Molecular Immunology 87 (2017) 240–248

Contents lists available at ScienceDirect

Molecular Immunology

journal homepage: www.elsevier.com/locate/molimm

Review

Pattern recognition receptors and coordinated cellular pathways involved in tuberculosis immunopathogenesis: Emerging concepts and perspectives

Abhishek Mishra[a], Shamim Akhtar[b], Chinnaswamy Jagannath[c], Arshad Khan[c,*]

[a] Department of Biotechnology, Goa University, Taleigao Plateau, Goa, 403206, India
[b] Department of Microbiology, Dr. D.Y. Patil College of Arts Commerce and Science, Saint Tukaram Nagar, Pimpri, Pune, 411018, India
[c] Department of Pathology and Laboratory Medicine, McGovern Medical School, University of Texas Health Sciences Center-Houston, Houston, TX, 77030, USA

ARTICLE INFO

Keywords:
Pattern recognition receptors
Innate sensing
Immune response
Autophagy
Phagosome maturation
Antigen presentation

ABSTRACT

Pattern Recognition Receptors (PRRs) play a central role in the recognition of numerous pathogens, including *Mycobacterium tuberculosis*, resulting in activation of innate and adaptive immune responses. Besides Toll Like Receptors, C-type Lectin Receptors and Nod Like Receptors are now being recognized for their involvement in inducing immune response against *M. tuberculosis* infection. Although, a functional redundancy of the PRRs has also been reported in many studies, emerging evidences support the notion that a cooperative and coordinated response generated by these receptors is critical to sustain the full immune control of *M. tuberculosis* infection. Many of the PRRs are now found to be involved in various cellular host defenses, such as inflammasome activation, phagosome biogenesis, endosomal trafficking, and antigen processing pathways that are all very critical for an effective immune response against *M. tuberculosis*. In support, polymorphism in several of these receptors has also been found associated with increased susceptibility to tuberculosis in humans. Nonetheless, increasing evidences also show that in order to enhance its intracellular survival, *M. tuberculosis* has also evolved multiple strategies to subvert and reprogram PPR-mediated immune responses. In light of these findings, this review analyzes the interaction of bacterial and host factors at the intersections of PRR signaling pathways that could provide integrative insights for the development of better vaccines and therapeutics for tuberculosis.

1. Introduction

Pattern Recognition Receptors (PRRs) are a family of receptor proteins through which mammalian cells sense the microbial infection by recognizing distinct molecular patterns associated with pathogens. Although, PRRs are one of the components of innate immune system and have been thought firstly to play a role in early host defense against invading pathogens, emerging evidences supports the notion that PRRs also play a crucial role in the initiation of adaptive immune response (Akira et al., 2006; Iwasaki and Medzhitov, 2015; Palm and Medzhitov, 2009). This is also based on the fact that activation of the innate immune system is a prerequisite for the induction of acquired immunity. A coordinated response of cells of innate and adaptive immune system is known to play a vital role in controlling the infection caused by *Mycobacterium tuberculosis* (O'Garra et al., 2013). Several PRRs, including Toll Like Receptors (TLRs), C-type Lectin Receptors (CLRs), Nucleotide oligomerization domain Like Receptors (NLRs), Dendritic Cell-Specific Intercellular adhesion molecule Grabbing Nonintegrin (DC-SIGN), Fc receptor, Mannose Receptor (MR) and Scavenger Receptors have been shown to mediate the recognition of *M. tuberculosis* (Killick et al., 2013; Stamm et al., 2015). However, the role of various PRRs in initiating innate and adaptive immune responses during *M. tuberculosis* infection is rather ambiguous. Within TLR family of PRRs, only TLR2 and TLR4 have been extensively studied and implicated in controlling the disease based on the evidences of increased bacterial burden and inflammation in lungs of mice deficient for these two receptors (Drennan et al., 2004; Heldwein et al., 2003). Mice deficient for MyD88 (an adaptor molecule required for TLR2 and TLR4 signaling) though could still acquire adaptive immune response against the pathogen, which suggested that other PRRs that employ MyD88 independent signaling could be involved during *M. tuberculosis* infection (Fremond et al., 2004). In order to better define the immune mechanisms and components critical for protection against tuberculosis (TB), signaling pathways of many more surface associated and intracellular PRRs that could be involved during *M. tuberculosis* infection have been dissected, in more recent time. It is also becoming clearer that the redundancy observed in PRRs functions may only be partial and a cooperation and coordination of immune response initiated by multiple PRRs assists in effective control of *M. tuberculosis* (Bafica et al., 2005; Court et al., 2010; Ferwerda et al., 2005; Trinchieri and Sher,

* Corresponding author.
E-mail addresses: arshubio@gmail.com, Arshad.Khan@uth.tmc.edu (A. Khan).

http://dx.doi.org/10.1016/j.molimm.2017.05.001
Received 21 February 2017; Received in revised form 28 April 2017; Accepted 1 May 2017
Available online 14 May 2017
0161-5890/ Published by Elsevier Ltd.

2007).From the inclusive analysis of mechanisms and molecules involved in various PRR mediated signaling, it has emerged that activation of many cellular processes such as apoptosis, antigen processing/presentation, inflammasome activation, phagosome maturation and autophagy are linked with stimulation of certain PRRs. Elucidation of molecular machinery involved in various PRR signaling and their crosstalk with key cellular processes critical for innate and adaptive immunity, has provided a closer insight about the mechanism through which multiple PRRs could orchestrate a successful protection against TB. Nonetheless, newer mechanisms that *M. tuberculosis* could employ to inhibit some of the PRR signaling mechanisms, have also been identified in recent time. This review first provides an updated illustration of the signaling pathways orchestrated by all PRRs that have been implicated in TB immunopathogenesis. PRR associated molecular and cellular events that are targeted by *M. tuberculosis* for immune evasion have also been analyzed to identify the critical bacterial and host components of therapeutic interest.

2. Current overview of pattern recognition receptors and mediated cellular processes implicated in immunity against *M. tuberculosis*

2.1. Toll like receptors

M. tuberculosis is known to produce several molecules that can activate mammalian PRRs during infection. Many of the mycobacterial cell wall components including Lipomannan (LM), Lipoarabinomannan (LAM) and Phosphatidyl-myo- inositol mannoside (PIM) are associated with activation of surface associated TLRs;TLR1, TLR2, TLR4, and TLR6 (Quesniaux et al., 2004). Non cell wall component of *M. tuberculosis*, such as lipoproteins, have also been found to ligate with certain TLRs (TLR2/1/6). While some mycobacterial cell wall ligands can activate an individual TLR, others may require cooperation between 2 different TLRs. For instance, di-acylated lipoproteins require heterodimer of TLR2 and 6 whereas tri-acylated lipoproteins require a heterodimer of TLR1 and TLR2 to stimulate the signaling downstream (Morr et al., 2002).

One of the most common downstream signaling used by many TLRs (TLR1/2, TLR2/6 and TLR4) after ligation with agonists, starts with binding of the adaptor protein MyD88 (Myeloid Differentiation protein 88) to the cytoplasmic TIR (Toll Interleukin Receptor) domain of TLRs, followed by recruitment of IL-1 receptor-associated kinases (IRAK4, 1 & 2), TNF receptor-associated factor (TRAF) 6, B cell lymphoma protein 10 (Bcl-10) and Mucosa-associated lymphoid tissue lymphoma translocation protein (1MALT1) in a protein complex. This complex further recruits TGF-β activated protein kinase 1 (TAK1), TAK1 binding protein (TAB) 2 & 3 to activate NF-κB (Nuclear Factor-κB) essential modulator (NEMO) and MAP kinase kinases (MKKs). NEMO and MKKs mediated signaling further downstream leads to nuclear translocation of transcription regulators NF-κB and Activator protein 1(AP1) respectively, which separately regulate expression of many pro-inflammatory cytokines (Akira and Takeda, 2004; Kawai and Akira, 2010). TLR4, on the other hand can transduce the signals independent of MyD88 as well. TLR4 signaling through MyD88 independent pathway involves another adaptor called Toll-interleukin-1 receptor containing adaptor inducing IFN-β (TRIF), which is also known as TIR containing adaptor molecule-1 (TICAM-1). TRIF dependent signaling through TLR4 is mediated by IRF (Interferon Regulatory Factor) 3 and leads to the activation of IFN-β inducible genes which can regulate the production of many pro-inflammatory cytokines (Fig. 1). Signaling through TLR1, TLR2, TLR4, and TLR6 has been demonstrated to occur during *M. tuberculosis* infection as evidenced by ligation of various mycobacterial cell wall components with these receptors and their essentiality for infection control (Krutzik and Modlin, 2004; Nicolle et al., 2004).

