononuclear cells against Mtb [77]. Live but not heat-killed Mtb activates the NOD2-mediated signaling pathway [78]. Live Mtb, though localized in the phagosomal compartment within macrophages, induces phagosomal membrane damage, results in Mtb interaction with cytosolic NOD2 receptor, and consequently stimulates the NOD2 pathway [79], which indicates that NLRs-mediated signaling pathway provides protection to host against Mtb infection.

**CD14 Receptors.** CD14 receptors mainly recognize LPS and play a role in phagocytosis. In fetal microglia, blocking of CD14 receptors by anti-CD14 antibodies causes inhibition of

Mtb phagocytosis [80]. Phagocytic cells expressing high levels of CD14 such as porcine alveolar macrophages preferentially ingest *M. bovis*, and anti-CD14 antibodies inhibit bacillary entry [81]. However, one study [80] suggested that CD14 is not essential in phagocytosis, but its expression is upregulated as a consequence of Mtb infection, which in turn may promote the pathogen's capability to modulate the immune response. Thus, the role of CD14 in Mtb internalization by macrophages is ambiguous.

**Dectin-1.** Dectin-1 is a PRR which consists of an extracellular carbohydrate recognition domain with an intracellular tyrosine activated motif. Macrophages, DCs, neutrophils, and a subset of T-cells are the main cells that express dectin-1 receptor.  $\beta$ -Glucans present in fungal pathogens are the ligands of dectin-1. However, this receptor can also recognize  $\alpha$ -glucan expressed on the surface of some species of Mtb [82]. Dectin-1-mediated recognition of Mtb induces Th1 and Th17 responses, and subsequent secretion of proinflammatory cytokines that promote bacterial killing [83]. Dectin-1 also promotes IL12p40 production by DCs in response to Mtb infection, and blocking of dectin-1-dependent activity or DCs from dectin-1<sup>-/-</sup> mice results in reduced production of Mtb induced IL12p40 production [84]. Although dectin-1 is suggested to play a protective role in Mtb infection [84, 85], Marakalala et al. [86] showed that dectin-1, that signals through the Syk/CARD9 pathway, may augment host susceptibility to Mtb as pulmonary bacilli burdens were observed lower in dectin-1-deficient mice. Moreover, CARD9-deficient mice were shown to be highly susceptible to Mtb and died early after high dose Mtb H37Rv aerosol challenge [87]. Dectin-1 is essential for production of TNF $\alpha$ , RANTES, IL-6, and G-CSF by murine macrophages upon mycobacterial infection [85, 88]. Further studies are necessary to reveal the exact role of this receptor in immunity against mycobacterial infection, in particular, to reveal the mycobacterial ligand(s) recognised by this receptor as mycobacteria do not possess  $\beta$ -glucans.

**Scavenger and Fc $\gamma$  Receptors.** Scavenger receptors (SRs) and Fc $\gamma$  receptors (Fc $\gamma$ R) play a less important role in Mtb pathogenesis. When uptake by CRs is being inhibited, Mtb may enter into phagocytic cells through binding with type-A scavenger receptors [89]. Fc $\gamma$ R mediates uptake of IgG-opsonized mycobacteria, induces generation of ROIs, and promotes formation of phagolysosome, thus aiding in Mtb killing [90].

**DC-SIGN.** Dendritic cell-specific intercellular adhesion molecule grabbing nonintegrin (DC-SIGN) is a carbohydrate recognition receptor expressed mainly on DCs. This receptor serves as PRR as well as adhesion receptor, because of its association with migration of DCs and interaction between DCs and T-cells [91, 92]. DC-SIGN recognizes Man-LAM and lipomannans expressed on the cell surface of mycobacteria and induces IL-10 production, thereby promoting an anti-inflammatory response by DCs [93]. DC-SIGN on DCs interacts with Man-LAM to internalize *M. bovis* BCG, and blocking of DC-SIGN by using

anti-DC-SIGN antibody restricts the infection of DCs [93]. However, the DC-SIGN homologue, SIGNR3 in a murine model, was shown to confer early resistance against Mtb infection, and the resistance was impaired in SIGNR3-deficient mice. During infection, SIGNR3 is expressed in lung phagocytes and interacts with Mtb bacilli and mycobacterial surface glycoconjugates and mediates host protection by inducing secretion of protective cytokines including TNF $\alpha$  and IL-6 [94, 95]. It was shown in an *in silico* study that two variants (-871G and -336A) in the promoter region of DC-SIGN gene (CD209) may confer protection against TB [96]. However, genetic studies on human population showed that sequence and length variation in DC-SIGN have no significant impact on TB susceptibility [97, 98].

