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REVIEW

C-type lectin receptors in tuberculosis: what we know

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Abstract *Mycobacterium tuberculosis* (Mtb), the etiologic agent of tuberculosis (TB), is recognized by a number of pathogen recognition receptors (PRRs), either soluble or predominantly expressed on the surface of various cells of innate and adaptive immunity. C-type lectin receptors (CTLRs) are a class of PRRs which can recognize a variety of endogenous and exogenous ligands, thereby playing a crucial role in immunity, as well as in maintaining homeostasis. Mtb surface ligands, including mannose-capped lipoarabinomannan and cord factor, are important immune modulators which recently have been found to be directly recognized by several CTLRs. Receptor ligation is followed by cellular activation, mainly via nuclear factor κB mediated by a series of adaptors with subsequent expression of pro-inflammatory cytokines. Mtb recognition by CTLRs and their cross talk with other PRRs on immune cells is of key importance for the better understanding of the Mtb-induced complexity of the host immune responses. Epidemiological studies have shown that single nucleotide polymorphisms (SNPs) in several PRRs, as well as the adaptors in their signaling cascades, are directly involved in the susceptibility for developing disease and the disease outcome. In addition, an increasing number of CTLRs have been studied for their functional effects in the pathogenesis of TB. This review summarizes current knowledge regarding the various roles played by different CTLRs in TB, as well as the role of their SNPs associated with disease susceptibility and outcome in different human populations.

Keywords PRRs · C-type lectin receptors · Cell signaling pathways · Tuberculosis · Single nucleotide polymorphisms

Introduction

Tuberculosis (TB), a communicable infectious disease, remains the second leading cause of deaths from an infectious disease worldwide. In 2014, TB claimed about 1.5 million deaths, according to the Global Tuberculosis Report 2015 [1]. The majority of infected individuals develop asymptomatic latent TB, while ∼5–10 % of latently infected individuals will progress to active TB, resulting in about 9 million new TB cases and 1.4 million deaths per year [2].

Mtb is transmitted via inhalation of tiny droplets/aerosols containing the bacteria. Once Mtb enters the lung, it is recognized by alveolar macrophages (AMs) and phagocytosed, whereupon it proliferates until either the cell dies or is instructed by an antigen-specific T cell to kill or at least limit the growth of the bacterium [3]. However, Mtb has also correspondingly coevolved and developed mechanisms to survive inside the macrophages, mainly by inhibiting the phagosome–lysosome fusion, macrophage activation, and utilizing host molecules for its own intracellular growth [4, 5]. AMs are thought to be the primary target of the bacterium, and progress of the infection depends on the interaction between these two. If the infection is established, the migratory cells take the bacteria to a nearby lymph node, where the T cells get activated by antigen-presenting dendritic cells (DCs). The role of antigen-specific T cells and that of activated macrophages, whose activation in turn

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depends on the antigen-specific T cells and secretion of activating cytokines from the cells at the site of infection, have been shown to be most important in clearing or stopping early infection. In addition to these, the invariant natural killer T cells (iNKT), which produce the macrophage-activating, granulocyte macrophage colony-stimulating factor (GM-CSF), and γδT cells, which respond rapidly to the mycobacterial antigens, are also potentially involved in limiting early infection [6]. The overall outcome of infection depends on the quality of innate immune response elicited by the host and for which the innate immunity cells are armed with a plethora of receptors and other mechanisms. Mtb has a complex hydrophobic cell wall composed mainly of peptidoglycan, arabinogalactan, mycolic acids, and glycolipids which are capable of influencing and resisting the innate and adaptive immune response of the human host cells [7]. The lipids present on the cell wall are highly immunomodulatory and can influence the innate immunity in a quest to establish a niche inside the phagocytes. Molecules like phthioceroldimycocerosate (PDIM) interfere with its recognition and thus the recruitment of activated macrophages to the infection site [6]. Trehalose-1,6-dimycolate (TDM) and lipoarabinomannan (LAM) are other powerful immunomodulators that interfere with phagosome maturation [8, 9]. Some of these bacterial surface molecules serve as pathogen-associated molecular patterns (PAMPs) that are detected by PRRs predominantly expressed on the cells of the innate immune system, such as monocytes and macrophages, DCs, as well as on some lymphocytes, and orchestrate Mtb-dependent innate and adaptive immune responses [10]. In this scenario, the best studied PRRs belong to the Toll-like receptor (TLR) family. TLR1, TLR2, TLR4, TLR6, and TLR9 have been reported to play an important initial role in the pathogenesis of TB [11–14].