Nonetheless, redundant function of some of the TLRs during *M. tuberculosis infection* has also been suggested in other studies. In a low dose aerosol based infection model of tuberculosis, mice deficient for TLR2 as well as TLR4 were able to resist *M. tuberculosis* infection in a manner similar to congenic wild type mice (Reiling et al., 2002). Immunopathological events such as secretion of pro-inflammatory cytokines, granuloma formation and macrophage activation in response to low-dose infection was found identical in mutant and control mice. Remarkably, during high dose aerosol challenge, TLR2 mutant mice were found susceptible to *M. tuberculosis* infection but not TLR4 defective mice. A later study also revealed that not only TLR2 and TLR4, but TLR9 was also not essential for induction of immunity against *M. tuberculosis* infection in mice (Hölscher et al., 2008). Post aerosol infection, both TLR2/4/9-deficient and wild-type mice were able to express pro-inflammatory cytokines secreting antigen-specific T cells and could produce IFN-γ, inducible nitric oxide synthase and anti-microbial peptide LRG-47 in infected lungs to similar extents. Even MyD88 deficient mice were able to express pro-inflammatory cytokines and expand IFN-γ producing antigen-specific T cells, though in a delayed fashion. However, mice that were deficient for MyD88, rapidly succumbed to unrestricted mycobacterial growth, whereas TLR2/4/9-deficient mice were able to control *M. tuberculosis* replication. These evidences suggest that during *M. tuberculosis* infection, neither TLR2/TLR4/TLR9 nor MyD88 might be required for the induction of adaptive T cell responses. Rather, MyD88, but not TLR2, TLR4 and TLR9, is critical for initiating macrophage effector mechanisms for anti-mycobacterial defense. It was also discovered later that post *M. tuberculosis* infection, expressions of IL-12, TNF-α, IFN-γ, and nitric oxide synthase 2 were markedly decreased in the MyD88 knockout mice compared to wild type (Scanga et al., 2004). Thus it could be perhaps contended that some of the TLRs may be redundant for protection against *M. tuberculosis* and resistance to this pathogen may also depend on MyD88-dependent signals that are mediated by other PRRs or through a combination of them. In humans as well, the critical role of surface TLRs; TLR1, TLR2, TLR4 and TLR6 in immunity against *M. tuberculosis* could be gauged from the association of polymorphisms in these genes and susceptibility to TB (Dittrich et al., 2015; Guo and Xia, 2015; Najmi et al., 2010; Randhawa et al., 2011).

Endosomal TLRs, TLR7/8 and TLR9 transduce signal in a MyD88 dependent manner, involving activation of NEMO as well as IRF7 downstream, which results in production of pro-inflammatory cytokines and INF-α respectively (Fig. 1). Since mycobacterial RNA/DNA must remain accessible to endosomes, TLR7 and TLR9, activated by ssRNA and CpG DNA, have been suggested to be stimulated as well during *M. tuberculosis* infection. An indirect evidence of involvement of TLR9 comes from the effective cooperation of this endosomal receptor with surface receptors TLR2 to regulate the Th1 responses in pursuit of optimal resistance against *M. tuberculosis* (Bafica et al., 2005). A clear association between polymorphism in TLR8 and TLR9 gene regions and susceptibility to pulmonary TB has also been reported in earlier studies, which further indicate the importance of endosomal TLRs in protection against *M. tuberculosis* infection (Davila et al., 2008; Graustein et al., 2015; Torres-García et al., 2013). In a more recent report, demonstration of increased antigen presentation by mouse macrophages when agonist of TLR7 and TLR9 were added externally as adjuvants with BCG, suggest that signaling through these endosomal PRRs by mycobacteria may remain inhibited or compromised during the normal course of infection (Bakhru et al., 2014). The exact mechanism through which TLR7 and TLR9 signaling induce antigen presentation remains to be understood though. Induction of autophagic pathways by endosomal TLRs have been reported during mycobacterial as well as other intracellular infection, and autophagy mediated increased phagosome maturation has been suggested as one possible mechanism through which antigen processing is enhanced (Crotzer and Blum, 2009; Delgado et al., 2008; Kuchtey et al., 2005). Autophagy, which is a specific biological process involved in maintaining homeostasis through the degradation of long-lived cellular proteins and organelles has been demonstrated to be induced by TLRs, resulting in enhanced phagosome

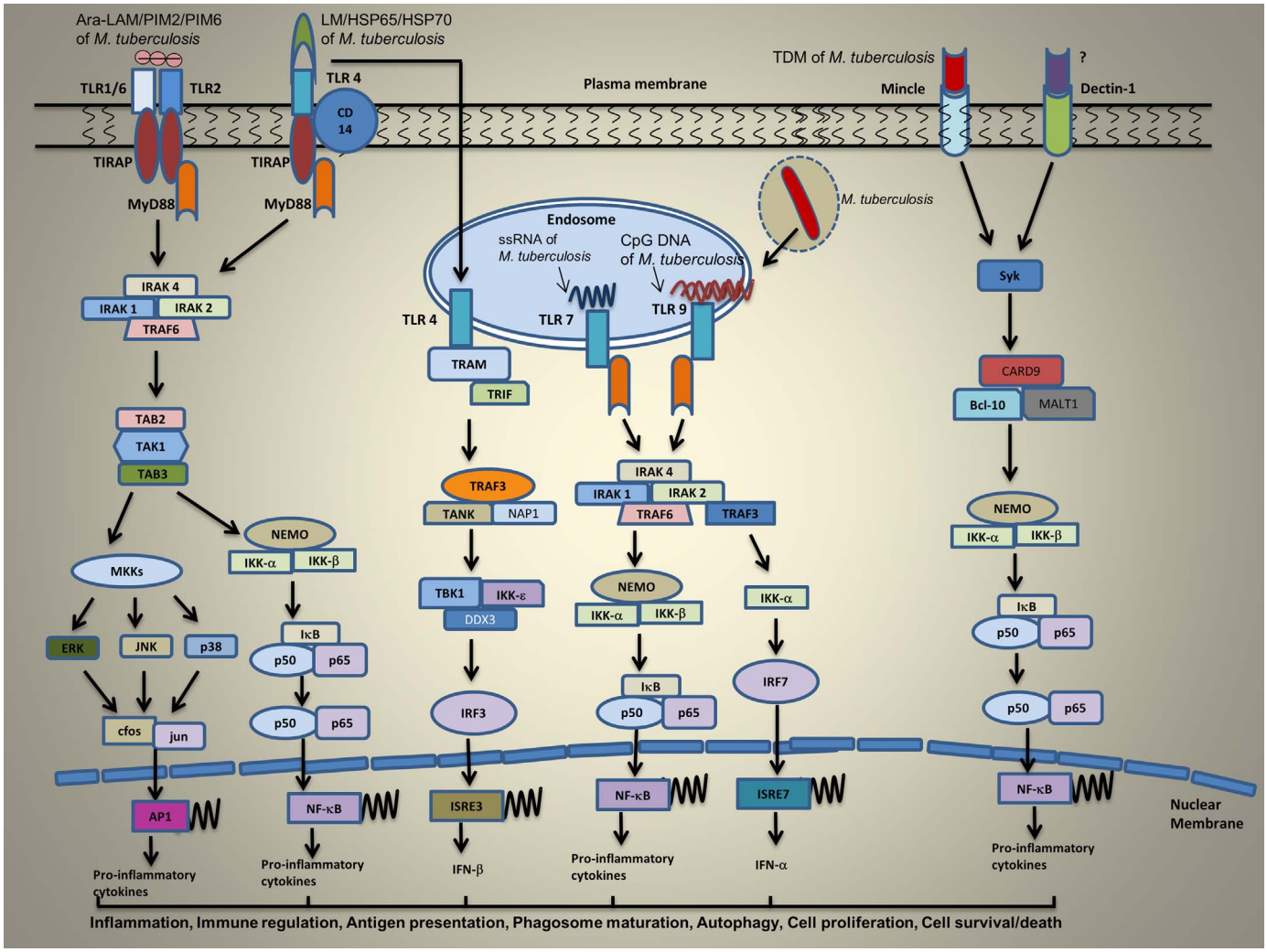

Fig. 1. A schematic representation of PRR signaling pathways activated during *M. tuberculosis* infection.Binding of mycobacterial ligand Ara-LAM/PIM2/PIM6 of *M. tuberculosis* to TLR 1 and 2 or 2 and 6 stimulates MyD88 dependent signaling cascade which eventually results in AP1 and NF-κB mediated secretion of pro-inflammatory cytokines (Quesniaux et al., 2004; Akira and Takeda, 2004; Kawai and Akira, 2010). Mycobacterial ligands of TLR4 such as Lipomannans/HSP65/HSP70 on the other hand induce signaling via MyD88 as well as MyD88 independent pathways by utilizing different adaptor molecules downstream. While MyD88 dependent signaling by TLR4 leads to secretion of AP1 and NF-κB mediated pro-inflammatory cytokines, MyD88 independent signaling of the same receptor on endosome results in secretion of IRF3 mediated type 1 interferon IFN-β. Endosomal TLR7 and TLR9 that respectively recognize ssRNA and CpG DNA of *M. tuberculosis* induce NF − κB mediated secretion of pro-inflammatory cytokines as well as IRF7 mediated IFN-α cytokine. Cell surface associated C type lectin receptors, Mincle and Dectine-1 upon respective recognition by TDM and unknown ligand of *M. tuberculosis*, lead to Syk and CARD9 mediated secretion of pro-inflammatory cytokines via NF-κB (Schoenen et al., 2010; Yadav and Schorey, 2006). **Abbreviations:** *Ara-LAM-Arabinosylated lipoarabinomannan; PIM- Phosphatidyl-myo-inositol mannoside; HSP- Heat shock protein; JNK-Jun amino-terminal kinases; ERK-Extracellular signal–regulated kinases; TANK- TRAF family member-associated NF-kappa-B activator; TBK1-TANK binding kinase1; NAP1-NAK/TBK-associated protein 1; IKK- I κB kinase; IκB- Inhibitor of NF-κB; ISRE- Interferon-sensitive response element; Syk- Spleen tyrosine kinase.*

maturation and antigen presentation during *M. tuberculosis* infection (Bento et al., 2015; Oh and Lee, 2014). TLR2/1/CD14 stimulation by Mycobacterial lipoprotein LpqH is also known to induce autophagy by triggering AMPK-p38 MAPK pathways via activating Vitamin D receptor and regulating Phosphoinositide 3-kinase class3 (PI3KC3) (Shin et al., 2010) (Fig. 1). Altogether, review of many studies and meta-analysis of the data clearly suggest significant associations between polymorphisms of several surface as well as endosomal TLRs and susceptibility to TB (Schurz et al., 2015; Sun et al., 2015; Thada et al., 2013).