**Surfactant Protein A.** Surfactant protein A (SP-A) is a soluble receptor protein present in abundance in host alveolar macrophages. SP-A induces an increased phagocytosis of Mtb by human macrophages [99]. HIV-positive patients with Mtb infection showed increased expression of SP-A in their lungs and resulted in a threefold higher risk of developing active disease [100]. SP-A mediated uptake of Mtb by human macrophages significantly reduces the generation of RNI in the macrophages and thereby decreases macrophage cytotoxicity and aids in intracellular survival of Mtb [99, 101].

Thus Mtb employs various mechanisms involving PRRs to get access into alveolar macrophages. The host cellular responses depend on the receptor used which determines the fate of Mtb infection whether the bacteria will survive or be destroyed by the initial inflammatory responses. Hence whether Mtb will be eliminated/contained or escape the host innate immunity may be dependent on the sum total of PRR interactions with the bacteria. Therefore, further studies are needed to assess whether some or all of these mechanisms are operative under *in vivo* conditions in order to gain a better understanding on the development of the disease.

## 5. *M. tuberculosis* Induced Cytokine Secretion: Protection for Host or for Pathogen?

Interaction of Mtb ligands with the PRRs on macrophages and DCs causes cell activation and secretion of cytokines which regulates the innate immune response as well as initiates the adaptive immune response to Mtb. Cytokines, produced in response to Mtb infection, are not always necessarily favorable to host protection, and some of these immune modulators favor the pathogen. Studies showed that cytokines, in response to a particular pathogen, produce beneficial as well as deleterious effects to the host. In this section, we discuss the importance of cytokines induced during Mtb infection under two major groups, proinflammatory cytokines (cytokines that are generally known to be beneficial to the host) and anti-inflammatory cytokines (cytokines that are generally deleterious to the host), with some cytokines displaying both pro- and anti-inflammatory properties.

**5.1. Proinflammatory Cytokines.** Th1 immunity plays a vital role for protection against TB. In response to Mtb infection,

immune cells produce several proinflammatory cytokines such as TNF $\alpha$ , IFN $\gamma$ , IL-1 $\beta$ , IL-6, IL-12, IL-18, and IL-23, which are involved in killing of the mycobacteria.

**Tumor Necrosis Factor- $\alpha$  (TNF $\alpha$ ).** TNF $\alpha$  is a prototype proinflammatory cytokine which is produced by phagocytic cells activated with mycobacteria or mycobacterial components and plays a key role in host defense against Mtb infection [102]. TNF $\alpha$  is crucial in containment of latent infection in mice granuloma [103] and protects the host from developing active TB. TNF $\alpha$  production is also detected at the site of infection in TB patients [104]. Mice deficient in either TNF $\alpha$  production or TNF $\alpha$  receptor exhibit increased susceptibility to Mtb infection [105, 106]. Mice treated with anti-TNF $\alpha$  antibody or lacking TNF $\alpha$  receptor are more vulnerable to infection with mycobacteria [107, 108]. TNF $\alpha$  secretion by Mtb-infected macrophages stimulates production of RNIs in conjunction with IFN $\gamma$  [109] and promotes apoptosis [110] and thereby induces killing of Mtb.

TNF $\alpha$  is the main cytokine that promotes granuloma formation which contains the infectious foci and thus prevents dissemination [103, 111]. Neutralization of TNF $\alpha$  activity during the latent phase of TB induces reactivation of the disease in C57BL/6 mice and causes severe tissue damage and death [103]. The most significant findings of this study were the apparent loss of granuloma structure and the infiltration of cells throughout the lungs which led to a destructive immunopathology [103]. Clay et al. [112] showed that loss of TNF signaling enhances mortality in *M. marinum* infected zebra fish. The authors also showed that intracellular bacterial growth and granuloma formation were increased in the absence of TNF, which were followed by necrotic death of macrophages and granuloma breakdown. These findings suggest that TNF is not required for granuloma formation but for maintaining the integrity of granuloma structure by limiting bacterial growth inside macrophages and for preventing their necrosis [112]. Treatment with anti-TNF $\alpha$  has also been shown to boost the reactivation of latent TB in patients with Crohn's disease and rheumatoid arthritis [113].