Recent findings demonstrated that polymorphisms in several TLRs are associated with an increased susceptibility to Mtb, suggesting the importance of innate immunity in tackling the infection [15–20]. CTLRs are increasingly being recognized to play an important role in modulating Mtb-mediated immune responses, and several of its PAMPs are detected by this family of receptors [21–25]. In this review, we will, therefore, emphasize the role of CTLRs in Mtb recognition, TB susceptibility, and immune pathology of TB.

C-type lectin receptors: general structure, function, and signaling mechanism

CTLRs comprise a large family of receptors that are characterized by the presence of one or more carbohydrate-recognition domains (CRDs) that can bind to carbohydrate

molecules in a Ca^{2+}-dependent manner [26]. In addition, lipids, proteins, and even inorganic compounds have been found to serve as ligands for this group of receptors in a Ca^{2+}-dependent or Ca^{2+}-independent manner. Thus, the more general term C-type lectin-like domains (CTLDs) was introduced for these domains [27]. The CTLD structure consists of a characteristic double loop stabilized at the base by highly conserved disulfide bridges, hydrophobic and polar interactions. The second loop exhibits structural and evolutionary flexibility and can bind to different carbohydrate species in the presence of Ca^{2+} ions, thus providing functional versatility [26]. For example, the EPN motif confers binding to sugars such as glucose, mannose, N-acetylglucosamine, whereas the QPD motif binds to galactose and N-acetylgalactosamine. Variations in CTLD fold structure have also been described [26].

The CTLR receptor family, which includes collectins, selectins, phagocytic receptors, and proteoglycans, has been classified into 17 groups, based on domain organization and phylogenetic features [26, 28]. CTLRs have roles in maintaining homeostasis, as well as in anti-microbial host defense. They have been reported to be involved in several cellular functions, such as cell–cell adhesion, lipid scavenging, orchestrating immunity against tumors, as well as virus-infected self-cells, allergy, and the development of autoimmune reactions [29–32]. In addition, they have been shown to play an important role as PRRs in the recognition of many fungal pathogens, as has been reported in several studies in the last decade [33–38]. It is notable that the polymorphisms in many of the CTLRs and also the adaptors involved in their pathways are being increasingly associated with the susceptibility and severity of the clinical courses of several fungal infections [39–43]. Members of this receptor family have also been shown to interact with each other and to cross talk with other PRRs, for example, TLRs to modulate pathogen-associated immune responses [44–47].

