



# Innate Immune Pattern Recognition Receptors of *Mycobacterium tuberculosis*: Nature and Consequences for Pathogenesis of Tuberculosis

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## 1 Introduction

Tuberculosis (TB), predominately caused by the bacterium *Mycobacterium tuberculosis*, remains one of the world's most significant infectious diseases, with a worldwide yearly burden of approximately 8.7 million new cases of active TB, 1.4 million deaths and a third of the world's population with latent TB infection (LTBI) (WHO 2019). The major burden for TB disease is still borne by developing countries, with Asia (e.g. China and India) having the highest number of cases of the disease. The epidemiological trend in developed countries continues to be that the majority of TB cases have originated from recent immigrants that have come from TB endemic areas of the world (Zumla et al. 2013; Zaheen and Bloom 2020). There are also significant numbers of TB patients co-infected with Human immunodeficiency virus (HIV), particularly in sub-Saharan Africa, resulting in the highest rates of

TB cases per capita (WHO 2019). The outbreak of the COVID-19 pandemic may also result in a similar dangerous synergy with TB, although the impact of co-infection of *M. tuberculosis* with the SARS-CoV-2 virus in patients remains to be determined (Ong et al. 2020). The frequency of multi-drug resistant tuberculosis (MDR-TB) to the main drugs used for treatment (e.g. rifampicin and isoniazid) is still worryingly high, particularly in India, Russia, China, Pakistan and South Africa (WHO 2019; Zaheen and Bloom 2020). Of further concern is the rise of extensively drug resistant (XDR-TB) in several countries to all current second and third-line therapies (Zaheen and Bloom 2020).

There continues to be a strong concerted effort to develop new interventions and therapies against TB with a particularly important focus on understanding innate immunity against TB particularly in the early stages of infection and the granuloma. It is well known that *M. tuberculosis* is able to persist as an intracellular parasite for years in the host as LTBI, mainly because of its ability to persist in the host macrophage by manipulating phagolysosome maturation, providing a favourable niche for it to be able to reside (Russell 2001; Gupta et al. 2012). *M. tuberculosis*-infected macrophages in LTBI are predominantly present within the granuloma, which is a complex structure of T cells, B cells,

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and giant epithelioid cells among others and a resectioning of tissue to contain these infected macrophages (Gupta et al. 2012). The formation and maintenance of this immune cordon against TB infection is crucial in preventing disseminated disease and transmission of the infection to other hosts. It is still not fully understood how the granuloma is formed and maintained in TB infection and the full extent of the contribution played by innate immunity. Here, we will discuss the latest advancements in the understanding of innate immune recognition of *M. tuberculosis* and how these contribute to both downstream protection and pathogenesis of TB.

The primary interactions of *M. tuberculosis* with the host upon inhalation remain to be determined fully, particularly the targeting and recognition by the innate immune response. The lungs are the main route of entry to the host for *M. tuberculosis* and is the main anatomical site for infection and pathogenesis, but not entirely as extra-pulmonary TB (EPTB) also relatively commonly occurs in 10–42% of cases (Caws et al. 2008). The establishment and dissemination of *M. tuberculosis* infection is dependent on several host and pathogen factors with the pathogen able to alter and circumvent facets of both the innate and adaptive immune responses. Initially, *M. tuberculosis* bacilli, within aerosol droplet nuclei (on average 4–7 $\mu$ m in size), are inhaled into the pulmonary alveoli where they come into primary contact and are phagocytosed by alveolar macrophages (Fennelly et al. 2004; Fennelly 2020). During this interaction, most of the bacilli are killed, but some can endure within the macrophage (Russell 2001; Gupta et al. 2012). The recognition and uptake of *M. tuberculosis* by the host is governed by several soluble and cell-bound factors such as pattern recognition receptors (PRRs) that recognise pathogen-associated molecular patterns (PAMPs) that are present on the surface of microbes and normally absent on host cells. Examples of PAMPs include lipopolysaccharide (LPS), porins, peptidoglycan, lipoteichoic acid (LTA), mannose-rich glycans, flagellin, bacterial and viral genomes, mycolic acid, and lipoarabinomannan (LAM). PRRs include phagocytic PRRs and signalling PRRs.

Examples of phagocytic PRRs include C-type lectins receptors (CTLRs) (e.g. collectins such as surfactant protein A (SP-A), surfactant protein D (SP-D), mannose receptor (MR), Dectin-1), scavenger receptors (e.g. CD-36, CD68, and SRB-1), opsonic receptors (e.g. plasma acute phase proteins like mannose binding lectin (MBL), C-reactive protein (CRP)) and complement proteins (e.g. C3b, iC3b, factor H and properdin). Signalling PRRs are either present on cell surface (e.g. Toll-like receptors (TLRs), CD14, on intracellular membranes (e.g. endosomes, lysosomes) or in the cytoplasm (e.g. nucleotide-binding oligomerization domain (NOD)-like receptors. In microbial infection and in particular *M. tuberculosis* infection the type of interaction of PRRs with PAMPs and innate immune cells (e.g. macrophages) also determine the subsequent cell signalling pathways (leading to production of cytokines/chemokines), which initiates inflammation and tissue modification (e.g. granuloma formation) (Feng et al. 2006; Lockhart et al. 2006; Eum et al. 2010). Furthermore, the formation of the granuloma occurs without the requirement for specific immunity (North and Izzo 1993; Hansch et al. 1996; Smith et al. 1997), with both tumour necrosis factor alpha (TNF- $\alpha$ ) and interferon gamma (IFN- $\gamma$ ) being the foremost signalling cytokines for cell infiltration, although they are not needed to begin the process of granuloma formation (Flynn et al. 1995; Smith et al. 1997).

After *M. tuberculosis* enters the alveoli space, the bacteria are internalized into alveolar macrophages by phagocytosis, a process triggered by receptor-ligand engagement. *M. tuberculosis* tends to target binding to macrophages in cholesterol-rich regions of the host cell membrane (Gatfield and Pieters 2000). Mycobacteria can be targeted via a wide variety of receptors that recognise opsonised and non-opsonised bacilli. These include collectins (SP-A, SP-D, conglutinin), MR (CD207), dendritic-cell-specific intercellular adhesion molecule-3 grabbing non-integrin (DC-SIGN), dectin-1, complement receptors (CR), surfactant protein (SP) receptors, scavenger receptors, and glycosylphosphatidylinositol (GPI)-anchored receptors such as CD14 (Schlesinger et al. 1990;

Schlesinger 1993; Stokes et al. 1993; Hirsch et al. 1994; Zimmerli et al. 1996; Ehlers and Daffe 1998; Ernst 1998; Peyron et al. 2000; Rooyackers and Stokes 2005). Various TLRs have also been shown to play important roles in *M. tuberculosis* interactions on the surface and within phagocytic cells (Means et al. 1999). In addition, *M. tuberculosis* can also recruit several host cell molecules on its surface that enhance its uptake by phagocytes.

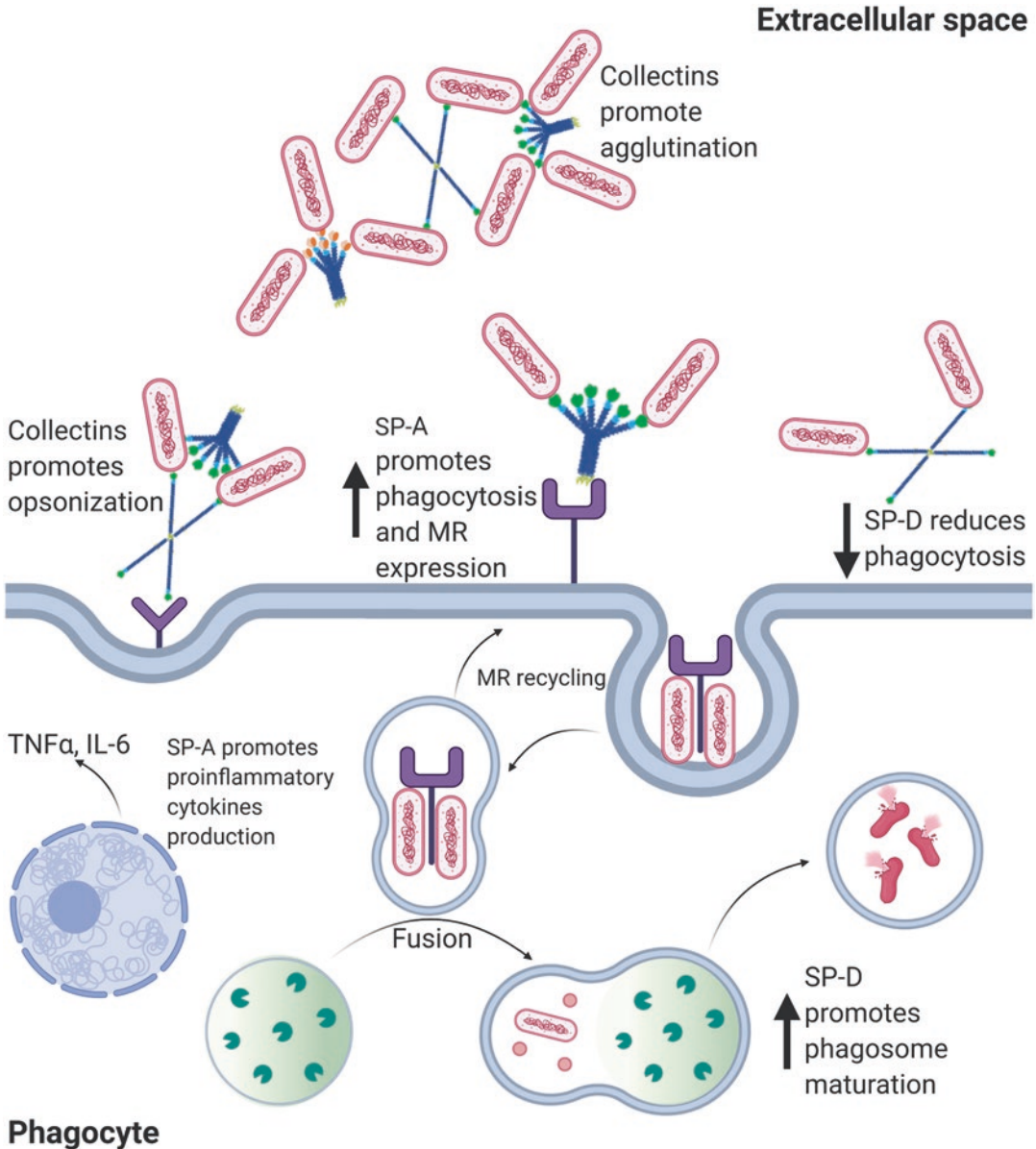
## 2 Collectins and Mycobacteria

Collectins are a group of soluble C-type (calcium-dependent) lectins, characterised by an N-terminal collagen region, an alpha helical coil neck motif, and a C-terminal carbohydrate recognition domain (CRD). Collectins can recognise and bind to PAMPs on variety of microbes via their CRD region and have a crucial role in their neutralisation and clearance but are also a critical bridge between the innate immunity and adaptive immunity (Kishore et al. 2006). The mammalian collectin family comprises of SP-A and SP-D, MBL, liver collectin (CL-L1), kidney collectin (CL-K1), CL-LK (composed of CL-L1 and CL-K1) and placenta collectin (CL-P1), conglutinin, CL-43 and CL-46, with the latter three found in Bovidae (Murugaiah et al. 2020; Tsolaki and Kishore 2020). Several of these collectins have a role in mycobacterial infection and pathogenesis.

Both SP-A and SP-D are the most relevant collectins for pulmonary TB as they are important components of pulmonary surfactant which is essential for the physiology of alveoli (Murugaiah et al. 2020). Furthermore, early observations also showed that pulmonary surfactant had anti-microbial properties being able to enhance clearance of *Staphylococcus aureus* by alveolar macrophages (AM) (Laforce et al. 1973). In fact, both SP-A and SP-D can target Gram-negative and Gram-positive bacteria enhancing their clearance through phagocytosis by AM (Pikaar et al. 1995).