**Interferon- $\gamma$  (IFN $\gamma$ ).** IFN $\gamma$  is a key cytokine that mediates antigen-specific T-cell immunity in response to Mtb infection. *In vitro* expression of mycobacterial antigen-specific IFN $\gamma$  can be a potential substitute marker of Mtb infection [114]. Various immune cells including CD4+ and CD8+ T cells, B cells, NK cells, NKT cells, and antigen presenting cells such as monocytes, macrophages, and DCs produce IFN $\gamma$ . IFN $\gamma$  promotes antigen presentation, recruits CD4+ T-lymphocytes and/or cytotoxic T lymphocytes (CTL), and thereby mediates mycobacterial killing. An *in vitro* study shows that IFN $\gamma$  is capable of inhibiting Mtb growth in mouse but not in human macrophages [115]. GKO mice lacking IFN $\gamma$  show greatest susceptibility to Mtb infection [116]. Exposure to Mtb induces severe infections to individuals defective in IFN $\gamma$  or IFN $\gamma$  receptor gene [117]. However, Mtb is shown to depress IFN $\gamma$  production in patients with active disease [118]. Mtb is also shown to inhibit macrophages from responding adequately to IFN $\gamma$  [119].

Production of IFN $\gamma$  is mostly regulated by two other cytokines such as IL-12 and IL-18 which mediate IFN $\gamma$  production upon infection with Mtb in cellular innate immune response [120, 121]. Upon recognition of mycobacterial ligands, macrophages secrete IL-12 and chemokines (e.g., macrophage-inflammatory protein-1 $\alpha$  (MIP-1 $\alpha$ )). These chemokines recruit NK cells at the infection site where IL-12 and IL-18 promote IFN $\gamma$  production which then exerts protective immune response [122, 123].

*Interleukin-12 (IL-12)*. IL-12 is a proinflammatory cytokine that plays a key role in host defense against Mtb infection. Phagocytic cells produced IL-12 upon phagocytosis of Mtb [124]. IL-12 together with IL-18 induces IFN $\gamma$  production and drives Th1 response that is essential for host defense against Mtb infection. IL-12-deficient mice are at high risk of Mtb infection. IL-12 supplementation to the Mtb susceptible Balb/c mice leads to killing of bacilli at the initial stage of the disease [125]. IL-12 expression is detected in lung infiltrates, pleurisy, and granulomas of patients with active TB [126, 127]. The expression of IL-12 receptors is also increased at the site of infection [128]. IL-12 receptor beta 1 deficiency has also been recognized in a patient with abdominal TB [129]. Deleterious mutations in IL-12 and IL-12 receptor genes have been reported in patients suffering from nontuberculous mycobacterial infections [130, 131]. These patients lacking effective IL-12 and IL-12 receptor show a reduced capacity of IFN $\gamma$  production. In fact, IL-12 exerts its protective roles against mycobacterial infection mainly through induction of IFN $\gamma$ , thus serving as a link between innate and adaptive host immune responses [132].

*Interleukin-18 (IL-18)*. IL-18 is a proinflammatory cytokine, which in synergy with IL-12 induces IFN $\gamma$  production. This cytokine can also induce production of other proinflammatory cytokines, chemokines, and transcription factors [133]. Thus, IL-18 plays a protective role against mycobacterial infections. IL-18 knockout mice show greater susceptibility to BCG and Mtb [134]. Higher expression of IL-18 correlates with resistance in mice against *M. leprae* infection [135]. In fact, both IL-18 and IFN $\gamma$  were expressed in TB pleurisy [136].