CTLRs can be found in soluble form in body fluids or in transmembrane form on cell surfaces. The soluble forms which are called collectins are mainly found in oligomeric forms in serum, and in the mucosal fluids, such as in lung alveoli. Collectins enhance the aggregation, uptake, and neutralization of pathogens by cross-linking their surface carbohydrate antigens, attracting phagocytes and activating complement [48–54]. The transmembrane CTLRs, especially those expressed on myeloid cells, have also been broadly divided on the basis of the signaling effect that they exert: (1) CTLRs signaling via immunoreceptor tyrosine-based activation motif (ITAM) domains; (2) CTLRs signaling via an immunoreceptor tyrosine-based inhibitory motif (ITIM) domains; and (3) the CTLRs that do not bear any ITAM or ITIM domains [26, 55]. An ITAM motif typically consists of a two *YxxL/I* (*Y* = tyrosine, *L* = leucine,
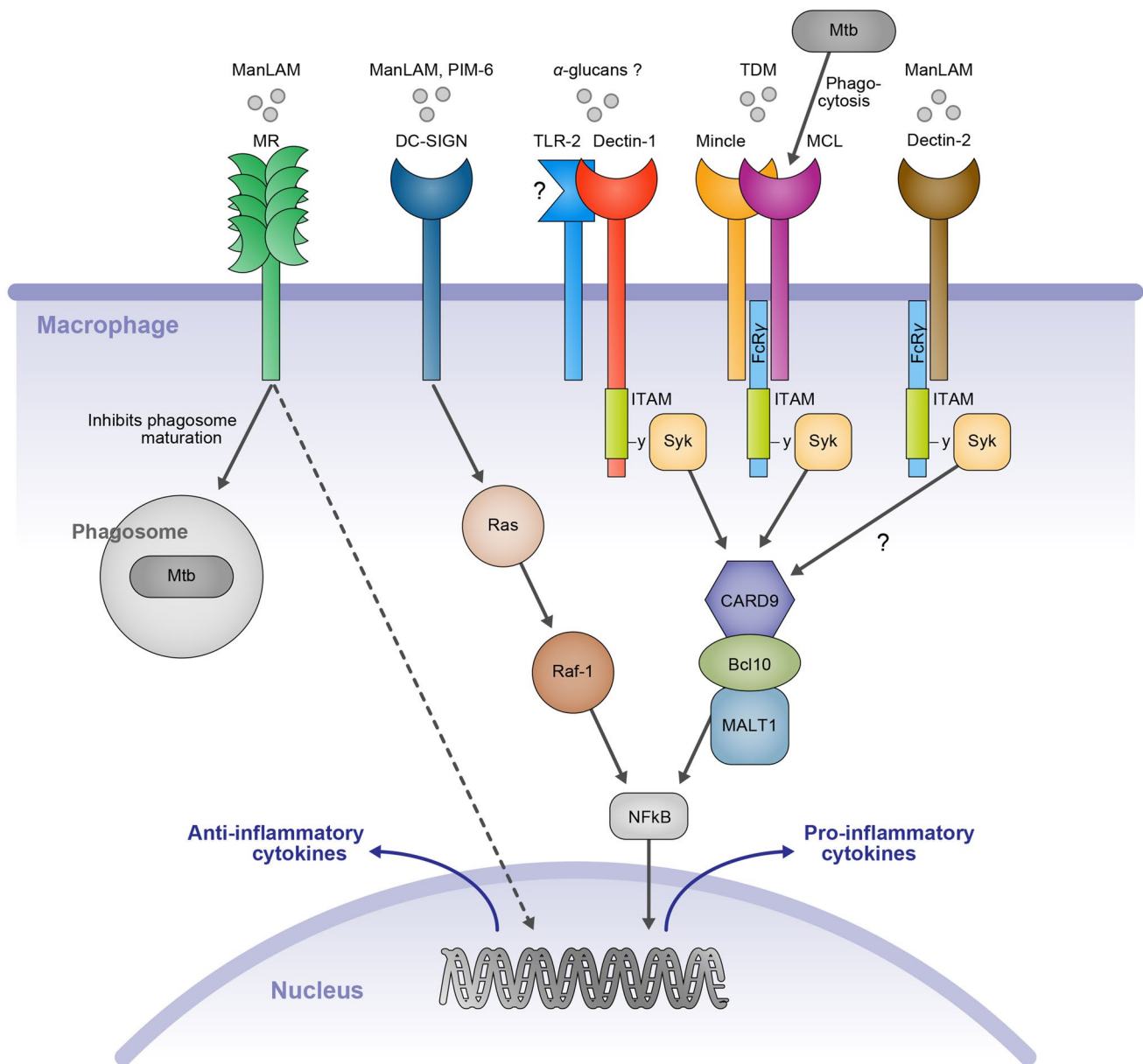
Fig. 1 Recognition of Mtb ligands (ManLAM, PIMs, TDM) by membrane-bound CLRs and subsequent signaling pathways activated by receptor–ligand interaction. MR recognizes the mannose-containing molecules, such as ManLAM, and causes bacterial internalization, but inhibits phagosome–lysosome fusion and may also contribute to anti-inflammatory response. DC-SIGN activates Raf-1, possibly through other adaptors which, in turn, activate the NF-κB. Dectin-1 may potentially bind to α-glucans of Mtb and may cross talk with TLR2 to signal via Syk. MCL and Mincle form heterodimers and lead to pro-inflammatory cytokine production mainly via NF-κB activation. MCL also plays a role in bacterial phagocytosis [25]. Dectin-2 also probably signals through the Syk-CARD9 pathway and produces both pro- and anti-inflammatory signals ('?' There are conflicting or no studies yet confirming these associations/pathways) [23, 25, 128, 130, 183]

