Microreview

Receptor-mediated recognition of mycobacterial pathogens

Kate E. Killick,1* Clíona Ní Cheallaigh,2 Clíona O’Farrelly,2 Karsten Hokamp,3 David E. MacHugh1,4 and James Harris5

1 Animal Genomics Laboratory, UCD School of Agriculture and Food Science, University College Dublin, Belfield, Dublin 4, Ireland.
2 School of Biochemistry and Immunology, Trinity Biomedical Sciences Institute, Trinity College Dublin, Dublin 2, Ireland.
3 Smurfit Institute of Genetics, Trinity College, Dublin 2, Ireland.
4 UCD Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Belfield, Dublin 4, Ireland.
5 Faculty of Medicine, Nursing and Health Sciences, Southern Clinical School, Monash Medical Centre, Monash University, Clayton, Victoria, Australia.

Summary

Mycobacteria are a genus of bacteria that range from the non-pathogenic Mycobacterium smegmatis to Mycobacterium tuberculosis, the causative agent of tuberculosis in humans. Mycobacteria primarily infect host tissues through inhalation or ingestion. They are phagocytosed by host macrophages and dendritic cells. Here, conserved pathogen-associated molecular patterns (PAMPs) on the surface of mycobacteria are recognized by phagocytic pattern recognition receptors (PRRs). Several families of PRRs have been shown to non-opsonically recognize mycobacterial PAMPs, including membrane-bound C-type lectin receptors, membrane-bound and cytosolic Toll-like receptors and cytosolic NOD-like receptors. Recently, a possible role for intracellular cytosolic PRRs in the recognition of mycobacterial pathogens has been proposed. Here, we discuss current ideas on receptor-mediated recognition of mycobacterial pathogens by macrophages and dendritic cells.

Introduction

Mycobacterium is a genus of Actinobacteria that includes more than 50 different species, ranging in virulence from the non-pathogenic M. smegmatis to the causative agent of tuberculosis (TB) in humans, M. tuberculosis (Table 1). Infection with mycobacteria most commonly occurs through inhalation or ingestion of bacilli. The bacilli are phagocytosed by host macrophages and dendritic cells (DCs) at the site of infection, for example by alveolar macrophages in M. tuberculosis-infected lungs or by intestinal macrophages in animals infected with M. avium subsp. paratuberculosis (MAP). Mycobacteria have evolved a range of mechanisms to circumvent phagosome maturation, preventing lysosomal degradation, and are therefore able to both survive and replicate inside the host phagosome (Ni Cheallaigh et al., 2012, Welin and Lerm, 2012).

In order for mycobacteria to be phagocytosed by macrophages and DCs, the pathogen is first recognized by pattern recognition receptors (PRRs) on the host cell (Medzhitov and Janeway, 2000; Gordon, 2002). This is achieved through the recognition of highly conserved molecular structures found on the surface of pathogens, often critical for microbial survival, termed pathogen-associated molecular patterns (PAMPs) (Akira et al., 2006). Several families of PRRs exist, all of which are capable of recognizing a different repertoire of PAMPs; including plasma membrane-bound and intracellular Toll-like receptors (TLRs) and cytosolic NOD-like receptors (NLRs) and RIG-I like receptors (RLRs) (Jo, 2008). This review examines some of the receptors that are involved in the non-opsonic recognition of mycobacteria by macrophages and DCs.

C-type lectin receptors

C-type lectin receptors are a family of membrane-bound calcium-dependent receptors that recognize
carbohydrate-rich molecules. Four C-type lectin receptors have been closely associated with responses to mycobacteria: the mannose receptor, DC-SIGN, Mincle and Dectin-1 (Fig. 1).