*Interleukin-1 $\beta$  (IL-1 $\beta$ )*. IL-1 $\beta$  is a proinflammatory cytokine which is mainly produced by monocytes, macrophages, and DCs [11] and is involved in host immune response to Mtb. IL-1 $\beta$  is expressed at the site of infection in TB patients and is important in Mtb control [137]. Mice unable to respond to IL-1 $\alpha$  and IL-1 $\beta$  display enhanced susceptibility to Mtb infection and induce defective granuloma formation [138, 139]. IL-1 was shown to mediate signals through IL-1 receptor (IL-1R) in response to mycobacterial infection [140]. Mice deficient in MyD88, the common adaptor molecule of TLR/IL-1R receptor family, were shown to be highly susceptible to Mtb infection, suggesting the importance of signaling through this pathway in innate defense against the bacterium [141, 142]. Although the importance of TLR/TLR-ligand interactions is well evidenced in immune response to Mtb, controversy remains on whether MyD88 mediated protection requires the

signaling from TLRs or via cytokine signaling through IL-1R [3, 41, 143]. To examine the particular role of TLR versus IL-1R mediated signals in MyD88 dependent defense against Mtb, Mayer-Barber et al. [144] used Mtb infected MyD88 $^{-/-}$ , TRIF/MyD88 $^{-/-}$ , IL-1R1 $^{-/-}$ , and IL-1 $\beta$  $^{-/-}$  mice and observed that all four groups showed highly increased pulmonary bacterial burden with acute mortality. These observations suggest that MyD88 regulates host protection to Mtb through IL-1 $\beta$ /IL-1R1 signaling rather than TLR-mediated signaling of cytokine production. These findings were further supported by the fact that the absence of IL-1R signal causes impairment in early control of Mtb infection similar to that seen in the absence of MyD88 [145]. The authors also concluded that IL-1/IL-1R mediated signaling is an important element of MyD88 dependent immune response and that IL-1/IL-1R mediated signal might be involved for the most part of MyD88-dependent host response to regulate acute Mtb infection.

*Interleukin-6 (IL-6)*. IL-6 possesses both pro- and anti-inflammatory properties and is produced by phagocytic cells at the onset of mycobacterial infection [137]. IL-6 plays multiple and sometimes seemingly opposing roles in the immune system, including inflammation, hematopoiesis, and differentiation of T cells. IL-6-deficient mice showed enhanced susceptibility during early infection with Mtb where T-cell mediated adaptive immunity is yet to fully develop [146]. On the contrary, IL-6 inhibits the production of protective cytokines such as TNF $\alpha$  and IL-1 $\beta$  and facilitates *M. avium* growth *in vitro* [147].

*Interleukin-23 (IL-23)*. IL-23 is a proinflammatory cytokine and is secreted by activated monocytes, macrophages, and DCs [148]. IL-23 together with IL-12 promotes activation of Ag-specific CD4 $^{+}$  T cells in the draining lymph nodes of Mtb-infected lungs [149]. Mice lacking in both IL-12 and IL-23 are markedly susceptible to infection with Mtb. However, mice deficient in IL-12 alone exhibit a partial compromise of protective immunity to Mtb, which suggests a protective role for IL-23 [150]. In contrast, mice deficient only in IL-23 showed effective control of Mtb infection, suggesting that IL-23 is not crucial for host protection [151]. IL-23 was shown not to be necessary for the early control of Mtb growth; however, it was implicated as an essential element for the control of Mtb growth late in infection as mice deficient in the p19 component of IL-23 (IL23a $^{-/-}$ ) exhibited increased bacterial growth at this stage [152]. IL-23 was also required for the development and maintenance of Th17 responses to Mtb infection [152]. Plasmids encoding both chains of IL-23 and IL-12 were reported to increase the protection induced by a DNA vaccine (namely, DNA85B) against Mtb aerosol challenge [153]. Another study showed that exogenous IL-23 is required for the development of IFN $\gamma$  secreting Th1 cells but not for the development of protective Th17 cells in IL12p40 $^{-/-}$  mice [154]. However, this group in a recent study showed that in the absence of IL-12 and IL-23, both Th17 and Th1 BCG-specific T cells neither were expanded nor provided protection against Mtb [155]. A reduced Th17 response was

observed to be directly correlated with the clinical outcome of Mtb infection, and the frequency of Th17 cells was lower in active TB patients than that of healthy individuals as well as individuals infected with latent TB [156]. Suppression of Th17 responses by inhibiting Th17 cell activation was also found to be associated with the incidence of active TB [157]. Therefore, further studies are needed to justify the role of IL-23 in the development of Th17 responses against Mtb infection.