I = isoleucine, and *x* = any residue) amino acid sequences separated by six to twelve intervening residues. Receptor ligation leads to the phosphorylation of the tyrosine residue in ITAM by Src family kinases. This further leads to the recruitment of spleen tyrosine kinase (Syk) which activates transcription factors including NFκB via a complex consisting of caspase recruitment domain-containing protein 9 (CARD9), B cell lymphoma 10 (Bcl10) and mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1) (Fig. 1) [56, 57]. PKCδ has been shown to be important for linking Syk activation with CARD9 signaling [58]. The consensus ITIM sequence consists of a I/V/L/

SxYxxI/L/V (V = valine; S = serine) motif. The tyrosine residue undergoes phosphorylation upon ligand recognition and recruits phosphatases Src homology 2 (SH2)-containing tyrosine phosphatase-1 (SHP-1), SHP-2, and/or SH2 domain-containing inositol phosphatase (SHIP-1) [59–61]. The ITIMs were previously proposed to exert an inhibitory effect on cellular activation especially those caused by the ITAM-containing receptors. However, later it was shown that ITAMs may also send inhibitory signals, while ITIMs may act in activation of certain cellular responses [62, 63]. ITIMs may also affect the TLR pathways by reducing the NFκB activity [55]. Some of the CLRs, such as Dectin-2, Mincle, MCL, C-type lectin domain family 5 member a (CLEC5a), which do not bear any signaling domains, have been shown to associate with ITAM-bearing adaptors such as FcRγ, DAP10, or DAP12 and mediate similar responses through Syk-CARD9-Bcl10-MALT-1 (Fig. 1) [27, 55]. Nevertheless, while the balance between both the activation and inhibition of immune responses is likely to play an important role in the fine-tuning of the pathogen-mediated immune response, the function of receptor clustering of several ITAM- and ITIM-bearing CTLRs on immune cells for the generation of immune responses is currently not well understood.

In several studies, it has been demonstrated that many CTLRs serve as important receptors for the recognition of Mtb ligands eliciting innate immune response against the pathogen (Fig. 1) [21, 23, 25, 64–67]. In the following sections, we will summarize current knowledge about each of those receptors which have been described as serving as PRR for Mtb. Taking each receptor individually, we will also collate the results of the studies associating SNPs in these CTLRs with the susceptibility to TB in different populations.

Soluble CTLRs: collectins

Collectins are collagenous soluble PRRs that mainly occur in mucosal lining fluids and in blood. They are a part of a first-line, non-specific defense system of innate immunity, that is able to recognize not only the gluco-conjugates, but also other type of ligands on the pathogen cell surface [68]. They consist of three chains, each with four domains—a cysteine-rich N-terminal which is required for oligomerization, a collagen-like region that maintains the overall structure and shape of the molecule, an α-helical neck domain that functions in protein trimerization, and a C-terminal carbohydrate-binding region which mediates ligand binding—and are generally found in multimeric forms [68, 69]. Among collectins, surfactant proteins SP-A and SP-D, and the complement protein MBL have been reported to recognize Mtb [65, 70–72].

