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Review

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

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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,

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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