**5.2. Anti-Inflammatory Cytokines.** Anti-inflammatory cytokines are the immunoregulatory molecules that inhibit cell activation and the induction of proinflammatory cytokines and thus counter the inflammatory process. These cytokines act mainly by inhibiting the production of proinflammatory cytokines or by opposing their biological effects. By the same token, overexpression of anti-inflammatory cytokines or dysregulation of their expression may compromise protection afforded by the proinflammatory cytokines. IL-4, IL-10, and TGF- $\beta$  are the major anti-inflammatory cytokines secreted by immune cells.

**Interleukin-4 (IL-4).** IL-4 is an anti-inflammatory cytokine which causes deleterious effects in TB causing deactivation of macrophage and suppression of IFN $\gamma$  production [158]. IL-4 in association with IL-13 can impair macrophage function by inducing alternative activation which causes downregulation of TLR2 and TNF and increases soluble TNF receptors, DC-SIGN, and IL-10 production [159–163]. IL-4 can be considered as a potential marker for active TB as it is expressed in high levels in TB patients especially in the tropics [164–166]. Overexpression of IL-4 induces progressive disease [167] and reactivation of latent infection [168] in mice infected with Mtb. Increased production of IL-4 has also been detected in TB patients, especially those with cavitory disease [169].

**Interleukin-10 (IL-10).** IL-10 is an anti-inflammatory cytokine which is produced by macrophages and T cells upon infection with Mtb. IL-10 deactivates macrophage function [170] by downregulating IL-12 and TNF $\alpha$  expression, which in turn reduces production of IFN $\gamma$  by T cells and thus aids in Mtb survival. IL-10 inhibits CD4+ T cell responses and opposes antigen presentation by cells infected with mycobacteria [171]. IL-10 impairs macrophage function in transgenic mice infected with mycobacteria and causes them to be susceptible to the infection [172]. Although CD8+ T cells are generally thought to provide protection against Mtb infection, IL-10 secreting phenotype of CD8+ T cells may occur during chronic infection which causes the cells to display a dysfunctional and immunosuppressive response [173]. IL-10 inhibits phagosome maturation, which in turn facilitates Mtb survival and disease outgrowth [174]. IL-10 also inhibits IFN $\gamma$  mediated activation of macrophages which leads to decreased secretion of ROIs and RNIs and thus impairs intracellular Mtb killing mechanisms [175–177]. Moreover, IL-10 was also shown to limit antigen presentation by downregulating major histocompatibility complex molecules [177]. DCs process mycobacterial antigens to carry them to draining lymph nodes in an IL-12p40 dependent mechanism, which was shown to be retarded by IL-10 [178]. DCs mediate T-cell

differentiation and promote recruitment of Th1 cells to the lungs of Mtb infected mice which were suggested to be restricted by the inhibitory effect of IL-10 on the production of the chemokine CXCL10 [179]. Neutralization of endogenous IL-10 in peripheral blood mononuclear cells (PBMC) of pulmonary TB patients enhanced T-cell proliferation and IFN $\gamma$  production [180]. Elevated levels of IL-10 and TGF- $\beta$  were found in bronchoalveolar lavage fluid and comprised mainly macrophages and neutrophils, in pulmonary TB patients [181]. Increased levels of IL-10 and Mtb antigen CFP32 were observed in the sputum of pulmonary TB patients suggesting a positive correlation between IL-10 and the progression of disease [182]. Overexpression of IL-10 by CD4+ T-cells in transgenic mice causes them to be more susceptible to *M. bovis* BCG and Mtb [172, 183]. Blocking of IL-10R signaling with anti-IL-10R monoclonal antibody during chronic infection boosts T-cell recruitment in the infection site and increases T-cell mediated IFN $\gamma$  production, thereby providing enhanced protection with reduced bacterial loads [184]. Treatment of Mtb infected IL-10<sup>-/-</sup> mice with anti-IL-10R monoclonal antibody leads to reduce bacterial burdens compared to the control counterparts [179]. Moreover, IL-10<sup>-/-</sup> mice were also shown to have increased level of protection against nontubular mycobacterial infections, such as *M. avium* and BCG [185, 186]. However, the role of IL-10 in TB remains controversial. IL-10<sup>-/-</sup> mice were shown to have similar bacterial loads in the lung and enhanced levels of IFN $\gamma$  production during early infection compared to wild type control mice, though the elevated IFN $\gamma$  failed to provide any additional protection [187, 188]. On the light of the above discussion, it can be concluded that IL-10 downregulates host Th1 immune responses and thereby favors mycobacterial infection.