2.2. Nod like receptors and cytosolic receptors

Lately importance of cytosolic receptors has also been recognized for their contribution in both innate and adaptive immune responses against TB. Individuals homozygous for the 3020insC NOD2 mutation, showed an 80% defective cytokine response after stimulation with *M. tuberculosis* bacilli, which underscores the importance NOD2 in host defense against the pathogen (Ferwerda et al., 2005). The signaling pathway of NOD2 is illustrated in Fig. 2. Cooperation between TLR2 and NOD2 was also observed for induction of pro-inflammatory cytokine response, and this synergism was abrogated in cells defective for either TLR2 or NOD2. This also demonstrated that TLR and NOD2 pathways are non-redundant mechanisms of *M. tuberculosis* recognition and host defense. Studies later on have extended the biological activity of NOD2 to include the induction of autophagy as well as in mediating direct T cell activation during *M. tuberculosis* and other viral infections (Shaw et al., 2011). NOD2-mediated autophagy was essential for both bacterial control and generation of major histocompatibility complex (MHC) class II antigen-specific CD4+ T cell response in Crohn's disease, which is now being associated with mycobacterial infections (Cooney et al., 2010; Greenstein, 2003). NOD2-induced autophagy was not dependent on NF-κB signaling but required interaction between NOD2 and a known autophagy protein, ATG16L1 (Travassos et al., 2010). Polymorphisms in NOD2 and ATG16L1 were also found associated with defective autophagy, bacterial killing, antigen presen-

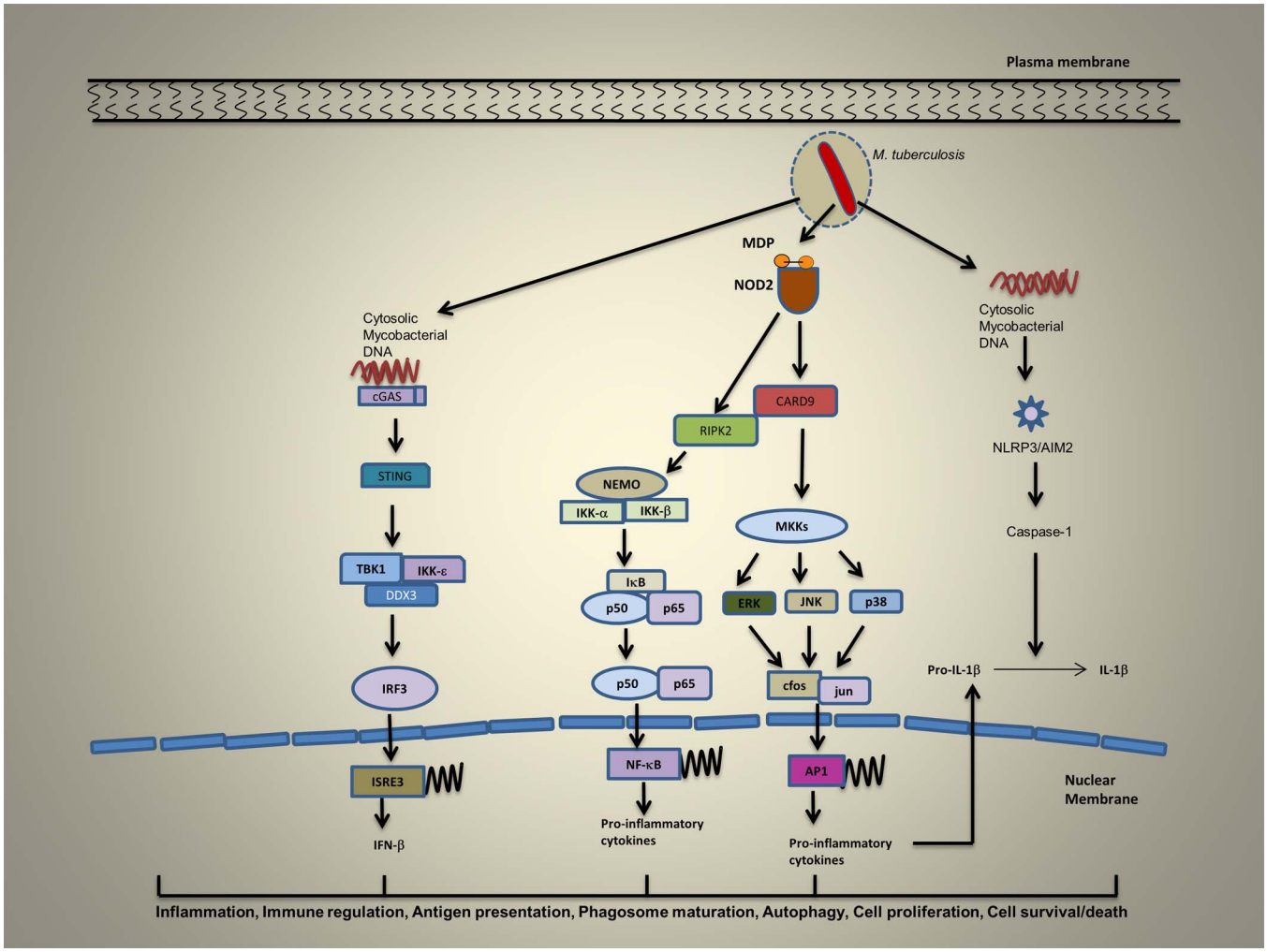

Fig. 2. A schematic representation of cytosolic PRR; NOD2, cGAS and Inflammasome signaling pathways activated during *M. tuberculosis* infection.Cytosolic receptor NOD2 which recognizes MDP of *M. tuberculosis* also utilizes the CARD9 dependent signaling but activates AP1 as well as NF-κB mediated pro-inflammatory cytokine secretion pathways (Caruso et al., 2014). Cytosolic DNA of *M. tuberculosis* could be recognized by cGAS/STING which stimulates IRF3 mediated secretion of IFN-β (Wassermann et al., 2015; Watson et al., 2012)· Cytosolic presence of *M. tuberculosis* DNA also activates the assembly of NLRP3 and AIM2 inflammasomes, which results in caspase-1 dependent maturation of pro-inflammatory cytokine IL-1β (Mishra et al., 2010; Shah et al., 2013)· **Abbreviations:***CARD9- Caspase recruitment domain-containing protein 9; RIPK2- Receptor-interacting serine/threonine-protein kinase 2; MDP-Muramyl dipeptide.*

tation in host DCs and increased risk for Crohn's disease (Homer et al., 2010). Polymorphism in some of the cytosolic and surface PRRs has also been found associated with altered immune response against leprosy, which is caused by *M. leprae*, a close relative of *M. tuberculosis* (Berrington et al., 2010; Kang and Chae, 2001; Kang et al., 2002). These evidences suggest an apparent link between PRR signaling, autophagy and antigen presentation which may prove to be valuable information in context of mechanisms of immune response against Mycobacterial infections.

In more recent past, other cytosolic PRRs have also been discovered to be involved in recognition of *M. tuberculosis* and induction of specific immune responses subsequently. Limited perforation of the phagosome membrane mediated by the ESX-1 secretion system of *M. tuberculosis* has been shown to allow the access of bacterial DNA and RNA to cytosolic nucleic acid sensors (Manzanillo et al., 2012). The host protein STING (Stimulator of interferon genes) was identified as a central signaling molecule involved in sensing unique bacterial dsDNA/cyclic dinucleotides, and upon activation induced signaling through the TBK1/IRF3 pathway to produce type 1 interferon IFN-β (Fig. 2). Type I IFN selectively have been reported to limit the production of IL-1β during *M. tuberculosis* infection (Novikov et al., 2011). The regulation of IL-1β through Type I interferon was found to occur at mRNA level and this mechanism was preferentially utilized by virulent mycobacteria. Since IL-1β is a critical pro-inflammatory cytokine, inhibition of its production through STING activation dependent type 1 interferon secretion could help in survival of *M. tuberculosis*. Irf3(-/-) mice, unable to respond to cytosolic DNA, were more resistant to long-term *M. tuberculosis* infection, indeed suggest that production of type 1 IFNs may promote *M. tuberculosis* infection (Manzanillo et al., 2012). Contrary to that however, recognition of extracellular mycobacterial DNA by the STING-dependent cytosolic pathway was demonstrated to assist in marking bacteria with ubiquitin, for delivery of bacilli to autophagosomes via ubiquitin-autophagy receptors p62 and NDP52 and the DNA-responsive kinase TBK1 (Watson et al., 2012). More recently it was also demonstrated that the cytosolic DNA sensor cyclic GMP-AMP synthase (cGAS) could also essentially initiate the recognition of cytosolic *M. tuberculosis* DNA which then engages STING as a secondary receptor (Wassermann et al., 2015). These results thus suggest that activation of cytosolic DNA sensing pathways lead to ubiquitin-mediated targeting of *M. tuberculosis* to autophagic process, which is known to play a critical role in generating immune response as well as resistance to *M. tuberculosis* infection.

Inflammasomes, that belong to NLR/ALR family of PRRs, have also been implicated in triggering immune responses against *M. tuberculosis* (Koo et al., 2008). Activation of NLRP3 (NACHT, LRR and PYD domains-containing protein 3) inflammasome through ESAT-6 of *M.*

tuberculosis leads to activation of caspase-1 and increased expression of IL-1β in human macrophages (Mishra et al., 2010). Via using IL-1α/β and IL-1R knockout (KO) mice, importance of pro-inflammatory function of IL-1β has been shown to be critical in limiting bacterial burden in the lung, regulating the subsequent expression of other cytokines and formation of granulomas (Bourigault et al., 2013; Sugawara et al., 2001).