Surfactant proteins (SP) A and D

SP-A and SP-D are large hydrophilic proteins of pulmonary surfactant that lines the alveolar epithelium in lungs and maintains the minimal surface tension preventing lung collapse. They are secreted by alveolar type II cells and Clara cells (Table 1). They can recognize a vast variety of carbohydrate ligands, such as mannose, glucose, *N*-acetylglucosamine (GlcNAc), *N*-acetylmannosamine (ManNAc), bacterial lipopolysaccharide (LPS), and pentoses. Lipid ligands include dipalmitoylphosphatidylcholine (DPPC), which is recognized by SP-A, while SP-D can bind to phosphatidylinositol (PI) [68, 69, 73]. SP-A and SP-D also serve as PRRs and are able to detect mycobacterial LAMs and other antigens of *Mycobacterium tuberculosis* (Table 1) [72, 74]. SP-A increased the phagocytosis of the Erdman strain, a virulent laboratory strain of Mtb, by human monocyte-derived macrophages (MDMs) which could be inhibited by anti-MR antibodies [75]. This observation was supported by another study demonstrating that SP-A upregulates the expression of mannose receptor (MR) on human MDMs [54]. SP-A levels were significantly decreased in BALF of TB patients and returned to normal in a month of therapy [65]. Low SP-A levels in patients' BALF were also associated with increased inflammation marked by high neutrophil numbers [65], while higher SP-A levels were observed in TB patients' serum [76]. However, the levels during the course or after the treatment were not investigated [76]. SP-A has also been shown to play a role in mediating oxidative burst of Mtb-infected macrophages. A study with rat AMs concluded that SP-A was able to suppress the production of reactive nitrogen intermediates in macrophages infected with the Mtb H37Ra strain [77]. In contrast, in another study, it was reported that SP-A enhanced the *Mycobacterium bovis* bacillus Calmette–Guérin (BCG)-induced production of nitric oxide synthase in rat BMMs [78]. The discrepancies in these studies might be attributed to the type of cells and the mycobacterial strains used.

SP-D can also cause agglutination of bacteria, but it has been associated with decreased adherence and phagocytosis of Erdman strain of Mtb by human MDMs. On the other hand, it has been demonstrated to enhance the fusion of bacteria-containing phagosomes with the lysosomes inside the macrophages, contributing to the intracellular mycobacterial growth control [53, 79]. Although the SP-A- and SP-D-deficient mice did not show any obvious differences compared to WT, an increased granulomatous infiltration was observed in SP-A-deficient mice. However, despite the many proved in vitro immunomodulatory roles, SP-A and SP-D seem to be dispensable in controlling immune status in response to mycobacterial infection, at least in murine infection models infected with the Erdman strain [80].

Table 1 CTLRs involved in Mtb recognition and subsequent responses as observed in human cells