**Mannose receptors**

Mannose receptors (MRs), encoded by the mannose receptor C type 1 and 2 (MRC1 and MRC2) genes, recognize lipoarabinomannan (LAM) and mannosylated LAM (ManLAM) glycolipids on the cell wall of mycobacteria and other microbes (Table 2) (Martinez-Pomares, 2012). Early work demonstrated a role for MRs in the recognition of virulent strains of *M. tuberculosis* (Schlesinger et al., 1996). More recent research has found that stimulation of human monocyte-derived macrophages (MDM) with either virulent *M. tuberculosis* or ManLAM resulted in upregulation of peroxisome proliferator-activated receptor γ (PPARγ) with a simultaneous increase in production of IL-8 and prostoglandin E2, as well as an increase in COX-2 expression. This was independent of NF-κB activation and TLR2 expression, which indicates the employment of an MR-specific signalling pathway. Interestingly, infection with BCG induced less PPARγ and was mediated via NF-κB activation. This indicates that MR-mediated PPARγ expression and the downstream signalling it initiates are specific to virulent *M. tuberculosis* (Rajaram et al., 2010).

Macrophage MRs may be targeted by mycobacteria to enhance survival within host macrophages. Binding of ManLAM by MRs has been shown to limit phagosome–lysosome fusion, favouring mycobacterial persistence within macrophages while blocking MRs during infection with virulent *M. tuberculosis* increased phagosome–lysosome fusion (Kang et al., 2005). While recognition of ManLAM by MRs may aid mycobacterial survival within the host macrophage, it is not clear whether differential binding via MRs is responsible for differences in virulence between strains. It has been shown that mannose capping of LAM was not crucial for mycobacterial survival in macrophages (Afonso-Barroso et al., 2013); murine bone marrow-derived macrophages (BMDM) were infected with mutant forms of *M. bovis* BCG and H37Rv *M. tuberculosis* lacking the mannose cap of LAM. No difference in the ability of these mutant strains to survive and proliferate in macrophages compared with the parental strains of *M. bovis* BCG and *M. tuberculosis* was observed (Afonso-Barroso et al., 2013). It also remains to be determined whether the differential signalling induced by virulent and non-virulent strains of mycobacteria (Rajaram et al., 2010) are responsible for differences in phagosome maturation. MRs have also been shown to be involved in the uptake of MAP (Souza et al., 2007). However, polymorphisms in *MRC1* have been associated with susceptibility to TB and leprosy, suggesting that MR
may have an important functional role in the immune response to mycobacteria (Azad et al., 2012; Wang et al., 2012; Zhang et al., 2013).

**DC-SIGN**

Dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN), encoded by the CD209 gene, is a type II transmembrane C-type lectin receptor found on the surface of immature DCs (Table 2) (Tailleux et al., 2003). DC-SIGN-specific antibodies have been shown to block DC interactions with *M. bovis* BCG. The receptor also interacts with ManLAM, found on the surface of *M. tuberculosis*, but not with non-mannosylated arabinofuranosyl-terminated LAM (AraLAM), found on the surface of *M. smegmatis* (Geijtenbeek et al., 2003). It has yet to be determined whether mannose capping of LAM affects the interaction between mycobacteria and DCs.

DC-SIGN appears to play a role in mycobacterial-induced immune suppression, as it mediates ManLAM-induced production of the anti-inflammatory cytokine IL-10 in DCs and inhibits lipopolysaccharide (LPS)-induced DC maturation/activation (Wu et al., 2011). Interestingly, cyanovirin-N (CV-N), a mannose binding lectin, has been found to compete with both MRs and DC-SIGN to bind LAM and inhibits the recognition of *M. tuberculosis* by DCs but not macrophages, indicating that recognition of *M. tuberculosis* by MR is less important to macrophages than recognition by DC-SIGN is to DCs.
Table 2. Pattern recognition receptors (PRRs) and mycobacterial infections.