Apart from regulation of cytokine production, autophagy, antigen presentation and inflammasome formation, maturation of bacteria containing phagosome has also been associated with PRR signaling. Modulation of phagosome biogenesis and maturation is one of the vital survival strategy employed by *M. tuberculosis* within macrophages (Fratti et al., 2003). It has been shown that fusion of phagosome with lysosome is accelerated by PRR signaling based on the evidences that it took much longer for phagolysosome formation and degradation of *M. tuberculosis* by macrophages which lacked either TLR2/4 or MyD88 compared to macrophages having functional TLR2/4 and MyD88 pathway (Blander and Medzhitov, 2004). Furthermore, the maturation of phagosomes in cells undergoing apoptosis was found slower compared to the cells infected with bacteria, which indicated that the presence of TLR signaling helps the acceleration of phagosome maturation. Morphological evidence suggests that lysosomes dock onto TLR or MyD88 deficient macrophages but do not fuse efficiently with them possibly due to the blockage in membrane addition. The fusogenic properties and biochemistry of bacterial phagosomes need to be studied in details to know how exactly PRR signaling helps in fusion of phagosomal and lysosomal membranes. It was also found in the subsequent studies that activation of p38 mitogen- activated protein (MAP) kinase that is essential of downstream signaling of many PRRs is needed for accelerated phagosome maturation during *M. tuberculosis* infection. One of the substrates for p38 is rab guanine nucleotide dissociation inhibitor (GD1), which becomes activated when phosphorylated by p38 (Vergne et al., 2004). Rab GD1 consequently controls the balance of membrane bound and soluble pool of rab (Ras related protein) 5 and rab7, that are key regulators of the endocytic pathways. The evidence of reduced uptake of bacteria in macrophages lacking TLR or MyD88, also supports the notion that TLR signaling is required for efficient phagocytosis and maturation of phagosome (Blander and Medzhitov, 2004). Th1 type pro-inflammatory cytokines TNF-α and IFN-γ produced due to activation of certain PRRs are also known to assist phagosome maturation process via induction of autophagy whereas Th2 cytokines IL-10 resulted in blockage of phagosome maturation in *M. tuberculosis* (Chauhan et al., 2015; Harris et al., 2008; O'Leary et al., 2011). NLRP3 inflammasome mediated production of IL-1β, has also been shown to enhance maturation of *M. tuberculosis* containing phagosomes in macrophages, though the mechanism remains unclear (Master et al., 2008). Thus, it could be suggested from above evidences that in addition to driving the long term transcriptional programs associated with macrophages and dendritic cells (DC) activation, selective PRR signaling also modulates phagosome maturation.

2.3. C-type lectin receptors

Mincle, a C-type lectin receptor, which is predominantly expressed on macrophages, has also been suggested as key PRR for defense against invading *M. tuberculosis*. Trehalose-6,6′-dimycolate (TDM), which is the most abundant glycolipid in the mycobacterial cell wall and a major mycobacterial virulence factor, is known to specifically ligate with Mincle (Ishikawa et al., 2009). Signaling through Mincle occurs via activation of CARD9–Bcl10–MALT1 complex which results in marked production of several cytokines including IL-6, MIP-2 and TNF-α in murine model of TB (Fig. 1) (Schoenen et al., 2010). Besides pro-inflammatory cytokines, generation of Th1/Th17 immune responses and contribution to granulomagenesis has been shown to be mediated through Mincle. However, 4 different Single nucleotide polymorphisms in the Mincle gene (CLEC4E) were not found associated with TB in African population in a very recent study, which indicates that perhaps function of Mincle in the human immune system could be dispensable (Bowker et al., 2016). On the other hand, Mincle encoded by CLEC4D gene was found to be a key component for antimycobacterial immunity in another study (Wilson et al., 2015). Mice deficient for CLEC4D exhibited neutrophilic inflammation, higher mycobacterial burdens, and increased mortality upon *M. tuberculosis* infection. Furthermore, a CLEC4D polymorphism in humans was also found associated with susceptibility to pulmonary tuberculosis.

Dectin-1 (encoded by gene CLEC7A), whose mycobacterial ligand remains unknown, is another CLR known to play a significant role in activating macrophage's pro-inflammatory response in cooperation with TLR2 (Yadav and Schorey, 2006). Dectin-1 operates through Syk/CARD9 dependent signaling mechanism that results in production of IL12p40, TNF-α, RANTES, G-CSF and IL-6 (Fig. 1). However, the role of Dectin-1 in host defense remains more controversial as evidenced by later study that intriguingly showed reduced microbial burden in Clec7a-/- knockout mice (Marakalala et al., 2011). Thus, further studies are required to clearly define the protective role of Dectin-1 against *M. tuberculosis* infection.

Collectin CL-LK, another soluble C-type lectin which recognizes mannose-capped lipoarabinomannan of *M. tuberculosis* has also been characterized recently (Troegeler et al., 2015). Although, mice deficient in CL-K1, one of the CL-LK subunits, did not display altered susceptibility to *M. tuberculosis*, the amount of CL-LK in the serum of patients with active TB was found much reduced, compared to that in controls. These findings indicate the possibility of polymorphism CL-CK and its link with susceptibility to TB in human population. *M. tuberculosis* has also been reported to produces a range of immunogenic β-gentiobiosyl diacylglycerides which could only induce a weak immune response in mice but much stronger in humans cells (Richardson et al., 2015). Dendritic Cell ImmunoReceptor (DCIR), a C-type lectin receptor expressed by DCs, was also recently found to modulate immunity to TB by sustaining type I IFN signaling (Troegeler et al., 2017). DCIR-deficient mice were able to control *M. tuberculosis* infection better than WT animals but also developed more inflammation through an increased production of TNF-α and inducible NOS (iNOS) in the lungs. Many members of C type lectin receptor family thus appear to play a non-redundant role in anti-mycobacterial immunity by participating in cross-talk with other PRRs to induce or modulate the inflammatory response during mycobacterial infection to maintain the equilibrium between infection-driven inflammation and pathogen's control (Lugo-Villarino et al., 2011; Troegeler et al., 2017).

3. Strategies of *M. tuberculosis* to evade PRR mediated host defense

Evidences summarized in the previous section delineate that a combined and concerted activation of various PRRs is required for an efficient immune response against *M. tuberculosis*. However, with the revelation of PRRs involved in TB immunopathogenesis and their crosstalk with key cellular pathways of host defense, survival strategies employed by pathogen to interfere with them are also being recognized concurrently. From increasing number of evidences, it is now clear that the pathogen has evolved multiple mechanisms to intercept PRR signaling at multiple steps which eventually helps the survival of bacterium (Goldberg et al., 2014; Khan et al., 2016). One such comprehensively documented PRR intervention mechanism employed by *M. tuberculosis* is to subvert antigen presentation by modulating PRR signaling via some of its lipoproteins (Baena and Porcelli, 2009). LprG and LprA lipoproteins of *M. tuberculosis* have been shown to exploit TLR-2 signaling to inhibit MHC-II Ag processing in human macrophages (Gehring et al., 2004; Pecora et al., 2006). TLR2-dependent inhibition of MHC class II transactivator expression, MHC class II molecule expression and antigen presentation by specific mycobacterial lipopro-

teins thus assisted in evading recognition of infected macrophages by CD4 T cells. However, antigen specific CD4+ T cell mediated immune response with substantial amount of IFN-γ production against TB antigens in human population exposed to *M. tuberculosis* suggests that inhibition of antigen presentation may not occur *in vivo* in humans unlike those seen in *in vitro* infection studies. Increased production of immunosuppressive IL-6 and IL-10 predominantly via TLR2, by DCs in response to *M. tuberculosis* infection indicated the inhibition of pro-inflammatory response as well through prolonged TLR signaling (Jang et al., 2004). Supporting the same, in a more recent study, the trisaccharide domain of the PGLs from *M. tuberculosis* has also been shown to inhibit TLR2-triggered NF-κB activation, and thus the production of inflammatory cytokines (Arbués et al., 2016). Inability of TLR2 knockout mice to recruit Foxp3+ T regulatory cells (Tregs) in pulmonary granulomas leading to inflammation and tissue damage further supports that extended TLR2 signaling mediates suppression of pro-inflammatory response and establishment of chronic *M. tuberculosis* infection (McBride et al., 2013). It is known that when a prolonged PRR signaling occurs, inhibition of antigen presentation is a general negative feedback mechanism employed by host cells to control inflammation. However, pathogen *M. tuberculosis* seems to have exploited TLR2 mediated feedback regulation of inflammation and antigen presentation for its own advantage to create a niche for survival in infected macrophages.

M. tuberculosis has also evolved tactics to protect itself against autophagy-mediated clearance. Many surface associated as well as cytosolic PRRs involve activation of ERK, JNK and p38 map kinases downstream which leads to stimulation of autophagy. *M. tuberculosis-Eis* gene that codes for a secreted protein with N-acetyltransferase activity, has been shown to inhibit autophagy by reducing the JNK phosphorylation (Kim et al., 2012). Being the last event triggering autophagy, JNK plays a critical role in induction of the autophagic signaling machinery. *M. tuberculosis*-Eis mediated blockade of JNK dependent autophagy also contributed to enhanced survival of *M. tuberculosis* within the macrophages (Wei et al., 2000). Moreover, inhibition of JNK pathway also results in upregulation of B cell lymphoma protein 2 (Bcl-2), which further contributes in inhibition of autophagy (Wei et al., 2008). Thus, inhibition of JNK by *M. tuberculosis* via interfering with PRR signaling could lead to blockade of multiple autophagic signaling.