C-type lectin receptor	Mtb ligand	Expression	Mtb-mediated signaling and effect on immune function			References
			Pro-inflammatory	Anti-inflammatory	Other effects	
SP-A	N-linked carbohydrates, LAM	Secreted by type II alveolar cells and Clara cells	TNFα↑, IL-6↑		Agglutination ↑, phagocytosis ↑ Oxidative burst^{ab}, MR expression ↑	[65, 68, 69, 72, 74, 75, 77, 78]
SP-D	LAM, LM, PILAM	Secreted by type II alveolar cells and Clara cells			Agglutination ↑, phagocytosis ↓, phagosome maturation ↑	[53, 68–70, 249]
MBL	ManLAM, PIMs	Liver cells			Agglutination and opsonophagocytosis ↑, lectin pathway activation	[71, 90]
MR	ManLAM, higher PIMs, mannosylated proteins	Macrophages, MDCs	IFNγ↑	IL-17↓, IL-12↓, IL-10↑, IL-1R type II↑	Phagosome maturation ↓	[121, 127, 128, 131, 133]
DC-SIGN	ManLAM, PIMs, α-glucan, LM, mannosylated 19-kDa and 45-kDa glycoproteins	Myeloid DCs, macrophage subsets	IFNγ↑, TLR-induced IL-12p40↓,	IL-17↓, TLR-induced IL-10↑	TLR-induced DC maturation↓, bacterial intake↑	[64, 131, 147, 148]
Dectin-1	Not defined	DCs, monocytes, macrophages, neutrophils, eosinophils, B cells, mast cells, lung epithelium	IL-6↑, IL-23↑, IL-1β↑, TNFα↑, TLR2-induced IL-12p40↑, IL-17↑		TLR-induced ROS↑, bacterial intake ↑	[55, 66, 131, 169–171, 184, 186]
Dectin-2	ManLAM	DCs (pDC), monocytes, tissue macrophages, CD8+ T cells, CD 19 + B cells	TNFα↑^{b}, MIP-2↑^{b}, IL-6↑^{b}, IL-17↑^{b}	IL-2↑^{b}, IL-10↑^{b}	DC maturation↑^{b}	[23, 192, 193, 195, 198, 200]
Mincle	TDM, β-gentiobiosyldiacyl-lglycerides, GroMM	Monocytes, macrophages, neutrophils, myeloid DCs, B cells	IL-8↑, G-CSF↑, IL-6↑, IL-1β↑^{a},	IL-10↑^{b}, IL-12p40↓^{b}	NO↑	[21, 220, 225, 250, 251]
MCL	TDM	Neutrophils, monocytes, DC subsets	IL-6↑^{b}, TNFα↑^{b}, MIP-2↑^{b}, IL-1β↑^{b}		Mincle expression ↑^{b}, bacterial intake↑^{b}	[232, 233]
CR3	LAM, Ag85C	Monocytes, alveolar macrophages, neutrophils, NK cells			Opsonic and non-opsonic phagocytosis ↑	[238, 240, 252]

a Increase or decrease, depending upon cell type and bacterial stain

b Effects studied in mice

SP-A consists of two isoforms SP-A1 and SP-A2 encoded by separate genes. Polymorphisms in both of these genes as well as in SP-D have been studied for their potential role in host susceptibility toward developing TB in different populations summarized in Table 2. A study in Mexican population revealed many marker alleles flanking SP-A and SP-D that were protective or conferred susceptibility toward pulmonary TB in the given population [81]. In replication to this study, another group found that SP-A1 alleles *SFTPA1* 307A, *SFTPA1* 776T and SP-A2 alleles *SFTPA2* 355C and *SFTPA2* 751C were significantly associated with TB in Ethiopian population. The SFTPA2 751A/C polymorphism is present in the CTLD of SP-A, leading to a change of lysine to glutamine which could be influencing its binding to Mtb. The haplotype 1A^3 in SP-A2, which also affects the amino acids in CTLD, was also found to be significantly associated with TB susceptibility [82]. In another study, two intronic SNPs SP-A2 G1649C and SPA2 A1660G in SP-A2 gene were identified to be associated with development of TB in an Indian population, whereas no association of SNPs in the SP-A1 gene was found [83]. In a more recent analysis, Yang et al. [84] also found a significant correlation of the SP-A2 1649G allele with pulmonary TB in Han Chinese population consistent with the results from studies in Ethiopian and Indian population. This allele leads to a transversion from proline to alanine at position 91 which may disturb the triple helical structure of SP-A, thus affecting its normal function [84]. An SP-D polymorphism, G459A in exon 7, has been reported to be significantly associated with TB susceptibility in an Indian population [85]. However, the molecular mechanism for these SNPs influencing the susceptibility to TB has not yet been elucidated.