| Protein/s | Gene symbol/s | Ligands | Cellular location | Gene variation and susceptibility/resistance | PRR/PAMP interactions reported for other microbes |
|-----------|---------------|---------|-------------------|---------------------------------------------|--------------------------------------------------|
| Mannose receptors | MRC1 | Lipoarabinomann (LAM) | Cell surface | Association between MRC1 polymorphism and susceptibility to TB and leprosy | Yes |
| | MRC2 | Manosylated LAM (ManLAM) | | Association between CD209 polymorphism and susceptibility to TB | None reported |
| | CD209 | | | | |
| DC-SIGN | | Lipoarabinomann (LAM) | | | |
| | | Manosylated LAM (ManLAM) | | | |
| | | | | | |
| | | | | | |
| Mincle | CLEC4E | Trehalose-6, 6-dimycolate (TDM) | Cell surface | No associations reported | None reported |
| Dectin-1 | CLEC7A | Oligosaccharide ligands | Cell surface | No associations reported | Yes |
| Scavenger receptors: | MSR1 | Wide variety of ligands | Cell surface | Polymorphism in MARCO has been shown to be associated with susceptibility to TB | Yes |
| SR-AI | MARCO | | | | |
| SR-AII | SCARB1 | | | | |
| MARCO | CD36 | | | | |
| NOD2 | CARD15 | Muramyl dipeptide | Cytoplasm | Conflicting evidence for an association between CARD15 polymorphisms and susceptibility to TB Association between CARD15 polymorphisms and leprosy in humans and to MAP infection in cattle Association between CARD15 polymorphisms and leprosy | Yes |
| TLR1 | TLR1 | Peptidoglycan and lipoproteins (forms a heterodimer with TLR2) | Cell surface | Association between TLR1 polymorphisms and susceptibility to leprosy TLR1 polymorphisms have also been associated with susceptibility to MAP infection in cattle | Yes |
| TLR2 | TLR2 | Lipoproteins and mycoplasma | Cell surface | Association between TLR2 polymorphisms and susceptibility to TB (particular extrapulmonary TB), leprosy and MAP infection in cattle | Yes |
| TLR4 | TLR4 | LPS | Cell surface | Association between TLR4 polymorphisms and TB susceptibility in HIV-positive patients (no association shown for HIV-negative patients) TLR4 polymorphisms associated with susceptibility to leprosy and MAP infections in cattle | Yes |
| TLR9 | TLR9 | CpG motifs on bacterial and viral DNA | Cytoplasm | Association between TLR9 polymorphisms and TB susceptibility | Yes |
| RIG-I | DDX58 | Viral double-stranded RNA | Cytoplasm | No associations reported | Yes |
Despite this, CV-N did not inhibit M. tuberculosis infection in a mouse model, suggesting that mannose-dependent C-type lectins, such as DC-SIGN and MRs, may not be essential during the early stages of murine M. tuberculosis infection. These findings demonstrate the functional redundancy of C-type lectin PRRs in the recognition of mycobacterial pathogens (Driessen et al., 2012).

Interestingly, despite these findings, it has been hypothesized that a variant of the CD209 gene contributes to susceptibility to TB infection (Vannberg et al., 2008; Zheng et al., 2011). However, a meta-analysis of the CD209 336A/G polymorphism and TB susceptibility that integrated ten independent association studies found no evidence for a genetic association at this locus (Miao et al., 2012). The apparent discrepancies between these studies could be due to differences in genotype distributions of CD209 variants in Asian or African populations compared with other human populations. Consequently, population-specific associations of susceptibility variants with TB infection could exist. It may be possible to clarify this by studying larger samples of geographically distinct human populations.

**Mincle**

The C-type lectin receptor Mincle, encoded by the C-type lectin domain family 4, member E gene (CLEC4E), is expressed on the surface of macrophages (Table 2) (Matsumoto et al., 1999). In 2009, Ishikawa and colleagues demonstrated Mincle to be an essential receptor for trehalose-6, 6-dimycolate (TDM), the mycobacterial cord factor (Ishikawa et al., 2009).

Recently, Mincle has been shown to play a role in CARD9-dependent signalling and inflammasome activation of IL-1β and subsequent induction of a T\(\alpha\)17 response (Shenderov et al., 2013). Upon exposure to M. bovis BCG, alveolar macrophages from Mincle-deficient mice demonstrated significantly reduced proinflammatory cytokine profile, decreased leucocyte infiltration and increased pulmonary and extrapulmonary bacterial load compared with wild-type mice (Behler et al., 2012). However, in another study, both low and high dose infection with H37Rv induced a similar granulomatous, T\(\alpha\)1 and T\(\alpha\)17 response in Mincle-deficient mice to that in wild-type controls. As well as suggesting that Mincle may play a different role in the response to different strains of mycobacteria, these results also indicate that the receptor is dispensable in an in vivo model of M. tuberculosis infection. It is probable that other receptors can compensate for Mincle deficiency and that other PRRs recognize TDM (Heilman et al., 2013). Indeed, macrophage C-type lectin (MCL), thought to have arisen from a gene duplication of Mincle, has been reported to recognize TDM (Miyake et al., 2013), as has the scavenger receptor macrophage receptor with a collagenous structure (MARCO) (Bowdish et al., 2009), discussed below.