Evasion of inflammasome activation is another key mechanism that *M. tuberculosis* has developed to intercept PRR signaling to enhance its intracellular survival. *M. tuberculosis* through its zinc metalloprotease Zmp1, inhibits NLRC4 (NLR family CARD domain-containing protein 4) and NLRP3 inflammasome signaling, though the exact mechanism remains unknown (Master et al., 2008). By inhibiting the inflammasome, *M. tuberculosis* limits the production and activation of IL-1β, which is an important pro-inflammatory cytokine implicated in anti-mycobacterial defenses. Prevention of IL-1β/inflammasome activation by *M. tuberculosis* was also found associated with decreased phagosome maturation, lower levels of reactive oxygen species and increased bacterial burden in macrophages compared to a zmp1 (Zinc metalloprotease) mutant strain of *M. tuberculosis* that was unable to inhibit NLRP3/NLRC4 inflammasome. *M. tuberculosis* is known to inhibit activation of AIM2 (Absent in melanoma 2)-inflammasome as well via its ESX-1 secretion system (Shah et al., 2013). Putative effectors secreted by *M. tuberculosis* via its ESX-1 system, either directly or indirectly inhibit AIM2-inflammasome to limit IL-1β and IL-18 production. Critical role of AIM2 for immunity has also been shown in an earlier study when AIM2-deficient mice were found highly susceptible to intratracheal infection with *M. tuberculosis* that was associated with defective IL-1β and IL-18 production together with impaired Th1 responses (Saiga et al., 2012). Association of inflammasome inhibition with virulence was also evident from the fact that non-virulent mycobacteria such as *M. smegmatis* could induce AIM2-inflammasome activation but not *M. tuberculosis*. These evidences overall suggest that disruption of inflammasome mediated intracellular PRR signaling by *M. tuberculosis* contributes in phagosome maturation block, intracellular survival and virulence of the pathogen.

Engagement of phagocytic receptors DC-SIGN and MR mediated signaling via its mannose-capped cell-wall component lipoarabinomannan (ManLAM), is another key evasion strategy that *M. tuberculosis* utilizes to compromise PRR signaling and enhance its survival (van Kooyk and Geijtenbeek, 2003). Increased secretion of ManLAM by infected macrophages results in inhibitory signals that interfere with the TLR-signaling and promote the secretion of immunosuppressive cytokine interleukin-10 (IL-10), thereby averting an efficient cellular immune response against *M. tuberculosis* infection (Teunis B H Geijtenbeek et al., 2003). MR mediated phagocytosis of *M. tuberculosis* has also been shown to limit phagosome lysosome fusion as the fusion of ManLAM microspheres with lysosome was significantly decreased in human macrophages and MR-expressing cell line but not in monocytes that lack the receptor (Kang et al., 2005). Moreover, phagocytosis of the virulent Erdman and H37Rv strains of *M. tuberculosis*, but not attenuated H37Ra strain, by human macrophages was mediated by the MR (Schlesinger et al., 1996). Similarly for DCs, *M. tuberculosis* ManLAM targets phagocytic receptor DC-SIGN to interfere with the TLR signaling which eventually results in inhibition of DC maturation and subsequent T cell response (Teunis B.H. Geijtenbeek et al., 2003). Thus via targeting certain phagocytic receptors of macrophages and DCs, *M. tuberculosis* inhibits the priming of T cells, production of inflammatory cytokines as well phagosome maturation.

4. Conclusions and perspectives

Although the significance of PRRs in generating innate and adaptive immune response to defend the host against microbial infections is well recognized, their role in protection against *M. tuberculosis* infection remained a rather debatable subject in the past. TLRs that were more extensively studied among PRRs in the earlier studies were found to be dispensable for adaptive immunity against *M. tuberculosis* in mice, but at the same time their contribution in controlling the infection was also clear (Quesniaux et al., 2004). Evidences of involvement of more and more PRRs in *M. tuberculosis* infection in subsequent studies support the emerging paradigm that in order to generate efficient immune response, activation of multiple cell defense mechanisms is required and blockage of any one of these pathways could significantly affect the ability of the host to resolve the infection (Ferwerda et al., 2005; Mortaz et al., 2015; Trinchieri and Sher, 2007). While activation of certain PRRs can lead to production of pro-inflammatory cytokines, other PRRs can regulate the inflammation by producing anti-inflammatory response. This could be one important mechanism of host to balance Th1/Th2 cytokine response, which has been suggested to be very critical in determining the outcome of TB disease (Hossain and Norazmi, 2013). Apart from that several critical cellular processes of host defense including, inflammation, antigen presentation, apoptosis, autophagy and phagosome maturation are now known to be induced individually as well as by combined effort of many PRRs during *M. tuberculosis* infection. Individual importance of many PRRs could be gauged by the fact that deficiency of a single PRR could lead to increased disease pathology/bacterial burden/inflammation and other defects in immune response in animal model of TB. Critical role of many of individual PRRs for their contribution in overall immunity is also being corroborated in humans with studies demonstrating a clear link between susceptibility to TB and polymorphism in many PRRs (Fol et al., 2015; Sun et al., 2015; Thada et al., 2013). On the other hand, many PRR variants also did not show any significant association with TB in other studies (Schurz et al., 2015). Many of these studies that evaluated the variation in PRRs and susceptibility to TB had the limitation of population size and included ethnic groups in the analysis. Demonstration of functional phenotype in PRR variants and its association with TB is also lacking in most of these polymorphism studies. Additional studies investigating immune function among PRRs

variants and their association with TB on a larger population size across all ethnic groups is thus required to gain a better understanding about the role of various receptors during *M. tuberculosis* infection in human host.

Nevertheless, we might underestimate the survival strategies evolved by *M. tuberculosis* based on the redundancy and time spatial role of PRR activation during infection. Although M. *tuberculosis* contains several Pathogen Associated Molecular Patterns which can be recognized by the host PRRs, the pathogen is still able to avoid the immune defense mechanisms of the host cells. The ability of mycobacteria to avoid PRR recognition by modifying or hiding the exposure of PRR agonists to host cells has been suggested as one of the major reason of their successful evasion of host immune system. The strategies, which mycobacteria have evolved to counteract the host immune system, revolve around their perspicacity to inhibit or block PRR mediated activation of cellular pathways. Inhibition of TLR2 signaling via specific lipoproteins of mycobacteria, is an example of how pathogen keeps the antigen presentation and T cell activation inhibited (Gehring et al., 2004; Pecora et al., 2006). This allows the pathogen to evade the immune system and cause chronic infection. Similarly *M. tuberculosis* can also inhibit phagosome maturation by interfering with other PRR signaling pathways (Kang et al., 2005). Targeting PRR mediated defense thus could be one key persistence mechanism of *M. tuberculosis*. Altogether, the discovery of various PRRs, their downstream signaling mechanism and regulated cellular pathways should greatly assist in translating these advances into designing novel vaccines and immunotherapies for TB. Natural bacterial agonists of various PRRs and other small molecule modulators of PRR signaling downstream could thus have great potential for development of adjuvants and therapeutics for TB and other infectious disease.

Conflict of interest

The authors have no conflict of interests to disclose.

Acknowledgement

We thank Dr. Robert L Hunter, Distinguished Professor, McGovern Medical School, University of Texas Health Science Center-Houston for comments that greatly helped in compilation of the manuscript.

References

Akira, S., Takeda, K., 2004. Toll-like receptor signalling. Nat. Rev. Immunol. 4, 499–511. http://dx.doi.org/10.1038/nri1391.

Akira, S., Uematsu, S., Takeuchi, O., 2006. Pathogen recognition and innate immunity. Cell 124, 783–801. http://dx.doi.org/10.1016/j.cell.2006.02.015.

Arbués, A., Malaga, W., Constant, P., Guilhot, C., Prandi, J., Astarie-Dequeker, C., 2016. Trisaccharides of phenolic glycolipids confer advantages to pathogenic mycobacteria through manipulation of host-Cell pattern-Recognition receptors. ACS Chem. Biol. 11, 2865–2875. http://dx.doi.org/10.1021/acschembio.6b00568.

Baena, A., Porcelli, S.A., 2009. Evasion and subversion of antigen presentation by Mycobacterium tuberculosis. Tissue Antigens 74, 189–204. http://dx.doi.org/10.1111/j. 1399-0039.2009.01301. x.

Bafica, A., Scanga, C.A., Feng, C.G., Leifer, C., Cheever, A., Sher, A., 2005. TLR9 regulates Th1 responses and cooperates with TLR2 in mediating optimal resistance to Mycobacterium tuberculosis. J. Exp. Med. 202, 1715–1724. http://dx.doi.org/10.1084/jem.20051782.

Bakhru, P., Sirisaengtaksin, N., Soudani, E., Mukherjee, S., Khan, A., Jagannath, C., 2014. BCG vaccine mediated reduction in the MHC-II expression of macrophages and dendritic cells is reversed by activation of Toll-like receptors 7 and 9. Cell. Immunol. 287, 53–61. http://dx.doi.org/10.1016/j.cellimm.2013.11.007.

Bento, C.F., Empadinhas, N., Mendes, V., 2015. Autophagy in the fight against tuberculosis. DNA Cell Biol. 34, 228–242. http://dx.doi.org/10.1089/dna.2014.2745.

Berrington, W.R., Macdonald, M., Khadge, S., Sapkota, B.R., Janer, M., Hagge, D.A., Kaplan, G., Hawn, T.R., 2010. Common polymorphisms in the NOD2 gene region are associated with leprosy and its reactive states. J. Infect. Dis. 201, 1422–1435. http://dx.doi.org/10.1086/651559.

Blander, J.M., Medzhitov, R., 2004. Regulation of phagosome maturation by signals from toll-like receptors. Science 304, 1014–1018. http://dx.doi.org/10.1126/science.1096158.