Overall, it can be said that the surfactant proteins may play a role in the local immune responses during early infection in the lung alveoli. One of the several reasons for the discrepancy in the results from mouse models and human cell models might be that TB pathogenesis differs in mouse and human systems [86]. On the other hand, several SNPs have been shown to be associated with the regulation of SP-A1 and SP-A2 expression and others affecting their overall structure or binding affinity [82]. The association of these SNPs with TB in different populations suggests that surfactant proteins may have some immunomodulatory role in active TB infection. However, more studies with human cell or tissue models are required to establish a concrete role for these proteins in TB pathology.

Mannose-binding lectin

Mannose-binding lectin, MBL, is a member of the lectin pathway of complement system that consists of a collagenous region and a lectin domain [85]. It circulates predominantly in the serum, but has also been detected at other sites, such as the synovial fluid of inflamed joints, nasopharyngeal secretions, amniotic fluid, and subcellular compartments, including endoplasmic reticulum (Table 1) [87]. MBL structure resembles that of the surfactant proteins, with the basic structure being a trimer. In serum, it circulates as an oligomer of trimers, most often as hexamers. MBL, in association with Ca^{2+} ions, is able to recognize terminal sugars such as D-mannose, L-fucose, and *N*-acetyl-D-glucosamine, but not D-galactose and sialic acid, on the surface of a wide variety of bacteria, viruses, fungal species, parasites, as well as apoptotic and tumor cells [88, 89]. A recent study demonstrated mannosylated lipoarabinomannan (ManLAM) to be one of the main cell wall components of slow-growing mycobacteria interacting with MBL [90]. MBL can directly act as an opsonin or, in association with MBL-associated serine proteases (MASPs), it can activate the lectin pathway of the complement system cleaving complement factor C3 in an antibody-independent manner, thereby enhancing the clearance of the pathogens via phagocytosis [89, 91]. In vivo studies have shown that the deficiency of MBL and other components of complement lectin pathway increase the susceptibility to certain bacteria, fungi, as well as viruses [92–95]. However, the role of MBL in TB has not yet been studied in murine infection models.

In humans, MBL is coded by the gene MBL2 on chromosome 10. Serum levels of this protein exhibit high interindividual variations, which have been attributed mainly to the polymorphisms found in the promoter and exon 1 of the MBL2 gene, although non-genetic factors like age, hormone levels, or inflammation may also influence the serum levels [96]. The missense mutations in codons 52, 54, and 57 in exon 1, respectively, called D, B, and C alleles (the wild type is denoted as A and the three variant alleles as O), are known to disrupt the normal collagen helix, while the alleles H/L (−619), Y/X (−290), and P/Q (−66), upstream in the promoter region, affect the serum levels by regulating protein expression [88, 96]. These polymorphisms are in linkage disequilibrium and give rise to different haplotypes and genotypes, which may appear in varying frequencies among individuals, depending upon ethnicity [91, 97]. About 5–30 % of healthy individuals have MBL-deficient alleles, suggesting that these mutations may confer some selective advantage, as they have not been wiped out by natural selection [96]. Nevertheless, these polymorphisms and serum MBL levels have been associated with TB and other infectious and inflammatory diseases in different ethnic groups [91, 97]. The variant alleles have been associated with susceptibility to TB in different populations, while in others no association was observed (Table 2) [98–106]. A meta-analysis carried out by Denholm et al. comparing 17 different studies

Table 2 Overview of the identified functional SNPs in CLRs in different populations associated with susceptibility/protection toward tuberculosis