Both SP-A and SP-D can bind and agglutinate mycobacteria but seem to have opposing effects

on the phagocytosis of *M. tuberculosis*. SP-A targets the putative surface adhesin Apa glycoprotein on *M. tuberculosis* (Ragas et al. 2007), whilst SP-D can also bind to LTA and peptidoglycan and to lipoarabinomannan (LAM) from *M. tuberculosis* and *Mycobacterium avium* (Ferguson et al. 1999; Van De Wetering et al. 2001; Kudo et al. 2004). SP-A can facilitate uptake of *M. tuberculosis* and *M. avium* by enhancing the expression of macrophage MR (Gaynor et al. 1995; Beharka et al. 2002; Kudo et al. 2004) (Fig. 9.1). Similarly, SP-A enhances expression of scavenger receptor A (SR-A), increasing the phagocytosis of *Streptococcus pneumoniae* by AM (Kuronuma et al. 2004). Additionally, bound SP-A can also facilitate uptake of *Mycobacterium bovis* bacillus Calmette-Guérin (BCG) by binding to specific 210-kDa SP-A receptor (SPR210) in U937 macrophages and rat AM (Chronoes et al. 1996; Weikert et al. 1997). Furthermore, this interaction led to increased mycobacterial killing and production of TNF- $\alpha$  and nitric oxide (Weikert et al. 2000). In contrast, SP-D inhibits phagocytosis of *M. tuberculosis* by blocking the interaction of LAM with macrophage MR, and is independent of agglutination by SP-D (Ferguson et al. 1999; Ferguson et al. 2002) (Fig. 9.1). Gene knockout mice (SP-A<sup>-/-</sup>, SP-D<sup>-/-</sup>, and SP-A/D<sup>-/-</sup>) infected with *M. tuberculosis*, still processed the ability for phagocytosis and bacterial clearance, suggesting that both SP-A and SP-D are not crucial for protection in this animal model for TB (Lemos et al. 2011). SP-A and SP-D can also influence the intracellular environment post phagocytosis, by stimulating and enhancing reactive oxygen and nitrogen species enabling the killing of intracellular pathogens such as mycobacteria (Fig. 9.1). SP-A enhances the intracellular killing of *M. bovis* BCG by enhancing nitric oxide (NO) levels and releasing TNF- $\alpha$  (Weikert et al. 2000). However, in *M. tuberculosis* and *M. avium*-infected AM primed by IFN- $\gamma$ , SP-A was able to suppress intracellular NO levels by inhibiting TNF- $\alpha$  production and nuclear factor-kappa B (NF- $\kappa$ B) activation (Pasula et al. 1999; Hussain, 2003). Thus, SP-A facilitates the intracellular survival of *M. tuberculosis* (Gaynor et al. 1995; Pasula et al. 1999). Moreover, HIV-1 infected



**Fig. 9.1** Role of collectins in recognising *M. tuberculosis* and subsequent consequences. SP-A and SP-D can bind and agglutinate mycobacteria but have opposing effects on phagocytosis. SP-A binds to *Apa* glycoprotein, whilst SP-D binds to lipoteichoic acid, peptidoglycan and to lipoarabinomannan (LAM) on *M. tuberculosis*. SP-A

enhances the expression of macrophage mannose receptor (MR) facilitating uptake of *M. tuberculosis*, increasing mycobacterial killing and production of inflammatory components TNF- $\alpha$  and IL-6. SP-D inhibits phagocytosis of *M. tuberculosis* by blocking the interaction of LAM with macrophage MR

patients, who had raised levels of pulmonary SP-A, had a significantly greater susceptibility to *M. tuberculosis* infection (Downing et al. 1995). Thus, SP-A appears to have pleiotropic effects being able to both enhance inflammation in the

presence of infected macrophages and inhibit inflammation in uninfected macrophages, thus possibly acting as a protective molecule against lung tissue damage from excessive and non-specific inflammation (Gold et al. 2004).

A number of genetic polymorphisms in the SP-A and SP-D genes are associated with TB susceptibility and protection in humans. SP-A is secreted as two distinct variants (SP-A1 and SP-A2) which are coded for by distinct genes. In individuals from Mexico, Ethiopia, India and China, mutations within and flanking the SP-A1 and SP-A2 genes are linked with protection or susceptibility toward pulmonary TB (Floros et al. 2000; Madan et al. 2002; Malik et al. 2006; Vaid et al. 2006; Yang et al. 2014). A study of Indian individuals identified a single mutation in the SP-D gene that was significantly associated with TB susceptibility (Vaid et al. 2006).

MBL is a serum protein and has a similar overall structure to SP-A and can target PAMPs on the surface of several Gram-positive and Gram-negative bacteria (Ip et al. 2009; Lugo-Villarino et al. 2011). MBL that is bound to microbial surfaces can activate complement via MBL-associated serine proteases (MASPs) of the lectin complement pathway, resulting in deposition of complement components (e.g. C3 and C4) that facilitates microbial phagocytosis and clearance. MBL also possesses complement-independent activity, acting directly as an opsonin, and an inhibitor of bacterial adhesion (Kuhlman et al. 1989; Polotsky et al. 1997; Jack et al. 2005). MBL can also bind to peptidoglycan and LTA from *Staphylococcus aureus* (Polotsky et al. 1996; Nadesalingam et al. 2005). In mycobacteria, MBL can bind to LAM from *M. avium* (Polotsky et al. 1997), antigen 85 (Ag85) of *M. tuberculosis* (Swierzko et al. 2016), and mannosylated lipoarabinomannan (ManLAM) from several mycobacterial species (*M. tuberculosis*, *M. bovis*, *M. kansasii*, *M. goodii* and *M. smegmatis*) (Bartlomiejczyk et al. 2014). MBL can also enhance the uptake of mycobacteria by macrophages (Polotsky et al. 1997). Both normal and elevated levels in serum MBL have been associated with recurrent infection with *M. tuberculosis* and *M. leprae*, probably driven by enhanced complement-mediated phagocytosis (Garred et al. 1994, 1997). Genetic polymorphisms associated with MBL serum-deficiency are common and some of these are linked to sus-

ceptibility to TB and other inflammatory diseases in several ethnicities (Takahashi and Ezekowitz 2005; Thiel et al. 2006; Goyal et al. 2016). Among the minor collectins, CL-L1, CL-K1 and CL-P1 bind to bacteria, with CL-K1 being able to bind *M. tuberculosis* (Troegeler et al. 2015). The heteromeric form CL-LK binds to ManLAM of *M. tuberculosis*, but not *M. smegmatis* because of the absence of capped mannose on its LAM (Troegeler et al. 2015). Furthermore, serum levels of CL-LK in TB patients are almost depleted, compared to normal healthy controls (Troegeler et al. 2015).

Of the bovine collectins, conglutinin has protective activity against several microbes, including mycobacteria. Conglutinin has a similar structure to SP-D (which targets mycobacterial LAM) (Murugaiah et al. 2020) but is predominantly a serum protein synthesised by the liver (Holmskov et al. 1998). Conglutinin has antimicrobial properties; low serum levels of conglutinin are linked with acute infections (e.g. pneumonia, metritis and other respiratory infection) (Ingram and Mitchell 1971; Holmskov et al. 1998). Conglutinin is able to bind to Gram-positive bacteria such as mycobacteria (Dec et al. 2012; Mehmood et al. 2019), and uniquely to complement C3 fragment iC3b, via the mannose residues (Laursen et al. 1994). A recombinant truncated form of conglutinin (rfBC), containing the  $\alpha$ -helical neck region and the CRD of conglutinin (Wang et al. 1995), is able to bind to *M. bovis* BCG and inhibit phagocytosis of the bacterium both in the presence and absence of complement deposition (Mehmood et al. 2019). Furthermore, there is a modulation of the inflammatory response with the elevation of pro-inflammatory cytokines (IL-1 $\beta$ , TNF- $\alpha$ , IL-6, IL-12) and suppression of anti-inflammatory cytokines (TGF- $\beta$  and IL-10) (Mehmood et al. 2019). Thus, it is probable that conglutinin interferes with the phagocytosis of *M. bovis* BCG by macrophages through two separate mechanisms: firstly, inhibiting binding of mycobacterial LAM (like SP-D) with mannose receptor, and secondly, inhibiting binding of iC3b with complement receptors CR3 and CR4 (Mehmood et al. 2019).

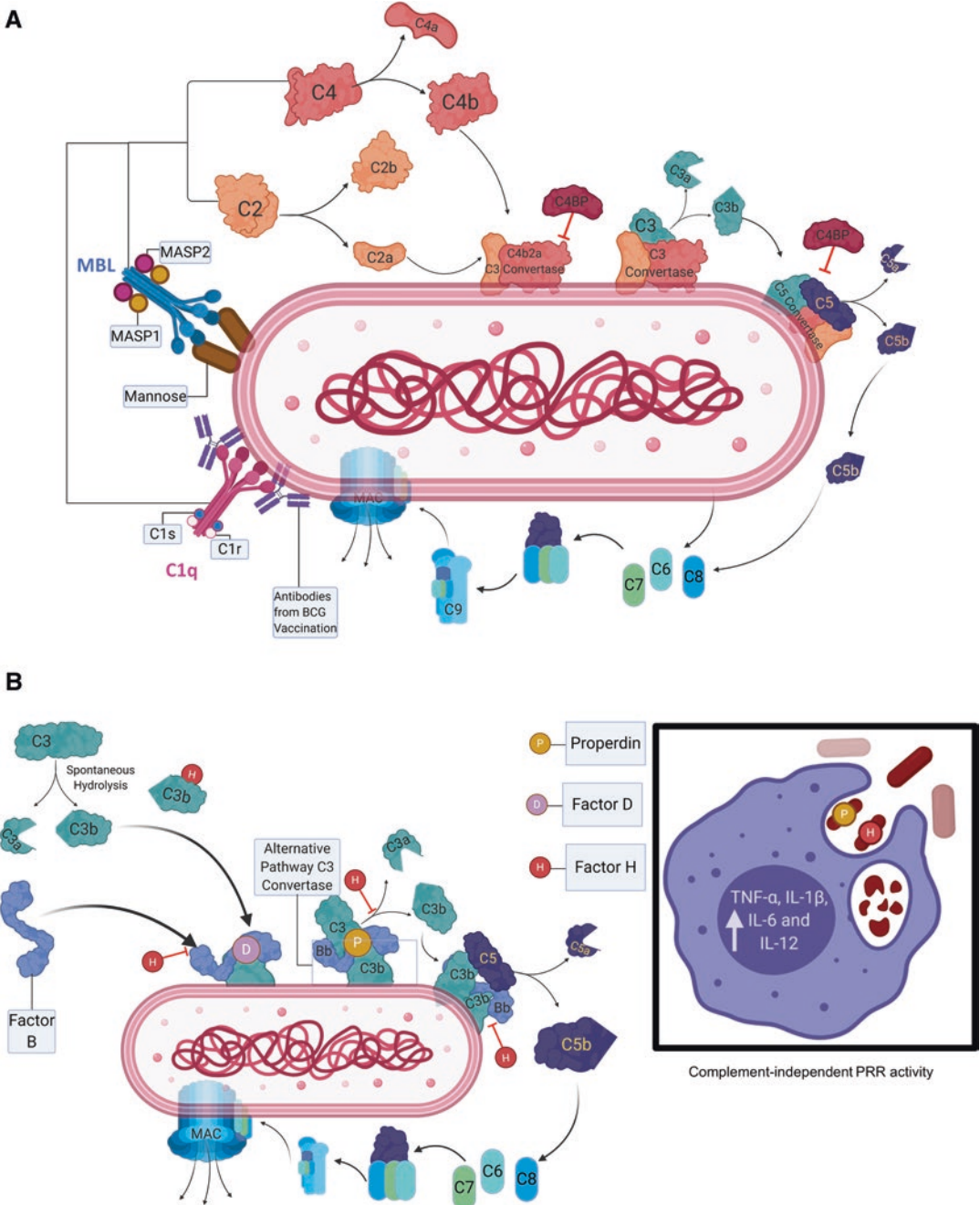
### 3 Complement and Mycobacteria

The complement system is a major arm of the innate immune response and is crucial for clearing microbial infection. The interactions between complement system and mycobacteria are not fully understood and this is probably more important in EPTB and disseminated disease than pulmonary TB. The complement system is composed of nearly 50 different proteins that are involved in three distinct pathways for activation: Alternative, Classical and Lectin (Carroll and Sim 2011) (Figs. 9.2a, b). Complement can be activated through several target surfaces including pathogens and altered-self cells or indirectly by pathogen-bound antibodies and results in the covalent binding of C3b component to the targeted cell, and subsequent cell lysis via the assembly of the membrane attack complex (MAC) (Carroll and Sim 2011). The classical pathway is activated by C1q binding to a target ligand either directly or to bound IgG/IgM antibodies (Fig. 9.2a). The lectin pathway is activated by the binding of MBL or ficolins to a target ligand (Matsushita and Fujita 1992; Matsushita et al. 2000; Matsushita and Fujita 2001) (Fig. 9.2a). However, the alternative pathway is activated differently and does not require an initiator like C1q or MBL but instead relies on the constant spontaneous hydrolysis of C3 to C3(H<sub>2</sub>O). The consequences of complement activation by any pathway is the formation of C3 convertase and the deposition of C3b on target surfaces to prompt opsonisation, the formation of the MAC and several other immunological functions (Carroll and Sim 2011) (Fig. 9.2b). There are also other complement regulatory proteins such as properdin (CFP) and factor H (CFH), where the latter is also a cofactor for factor I that is involved in the cleavage of C3b to iC3b (Whaley and Ruddy 1976a; Sim et al. 1993) (Fig. 9.2b).