Bourigault, M.-L., Segueni, N., Rose, S., Court, N., Vacher, R., Vasseur, V., Erard, F., Le Bert, M., Garcia, I., Iwakura, Y., Jacobs, M., Ryffel, B., Quesniaux, V.F.J., 2013. Relative contribution of IL-1α, IL-1β and TNF to the host response to Mycobacterium tuberculosis and attenuated M. bovis BCG. Immun. Inflamm. Dis. 1, 47–62. http://dx.doi.org/10.1002/iid3.9.

Bowker, N., Salie, M., Schurz, H., van Helden, P.D., Kinnear, C.J., Hoal, E.G., Möller, M., 2016. Polymorphisms in the pattern recognition receptor mincle gene (CLEC4E) and association with tuberculosis. Lung 194, 763–767. http://dx.doi.org/10.1007/s00408-016-9915-y.

Caruso, R., Warner, N., Inohara, N., Núñez, G., 2014. NOD1 and NOD2: signaling, host defense, and inflammatory disease. Immunity 41, 898–908. http://dx.doi.org/10.1016/j.immuni.2014.12.010.

Chauhan, S., Mandell, M.A., Deretic, V., 2015. IRGM governs the core autophagy machinery to conduct antimicrobial defense. Mol. Cell 58, 507–521. http://dx.doi.org/10.1016/j.molcel.2015.03.020.

Cooney, R., Baker, J., Brain, O., Danis, B., Pichulik, T., Allan, P., Ferguson, D.J.P., Campbell, B.J., Jewell, D., Simmons, A., 2010. NOD2 stimulation induces autophagy in dendritic cells influencing bacterial handling and antigen presentation. Nat. Med. 16, 90–97. http://dx.doi.org/10.1038/nm.2069.

Court, N., Vasseur, V., Vacher, R., Frémond, C., Shebzukhov, Y., Yeremeev, V.V., Maillet, I., Nedospasov, S.A., Gordon, S., Fallon, P.G., Suzuki, H., Ryffel, B., Quesniaux, V.F.J., 2010. Partial redundancy of the pattern recognition receptors, scavenger receptors, and C-type lectins for the long-term control of Mycobacterium tuberculosis infection. J. Immunol. 184, 7057–7070. http://dx.doi.org/10.4049/jimmunol.1000164.

Crotzer, V.L., Blum, J.S., 2009. Autophagy and its role in MHC-Mediated antigen presentation. J. Immunol. 182, 3335–3341. http://dx.doi.org/10.4049/jimmunol.0803458.

Davila, S., Hibberd, M.L., Hari Dass, R., Wong, H.E.E., Sahiratmadja, E., Bonnard, C., Alisjahbana, B., Szeszko, J.S., Balabanova, Y., Drobniewski, F., van Crevel, R., van de Vosse, E., Nejentsev, S., Ottenhoff, T.H.M., Seielstad, M., 2008. Genetic association and expression studies indicate a role of toll-like receptor 8 in pulmonary tuberculosis. PLoS Genet. 4, e1000218. http://dx.doi.org/10.1371/journal.pgen.1000218.

Delgado, M.A., Elmaoued, R.A., Davis, A.S., Kyei, G., Deretic, V., 2008. Toll-like receptors control autophagy. EMBO J. 27, 1110–1121. http://dx.doi.org/10.1038/emboj.2008.31.

Dittrich, N., Berrocal-Almanza, L.C., Thada, S., Goyal, S., Slevogt, H., Sumanlatha, G., Hussain, A., Sur, S., Burkert, S., Oh, D.-Y., Valluri, V., Schumann, R.R., Conrad, M.L., 2015. Toll-like receptor 1 variations influence susceptibility and immune response to Mycobacterium tuberculosis. Tuberculosis (Edinb) 95, 328–335. http://dx.doi.org/10.1016/j.tube.2015.02.045.

Drennan, M.B., Nicolle, D., Quesniaux, V.J.F., Jacobs, M., Allie, N., Mpagi, J., Frémond, C., Wagner, H., Kirschning, C., Ryffel, B., 2004. Toll-like receptor 2-deficient mice succumb to Mycobacterium tuberculosis infection. Am. J. Pathol. 164, 49–57. http://dx.doi.org/10.1016/S0002-9440(10)63095-7.

Ferwerda, G., Girardin, S.E., Kullberg, B.-J., Le Bourhis, L., de Jong, D.J., Langenberg, D.M.L., van Crevel, R., Adema, G.J., Ottenhoff, T.H.M., Van der Meer, J.W.M., Netea, M.G., 2005. NOD2 and toll-like receptors are nonredundant recognition systems of Mycobacterium tuberculosis. PLoS Pathog. 1, 279–285. http://dx.doi.org/10.1371/journal.ppat.0010034.

Fol, M., Druszczynska, M., Wlodarczyk, M., Ograczyk, E., Rudnicka, W., 2015. Immune response gene polymorphisms in tuberculosis. Acta Biochim. Pol. 62, 633–640. http://dx.doi.org/10.18388/abp.2015_1130.

Fratti, R.A., Chua, J., Vergne, I., Deretic, V., 2003. Mycobacterium tuberculosis glycosylated phosphatidylinositol causes phagosome maturation arrest. Proc. Natl. Acad. Sci. U. S. A. 100, 5437–5442. http://dx.doi.org/10.1073/pnas.0737613100.

Fremond, C.M., Yeremeev, V., Nicolle, D.M., Jacobs, M., Quesniaux, V.F., Ryffel, B., 2004. Fatal Mycobacterium tuberculosis infection despite adaptive immune response in the absence of MyD88. J. Clin. Invest. 114, 1790–1799. http://dx.doi.org/10.1172/JCI21027.

Gehring, A.J., Dobos, K.M., Belisle, J.T., Harding, C.V., Boom, W.H., 2004. Mycobacterium tuberculosis LprG (Rv1411c): a novel TLR-2 ligand that inhibits human macrophage class II MHC antigen processing. J. Immunol. 173, 2660–2668.

Geijtenbeek, T.B.H., Van Vliet, S.J., Koppel, E.A., Sanchez-Hernandez, M., Vandenbroucke-Grauls, C.M.J.E., Appelmelk, B., Van Kooyk, Y., 2003. Mycobacteria target DC-SIGN to suppress dendritic cell function. J. Exp. Med. 197, 7–17.

Goldberg, M.F., Saini, N.K., Porcelli, S.A., 2014. Evasion of innate and adaptive immunity by mycobacterium tuberculosis. Microbiol. Spectr. 2. http://dx.doi.org/10.1128/microbiolspec.mgm2-0005-2013.

Graustein, A.D., Horne, D.J., Arentz, M., Bang, N.D., Chau, T.T.H., Thwaites, G.E., Caws, M., Thuong, N.T.T., Dunstan, S.J., Hawn, T.R., 2015. TLR9 gene region polymorphisms and susceptibility to tuberculosis in Vietnam. Tuberculosis (Edinb) 95, 190–196. http://dx.doi.org/10.1016/j.tube.2014.12.009.

Greenstein, R.J., 2003. Is Crohn's disease caused by a mycobacterium? Comparisons with leprosy, tuberculosis, and Johne's disease. Lancet Infect. Dis. 3, 507–514.

Guo, X.-G., Xia, Y., 2015. The rs5743708 gene polymorphism in the TLR2 gene contributes to the risk of tuberculosis disease. Int. J. Clin. Exp. Pathol. 8, 11921–11928.

Hölscher, C., Reiling, N., Schaible, U.E., Hölscher, A., Bathmann, C., Korbel, D., Lenz, I., Sonntag, T., Kröger, S., Akira, S., Mossmann, H., Kirschning, C.J., Wagner, H., Freudenberg, M., Ehlers, S., 2008. Containment of aerogenic Mycobacterium tuberculosis infection in mice does not require MyD88 adaptor function for TLR2, −4 and −9. Eur. J. Immunol. 38, 680–694. http://dx.doi.org/10.1002/eji.200736458.

Harris, J., Hope, J.C., Keane, J., 2008. Tumor necrosis factor blockers influence macrophage responses to Mycobacterium tuberculosis. J. Infect. Dis. 198, 1842–1850. http://dx.doi.org/10.1086/593174.