**Transforming Growth Factor- $\beta$  (TGF- $\beta$ ).** Like IL-4 and IL-10, TGF- $\beta$  is also an anti-inflammatory cytokine that counteracts protective immunity in TB. Upon stimulation with Mtb ligands, human monocytes and DCs produce TGF- $\beta$  which is found in the granulomatous lesions of TB patients [189, 190]. TGF- $\beta$  exerts various anti-inflammatory effects that include inhibition of macrophage-mediated production of ROI and RNI [191], suppression of T cell proliferation [192], interference with NK and cytotoxic T lymphocyte function, and downregulation of proinflammatory cytokine release [193]. Addition of TGF- $\beta$  in coculture of mononuclear phagocytes and Mtb causes inhibition of phagocytosis and facilitates Mtb growth in a dose-dependent manner [189]. Inhibitors of TGF- $\beta$  abolish the anti-inflammatory effects of the cytokine and thereby protect the host from Mtb infection [194].

Thus like PRRs, the balance of various cytokine production may influence the outcome of infection and disease progression.

**5.3. Type I Interferons: Friend or Foe?** Type I IFNs are a group of cytokines that mainly include multiple forms of IFN $\alpha$  and one IFN $\beta$ , which mediate signals through a common receptor (IFN- $\alpha/\beta$  receptor (*Ifnar*)). Type I IFNs are generally associated with innate immune response to viral infection.

However, the innate immune response of type I IFNs can also be induced by bacterial infections [195].

The role of type I IFNs in TB is not completely understood. In contrast to the well-known role of type II IFN (IFN $\gamma$ ) in the immune control of TB, type I IFNs are reported to promote rather than to control Mtb infection. Monocytes of patients with active but not latent TB produce type I IFN. Furthermore, transcriptional activities of leukocytes induced by type I IFNs were observed in active but not latent infection. These findings are suggestive of type I IFN to be involved directly in causing active TB [196, 197]. TPL2-ERK1/2 signaling pathway mediates host protection against Mtb infection through negative regulation of type I IFN production [198]. An increased level of type I IFNs was produced in the absence of TPL2 which promoted IL-10 production and exacerbated disease [198]. However, a recent study showed that type I IFNs play a nonredundant protective role against TB. Mice deficient in both type I and type II IFN receptors (Ifnar<sup>-/-</sup>Ifngr<sup>-/-</sup>) showed more severe lung histopathology and died significantly earlier than did mice with impaired type II IFN signaling (Ifngr<sup>-/-</sup>) alone [195]. Type I IFNs showed beneficial effect against pulmonary TB [199] and have been suggested to be used as a potential therapy against infections with MDR strains [200] or in patients lacking IFN $\gamma$  receptor [201]. However, IFN $\alpha$  treatment in a patient with viral hepatitis was found to upregulate the severity of TB [202]. Redford et al. [203] showed that type I IFN signaling leads to the enhancement of mycobacterial growth in mice coinfecting with influenza A virus and Mtb.