In the classical pathway, C1q seems to bind in the presence of IgG and IgM from serum, presumably because of *M. bovis* BCG vaccination (Carroll et al. 2009). Experiments using C1q-deficient serum result in a reduction of C3 bind-

ing to mycobacteria (Ferguson et al. 2004). The levels of C1q are significantly elevated in the lungs (determined by bronchoalveolar lavage (BAL) and sera of active TB patients), compared to control patients and those with LTBI, indicating that C1q is an important biomarker for TB (Lubbers et al. 2018). The classical pathway may be more relevant in EPTB where C1q is predominantly a serum protein, however, local pulmonary synthesis occurs in the lungs during active TB accounting for the raised levels of C1q observed. Furthermore, systemic and local C1q levels are raised significantly upon vaccination with BCG in non-human primates (Dijkman et al. 2020). Complement receptor CR3 deficient mice (CR3<sup>-/-</sup>), infected with *M. tuberculosis*, had a lower percentage of infected macrophages at 2 h but not at 4 h post infection, suggesting the opsonisation and uptake via complement and receptors may be key during the early stages of infection (Hu et al. 2000). Genetic polymorphisms in complement receptor CR1 have been reported to increase susceptibility to *Mycobacterium leprae* infection and TB disease (Fitness et al. 2004a, b; Kretzschmar et al. 2018), whilst a congenital deficiency of the classical pathway did not seem to affect susceptibility to TB (Kumararatne 1997). In contrast, a recent study has shown that polymorphisms in the C1q gene cluster are significantly associated with TB susceptibility and differing plasma levels of C1qA in South African TB patients (Bruiners et al. 2020).

The alternative pathway differs from the classical and lectin pathways because it does not need a specific stimulus for activation, since the alternative pathway is constantly active at low levels and able to target pathogens promptly (Kouser et al. 2013). Properdin (CFP) is a key regulatory protein of the alternative pathway and contains thrombospondin (TSR) type 1 repeats (TSR1-TSR6), which are crucial for its function; TSR4 stabilises C3bBb; whilst TSR5 binds to C3b (Higgins et al. 1995; Kouser et al. 2013). Both CFP and recombinant TSR4 + 5 are able to bind to *M. bovis* BCG, inhibiting its uptake by macrophages (Al-Mozaini et al. 2018). In contrast, CFH downregulates complement activation



**Fig. 9.2** Role of complement activation and complement proteins in recognising *M. tuberculosis* and subsequent consequences. (a) The classical pathway is activated by C1q binding to a target ligand either directly or to bound or anti-mycobacterial antibodies. The lectin pathway is activated by the binding of MBL or ficolins to target myco-

bacterial ligands. (b) The alternative pathway is activated via the constant spontaneous hydrolysis of C3 to C3(H<sub>2</sub>O). Properdin and factor H both act as pattern recognition receptors (PRR) and have complement independent functions on mycobacteria, being able to inhibit phagocytosis and alter the subsequent inflammatory response

but has also been shown to bind to *M. bovis* BCG and inhibit its uptake by macrophages in a similar manner (Carroll et al. 2009; Abdul-Aziz et al. 2016). Both CFP and CFH are also able to modulate the immune response from the macrophage during *M. bovis* BCG phagocytosis by enhancing the pro-inflammatory response (TNF- $\alpha$ , IL-1 $\beta$ , IL-6 and IL-12) and dampening the anti-inflammatory response (TGF- $\beta$  and IL-10). This suggests consequences for the adaptive immune response to follow against *M. tuberculosis* infection, particularly in the formation and maintenance of the protective granuloma.

The lectin pathway is primarily triggered by MBL and ficolins that recognise terminal sugar residues on the surface of bacteria (e.g. mannose, fucose and N-acetyl-glucosamine) and subsequently activates MASPs resulting in the cleavage of complement components C4 and C2 to C4bC2a. There are three human ficolins: L-ficolin and H-ficolin, which are synthesised by the liver and predominantly circulate in the serum and M-ficolin which exist in granules of monocytes, neutrophils, and type II alveolar epithelial cells. All three human ficolin can associate with MASPs and activate the complement cascade (Liu et al. 2005). MBL and ficolins can bind to several mycobacteria (*M. tuberculosis*, *M. goodii*, *M. kansasii* and *M. smegmatis*) (Bartlomiejczyk et al. 2014). Direct binding of L-ficolin from human serum to *M. bovis* BCG and subsequent MASP-2 activation has been reported, but no binding was detected for H-ficolin (Carroll et al. 2009). L-ficolin is also able to bind with higher affinity to *M. tuberculosis* than to non-virulent mycobacteria and inhibit infection of human lung A549 epithelial cells (Luo et al. 2013). In mice, exogenously administered L-ficolin had a significant protective effect against virulent *M. tuberculosis* infection, whilst Ficolin-A (homologous to human L-ficolin in mouse) demonstrated increased susceptibility to *M. tuberculosis* infection (Luo et al. 2013). Furthermore, L-ficolin also modulates the immune response against *M. tuberculosis* infection by partially activating c-Jun N-terminal kinase (JNK) phosphorylation, stimulating the secretion of IFN- $\gamma$ , IL-17, IL-6, TNF- $\alpha$ , and NO

production by macrophages (Luo et al. 2013). Clinically, L-ficolin serum levels in pulmonary TB patients are much lower than compared to healthy controls (Luo et al. 2013), suggesting an important role for L-ficolin in *M. tuberculosis* infection.

The cell wall of mycobacteria is complex and is composed of a thick peptidoglycan layer, which covers the bacteria plasma membrane and is the scaffold to which various components are covalently attached (e.g. LAM, arabinogalactans, arabinomannans, glycolipids and mycolic acids) (Daffe and Draper 1998). Furthermore, there is also a capsule layer surrounding the mycolates made up of additional proteins, polysaccharides and lipids (e.g. phospholipids and glycolipids) (Daffe and Etienne 1999). One of these components is trehalose dimycolate (TDM) (also known as cord factor), which activates complement (Ramanathan et al. 1980). The complex mycobacterial cell wall has evolved to protect the bacterium from immunological attack (particularly intracellularly), but also plays a major role in determining ant-mycobacterial drug efficacy (Besra 1998). Several bacteria have evolved strategies to circumvent the immune response by interfering and inhibiting complement activation by either producing bacterial complement inhibitors, inactivating host complement inhibitors (e.g. CFH), or secreting bacterial proteases that break-down complement proteins (e.g. *Salmonella enterica* and *Porphyromonas gingivalis*) (Wingrove et al. 1992; Jagels et al. 1996; Ramu et al. 2007). *M. tuberculosis* is a highly evolved intracellular pathogen, being able to persistently reside in the phagosome of macrophages. Nevertheless, the interaction of complement and mycobacteria and the implications for pathogenesis and protection against TB are not well understood.

*M. bovis* BCG can activate the classical, lectin and alternative pathways (Ramanathan et al. 1980; Ferguson et al. 2004; Carroll et al. 2009). Activation via the alternative pathway also occurred in the absence of antibody, but intriguingly CFH was also found to bind to the mycobacterial surface, possibly indicating a means for complement moderation (Carroll et al. 2009).



Although C3b is deposited on the mycobacterial surface (Carroll et al. 2009), it is not clear if MAC formation occurs. The fixation of complement proteins on the mycobacterial surface may enhance the phagocytosis of mycobacteria via complement receptors. Several studies have reported C3b deposition on mycobacteria and its role in phagocytosis via complement receptors CR1, CR3 or CR4 on macrophages (Hetland and Wiker 1994; Schlesinger and Horwitz 1994; Cywes et al. 1996; Hetland et al. 1998; Mueller-Ortiz et al. 2001; Ferguson et al. 2004). However, the specific importance of C3b and iC3b deposition on mycobacteria is not well understood. Complement activation by classical and alternative pathways has been shown on *M. tuberculosis* and *M. bovis* BCG resulting in C3b and iC3b deposition, but the target ligands are not known (Ferguson et al. 2004; Carroll et al. 2009). During the alternative pathway, CFH plays a major role in the cleavage of C3b to iC3b by acting as a cofactor of factor I, whilst also controlling the formation of the C3 and C5 convertases (Whaley and Ruddy 1976b; Whaley et al. 1976). C3b component is essential for the complement cascade to proceed to the terminal MAC, whilst iC3b is unable to facilitate this. Also, both C3b and iC3b have different complement receptors (C3b is a ligand for CR1; iC3b is a ligand for CR3 and CR4) (Ross 1986). iC3b exists as a cleavage product from C3b produced by factor I with cofactors CFH and CR1 (Figuroa and Densen 1991). Thus, both opsonic C3b or iC3b complement components may facilitate phagocytosis of host cells by mycobacteria, either promoting clearance or intracellular persistence. Indeed, a recent study showed enhanced uptake of complement-deposited *M. bovis* BCG by THP-1 macrophages compared to non-deposited *M. bovis* BCG (Mehmood et al. 2019). This same study also observed that phagocytosis of complement-deposited *M. bovis* BCG bacteria are inhibited from phagocytosis by THP-1 macrophages by rfBC (a recombinant truncated form of bovine conglutinin) which uniquely binds to iC3b (Mehmood et al. 2019). These observations suggest that the blocking of iC3b by conglutinin may be indicative of a protective mechanism against

mycobacterial infection in the bovine host, by inhibiting phagocytosis via macrophage receptors CR3 and CR4 (Mehmood et al. 2019).