**Dectin-1**

Dectin-1, encoded by the C-type lectin domain family 7, member A gene (CLEC7A), has been shown to play a role in the recognition of the non-tuberculous M. abscessus (Shin et al., 2008). A more recent study using human MDM has demonstrated that Dectin-1 is required for activation of the NLRP3 inflammasome in response to infection with M. abscessus (Lee et al., 2012). Dectin-1 has also been shown to play a role in infection with M. tuberculosis. A study by Lee and colleagues demonstrated that M. tuberculosis H37Rv induced the expression of Dectin-1 in A549 alveolar epithelial cells in a TLR2-dependent manner (Lee et al., 2009). Moreover, Dectin-1 is required for TLR2-mediated production of TNF-\(\alpha\) by murine BMDM in response to infection with the attenuated mycobacterial strains M. bovis BCG and M. tuberculosis H37Ra, as well as the avirulent M. smegmatis and M. phlei, although this was not the case for the virulent M. avium and M. tuberculosis H37Rv strains (Yadav and Schorey, 2006). However, a role for Dectin-1 in M. tuberculosis-induced production of IL-12p40 in splenic DCs, a cytokine subunit previously shown to be important in granuloma formation, has also been proposed (Rothfuchs et al., 2007).

Interestingly, Dectin-1 activation by M. tuberculosis has been shown to promote a mixed T\(\alpha\)1/T\(\alpha\)17 response; driving the secretion of IL-1, IL-23, TNF-\(\alpha\) and IL-6 by monocyte-derived DC, which in turn drives IFN-\(\gamma\) and IL-17 secretion by CD\(^+\) T cells in vitro (Zenaro et al., 2009). Co-stimulation of MR or DC-SIGN, on the other hand, inhibits the secretion of these cytokines and drives a predominantly TH1 phenotype in CD4+ Cells (Zenaro et al., 2009). T\(\alpha\)1-type responses, typified by the secretion of IFN-\(\gamma\), TNF-\(\alpha\) and IL-12 are essential for protective immunity to M. tuberculosis (Harris and Keane, 2010). The role of IL-17 in M. tuberculosis infection is not clear, although studies suggest that high numbers of IFN-\(\gamma\)/IL-17-producing T lymphocytes correspond with more severe disease and low responders (Jurado et al., 2012). However, IL-17 may have an important role to play in protective responses following vaccination (Chatterjee et al., 2011; Gopal et al., 2012). Thus, targeting Dectin-1 during vaccination may represent a therapeutically advantageous approach. However, a study by Marakalala and colleagues detected no differences in pulmonary cytokine expression between wild-type and Clec7a\(+\) mice infected with M. tuberculosis H37Rv (Marakalala et al., 2011), suggesting that Dectin-1 may be functionally redundant for proinflammatory cytokine production during M. tuberculosis infection in vivo.

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Scavenger receptors

Scavenger receptors (SRs) are expressed on the cell surface of mammalian monocytes and macrophages and recognize a wide range of ligands. SR sub-group A consists of SR-AI, SR-All and MARCO, while SR sub-group B consists of SR-B1 and CD36 (Fig. 1) (Peiser et al., 2002). It has been demonstrated that SR-A-deficient mice infected with M. tuberculosis H37Rv survive significantly longer than their wild-type cohorts (Sever-Chroneos et al., 2011), suggesting that recognition by these receptors may favor subversion of the immune response by the bacilli. Evidence exists for a role of the SR-B1 as a macrophage receptor involved in BCG recognition. However, this was shown to be only a minor role in vivo, possibly due to the ability of other PRRs to compensate for the SR-B1 function (Schafer et al., 2009). Similarly, mice deficient in CD36 were found to be less susceptible to infection with M. bovis BCG, while Cd36−/− macrophages demonstrated increased intracellular killing of M. tuberculosis H37Rv and M. marinum in vitro (Hawkes et al., 2010). The mechanism through which CD36 deficiency confers greater protection against infection is not clear, but it does not involve differences in phagocytic uptake, macrophage apoptosis, TNF-α or IL-10 production, or the generation of reactive oxygen or nitrogen intermediates (Hawkes et al., 2010).