Heldwein, K.A., Liang, M.D., Andresen, T.K., Thomas, K.E., Marty, A.M., Cuesta, N., Vogel, S.N., Fenton, M.J., 2003. TLR2 and TLR4 serve distinct roles in the host immune response against Mycobacterium bovis BCG. J. Leukoc. Biol. 74, 277–286.
Homer, C.R., Richmond, A.L., Rebert, N.A., Achkar, J.-P., McDonald, C., 2010. ATG16L1 and NOD2 interact in an autophagy-dependent antibacterial pathway implicated in Crohn's disease pathogenesis. Gastroenterology 139, 1630–1641. http://dx.doi.org/10.1053/j.gastro.2010.07.006. e1–2.
Hossain, M.M., Norazmi, M.-N., 2013. Pattern recognition receptors and cytokines in mycobacterium tuberculosis Infection—The double-Edged sword? Biomed. Res. Int. 2013, 1–18. http://dx.doi.org/10.1155/2013/179174.
Ishikawa, E., Ishikawa, T., Morita, Y.S., Toyonaga, K., Yamada, H., Takeuchi, O., Kinoshita, T., Akira, S., Yoshikai, Y., Yamasaki, S., 2009. Direct recognition of the mycobacterial glycolipid, trehalose dimycolate, by C-type lectin Mincle. J. Exp. Med. 206, 2879–2888. http://dx.doi.org/10.1084/jem.20091750.
Iwasaki, A., Medzhitov, R., 2015. Control of adaptive immunity by the innate immune system. Nat. Immunol. 16, 343–353. http://dx.doi.org/10.1038/ni.3123.
Kang, T.J., Chae, G.T., 2001. Detection of Toll-like receptor 2 (TLR2) mutation in the lepromatous leprosy patients. FEMS Immunol. Med. Microbiol. 31, 53–58.
Kang, T.J., Lee, S.B., Chae, G.T., 2002. A polymorphism in the toll-like receptor 2 is associated with IL-12 production from monocyte in lepromatous leprosy. Cytokine 20, 56–62.
Kang, P.B., Azad, A.K., Torrelles, J.B., Kaufman, T.M., Beharka, A., Tibesar, E., DesJardin, L.E., Schlesinger, L.S., 2005. The human macrophage mannose receptor directs Mycobacterium tuberculosis lipoarabinomannan-mediated phagosome biogenesis. J. Exp. Med. 202, 987–999. http://dx.doi.org/10.1084/jem.20051239.
Kawai, T., Akira, S., 2010. The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. Nat. Immunol. 11, 373–384. http://dx.doi.org/10.1038/ni.1863.
Khan, N., Vidyarthi, A., Pahari, S., Agrewala, J.N., 2016. Distinct strategies employed by dendritic cells and macrophages in restricting mycobacterium tuberculosis infection: different philosophies but same desire. Int. Rev. Immunol. 35, 386–398. http://dx.doi.org/10.3109/08830185.2015.1015718.
Killick, K.E., Ní Cheallaigh, C., O'Farrelly, C., Hokamp, K., MacHugh, D.E., Harris, J., 2013. Receptor-mediated recognition of mycobacterial pathogens. Cell. Microbiol. 15, 1484–1495. http://dx.doi.org/10.1111/cmi.12161.
Kim, K.H., An, D.R., Song, J., Yoon, J.Y., Kim, H.S., Yoon, H.J., Im, H.N., Kim, J., Kim, D.J., Lee, S.J., Kim, K.-H., Lee, H.-M., Kim, H.-J., Jo, E.-K., Lee, J.Y., Suh, S.W., 2012. Mycobacterium tuberculosis Eis protein initiates suppression of host immune responses by acetylation of DUSP16/MKP-7. Proc. Natl. Acad. Sci. U. S. A. 109, 7729–7734. http://dx.doi.org/10.1073/pnas.1120251109.
Koo, I.C., Wang, C., Raghavan, S., Morisaki, J.H., Cox, J.S., Brown, E.J., 2008. ESX-1-dependent cytolysis in lysosome secretion and inflammasome activation during mycobacterial infection. Cell. Microbiol. 10, 1866–1878. http://dx.doi.org/10.1111/j. 1462-5822.2008.01177. x.
Krutzik, S.R., Modlin, R.L., 2004. The role of Toll-like receptors in combating mycobacteria. Semin. Immunol. 16, 35–41.
Kuchtey, J., Chefalo, P.J., Gray, R.C., Ramachandra, L., Harding, C.V., 2005. Enhancement of dendritic cell antigen cross-presentation by CpG DNA involves type I IFN and stabilization of class I MHC mRNA. J. Immunol. 175, 2244–2251.
Lugo-Villarino, G., Hudrisier, D., Tanne, A., Neyrolles, O., 2011. C-type lectins with a sweet spot for Mycobacterium tuberculosis. Eur. J. Microbiol. Immunol. 1, 25–40. http://dx.doi.org/10.1556/EuJMI.1.2011.1.6.
Manzanillo, P.S., Shiloh, M.U., Portnoy, D.A., Cox, J.S., 2012. Mycobacterium tuberculosis activates the DNA-dependent cytosolic surveillance pathway within macrophages. Cell Host Microbe 11, 469–480. http://dx.doi.org/10.1016/j.chom.2012.03.007.
Marakalala, M.J., Guler, R., Matika, L., Murray, G., Jacobs, M., Brombacher, F., Rothfuchs, A.G., Sher, A., Brown, G.D., 2011. The Syk/CARD9-coupled receptor Dectin-1 is not required for host resistance to Mycobacterium tuberculosis in mice. Microbes Infect. 13, 198–201. http://dx.doi.org/10.1016/j.micinf.2010.10.013.
Master, S.S., Rampini, S.K., Davis, A.S., Keller, C., Ehlers, S., Springer, B., Timmins, G.S., Sander, P., Deretic, V., 2008. Mycobacterium tuberculosis prevents inflammasome activation. Cell Host Microbe 3, 224–232. http://dx.doi.org/10.1016/j.chom.2008.03.003.
McBride, A., Konowich, J., Salgame, P., 2013. Host defense and recruitment of Foxp3$^+$ T regulatory cells to the lungs in chronic Mycobacterium tuberculosis infection requires toll-like receptor 2. PLoS Pathog. 9, e1003397. http://dx.doi.org/10.1371/journal.ppat.1003397.
Mishra, B.B., Moura-Alves, P., Sonawane, A., Hacohen, N., Griffiths, G., Moita, L.F., Anes, E., 2010. Mycobacterium tuberculosis protein ESAT-6 is a potent activator of the NLRP3/ASC inflammasome. Cell. Microbiol. 12, 1046–1063. http://dx.doi.org/10.1111/j. 1462-5822.2010.01450. x.
Morr, M., Takeuchi, O., Akira, S., Simon, M.M., Mühlradt, P.F., 2002. Differential recognition of structural details of bacterial lipopeptides by toll-like receptors. Eur. J. Immunol. 32, 3337–3347. http://dx.doi.org/10.1002/1521-4141(200212)32:12<3337:AID-IMMU3337>3.0.CO;2-#.
Mortaz, E., Adcock, I.M., Tabarsi, P., Masjedi, M.R., Mansouri, D., Velayati, A.A., Casanova, J.-L., Barnes, P.J., 2015. Interaction of pattern recognition receptors with mycobacterium tuberculosis. J. Clin. Immunol. 35, 1–10. http://dx.doi.org/10.1007/s10875-014-0103-7.
Najmi, N., Kaur, G., Sharma, S.K., Mehra, N.K., 2010. Human Toll-like receptor 4 polymorphisms TLR4 Asp299Gly and Thr399Ile influence susceptibility and severity of pulmonary tuberculosis in the Asian Indian population. Tissue Antigens 76, 102–109. http://dx.doi.org/10.1111/j. 1399-0039.2010.01481. x.
Nicolle, D., Fremond, C., Pichon, X., Bouchot, A., Maillet, I., Ryffel, B., Quesniaux, V.J.F., 2004. Long-term control of Mycobacterium bovis BCG infection in the absence of Toll-like receptors (TLRs): investigation of TLR2-, TLR6-, or TLR2-TLR4-deficient mice. Infect. Immun. 72, 6994–7004. http://dx.doi.org/10.1128/IAI.72.12.
Novikov, A., Cardone, M., Thompson, R., Shenderov, K., Kirschman, K.D., Mayer-Barber, K.D., Myers, T.G., Rabin, R.L., Trinchieri, G., Sher, A., Feng, C.G., 2011. Mycobacterium tuberculosis triggers host type I IFN signaling to regulate IL-1 production in human macrophages. J. Immunol. 187, 2540–2547. http://dx.doi.org/10.4049/jimmunol.1100926.
O'Garra, A., Redford, P.S., McNab, F.W., Bloom, C.I., Wilkinson, R.J., Berry, M.P.R., 2013. The immune response in tuberculosis. Annu. Rev. Immunol. 31, 475–527. http://dx.doi.org/10.1146/annurev-immunol-032712-095939.
O'Leary, S., O'Sullivan, M.P., Keane, J., 2011. IL-10 blocks phagosome maturation in mycobacterium tuberculosis-infected human macrophages. Am. J. Respir. Cell Mol. Biol. 45, 172–180. http://dx.doi.org/10.1165/rcmb.2010-0319OC.
Oh, J.E., Lee, H.K., 2014. Pattern recognition receptors and autophagy. Front. Immunol. 5. http://dx.doi.org/10.3389/fimmu.2014.00300.
Palm, N.W., Medzhitov, R., 2009. Pattern recognition receptors and control of adaptive immunity. Immunol. Rev. 227, 221–233. http://dx.doi.org/10.1111/j.1600-065X.2008.00731. x.
Pecora, N.D., Gehring, A.J., Canaday, D.H., Boom, W.H., Harding, C.V., 2006. Mycobacterium tuberculosis LprA is a lipoprotein agonist of TLR2 that regulates innate immunity and APC function. J. Immunol. 177, 422–429.
Quesniaux, V., Fremond, C., Jacobs, M., Parida, S., Nicolle, D., Yeremeev, V., Bihl, F., Erard, F., Botha, T., Drennan, M., Soler, M.-N., Le Bert, M., Schnyder, B., Ryffel, B., 2004. Toll-like receptor pathways in the immune responses to mycobacteria. Microbes Infect. 6, 946–959. http://dx.doi.org/10.1016/j.micinf.2004.04.016.
South African Tuberculosis Vaccine Initiative Team,Randhawa, A.K., Shey, M.S., Keyser, A., Peixoto, B., Wells, R.D., de Kock, M., Lerumo, L., Hughes, J., Hussey, G., Hawkridge, A., Kaplan, G., Hanekom, W.A., Hawn, T.R., 2011. Association of human TLR1 and TLR6 deficiency with altered immune responses to BCG vaccination in South African infants. PLoS Pathog. 7, e1002174. http://dx.doi.org/10.1371/journal.ppat.1002174.
Reiling, N., Hölscher, C., Fehrenbach, A., Kröger, S., Kirschning, C.J., Goyert, S., Ehlers, S., 2002. Cutting edge: toll-like receptor (TLR)2- and TLR4-mediated pathogen recognition in resistance to airborne infection with Mycobacterium tuberculosis. J. Immunol. 169, 3480–3484.
Richardson, M.B., Torigoe, S., Yamasaki, S., Williams, S.J., 2015. Mycobacterium tuberculosis (-gentiobiosyl diacylglycerides signal through the pattern recognition receptor Mincle: total synthesis and structure activity relationships. Chem. Commun. 51, 15027–15030. http://dx.doi.org/10.1039/C5CC04773K.
Saiga, H., Kitada, S., Shimada, Y., Kamiyama, N., Okuyama, M., Makino, M., Yamamoto, M., Takeda, K., 2012. Critical role of AIM2 in Mycobacterium tuberculosis infection. Int. Immunol. 24, 637–644. http://dx.doi.org/10.1093/intimm/dxs062.
Scanga, C.A., Bafica, A., Feng, C.G., Cheever, A.W., Hieny, S., Sher, A., 2004. MyD88-Deficient mice display a profound loss in resistance to mycobacterium tuberculosis associated with partially impaired th1 cytokine and nitric oxide synthase 2 expression. Infect. Immun. 72, 2400–2404. http://dx.doi.org/10.1128/IAI.72.4.
Schlesinger, L.S., Kaufman, T.M., Iyer, S., Hull, S.R., Marchiando, L.K., 1996. Differences in mannose receptor-mediated uptake of lipoarabinomannan from virulent and attenuated strains of Mycobacterium tuberculosis by human macrophages. J. Immunol. 157, 4568–4575.
Schoenen, H., Bodendorfer, B., Hitchens, K., Manzanero, S., Werninghaus, K., Nimmerjahn, F., Agger, E.M., Stenger, S., Andersen, P., Ruland, J., Brown, G.D., Wells, C., Lang, R., 2010. Cutting edge: mincle is essential for recognition and adjuvanticity of the mycobacterial cord factor and its synthetic analog trehalose-Dibehenate. J. Immunol. 184, 2756–2760. http://dx.doi.org/10.4049/jimmunol.0904013.
Schurz, H., Daya, M., Möller, M., Hoal, E.G., Salie, M., 2015. TLR1, 2, 4, 6 and 9 Variants Associated with Tuberculosis Susceptibility: A Systematic Review and Meta-Analysis. PLoS One 10, e0139711.
Shah, S., Bohsali, A., Ahlbrand, S.E., Srinivasan, L., Rathinam, V.A.K., Vogel, S.N., Fitzgerald, K.A., Sutterwala, F.S., Briken, V., 2013. Cutting edge: mycobacterium tuberculosis but not nonvirulent mycobacteria inhibits IFN- and AIM2 inflammasome-Dependent IL-1 production via its ESX-1 secretion system. J. Immunol. 191, 3514–3518. http://dx.doi.org/10.4049/jimmunol.1301331.
Shaw, M.H., Kamada, N., Warner, N., Kim, Y.-G., Nuñez, G., 2011. The ever-expanding function of NOD2: autophagy, viral recognition, and T cell activation. Trends Immunol. 32, 73–79. http://dx.doi.org/10.1016/j.it.2010.12.007.
Shin, D.-M., Yuk, J.-M., Lee, H.-M., Lee, S.-H., Son, J.W., Harding, C.V., Kim, J.-M., Modlin, R.L., Jo, E.-K., 2010. Mycobacterial lipoprotein activates autophagy via TLR2/1/CD14 and a functional vitamin D receptor signalling. Cell. Microbiol. 12, 1648–1665. http://dx.doi.org/10.1111/j. 1462-5822.2010.01497. x.
Stamm, C.E., Collins, A.C., Shiloh, M.U., 2015. Sensing of Mycobacterium tuberculosis and consequences to both host and bacillus. Immunol. Rev. 264, 204–219. http://dx.doi.org/10.1111/imr.12263.
Sugawara, I., Yamada, H., Hua, S., Mizuno, S., 2001. Role of interleukin (IL)-1 type 1 receptor in mycobacterial infection. Microbiol. Immunol. 45, 743–750.
Sun, Q., Zhang, Q., Xiao, H., Bai, C., 2015. Toll-like receptor polymorphisms and tuberculosis susceptibility: a comprehensive meta-analysis. J. Huazhong Univ. Sci. Technol. Med. Sci. 35, 157–168. http://dx.doi.org/10.1007/s11596-015-1405-6.
Thada, S., Valluri, V.L., Gaddam, S.L., 2013. Influence of Toll-like receptor gene polymorphisms to tuberculosis susceptibility in humans. Scand. J. Immunol. 78, 221–229. http://dx.doi.org/10.1111/sji.12066.
Torres-García, D., Cruz-Lagunas, A., García-Sancho Figueroa, M., Fernández-Plata, R., Baez-Saldaña, R., Mendoza-Milla, C., Barquera, R., Carrera-Eusebio, A., Ramírez-Bravo, S., Campos, L., Angeles, J., Vargas-Alarcón, G., Granados, J., Gopal, R., Khader, S.A., Yunis, E.J., Zuñiga, J., 2013. Variants in toll-like receptor 9 gene