Both properdin (CFP) and factor H (CFH) are complement components that have also been observed to bind to mycobacteria in a dose-dependent manner and independently of C3b deposition (Carroll et al. 2009; Abdul-Aziz et al. 2016; Al-Mozaini et al. 2018). Both CFP and CFH have been shown to be PRRs for mycobacteria that have complement-independent functions. *M. bovis* BCG bound with CFP or CFH are inhibited for phagocytosis by THP-1 macrophages compared to *M. bovis* BCG alone (Al-Mozaini et al. 2018; Abdul-Aziz et al. 2016). Moreover, the subsequent macrophage inflammatory response was altered in terms of enhanced secretion of TNF- $\alpha$ , IL-1 $\beta$ , IL-6 and IL-12, whilst simultaneously dampening anti-inflammatory cytokines (TGF- $\beta$  and IL-10) (Al-Mozaini et al. 2018; Abdul-Aziz et al. 2016). CFH binding has been reported in other bacteria where it serves to circumvent complement activation and thus opsonisation and killing through MAC (e.g. *S. pyogenes*, *Streptococcus pneumoniae*, *Yersinia enterocolitica*, *Haemophilus influenza*, *Neisseria gonorrhoea* and *N. meningitidis* (China et al. 1993; Diaz et al. 1997; Ram et al. 1998a, b; Dave et al. 2001; Meri et al. 2002; Schneider et al. 2006). In the case of mycobacterial infection, the ability to bind CFH may serve its immune evasion by activating C3 and using C3b opsonisation to enhance phagocytosis by macrophages via complement receptors (Schlesinger et al. 1990; Ferguson et al. 2004). These intriguing results describe potentially novel mechanisms in shaping the adaptive immune response against mycobacterial infection. For *M. tuberculosis*, there is a fine balance in activating complement to an optimum limited level to allow for enhanced opsonisation and uptake into macrophages, whilst avoiding being killed. Thus, the complex interactions between *M. tuberculosis* and complement is a major mechanism through which mycobacteria can evade the immune response by persistently intracellularly in the macrophage.

CR3 is an integrin (also known as  $\alpha_M\beta_2$ ; CD11b/CD18), commonly expressed on

neutrophils, macrophages, NK cells, and monocytes and is involved in both opsonic and non-opsonic phagocytosis (Le Cabec et al. 2002; Velasco-Velazquez et al. 2003). CR3 can bind iC3b (particularly on complement-deposited mycobacteria), mycobacterial LAM, Ag85C, PIMs, ICAM-1, several bacterial ligands and other carbohydrate residues (e.g.  $\beta$ -glucan, glucose, N-acetylglucosamine (GlcNAc) (Arnaout 1990; Ehlers and Daffe 1998; Velasco-Velazquez et al. 2003; Villeneuve et al. 2005). Elevated levels of CR3 in tuberculosis patients have been reported in several studies, particularly in phagocytic cells in the peripheral blood and AMs, suggesting a probable role in pathogenesis (Yassin and Hamblin 1994; Kuo et al. 1996; Juffermans et al. 2001). Indeed, complement activation via classical pathway in the lungs may also be a major mechanism for opsonin-mediated uptake of *M. tuberculosis* by AMs (Watford et al. 2000; Ferguson et al. 2004). However, CR3 deficiency in mice does not appear to affect the intracellular killing mechanisms (induction of reactive oxygen and nitrogen intermediates), or on the survival of the mycobacteria inside the cell, but it did result in reduced opsonisation and phagocytosis (Hu et al. 2000; Melo et al. 2000; Rooyackers and Stokes 2005). CR3 has been found associated with several GPI-anchored proteins localized in cholesterol-rich rafts of the plasma membrane in neutrophils and is involved in the uptake of *Mycobacterium kansasii* (Peyron et al. 2000). Moreover, the existence of host plasma membrane cholesterol appears to be critical for CR3-mediated uptake of *M. tuberculosis* (Gatfield and Pieters 2000; Peyron et al. 2000). *M. tuberculosis* may also use cholesterol as an energy source during intracellular survival in macrophages (Van Der Geize et al. 2007). Furthermore, survival of mycobacteria within the macrophage may depend on the receptor involved in phagocytosis, since pro-inflammatory responses and respiratory burst occurs when mycobacteria are phagocytosed via Fc receptors (Russell 2001), whilst macrophage activation is inhibited when mycobacteria are phagocytosed via CR3 receptors (Caron and Hall 1998).

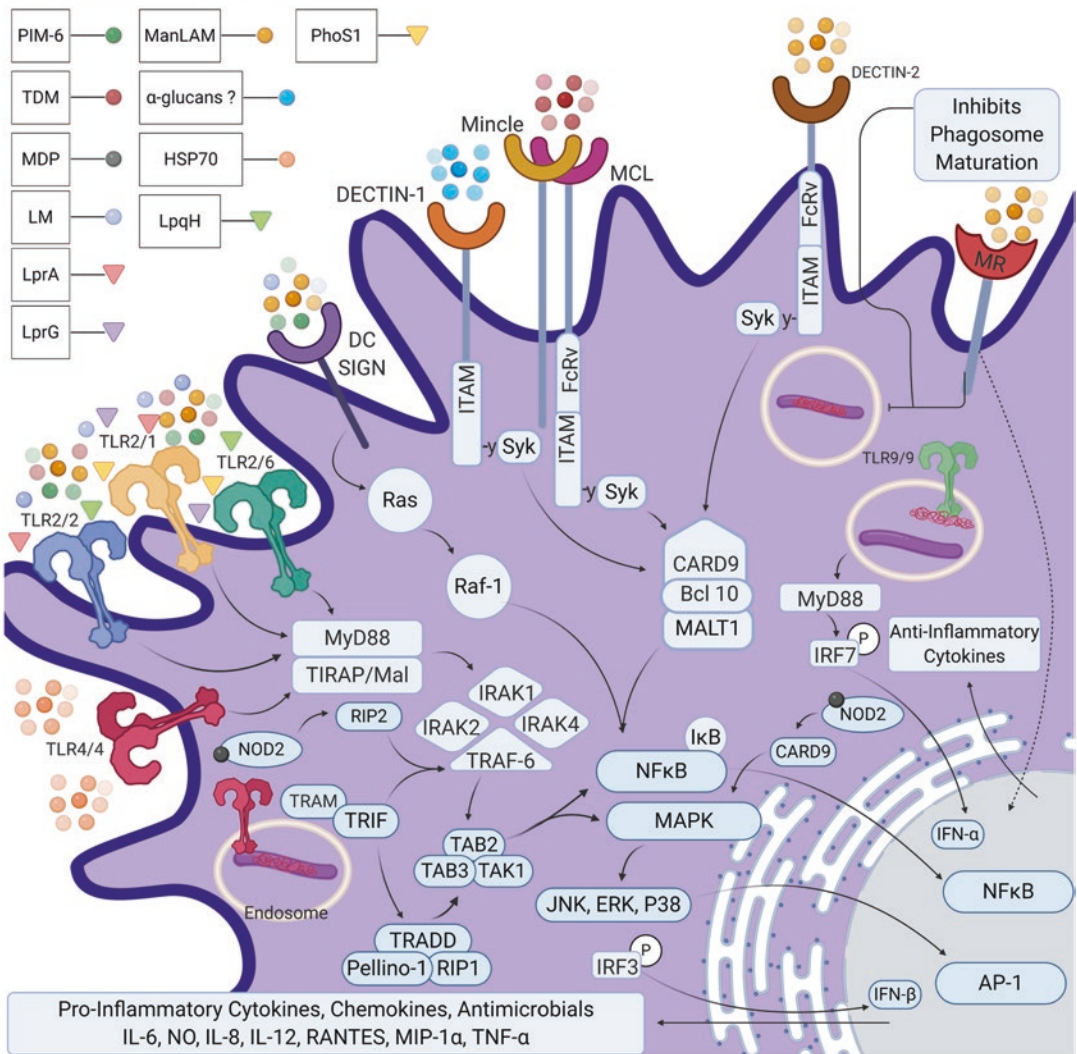
CR3 mediates the phagocytosis of ~80% of complement-opsonized *M. tuberculosis* (Schlesinger et al. 1990). CR3 is also able to facilitate phagocytosis of non-opsonized mycobacteria (Velasco-Velazquez et al. 2003). CR3 is mainly expressed on the cell surface of macrophages, neutrophils, monocytes, and natural killer cells. In lung alveolar macrophages, expression of CR3 is relatively low, whilst *in vitro*, differentiated macrophages have increased expression of CR3, enhancing their capacity to bind mycobacteria (Stokes et al. 1998). Several mycobacterial ligands are recognised by CR3, including Ag85C and LAM from *M. tuberculosis*, with the latter being the main ligand for CR3 (Velasco-Velazquez et al. 2003). Whilst CR3 plays a major role in facilitating the phagocytosis of *M. tuberculosis*, it does not necessarily result in the intracellular killing of the pathogen (Velasco-Velazquez et al. 2003; Rooyackers and Stokes 2005). Furthermore, it may also not be essential in protection against *M. tuberculosis* infection, since CR3-deficient and wild-type mice are equally resistant to *M. tuberculosis* infection, suggesting that *M. tuberculosis* phagocytosis may occur efficiently through alternative receptors (Hu et al. 2000). Therefore, the role of CR3 in TB pathogenesis may be redundant. To date, no genetic polymorphisms in the CR3 genes have been associated with susceptibility to TB.

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#### 4 Toll-like Receptors (TLRs) and Mycobacteria

TLRs are key signalling PRRs present on several immune and non-immune cells (e.g. monocytes/macrophages, B and T cells, dendritic cells, neutrophils, epithelial and endothelial cells). TLRs recognise a wide variety of microbial ligands (PAMPs) and host danger signals (DAMPs). TLRs have key roles in innate immunity and are an important bridge to adaptive immunity (Fig. 9.3). 13 TLRs have been described in human and mouse so far. TLRs are transmembrane proteins that have ligand sensing N-terminal leucine-rich extracellular domains and a cytoplasmic

**Mycobacterial ligands**



**Fig. 9.3** C-type lectin receptors (CTLRs) involved in the recognition of *M. tuberculosis* and subsequent consequences. Several mycobacterial ligands are recognised

by a variety of host CTLR PRRs that can stimulate a multitude of signalling pathways involved in mycobacterial phagocytosis, clearance, and inflammatory responses

Toll/IL-1R (TIR) C-terminal domain. The TIR domain mediates interactions between TLRs and adaptor proteins (e.g. myeloid differentiation primary response protein (MyD88), TIR domain-containing adaptor inducing IFN-β (TRIF), TIRAP/MAL, and TRAM) (Lim and Staudt 2013). Several kinases are also activated and involved in signalling, e.g. Interleukin-1 receptor-associated kinases (IRAK4, IRAK1, IRAK2), IκB kinase-ε (IKKε) and TANK-binding kinase-1

(TBK1), and ubiquitin ligases TNF receptor associated factor 6 (TRAF6) and Pellino-1. Upon ligand recognition, TLR signalling progresses via two distinct signalling pathways: either MyD88-dependent or TRIF-dependent pathway. Of the two, MyD88 is the most involved in TLR signalling. The triggering of the MyD88-dependent pathways ultimately results in the translocation of transcription factors NF-κB (RelA/p50) and activator protein 1 (AP1), inducing pro-

inflammatory cytokine production (IL-6, TNF- $\alpha$ , and IL-1 $\beta$ ). For the TRIF-dependent pathway (most relevant for TLR3 and TLR4), its signalling involves either 1) interaction with TRAF6 which goes on to activate transforming growth factor- $\beta$ -activated kinase (TAK1) complex that in turn activates NF- $\kappa$ B and mitogen-activated protein kinases (MAPKs), or 2) interaction of TRAF3 which induces activation of interferon-regulatory factor 3 (IRF3) transcription factor that leads to the production of type I interferon (IFN- $\alpha$  and IFN- $\beta$ ) (Kawai and Akira 2010).

In humans, TLR1, 2, 4, 5, 6, and 10 are found on the host cell surface and mainly target microbial surface components (e.g. membrane of cell wall ligands), whilst TLR3, 7, 8, and 9 are found intracellularly in the endolysosomal membrane compartments and target nucleic acids (Akira et al. 2006; Triantafilou et al. 2006; Seo et al. 2018). TLRs are key downstream signalling molecules which can stimulate the production of pro-inflammatory cytokines, chemokines, and interferons (type I IFN) (Kawai and Akira 2010). These pathways are sometimes over-activated, in an uncontrolled manner, in response to stimuli, generating severe immunopathology (Vijay 2018).