MARCO has been found to be involved, at least in part, in the recognition of TDM (Bowdish et al., 2009). However, mice deficient in MARCO show no differences in response to acute or chronic infection with M. tuberculosis compared with WT controls (Court et al., 2010). Interestingly, in this same study, no difference in response to infection were observed in CD36−/−, SRA−/−, or MR−/− mice, in contrast to the studies discussed above. The reasons for these differences are not clear, but there may be some functional redundancy within the different classes of SR. However, a polymorphism in MARCO has been shown to be associated with susceptibility to TB infection in a Gambian population (Bowdish et al., 2013).

Nod-like receptors

There are two human NOD genes, NOD1 and NOD2, both of which detect peptidoglycan, a structural component essential to the bacterial cell wall (Kanneganti et al., 2007). NOD-2 also senses muramyl dipeptide (MDP), which is a common cell wall component of Gram-negative and Gram-positive bacteria (Girardin et al., 2003). A role for NOD-2 in the recognition of M. tuberculosis was first demonstrated using BMDM and DCs from Nod2−/− mice. NOD-2 was found to be required for optimal production of proinflammatory cytokines in response to M. tuberculosis in vitro (Gandotra et al., 2007), suggesting that NOD-2 is at least one of the receptors required for sensing of the bacillus. Moreover, Nod2−/− mice have been shown to display decreased immunopathology and T cell recruitment to the lungs upon infection with M. bovis BCG, coupled with higher bacterial burdens and increased mortality. In this model, M. bovis BCG-infected alveolar macrophages from Nod2−/− mice released significantly less TNF-α than wild-type cells (Divangahi et al., 2008). Similarly, Brooks and colleagues studied the NOD-2 receptor in both human MDM and alveolar macrophages in response to infection with M. tuberculosis. Survival of the bacteria within Nod2−/− macrophages was higher than in controls, suggesting that NOD-2 plays an important role in the recognition and control of mycobacterial infection (Brooks et al., 2011).

In addition, activation of NOD-2 with MDP in human alveolar macrophages infected with M. tuberculosis has been shown to increase intracellular control of bacterial growth and lead to the recruitment of proteins linked with autophagy to the bacteria-containing phagosome/autophagosome (Juarez et al., 2012). It is well established that autophagy represents an important mechanism for the intracellular killing of mycobacteria by macrophages (Gutierrez et al., 2004; Castillo et al., 2012). These data highlight the possibility of a PRR-dependent mechanism for the activation of autophagy, unlike previous studies that have shown that autophagic killing of mycobacteria is regulated by cytokines – particularly IFN-γ (Gutierrez et al., 2004; Harris et al., 2007). However, the role of macrophage-derived cytokines, such as TNF-α and IL-1, which can also induce autophagy, was not assessed in this study (Harris, 2011, 2013).

In a case-control study of an African-American population in the United States, three common nonsynonymous polymorphisms in the NOD2 gene were significantly associated with a genetic susceptibility to TB infection (Austin et al., 2008). An association has also been found between TB susceptibility and the NOD2 synonymous Arg5878Arg SNP in the Chinese Han population (Zhao et al., 2012). This association was further validated in a larger Chinese population (Pan et al., 2012). Genetic associations between allelic variants of NOD2 and susceptibility to infection have also been reported for other mycobacterial species. For example, a highly significant association (P < 0.0001) with MAP infection for genotypes at a nonsynonymous SNP in the bovine NOD2 gene has been reported in a mixed population of domestic cattle (Pinedo et al., 2009) and in Holstein-Friesian cattle (Ruiz-Larranaga et al., 2010). In addition, it has been proposed that several NOD2 polymorphisms are associated with susceptibility to leprosy, an infectious disease of the peripheral nerves and skin, caused by the mycobacterial pathogen M. leprae (Berrington et al., 2010) (Fig. 1).
RIG-I-like receptors and cytosolic DNA sensors