Type I IFNs also display both useful and harmful effects during mycobacterial infections *in vitro*. Type I IFNs impair normal macrophage function and promote BCG growth in human macrophages [204], whereas IFN $\beta$  inhibits growth of BCG by increasing human DC maturation [205]. Mtb-induced type I IFNs can selectively limit the production of IL-1 $\beta$  in human macrophages, thus promoting TB infection [206]. These controversies are probably due to the fact that type I IFNs act differently on distinct cell types [207]; hence more extensive *in vivo* investigation may need to be carried out to further delineate their function. Type I IFNs also show distinct effects in response to infection by different strains of mycobacteria. IFN- $\beta$  increases the resistance of mice to *M. avium* infection [208], whereas mice infected with the virulent Mtb HN878 strain become vulnerable by intranasal treatment with IFN- $\alpha/\beta$  [209]. A recent study also showed that different strains of Mtb result in distinct profile of IFN- $\beta$  production by bone marrow derived macrophages during infection [30]. Type I IFNs are able to control early infection with BCG in Ifnar<sup>-/-</sup> mice [210], but late infection with the Mtb HN878 strain [211]. This time-dependent relationship between type I IFNs and their overlapping biological activities requires further investigation.

The role of type I IFNs as pro- or anti-inflammatory effectors is still uncertain. It is assumed that type I IFNs demonstrate anti-inflammatory effects when IFN $\gamma$  is present in abundance during TB. Type I IFNs inhibit inflammasome activation and thereby inhibit inflammasome-mediated IL-1 $\beta$  production [212]. In addition, type I IFNs activate signal

transducers and activators of transcription 3 (STAT3) which in turn inhibits STAT1-dependent gene activation and thereby downregulates the activities of immune inflammatory mediators in myeloid cells [213]. Type I IFNs-activated STAT3 also induces IL-10 production and intensifies anti-inflammatory responses [213]. Finally, the ubiquitous presence of both type I and type II IFN receptors implies that many cell types can respond to these cytokines but with distinct outcomes.

## 6. Concluding Remarks

We have gained a better understanding of innate immune mechanisms with the discovery of TLRs at the end of last century. TLRs are largely involved in mycobacterial uptake which initiates a signaling pathway to trigger production of innate immune effector molecules, cytokines, and chemokines. These molecules dictate the innate immune system, initiate the adaptive immune response to Mtb, and finally mediate Mtb growth arrest or killing. The non-TLRs-mediated or TLR independent mechanisms of Mtb phagocytosis have also been shown to induce protective innate immune response to mycobacteria and subsequently initiate adaptive immune defense. Both innate and adaptive immunity are synergistic in biological systems and exert protective response against invading pathogen. Therefore, both innate and adaptive immune responses are important and have pivotal roles in host defense against mycobacteria. However, there still remain some fundamental issues to be answered regarding the innate immune responses to Mtb.

One such issue is how Mtb is able to evade innate immune defense mechanisms. Mtb can maintain intracellular growth inside the phagosome by inhibiting phagolysosome formation. Recognition of PRRs and the consequent innate immune response in killing Mtb is well reported, but the reasons why it fails to restrict Mtb growth and infection remain incompletely understood. Further studies are thus needed to elucidate why some people develop active TB upon infection while others do not.

Another vital concern in TB is the latent infection and its reactivation. It is believed that innate immunity is primarily needed to restrict Mtb growth in the initial phase of infection. After inhalation, alveolar resident macrophages engulf Mtb bacilli, where it faces a series of immunological events and the immune machinery finally provides protection to the host. However, this protection sometimes leads to latent infection by containment of mycobacteria within granulomas, which may reactivate in immunocompromised individuals. However, the role of innate immune systems in latency and in reactivation is still poorly understood. Therefore, a precise understanding of the innate immune response to Mtb infection is crucial to design novel vaccination strategies that can enhance preexisting immunity or can prevent reactivation of latent TB.

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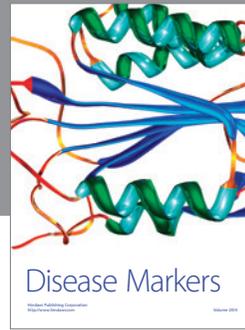
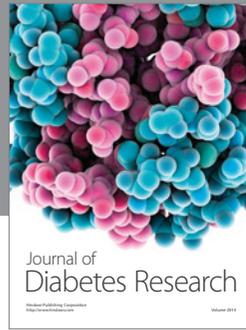
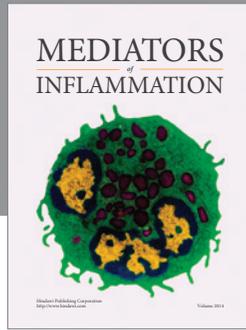
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