TLRs play several important roles in TB. In blood samples from patients with active pulmonary TB, the expression of several TLRs are upregulated (Chang et al. 2006). TLRs recognise *M. tuberculosis* or a variety of its components and can initiate a set of innate and adaptive immune responses (Jo et al. 2007). The main TLRs involved in host-pathogen interaction in TB are TLR2, TLR4, TLR9 and TLR1/TLR6 (Jo et al. 2007; Kim et al. 2019). The precise nature and consequence of the signalling pathways induced by mycobacteria remain to be fully understood (Berrington and Hawn 2007; Holscher et al. 2008). Although TLRs target *M. tuberculosis*, this does not occur directly, but is triggered intracellularly by TLR signalling via MyD88-dependant pathway (Quesniaux et al. 2004). This also results in the activation of pro- and anti-inflammatory responses via enhanced NF- $\kappa$ B expression and MAPKs activation generating secretion of TNF- $\alpha$ , IL-1 $\beta$  and IL-12, and production of nitric oxide (Yamamoto et al. 2003;

Jo et al. 2007; Xu et al. 2007; Jo 2008; Garlanda et al. 2007).

TLR2 plays a key role in recognising mycobacteria PAMPs and is central to activating the intracellular signalling that triggers NF- $\kappa$ B and MAPKs pathways, inducing secretion of pro-inflammatory cytokines and chemokines and initiating phagocytosis, intracellular killing of *M. tuberculosis*, and antigen presentation. TLR2 also works together with TLR4 and TLR9 during *M. tuberculosis* infection (Jung et al. 2006). TLR2 can bind to several mycobacterial ligands, such as LpqH, LprA, LprG, LAM, lipomannan (LM), 38-kDa lipoprotein, 19-kDa lipoprotein, phosphatidylinositol mannoside (PIMs) (Quesniaux et al. 2004; Kawai and Akira 2011; Kleinnijenhuis et al. 2011; Basu et al. 2012; Kim et al. 2019) (Fig. 9.3). However, TLR2 does not seem to be necessary for protection in mice during acute *M. tuberculosis* infection (Reiling et al. 2002; Sugawara et al. 2003; McBride et al. 2011). However, TLRs are important for the long-term control of the *M. tuberculosis* infection in mice (Abel et al. 2002; Drennan et al. 2004). TLR2 knockout mice (but not TLR6 knockout mice) have an impaired ability to clear *M. tuberculosis* infection and form granulomas compared to wild-type animals; TLR2-deficient mice have significantly lower pro-inflammatory cytokine production in response to *M. tuberculosis* infection (Reiling et al. 2002; Sugawara et al. 2003; Drennan et al. 2004). TLR2 knockout mice also exhibit increased *M. tuberculosis* bacterial load and impaired neutrophil inflammation via the downregulation of CXCL5 during infection (Gopalakrishnan et al. 2019). During *M. tuberculosis* infection, TLR2 is critical for the expression of TNF- $\alpha$  (Underhill et al. 1999), whilst both TLR2 and TLR6 are key in the expression IL-1 $\beta$  via MyD88 (Kleinnijenhuis et al. 2009). Another key cytokine in TB, IL-12, which is also dependent on TLR2 in macrophages and dendritic cells (Pompei et al. 2007). Indeed, the production of TNF- $\alpha$  and IL-12 is mainly dependent on TLR2 rather than TLR4 signalling during *M. tuberculosis* infection (Means et al. 2001), with TLR2 and TLR9 also being involved in controlling dendritic cell-derived IL-12 secretion in mice infected with

*M. tuberculosis* (Bafica et al. 2005). Furthermore, in monocytes, reactive oxygen species (ROS) production and the expression of CXCL8 and CCL2 is also dependant on TLR2 during *M. tuberculosis* infection (Lee et al. 2009a). In dendritic cells, TLR2 induces ROS production, facilitating dendritic cell maturation and subsequent lymphocyte proliferation during *M. tuberculosis* infection (Romero et al. 2016). *M. tuberculosis* lipoproteins induce significant signalling of TLR2 which inhibits macrophage major histocompatibility complex (MHC) class II (MHC-II) expression and antigen presentation (Fulton et al. 2004; Pai et al. 2004), resulting in poor activation of CD4<sup>+</sup> T cell responses (Noss et al. 2001; Jo 2008). TLRs gene polymorphisms also seem to have an influence on the immune response in TB (Mukherjee et al. 2019; Zhang et al. 2013b; Sun et al. 2015). A single nucleotide polymorphism (SNP) in the TLR2 gene resulting in an amino acid change (T597C) has been reported to be associated with the development of TB meningitis and miliary TB, suggesting that TLR2 may have relevance for the dissemination of *M. tuberculosis* infection (Thuong et al. 2007). Another gene polymorphism (rs5743708) in the TLR2 gene is also associated with higher risk for TB (Guo and Xia 2015).

TLR4 is an important sensor for bacterial endotoxins, particularly those derived from Gram-negative bacteria (e.g. LPS) (Pandey et al. 2014). In mycobacterial infection, the TLR4 signalling pathway plays a central role in immune response (Sepehri et al. 2019). Blocking interaction of *M. tuberculosis* with TLR4, using anti-TLR4 antibody and an endotoxin antagonist, inhibits macrophage-dependent killing of intracellular bacteria as well as the pro-inflammatory response (Means et al. 2001; Lv et al. 2017). TLR4 can target several *M. tuberculosis* ligands, such as heat shock proteins GrpE, Hsp65 and Resuscitation promoting factor (RpfB) (Kim et al. 2019). Additionally, mycobacterial LM can modulate macrophages inflammatory response via the TLR4 signalling (Doz et al. 2007). Both TLR4 and TLR2 expression is significantly upregulated in lymphocytes from patients with active pulmonary TB compared to healthy con-

trols (Chang et al. 2006). Furthermore, increased expression of TLR4, CD14 and MR on monocytes (but not TLR2) was observed in *M. bovis* BCG vaccinated individuals compared to those who were not vaccinated; BCG-vaccinated individuals showed elevated Th1 and Th17 immune responses (Kleinnijenhuis et al. 2014). However, *M. tuberculosis* H37Rv strain was able to significantly enhance the expression of TLR4, TNF- $\alpha$ , and scavenger receptors in neutrophils when compared to mycobacterial vaccine strains (Hilda et al. 2012). The importance of TLR4 in protecting mice from TB infection is controversial. TLR4-mutant mice were observed to be more susceptible to pulmonary TB than wild-type mice, and had a reduced capacity to produce IFN- $\gamma$  (Branger et al. 2004). After infection with *M. tuberculosis*, TLR4-mutant mice were observed to have lower pulmonary expression of TNF- $\alpha$ , IL-12p40, and monocyte chemoattractant protein 1, compared with the wild-type controls (Abel et al. 2002). In mice, cooperation between TLR4- and TLR2-dependent signalling is critical in macrophage apoptosis induced by *M. tuberculosis* infection, with the absence of TLR4 favouring necrosis instead (Sanchez et al. 2010). However, there are studies that report no significant difference in protection to *M. tuberculosis* infection between wild-type and TLR4-mutant mice (Shim et al. 2003; Gopalakrishnan et al. 2019). Thus, the precise role of TLR4 in TB remains to be fully determined (Reiling et al. 2002; Shim et al. 2003).

It is well known that TLR9 recognizes bacterial DNA, including *M. tuberculosis* DNA, with TLR9 signalling subsequently activating the macrophage pro-inflammatory response and induction of T-cell differentiation (Hemmi et al. 2000; Latz et al. 2004; Jo et al. 2007; Rahman et al. 2009). Cooperation between TLR9 and TLR2 have a protective role against *M. tuberculosis* infection, with TLR2/TLR9 knockout mice showing significantly enhanced susceptibility to infection, coupled together with suppressed levels of IL-12p40 and IFN- $\gamma$  production (Bafica et al. 2005). Interestingly, TLR9 knockout mice have modest susceptibility to *M. tuberculosis* infection compared to the TLR2/TLR9 double knockout

mice (Bafica et al. 2005). Macrophages, pre-treated with vitamin D, were able to significantly up-regulate TLR9 expression, which boosted the pro-inflammatory response to DNA from different evolutionary lineages of *M. tuberculosis* (Cervantes et al. 2019). TLR9 genetic polymorphisms in the human population may be linked to susceptibility to TB. In a meta-analysis of 1745 scientific articles, a single TLR9 polymorphism (rs352139) was identified that may be associated with decreased TB risk in Indonesians individuals, whilst increased risk in Mexican individuals (Chen et al. 2015). In a study of Vietnamese individuals, two further polymorphisms were identified, with the first (rs352142) strongly associated with meningeal TB, and the second (rs352143) associated with pulmonary TB (Graustein et al. 2015). Another single-nucleotide polymorphism (rs187084) has been associated with susceptibility to pulmonary TB amongst an Indian tribe (Bharti et al. 2014).

Other TLRs that may have a significant role in TB include TLR7 and TLR8. The upregulation of TLR7 was observed to eliminate intracellular *M. tuberculosis* through autophagy (Bao et al. 2017). TLR7 in *M. tuberculosis* infected macrophages was upregulated and this also increase viability of infected host cells, whilst down-regulation of TLR7 decrease cell viability (Bao et al. 2017). Furthermore, the autophagosome was significantly increased in the *M. tuberculosis*-infected macrophages after upregulation of TLR7, but in contrast, the autophagosome was not observed in macrophages following down-regulation of TLR7 (Bao et al. 2017). Interestingly, TLR8 expression is also upregulated in *M. bovis* BCG infected THP-1 macrophages (Davila et al. 2008), whilst TLR8 expression is significantly upregulated in pulmonary TB patients during the acute phase of disease (Davila et al. 2008). Genetic polymorphisms in TLR7 and TLR8 genes are associated with increased susceptibility to *M. tuberculosis* infection as a result of impaired phagocytosis and TLR signalling (Davila et al. 2008; Lai et al. 2016).

The overall role of TLRs in TB pathogenesis and protection is complex. TLR-mediated signalling in TB results in an inflammatory and protective immune response, instead of a *M. tuberculosis*

LAM-(host receptor)-mediated signalling involving C-type lectins such as MR and DC-SIGN, which tends to result in a more anti-inflammatory and suppressive immune response (Kaufmann and Schaible 2003). Furthermore, *M. tuberculosis* ManLAM, which is predominantly recognised by MR and DC-SIGN, results in an anti-inflammatory response and is not recognized by any TLR, suggesting that the type of cap modification on the LAM antigen has an important effect on the downstream immune response against mycobacterial infection (Quesniaux et al. 2004). An optimum IFN- $\gamma$  secretion in *M. tuberculosis* infection requires crosstalk between TLR2, TLR4 and MR (Mukhopadhyay et al. 2004).