influence susceptibility to tuberculosis in a Mexican population. J. Transl. Med. 11, 220. http://dx.doi.org/10.1186/1479-5876-11-220.

Travassos, L.H., Carneiro, L.A.M., Ramjeet, M., Hussey, S., Kim, Y.-G., Magalhães, J.G., Yuan, L., Soares, F., Chea, E., Le Bourhis, L., Boneca, I.G., Allaoui, A., Jones, N.L., Nuñez, G., Girardin, S.E., Philpott, D.J., 2010. Nod1 and Nod2 direct autophagy by recruiting ATG16L1 to the plasma membrane at the site of bacterial entry. Nat. Immunol. 11, 55–62. http://dx.doi.org/10.1038/ni.1823.

Trinchieri, G., Sher, A., 2007. Cooperation of Toll-like receptor signals in innate immune defence. Nat. Rev. Immunol. 7, 179–190. http://dx.doi.org/10.1038/nri2038.

Troegeler, A., Lugo-Villarino, G., Hansen, S., Rasolofo, V., Henriksen, M.L., Mori, K., Ohtani, K., Duval, C., Mercier, I., Bénard, A., Nigou, J., Hudrisier, D., Wakamiya, N., Neyrolles, O., 2015. Collectin CL-LK is a novel soluble pattern recognition receptor for mycobacterium tuberculosis. PLoS One 10, e0132692. http://dx.doi.org/10.1371/journal.pone.0132692.

Troegeler, A., Mercier, I., Cougoule, C., Pietretti, D., Colom, A., Duval, C., Vu Manh, T.-P., Capilla, F., Poincloux, R., Pingris, K., Nigou, J., Rademann, J., Dalod, M., Verreck, F.A.W., Al Saati, T., Lugo-Villarino, G., Lepenies, B., Hudrisier, D., Neyrolles, O., 2017. C-type lectin receptor DCIR modulates immunity to tuberculosis by sustaining type I interferon signaling in dendritic cells. Proc. Natl. Acad. Sci. 114, E540–E549. http://dx.doi.org/10.1073/pnas.1613254114.

Vergne, I., Chua, J., Singh, S.B., Deretic, V., 2004. Cell biology of mycobacterium tuberculosis phagosome. Annu. Rev. Cell Dev. Biol. 20, 367–394. http://dx.doi.org/10.1146/annurev.cellbio.20.010403.114015.

Wassermann, R., Gulen, M.F., Sala, C., Perin, S.G., Lou, Y., Rybniker, J., Schmid-Burgk, J.L., Schmidt, T., Hornung, V., Cole, S.T., Ablasser, A., 2015. Mycobacterium tuberculosis differentially activates cGAS- and inflammasome-Dependent intracellular immune responses through ESX-1. Cell Host Microbe 17, 799–810. http://dx.doi.org/10.1016/j.chom.2015.05.003.

Watson, R.O., Manzanillo, P.S., Cox, J.S., 2012. Extracellular M. tuberculosis DNA targets bacteria for autophagy by activating the host DNA-Sensing pathway. Cell 150, 803–815. http://dx.doi.org/10.1016/j.cell.2012.06.040.

Wei, J., Dahl, J.L., Moulder, J.W., Roberts, E.A., O'Gaora, P., Young, D.B., Friedman, R.L., 2000. Identification of a Mycobacterium tuberculosis gene that enhances mycobacterial survival in macrophages. J. Bacteriol. 182, 377–384.

Wei, Y., Pattingre, S., Sinha, S., Bassik, M., Levine, B., 2008. JNK1-mediated phosphorylation of Bcl-2 regulates starvation-induced autophagy. Mol. Cell 30, 678–688. http://dx.doi.org/10.1016/j.molcel.2008.06.001.

Wilson, G.J., Marakalala, M.J., Hoving, J.C., van Laarhoven, A., Drummond, R.A., Kerscher, B., Keeton, R., van de Vosse, E., Ottenhoff, T.H.M., Plantinga, T.S., Alisjahbana, B., Govender, D., Besra, G.S., Netea, M.G., Reid, D.M., Willment, J.A., Jacobs, M., Yamasaki, S., van Crevel, R., Brown, G.D., 2015. The C-type lectin receptor CLECSF8/CLEC4D is a key component of anti-mycobacterial immunity. Cell Host Microbe 17, 252–259. http://dx.doi.org/10.1016/j.chom.2015.01.004.

van Kooyk, Y., Geijtenbeek, T.B.H., 2003. DC-SIGN: escape mechanism for pathogens. Nat. Rev. Immunol. 3, 697–709. http://dx.doi.org/10.1038/nri1182.

Yadav, M., Schorey, J.S., 2006. The beta-glucan receptor dectin-1 functions together with TLR2 to mediate macrophage activation by mycobacteria. Blood 108, 3168–3175. http://dx.doi.org/10.1182/blood-2006-05-024406.