Retinoic acid-induced gene (RIG)-I-like receptors (RLRs) are a family of PRRs located in the cytoplasm. The involvement of RLRs in the detection of intracellular bacteria has been previously demonstrated (Monroe et al., 2009; Chiliveru et al., 2010). Moreover a RIG-I signalling pathway was over-represented in a genome-wide transcriptomics study of M. bovis-infected bovine MDM (Magee et al., 2012). A murine cytosolic DNA sensor, IFI204, has also been shown to recognize M. tuberculosis and activates the STING/Tbk1/Irf3 axis, resulting in IFN-β secretion (Manzanillo et al., 2012). This pathway is activated by multiple receptors, including NLRs, TLRs and RLRs (Barber, 2011). The STING/Tbk1 axis has been shown to be required for targeting of M. tuberculosis to the autophagosome (Watson et al., 2012). Interestingly, Ifi3−/− mice are resistant to infection with M. tuberculosis, suggesting that cytosolic DNA receptors may be specifically targeted by the bacteria to promote their intracellular survival (Manzanillo et al., 2012). A role for intracellular PRRs in the recognition of mycobacterial pathogens may also tally with recent evidence that M. tuberculosis has the potential to escape from the phagosome (Harriff et al., 2012; Watson et al., 2012). Further research in this area may reveal the full extent to which intracellular PRRs are involved in the sensing of mycobacterial pathogens.

Toll-like receptors

Toll-like receptors (TLRs) are a conserved family of ten human (TLRs 1–10) and twelve murine (TLRs 1–9 and TLRs 11, 12, 13) PRRs that have a fundamental role in non-opsonic phagocytosis and recognition of both intracellular and extracellular ligands (Kawai and Akira, 2010). TLRs 1, 2, 4, 5 and 6 are located on the cell surface, while TLRs 3, 7, 8 and 9 are located intracellularly, mainly on the endoplasmic reticulum (ER) membrane. TLR-10 is an orphan member of the human TLRs, expressed on B cells and plasmacytoid DCs and non-functional in mice (Hasan et al., 2005).

TLRs have been shown to play a role in the cellular response to mycobacterial pathogens (Basu et al., 2012). Interestingly, whereas live M. tuberculosis activates NF-κB via TLR-2 and TLR-4, heat-killed M. tuberculosis only activates through TLR-2. Expression of a dominant-negative TLR-2 construct in RAW 264.7 macrophages consistently blocked M. tuberculosis-induced NF-κB activation by 70–80%, whereas expression of a dominant-negative TLR-4 construct blocked NF-κB activation by 30–40%. Coexpression of both TLR-2 and TLR-4 dominant-negative constructs resulted in almost complete absence of NF-κB activation (Means et al., 2001). Moreover, a TLR-4 inhibitor inhibited mycobacteria-induced TNF-α and primary human alveolar macrophages (Means et al., 2001). A role for TLR-2 and TLR-4 in the induction of apoptosis has subsequently been confirmed by other groups (Lopez et al., 2003; Sanchez et al., 2010). TLR-2 is also involved in the production of IL-1β following infection by M. tuberculosis (Kleinnijenhuis et al., 2009).

In human cells, stimulation of TLR-2 triggers a pathway that involves upregulation of the vitamin D receptor and the vitamin D-activating enzyme CYP2R1, transcription of cathelicidin and beta 4 defensin, and culminates in the colocalization of cathelicidin and mycobacteria and intracellular killing of bacteria (Liu et al., 2006). Similarly, autophagy in response to the mycobacterial lipoprotein LpqH is TLR1/2- and vitamin D receptor-dependent (Shin et al., 2010). TLR-2 may also be involved in mycobacterial inhibition of host immune responses; Noss and colleagues reported that inhibition of MHC-II antigen processing by the 19 kDa mycobacterial lipoprotein was TLR2-dependent (Noss et al., 2001). Further work demonstrated that this was mediated via TLR2-dependent inhibition of IFN-γ-regulated HLA-DR protein and mRNA expression (Gehring et al., 2003). It has subsequently been shown that exposure of the murine J774 macrophage cell line to the TLR2 ligands 19 kDa mycobacterial lipoprotein or zymosan, but not the TLR4 ligand LPS, inhibits IFN-γ-induced killing of M. bovis BCG in a TLR2-dependent manner (Arko-Mensah et al., 2007). In addition, mycobacterial CpG motifs have been found to be recognized by TLR-9 (Carvalho et al., 2011), and classical TLR-9 signalling has been shown to be blocked by MAP in bovine monocytes (Arsenault et al., 2013).