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## 5 Other PRRs and Mycobacteria

### 5.1 Dendritic Cell-Associated C-Type Lectin (Dectin)

#### 5.1.1 Dectin-1

Dectin-1, coded by the CLEC7 gene, is a non-TLR PRR and a type II transmembrane receptor involved in cellular activation; it is expressed on macrophages, dendritic cells, neutrophils, eosinophils, B cells, and mast cells in the lung (Brown 2006). Dectin-1 tends to target  $\beta$ -glucans on fungal pathogens but can also interact with *M. tuberculosis*, although its specific mycobacterial ligands are not known. During the recognition of fungal ligands, Dectin-1 can induce production of cytokines/chemokines, intracellular killing, phagocytosis, and DC maturation (Brown 2006) (Fig. 9.3). Downstream signalling by Dectin-1 occurs via Spleen tyrosine kinase (Syk)-dependent or -independent mechanisms involving several transcription factors (e.g. NF- $\kappa$ B, MAPK, NFAT, IRF1, IRF5) and the intracellular sensor NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3), central to the NLRP3 inflammasome (Kerrigan and Brown 2011; Dambuzza and Brown 2015). Dectin-1 can also associate with TLR2 when recognising several mycobacteria facilitating the production of pro-inflammatory cytokines (Yadav and Schorey

2006; Shin et al. 2008; Romero et al. 2016). Dectin-1 is necessary for the TLR2-dependent production of TNF- $\alpha$ , IL-6, RANTES, and GM-CSF by murine macrophages infected with non-pathogenic mycobacteria (*M. tuberculosis* H37Ra, *M. smegmatis* and *M. bovis* BCG), but not for *M. tuberculosis* H37Rv (Yadav and Schorey 2006). In DCs derived from TLR2<sup>-/-</sup> mice, *M. tuberculosis*-induced IL-12p40 was dampened by inhibition of Dectin-1 by laminarin and by the inhibition of Syk (Rothfuchs et al. 2007). Similarly, enhanced phagocytosis and expression of Dectin-1, Src kinase, and induction of ROS occurs via TLR2 in *M. tuberculosis*-infected human lung epithelial cells (Lee et al. 2009b). *M. tuberculosis*-induced ROS production in human DCs occurs via Dectin-1 associating with TLR2 (Romero et al. 2016). *M. tuberculosis*:Dectin-1 interaction also appears to be the key in inducing Th1/Th17 responses in human monocyte derived DCs, but is inhibited by MR and Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin (DC-SIGN) co-expression in the cell (Zenaro et al. 2009). In human PBMCs, *M. tuberculosis* induction of Th17 responses is mediated by Dectin-1 and TLR4, but not TLR2, with IL-17A production requiring the IL-1 pathway (Van De Veerdonk et al. 2010). Thus, Dectin-1 plays a role in the innate immune response against *M. tuberculosis*. However, in knockout (Dectin-1<sup>-/-</sup>) mice, there does not seem to be a difference in survival to *M. tuberculosis* infection compared to wild type animals (Marakalala et al. 2011). Although a genetic deficiency resulting in a truncated Dectin-1 has been associated with susceptibility to several fungal infections (Rosentul et al. 2011; Sainz et al. 2012), no polymorphisms in the Dectin-1 gene have been reported to be involved in TB susceptibility.

### 5.1.2 Dectin-2

Dectin-2, coded by the Clec4n gene, is also a CTLR similar in structure to Dectin-1, composed of an N-terminal cytoplasmic domain, a trans-membrane domain, and a C-terminal extracellular Ca<sup>2+</sup>- dependant CRD region (Ariizumi et al. 2000; Kanazawa et al. 2004; Sato et al. 2006). Dectin-2 is predominantly expressed in the lungs,

but its expression has also been reported in spleen and lymph tissues and on DCs, monocytes, macrophages and B cells (Kanazawa et al. 2004; Sancho et al. 2012). Dectin-2 acts as an adaptor molecule recognising the  $\gamma$ -chain of Fc receptor triggering the activation of cells (Sato et al. 2006). Dectin-2 expression can be influenced by different ligands, with its CRD region targeting mannose residues (Gavino et al. 2005; Taylor et al. 2005; Mcgreal et al. 2006). Moreover, soluble recombinant Dectin-2 has been reported to bind to *M. tuberculosis* (Mcgreal et al. 2006) via ManLAM, although dectin-2 does not bind mycobacteria lacking mannose-capped LAM (Yonekawa et al. 2014; Decout et al. 2018) (Fig. 9.3). Expression of Dectin-2 on macrophages is upregulated by TNF (Decout et al. 2018). Dectin-2 elicits pro- and anti-inflammatory cytokine production (e.g. IL-6, TNF- $\alpha$ , MIP-2, IL-2, and IL-10) in bone marrow-derived DCs and seems to be important for DC maturation and IL-17 secretion (Yonekawa et al. 2014). This effect of ManLAM was completely negated in Clec4n<sup>-/-</sup> bone marrow-derived DCs, whilst Clec4n<sup>-/-</sup> mice infected with *M. tuberculosis* showed significantly greater lung pathology than wild-type mice (Yonekawa et al. 2014). To date, no polymorphisms in the human population have been described in the Clec4n gene that are linked to TB susceptibility. Thus, the role of Dectin-2 receptor in TB pathogenesis remains intriguing.

## 5.2 Macrophage-Inducible C-Type Lectin (Mincle)

The Macrophage-inducible C-type lectin (Mincle), coded by the CLEC4E gene, is a PRR that is found on the surface of macrophages, myeloid DCs, monocytes, neutrophils, and certain B cells and binds to several target PAMPs (e.g. mannose and fucose, among others) (Lee et al. 2011; Kerscher et al. 2013). Mincle is an LPS inducible transcriptional target in macrophages and is able to stimulate pro-inflammatory cytokines via the Syk-CARD9 pathway (Matsumoto et al. 1999; Yamasaki et al. 2008; Schoenen et al. 2010) (Fig. 9.3). Mincle can bind to trehalose dimycolate (cord factor), a key com-

ponent of the mycobacterial cell wall that has also been implicated in lung granuloma formation in mice (Ishikawa et al. 2009). Trehalose dimycolate can inhibit phagosome maturation, promoting intracellular persistence and interfering with antigen presentation (Spargo et al. 1991; Actor et al. 2002; Indrigo et al. 2003; Hunter et al. 2006; Axelrod et al. 2008). Mincle, being a key receptor for the trehalose dimycolate, regulates Th1/Th17 responses in mice (Schoenen et al. 2010). In neutrophils, trehalose dimycolate-induced Mincle signalling increased cell adherence (important in early stages of granuloma formation), CR3 (CD11b/CD18) expression, together with TLR2 activation leading to reactive oxygen species and TNF- $\alpha$  production (Lee et al. 2012). Mincle<sup>-/-</sup> mice had impaired immune responses when challenged by aerosol *M. tuberculosis*, and exhibited increased inflammation and mycobacterial load than wild-type mice (Lee et al. 2012). Neutrophil depletion (using anti-Ly6G antibody) showed inhibition of IL-6 and MCP-1 (monocyte chemotactic protein-1) following trehalose dimycolate treatment, thus reducing immune cell recruitment (Lee et al. 2012). Therefore, Mincle may modulate neutrophils during the early stage of mycobacterial infection. However, another study concluded that Mincle was not essential for controlling *M. tuberculosis*; Mincle<sup>-/-</sup> mice could still form granulomas, had Th1 and Th17 responses, and a similar mycobacterial burden after aerosol infection to wild-type mice (Heitmann et al. 2013). Another study using Mincle<sup>-/-</sup> mice found that inoculation of mycobacteria (*M. bovis* BCG) intravenously, rather than intratracheally, resulted in higher mycobacterial burden in the lungs and other tissues, suggesting Mincle may play a greater role in systemic mycobacterial infection (Behler et al. 2012). Interestingly, in Mincle<sup>-/-</sup> mice, DCs induced Th1 responses in the spleen, but not in the liver, suggesting a role in systemic mycobacterial infection (Behler et al. 2015). The interaction of Mincle with trehalose dimycolate and *M. bovis* BCG can also promote anti-inflammatory IL-10 but conversely alter pro-inflammatory IL-12p40 secretion from murine

bone-derived macrophages *in vitro* (Patin et al. 2016).

Mincle recognises trehalose-6,6-dibehenate (TDB) (a synthetic analogue of trehalose dimycolate), which is involved in NLRP3 inflammasome activation and Myd88-dependent Th1 and Th17 responses through IL-1R-signalling in mice bone-derived DCs (Desel et al. 2013; Schweneker et al. 2013; Shenderov et al. 2013). Mincle appears to be a crucial switch for macrophages to shift from cytokine expression to high nitric oxide (NO) production. Mincle can have dual functions in mycobacterial infection: 1) having a stimulatory role on TLR-mediated transcription, and 2) enhancing the translation of key genes required for NO synthesis, thus in the promotion of NO production and subsequent resolution of inflammation and the granuloma (Lee et al. 2016b). In fact, in resting murine macrophages, Mincle is expressed at low levels but is upregulated by LPS (a TLR ligand), leading to Myd88-dependent NO production (Matsumoto et al. 1999; Schoenen et al. 2014; Kerscher et al. 2016a). Together with TLR4, Mincle has been reported to induce autophagy through Myd88, which facilitates *M. tuberculosis* intracellular growth (Pahari et al. 2020).

Much of the above data on Mincle has come from the mouse model of *M. tuberculosis* infection, but there are several studies that show similar immune responses in humans. Human antigen presenting cells have a similar response to trehalose dimycolate/TDB, inducing various cytokines via Syk-signalling (Ostrop et al. 2015), whilst the CRDs of human and mouse Mincle are similar in structure, having comparable affinity to trehalose dimycolate, but not other mycobacterial ligands (Rambaruth et al. 2015; Richardson et al. 2015; Van Der Peet et al. 2015). The downstream signalling resulting from trehalose dimycolate-Mincle interaction seems to be more complex. A recent study used quantitative phosphoproteome analysis and showed substantial reprogramming of macrophages by trehalose dimycolate and revealed both Mincle-dependent and Mincle-independent signalling mechanisms (Hansen et al. 2019).



There have been a few reports of genetic polymorphisms in the CLEC4E gene and susceptibility to TB in the human population. In one study in South African, 4 SNPs (rs10841845, rs10841847, rs10841856 and rs4620776) were described in the CLEC4E gene, but no association was found with TB susceptibility (Bowker et al. 2016). However, two of the SNPs in CLEC4E (rs10841845 and rs10841847) described earlier, were found to be associated with increased individual protection against pulmonary TB in the northern Chinese population (Kabuye et al. 2019). Furthermore, SNP rs10841847 in the CLEC4E gene was also associated with pulmonary TB risk in a study population from Guinea-Bissau (West Africa) (Olvany et al. 2020).

Mincle remains a fascinating PRR and its involvement in tuberculosis pathogenesis remains to be fully elucidated. Further studies are needed on Mincle's involvement with genetically diverse *M. tuberculosis* strains, other mycobacterial ligands and in resolving the complex Mincle-dependent and Mincle-independent intracellular pathways that can be elicited in immune cells.

### 5.3 Macrophage C-Type Lectin (MCL)

Macrophage C-type lectin (MCL; also known as Clec4e, Dectin-3 and CD368) is a membrane-bound PRR coded by the CLEC4D gene. First described in mice (Balch et al. 1998), MCL was subsequently characterised in humans as a type II membrane glycoprotein composed of an N-terminal cytoplasmic region lacking the consensus signalling motifs and an extracellular C-terminal region with a single CRD (Arce et al. 2004). MCL is commonly expressed on myeloid cells but it is also found on neutrophils, monocytes and DCs (Graham et al. 2012). MCL expression is downregulated upon DC maturation or monocyte/macrophage differentiation (Graham et al. 2012). The CLEC4D gene is proximal to the CLEC4E gene, and thus, the MCL gene may have originated from Mincle gene duplication. Like Mincle, MCL can also bind to trehalose dimycolate (but with lower affinity) as

well as some fungal species (Arce et al. 2004; Miyake et al. 2013; Zhu et al. 2013) (Fig. 9.3).

The expression of MCL and Mincle are co-regulated, induced via Myd88 (Lobato-Pascual et al. 2013; Miyake et al. 2015; Kerscher et al. 2016a). Thus, MCL is closely linked with Mincle function, with the FcRγ region of MCL being essential for inducing Mincle expression upon binding to trehalose dimycolate (Graham et al. 2012). Furthermore, MCL cross-linking can lead to initiation of phagocytosis, intracellular respiratory burst, and cytokine secretion via Syk-signalling (Graham et al. 2012). In contrast, MCL knockout mice (Clec4d<sup>-/-</sup>) have compromised trehalose dimycolate-induced responses, cytokine production and a reduced ability to form granulomas (Miyake et al. 2013; Zhao et al. 2014). An alternative idea is that MCL and Mincle do not co-associate, but instead, MCL's function is to induce initial Mincle expression (Zhao et al. 2014).

MCL appears to be a key, non-redundant PRR in anti-mycobacterial immunity; MCL knockout mice (Clec4d<sup>-/-</sup>) show significantly higher mycobacterial loads and increased mortality after *M. tuberculosis* infection (Wilson et al. 2015), concomitant with enhanced pulmonary inflammation and neutrophil recruitment (Wilson et al. 2015). Phagocytes derived from MCL knockout mice show impaired phagocytosis of mycobacteria, but this defect is restored when MCL-opsonized mycobacteria are challenged (Wilson et al. 2015).

A single genetic polymorphism (rs4304840) in MCL in humans (Indonesian cohort) has been associated with an increased susceptibility to pulmonary TB (Wilson et al. 2015). MCL seems to play a central role, together with Mincle, in the protective anti-mycobacterial immune response.

### 5.4 Dendritic Cell-Specific Intercellular Adhesion Molecule-3-Grabbing Non-integrin (DC-SIGN)

DC-SIGN (encoded by CD209 gene; Geijtenbeek et al. 2000) is a type II transmembrane receptor expressed predominantly on some macrophages

(alveolar), DCs (myeloid) cells and activated B lymphocytes (Rappocciolo et al. 2006; Lugo-Villarino et al. 2011). DC-SIGN recognizes PAMPs such as N-linked high-mannose and branched fucosylated residues. DC-SIGN has a key role in the clearance of microbial infections, but conversely, pathogens can also manipulate DC-SIGN to alter DCs in their favour for their survival. DC-SIGN is made up of four domains: the N-terminal cytoplasmic domain, transmembrane domain, extracellular domain comprising the neck region, and a single C-terminal CRD (Garcia-Vallejo and Van Kooyk 2013).

DC-SIGN is a PRR for several microbes, most notably HIV-1 (Curtis et al. 1992; Geijtenbeek et al. 2002), but can also bind to bacterial and fungal species (Van Kooyk and Geijtenbeek 2003). DC-SIGN recognises and binds the ManLAM from *M. tuberculosis* (Appelmek et al. 2003; Maeda et al. 2003), and enhances the internalization of both *M. bovis* BCG and *M. tuberculosis* (Geijtenbeek et al. 2003; Tailleux et al. 2003). Interestingly, mycobacteria are able to subvert DC-SIGN function by altering TLR-mediated activation of DCs. Mycobacteria are strong inducers of the Th1 response and can also facilitate the expression of downstream co-stimulatory molecules and cytokines (e.g. IL-12) by DCs via TLR2 and TLR4 PRRs (Nigou et al. 2001). Despite alveolar macrophages being the predominate targets of mycobacteria in the lungs, the role of DCs is becoming increasingly key in understanding the pathogenesis of TB since DCs expressing DC-SIGN are present in the airway mucosa and interstitial sites of the respiratory system (Soilleux et al. 2002; Tailleux et al. 2003).

The importance of DC-SIGN in TB pathogenesis is also shown in several studies involving transgenic mice. In fact, mice have eight different DC-SIGN homologues (SIGNR1-8). Gene knockout studies have shown that SIGNR3 (the most similar to human DC-SIGN) has a key role in resistance to early *M. tuberculosis* infection (Tanne et al. 2009; Tanne and Neyrolles 2010; Lugo-Villarino et al. 2011). Furthermore, transgenic mice expressing human DC-SIGN showed decreased pathology and prolonged survival following mycobacterial infection (Schaefer et al. 2008).

Capped ManLAM is the main PAMP for DC-SIGN (Geijtenbeek et al. 2003; Kaufmann and Schaible 2003; Maeda et al. 2003). DC-SIGN does not bind to non-capped LAM (AraLAM), which is present on fast-growing mycobacterial species (*M. smegmatis*, *M. fortuitum* and *M. chelonae*) (Geijtenbeek et al. 2003; Tailleux et al. 2003). DC-SIGN appears to be the main DC receptor for mycobacteria (Geijtenbeek et al. 2003); competitive inhibition using anti-DC-SIGN antibodies inhibited *M. bovis* BCG and ManLAM binding by 80% (Geijtenbeek et al. 2003). DC-SIGN also binds to other mycobacterial PAMPs (mannosylated and  $\alpha$ -glucan cell wall components, and PIMs). However, mycobacteria can be phagocytosed by DCs in a non-DC-SIGN dependent manner, showing a degree of redundancy in the host-pathogen interaction (Gagliardi et al. 2005; Pitarque et al. 2005; Appelmek et al. 2008; Driessen et al. 2012; Geurtsen 2009 #972).

DC-SIGN-mediated DC responses requires prior activation of NF- $\kappa$ B via TLR signalling (Geijtenbeek and Gringhuis 2009; Gringhuis et al. 2009; Sancho et al. 2012; Garcia-Vallejo and Van Kooyk 2013), whilst several different PAMPs can trigger a variety of intracellular signalling from DC-SIGN (Gringhuis et al. 2009; Sancho et al. 2012) (Fig. 9.3). DC-SIGN-ManLAM interaction results in Raf-1 phosphorylation and then phosphorylation of transcription factor NF- $\kappa$ B, inducing cytokine production (e.g. IL-12, IL-10, IL-6, and CXCL8) and other co-stimulatory molecules (e.g. CD80, CD83 and CD86) (Gringhuis et al. 2007, 2009). Infection of immature monocyte-derived DCs by *M. tuberculosis* facilitated the maturation of DCs, producing TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and IL-23, and stimulated CD4<sup>+</sup> T cells to produce IFN- $\gamma$  and IL-17 (Zenaro et al. 2009). Furthermore, DC-SIGN interferes negatively with the pro-inflammatory responses and control of *M. tuberculosis* intracellular growth in human macrophages mediated by Dectin-1 (Lugo-Villarino et al. 2018).

In immature DCs, internalisation of *M. tuberculosis* via ManLAM-DC-SIGN interaction results in the pathogen being directed to the late endosomes/lysosomes and suppression of LPS-

induced IL-12 secretion (Nigou et al. 2001). ManLAM-DC-SIGN interaction on immature DCs also interferes with TLR4 signalling, since LPS binding and signalling is via TLR4 (Akira et al. 2001). *M. tuberculosis* interferes between the balance of TLR signalling (DC maturation and inflammation) and DC-SIGN signalling (inhibition of DC maturation and immunosuppression) (Nigou et al. 2001; Engering et al. 2002a, b; Geijtenbeek et al. 2003). Both *M. tuberculosis*-infected DCs and macrophages can secrete the ManLAM that can bind to DC-SIGN on other proximal DCs (Sada et al. 1990; Chatterjee and Khoo 1998); this interferes with the TLR-signalling, inhibiting DC maturation and inducing anti-inflammatory IL-10 cytokine production (Tsuji et al. 2000; Geijtenbeek et al. 2003). Thus, *M. tuberculosis* is able to modulate the DC response to immune suppression to facilitate its intracellular survival (Fortsch et al. 2000; Jiao et al. 2002).

Two genetic polymorphisms have been reported in the DC-SIGN promoter region (-336A/G and -871A/G) but it is unclear as to their effect on TB susceptibility. The polymorphism -336G results in reduced expression of DC-SIGN, which also correlates with the severity of dengue disease (Despres et al. 2005). In a meta-analysis study, polymorphisms (-336A/G, -871A/G) were found not to substantially contribute to TB susceptibility, except that the genotype -336G/G might be associated with increased TB susceptibility for the Asians population (Chang et al. 2012). In another meta-analysis study, the -871A/G polymorphism was associated with decreased susceptibility to pulmonary TB, whilst the -336A/G polymorphism was associated with increased susceptibility of pulmonary TB in the Asian population (Yi et al. 2015). However, an additional polymorphism (-139G/A) was not found to be associated with susceptibility to pulmonary TB (Yi et al. 2015). Moreover, two other genotypes (-871G and -336A) seem to be associated with protection against TB and may have an increased frequency in non-African populations, possibly due to host genetic adaptation as a result of longer history of exposure to *M. tuberculosis* (Barreiro et al. 2006). In the Russian

population, -336A genotypes were more sensitive to infection with an *M. tuberculosis* lineage 2 (Beijing/W) strain, whilst those with the -336G genotype and *M. tuberculosis* lineage 2 genotype had increased frequency of death due to pulmonary TB (Ogarkov et al. 2012).

DC-SIGN plays a key role in host-pathogen interactions in TB. Whether DC-SIGN plays a protective role for the host, or is manipulated by the *M. tuberculosis* to circumvent immune responses needs further study. Further data is needed from GWAS as to the genetic susceptibility to TB from CD209 polymorphisms in the human population. Further studies are also required that investigate the interaction of DC-SIGN with different phylogeographic lineages of *M. tuberculosis* strains.

## 5.5 NOD-like Receptors (NLRs)

NOD-Like Receptors (NLRs) are a large family of intracellular PRRs that contain a nucleotide binding oligomerization domain (NOD). Structurally, NLRs have a variable N-terminal interaction domain, a central NACHT domain (NTPase domain that is evolutionarily conserved), and a C-terminal leucine-rich repeat domain (Fritz et al. 2006; Werts et al. 2006; Franchi et al. 2008) (Fig. 9.3). NLRs are cytosolic sensors that tend to target bacterial cell wall components such as peptidoglycan (containing N-acetylglucosamine and N-acetylmuramic acid) and muramyl dipeptide (MDP) (Girardin et al. 2003a, b; Chen et al. 2009; Franchi et al. 2009). Some NLRs have an amino-terminal caspase recruitment domain (CARD), which is critical to initiate NF- $\kappa$ B signalling, resulting in the release of pro-inflammatory cytokines (e.g. IL-1 $\beta$ , IL-6, TNF- $\alpha$ , and IL-8), antimicrobial peptides ( $\beta$ -defensin 2), other chemokines, NO and upregulation of adhesins (Darcissac et al. 1996; Heinzelmann et al. 2000; Chin et al. 2002; Guo et al. 2006; Kramer et al. 2006; Uehara et al. 2007). Some of the most prominent members involved in innate immune detection of *M. tuberculosis* in the cytosol are NOD1, NOD2, NLRP3 and NLR family CARD domain containing 4

(NLR4). This stems from the ability of *M. tuberculosis* to escape from phagosomes into macrophage cytosol via the early secretory antigenic target-6 (ESAT-6) secretion system-1 (ESX-1) mechanism (Simeone et al. 2012). NOD2<sup>-/-</sup> knockout mice have impaired resistance to *M. tuberculosis* infection because of decreased production of type 1 cytokines and reduced recruitment of CD8<sup>+</sup> and CD4<sup>+</sup> T cells; there is a higher bacterial burden in the lungs, 6 months after infection than wild-type controls (Divangahi et al. 2008). MDP treatment of AMs also activates NOD2, which enhances the control of intracellular growth of *M. tuberculosis* and the release of TNF- $\alpha$ , IL-6 and bactericidal LL37 (Juarez et al. 2012). Furthermore, an increase in autophagy proteins (e.g. IRGM, LC3 and ATG16L1) was observed in the mycobacteria-containing autophagosome, suggesting a PRR-dependent mechanism for autophagy activation (Juarez et al. 2012). The CARD9 domain plays a central role in NOD2-mediated activation of p38 and JNK signalling during innate immune responses to intracellular pathogens (Hsu et al. 2007). NOD2 can act in synergy with TLR2 to induce inflammatory cytokines during *M. tuberculosis* infection, and this synergism is lost in mononuclear cells defective in either TLR2 or NOD2, suggesting a non-redundant recognition mechanisms (Ferwerda et al. 2005). Similarly, NOD2 and TLR4 also work synergistically in stimulating the activity of DCs, enhancing T cell recruitment by inducing autophagy and bolstering IL-12p40/70, IL-6, IFN- $\gamma$  and CD40, CD80 and CD86 co-stimulatory molecules (Khan et al. 2016b). Activating DCs through NOD2 and TLR4 restricts *M. tuberculosis* intracellular survival through strong release of cytokines, nitric oxide, autophagy and enhanced DC migration to lymph nodes (Khan et al. 2016a). NOD1 seems to co-operate with NOD2 or TLRs to produce cytokines (IL-6 and IL-1 $\beta$ ) in bone-marrow derived macrophages in response to *M. tuberculosis* infection (Lee et al. 2016a). Similarly, NOD1 is involved in AM and MDM innate responses, which include pro-inflammatory cytokines (e.g. IL-1 $\beta$ , IL-6, IL-8, and TNF- $\alpha$ ) and

autophagy (Juarez et al. 2014). Intriguingly, an approach using adjunct therapy (with ligands of NOD2 and TLR4) to treat *M. tuberculosis*-infected mice in conjunction with isoniazid, improved drug efficacy against *M. tuberculosis* (Khan et al. 2016a). A therapeutic role for NOD-2 has also be suggested in augmenting T cells responses to *M. tuberculosis* infection (Pahari et al. 2017).