Genetic associations between TLR gene polymorphisms and TB susceptibility have been reviewed previously (Azad et al., 2012). Briefly, associations between TLR2 gene polymorphisms and TB, particularly extrapulmonary TB, have been reported for a range of different human populations in Africa and Asia (Chen et al., 2010; Motsinger-Reif et al., 2010). No studies have yet shown an association between TLR4 polymorphisms and TB in HIV-negative patients; however, a link between a TLR4 SNP and TB susceptibility in HIV-infected individuals has been reported (Pulido et al., 2010). Two studies have also reported an association between a TLR9 polymorphism and TB (Velez et al., 2010; Kobayashi et al., 2012). A study on a Columbian population found no association between TB susceptibility and polymorphisms in either TLR2, TLR4 or TLR9. However, this study may have been underpowered to detect minor associations (Sanchez et al., 2012). In addition, SNPs within the TIR domain containing adaptor protein gene (TIRAP, or Mal), which encodes a signalling adaptor protein downstream of TLR-2 and TLR-4, have also been associated with TB susceptibility in some studies (Selvaraj et al., 2010; Zheng et al., 2011).
The importance of TLRs in infection with *M. tuberculosis* in the murine model, particularly the key role of TLR-2 has previously been demonstrated (Drennan et al., 2004; Bafica et al., 2005; Mayer-Barber et al., 2010). However, these results do vary by model: Hölscer and colleagues report that *Thr2/4/9* triple knockout mice infected with 100 cfu (colony-forming unit) H37Rv have normal production of TNF-α, IL-12p40, normal CD4+ and CD8+ responses to stimulation with *M. tuberculosis* peptides, and no difference in bacterial burden at 150 days compared with wild-type mice (Holscher et al., 2008). These conflicting results may be due to different H37Rv exposure times. MyD88 is a signalling adaptor protein downstream of all TLRs, with the exception of TLR-3; it is also involved in other signalling pathways including IFN-γ and IL-18 (Sun and Ding, 2006; Schneider et al., 2010). In addition, MyD88−/− mice show a markedly increased susceptibility to infection with *M. tuberculosis*, which is thought to primarily reflect its role in IL-1β signalling (Holscher et al., 2008; Mayer-Barber et al., 2010).

With regards to other mycobacterial infections, genetic variants of the TLR1 gene have been identified as a major determinant of leprosy susceptibility (Wong et al., 2010). DNA sequence polymorphisms in TLR2 and TLR4 have also been associated with susceptibility to *M. leprae* infection (Hart and Tapping, 2012). In addition, susceptibility to MAP infection in cattle has been associated with polymorphisms in the bovine TLR1, TLR2 and TLR4 genes (Fig. 1) (Mucha et al., 2009).

**Conclusion**

Host macrophage and DC recognition of mycobacterial pathogens is a complex process: different populations of myeloid immune cells use different receptors or combinations of receptors and act in conjunction with other molecules to successfully identify and phagocytose mycobacteria, while the bacteria themselves may preferentially target-specific receptors to manipulate the host response and promote their own survival. Understanding these processes will help us to better understand the co-evolution of host immune genes and mycobacterial genomes. The development of effective vaccines against mycobacterial diseases will be paramount to the future of human and animal health. Deciphering the mycobacterial-specific mechanisms for evading macrophage and DC recognition will be key to this, including a greater knowledge of the relationship between different PRRs and mycobacterial disease prevalence across global populations. Future studies targeting different combinations of receptors may lead to a better appreciation of the complex interactions between phagocyte and mycobacterium. Ultimately, increasing our understanding of innate immune recognition of mycobacterial pathogens will aid in our ability to treat and prevent mycobacterial diseases.

**Conflict of interest**

The authors declare that they have no conflict of interest.

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