ESAT-6 is a potent activator of the NLRP3/ASC inflammasome and NLRs and CARD proteins play a central role in IL-1 $\beta$  secretion during *M. tuberculosis* infection, via an NLRP3, ASC and caspase-1 infection-inducible inflammasome complex (Mishra et al. 2010). Mycobacterial PPE13 triggers the inflammasome-response in macrophages, by binding to the LRR and NATCH domains of NLRP3 via its MPTR domain (Yang et al. 2020). In DCs, PPE60 was observed to activate the NLRP3 inflammasome, followed by caspase-1-dependent IL-1 $\beta$  and IL-18 synthesis (Su et al. 2018). However, NLRP3 may not be essential for survival in the early stages of *M. tuberculosis* infection or in granuloma formation (Allen et al. 2010; Mcelvania Tekippe et al. 2010; Walter et al. 2010).

Mutations in the NLR genes suggest their importance in protection against several microbial infections, granulomatous inflammatory disorders and inflammatory bowel disease (e.g. Crohn's disease) (Hugot et al. 2001; Miceli-Richard et al. 2001; Ogura et al. 2001). Several polymorphisms in NLR genes linked to TB susceptibility have been reported. Two polymorphism in the NOD1 gene (rs751770147 and chr7:30477156(T)) are associated with TB progression in the Ethiopian population (Mekonnen et al. 2018). Three polymorphisms (Pro268Ser, Arg702Trp, and Ala725Gly) in the NOD2 gene are significantly associated with TB disease in African-American subjects in the USA (Austin et al. 2008). Another polymorphism (Arg587Arg) in the NOD2 gene has been associated with TB susceptibility in the Chinese population but not in the Uyghur and Kazak populations (Zhao et al. 2012). In a recent meta-analysis of NOD2 polymorphisms, no significant association was found

between the Arg587Arg polymorphisms and TB risk; however, Arg702Trp polymorphism was found to be likely associated with protection against TB (Wang et al. 2013). For NLRP3, a single polymorphism (rs34298354) was associated with protection against TB (Liu et al. 2020). A single polymorphism (Q705K) in the NLRP3 gene was associated with poor TB treatment outcome in the Ethiopia population (Abate et al. 2019). Interestingly, in TB/HIV patients from Botswana, a NLRP3 polymorphism (rs10754558-G) was associated with an increased risk for early mortality after starting initiating anti-retroviral therapy (ART), suggesting that these patients may benefit from interventions that decrease inflammasome-mediated inflammation (Ravimohan et al. 2018).

NLRs have given significant insight into the innate immune recognition of *M. tuberculosis* in the cytosol. The role of the inflammasome in protection/pathogenesis is unclear and its activation may be triggered by *M. tuberculosis* as a means of latent infection.

## 5.6 Mannose Receptor (MR)

Mannose receptor (MR; CD206), coded for by the MRC1 gene, is a type I transmembrane glycoprotein of 165 kDa made up of a C-terminal cytoplasmic domain containing a tyrosine-based motif and three types of extracellular domains (an N-terminal cysteine-rich R-type domain, a fibronectin type II repeat (FNII), and eight consecutive CRDs) (Taylor et al. 1990; Stahl and Ezekowitz 1998). MR is mainly expressed on the surface of macrophages (particularly AMs), monocyte-derived DCs and other cells (e.g. non-vascular endothelial cells) (Martinez-Pomares 2012). MR is also commonly found in intracellular membranes; only 10–30% is constitutively expressed at the cell surface, which reflects its role in recycling and internalization (Schweizer et al. 2000). MR is unique in that its multiple CRDs recognise different PAMPs. The R-type domain can bind to glycans (without the need for Ca<sup>2+</sup>) (Leteux et al. 2000), whilst the FNII domain binds to collagens

(Martinez-Pomares et al. 2006). MR is able to bind to mannose via CRDs 4 to 8, with CRD4 having the primary preference for terminal mannose-containing glycoconjugates, fucose, and N-acetylglucosamine, but less well to glucose (Lennartz et al. 1987; Taylor et al. 1990). In contrast, CRD5 and CRD7 are involved in binding to mannose-containing glycans, whilst CRDs 1 to 3 seem to play less of a role in binding sugars (Kery et al. 1992; Taylor and Drickamer 1993).

MR recognises complex glycoproteins or glycolipids with multiple sugar moieties endogenously and exogenously. MR may interact with an additional receptor, or soluble MR (as a result of proteolytic cleavage) to facilitate phagocytosis (Le Cabec et al. 2005; Martinez-Pomares 2012) (Fig. 9.3). Intriguingly, pulmonary TB patients with poor prognosis show significantly higher levels of serum soluble MR; pathological analysis revealed enhanced levels of soluble MR in the lung and pleural tissues with caseating granulomas (Suzuki et al. 2018).

ManLAM is a major ligand for MR and this interaction on DCs initiates uptake of the mycobacterium, with probable antigen presentation via CD1b and the major histocompatibility complex class II (MHC-II) (Prigozy et al. 1997). In addition to ManLAM, MR can also bind to PIM, lipomannan (LM), and other mannosylated proteins on *M. tuberculosis* (Schlesinger et al. 1994; Diaz-Silvestre et al. 2005; Torrelles et al. 2006). MR is a major macrophage phagocytic receptor for virulent *M. tuberculosis* strains (H37Rv and Erdman) but not the attenuated strain H37Ra (Schlesinger 1993). Additionally, structural differences in LAM from different *M. tuberculosis* strains seem to alter adherence during the initial interactions with macrophage MR (Schlesinger et al. 1996).

Binding and phagocytosis of ManLAM or mannosylated beads via MR can inhibit phagosome-lysosome fusion, facilitating intracellular persistence of *M. tuberculosis* (Astarie-Dequeker et al. 1999, 2002; Kang et al. 2005). In DCs, ManLAM facilitates intracellular persistence of *M. tuberculosis* and *M. bovis* BCG by inhibiting IL-12 responses via interfering

with the LPS-induced signalling from TLR2 (Nigou et al. 2001). This indicates a cross-linking between MR and TLR2 when binding to ManLAM (Nigou et al. 2001). Cross-linking of MR using a specific anti-MR monoclonal antibody during binding of ManLAM inhibited IL-12 production, but also induced the production of anti-inflammatory IL-10, IL-1R antagonist, and IL-1R type II in DCs (Chieppa et al. 2003). A recurring theme during TB host-pathogen interaction is the degree of cross-linking between various PRR in the recognition of *M. tuberculosis*, via its several PAMPs. In addition to TLRs, MR and DC-SIGN co-stimulation inhibits Dectin-1-induced Th17 responses, whilst enhancing the Th1 responses in *M. tuberculosis*-infected DCs (Zenaro et al. 2009). In macrophages, binding of *M. tuberculosis* mannosylated ligands to MR results in receptor-mediated signalling mechanisms (modulation of cytoskeleton, activation of protein kinases, and transcriptional activation by AP-1), leading to production of matrix metalloproteinase-9 (MMP-9) that may contribute to lung tissue pathology during TB *in vivo* (Rivera-Marrero et al. 2002). SP-D is able to bind to *M. tuberculosis* and inhibit its MR-mediated uptake by macrophages (Ferguson et al. 2002), suggesting that SP-D may be masking mycobacterial ligands and inhibiting phagocytosis of mycobacteria by macrophages. MR may benefit *M. tuberculosis* intracellular persistence; however, in mouse models of TB infection, MR does not seem to be implicated in determining survival or disease severity (Court et al. 2010).

The frequency of a polymorphism of the MRC1 gene (rs34039386), allele G1186A, was higher in individuals with pulmonary TB than healthy controls (Zhang et al. 2012), including in the Uygur population (Zhang et al. 2013a). The G1186A polymorphisms (in exon 7 for CRD2 of MR) may affect the affinity of MR binding to mycobacterial ligands (Zhang et al. 2013a). MR is undoubtedly a major phagocytotic receptor for *M. tuberculosis*, but its importance is overshadowed by many other PRRs. However, entry of *M. tuberculosis* via MR may be a key

route for the pathogen to manipulate and circumvent the immune response and prolong its intracellular survival.

## 5.7 CD14

CD14 receptor is a lipid-anchored glycan-linked protein lacking transmembrane and cytoplasmic domains and is mainly expressed on myeloid monocytic cells. CD14 can bind to *M. tuberculosis* LAM, resulting in the macrophage production of IL-8 (Pugin et al. 1994). CD14 binding of bacterial ligands (LPS, lipoteichoic acid and peptidoglycan) requires co-interaction with other host receptor and cell surface components (TLRs) to facilitate phagocytosis, cell activation and cytokine secretion (Dziarski et al. 2000; Kaisho and Akira 2000). CD14 has also been shown to mediate uptake of non-opsonised *M. tuberculosis* by microglia cells, suggesting that this may be important in the pathogenesis of cerebral TB (Peterson et al. 1995). In AMs expressing high levels of CD14, the phagocytosis of *M. bovis* was enhanced (Khanna et al. 1996); however, *M. tuberculosis* merely up-regulates CD14 expression in macrophages without mediating phagocytosis (Shams et al. 2003). *M. tuberculosis* molecular chaperone chaperonin 60.1 protein partially activates human peripheral blood mononuclear cells via a CD14-mediated mechanism (Lewthwaite et al. 2001).

In mice, CD14 deficiency seems to be protective against chronic *M. tuberculosis* infection by suppressing inflammatory responses. Mouse bone marrow derived macrophages deficient in CD14 exhibited a significant reduction in TNF- $\alpha$  secretion when infected with *M. avium* compared to controls, but infection of CD14-deficient mice with *M. avium* or *M. tuberculosis* showed no difference in controlling mycobacterial infection compared to controls (Reiling et al. 2001, 2002). However, another study found CD14<sup>-/-</sup> mice survive chronic *M. tuberculosis* infection, although their wild type counterparts succumbed to infection due to reduced pulmonary inflammation (Wieland et al. 2008).

Soluble CD14, produced from proteolytic cleavage of membrane CD14, seems to be significantly elevated in patients with pulmonary TB (Hoheisel et al. 1995). A SNP in the promoter region (C(-159)T) of the CD14 gene has been found to be associated with high levels of soluble CD14 and increased probably of developing pulmonary TB in the Mexican population (Rosas-Taraco et al. 2007). In another study, the -159TT allele in the CD14 promoter was also significantly associated with TB risk in the Korean population, probably from higher promoter activity resulting in higher level of soluble CD14, but also decreased IFN- $\gamma$  secretion in individuals with this genotype (Kang et al. 2009).

## 6 Concluding Remarks

The nature of host-pathogen interaction is complex in tuberculosis. At the very heart of this is the host receptor-mycobacterial ligand interaction, which is the critical molecular dialogue in the early stages of *M. tuberculosis* infection. Understanding this molecular dialogue is profoundly important in determining the infection outcome. In vitro studies have proven an essential first step, but they often only involve one receptor-ligand interaction. In vivo, the host-pathogen communication is undoubtedly more complex involving an array of mycobacteria ligands that interact with several host PRRs, both soluble and membrane bound. There is indeed redundancy in both the mycobacterial ligands and host PRRs. In vivo, internalisation of *M. tuberculosis* involves multiple routes of cellular entry and crosstalk and co-operation between different PRRs. There seems to be a balance between TLR and CTLR entry with TLR often favouring a pro-inflammatory response, whereas CTLR favouring an anti-inflammatory response. Furthermore, the favoured target cell of *M. tuberculosis* (macrophage or dendritic cell) adds an additional layer of complexity. Fully understanding the host-pathogen dialogue in the early stages of infection is the 'holy grail' in preventing tuberculosis, because only then can we devise strategies to fully block mycobacterial interaction and entry into human cells.

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