CTLR	SNP and location	Effect of SNP	References
SP-A	SPA-1 rs1059047 (exon 3) rs1136450 (exon 3) rs1136451 (exon 4) rs1059057(exon 6) rs4253527 (exon 6) SPA-2 rs17886395 (exon 4) rs1965707 (exon 6) rs17886221 (exon 4) rs1965708 (exon 6)	C allele—risk in Mexicans G allele—protection in Mexicans A allele—risk in Ethiopians, protection in Mexicans G allele—risk in Mexicans T allele—risk in Mexicans and Ethiopians Haplotypes 6A^4—risk in Mexicans 6A^2—protection in Mexicans CGAAC—protection in Chinese Han G allele—risk in Indians and Chinese Han, protection in Ethiopians T allele—risk in Chinese Han A allele—protection in Indians C allele—risk in Ethiopians Haplotypes 1A^3—risk in Mexicans and Ethiopians 1A—risk in Mexicans 1A^6, 1A^{10}, 1A^9, 1A^2—risk in Chinese Han 1A^3, 1A^5, 1A^{12}, 1A^{11}—protection in Chinese Han	[81–84]
SP-D	aa307 (exon 7)	G allele—protection in Indian population	[85]
MBL	Exon 1 variations (B, C D, O and A alleles) Promoter variations (H/L, X/Y, P/Q)	O allele—no association in Hispanic, white Americans, South African colored Risk in Indians B allele—risk and protection in two different Indian populations and African Americans, protection and no association in two different Turkish children populations. C allele—protection in Gambian population and Ghanaian (*M. africanum* infection) population D allele—risk in Indians XA/O haplotype—protection in white and non-white Americans XY genotype—risk in Chinese HYA/HYA haplotype—protection in Italians YA/YA—protection in Vietnamese LYB/LYD haplotype—risk in Italians XB haplotype—risk in Chinese Han HPYA, LPXA, LQYA, LPYB haplotypes—risk in Chinese	[98–106, 109, 110, 112, 113, 115, 253]
MR	rs34039386 (exon 7)	G allele—risk in a Chinese population Risk in Chinese Uygur No association in Chinese Kazak	[135, 136]
DC-SIGN	Promoter variations 336A/G 871A/G 939G/A	A allele—protection in South African colored, Iranian Risk in sub-Saharan Africans No association in Colombians, Tunisians, Indians, Chinese, West Africans, Moroccans G allele—protection in South African colored No association in Indonesians, Chinese, West Africans G allele—risk in Indonesians No association in Vietnamese	[161, 254] [254, 255] [256–261] [161] [259, 260, 262] [262]

Table 2 continued

CTLR	SNP and location	Effect of SNP	References
L-SIGN	Neck region variations 5 repeats 9 repeats 7 or 6 repeats (exon 4)	Protection in Brazilians Susceptibility in Brazilians No association in South Africans	[166, 167]
Mincle	rs10841845, rs10841847, rs10841856, rs4620776	No association in South African Population	[229]
MCL	rs4304840 (exon 3)	G allele—risk in Indonesians	[25]

and considering the effect of MBL polymorphisms and/or serum levels found no significant association of MBL polymorphisms with TB, although a consistent increase in the serum MBL levels in TB patients was observed, which may have been an acute phase response during infection. It is worth noting that most of the studies included in this analysis did not investigate the MBL haplotypes including promoter polymorphisms and the cohort, and the study design in these investigations were of highly heterogeneous nature [107]. In contrast, a meta-analysis involving Chinese populations concluded that presence of allele B might be a risk factor for developing TB [108]. In addition, more recent studies have focused on correlating the serum MBL levels with these genotypes and studying the effect of SNPs on factors, such as treatment progression and outcome, interaction with environment, or other genes, and on TB caused by other mycobacterial species [109–114]. In a recent study in Vietnam, it was found that the YA/YA haplotype had a protective effect against developing new pulmonary TB in young adults. They also found that the MBL levels decreased over the course of treatment after seven months, again pointing to the fact that high MBL levels in TB patients may be the result of acute phase response and that this decrease was highly dependent upon the genotype [115].

Given that MBL is one of the acute phase proteins and its levels can be affected by several other factors and pathogens, as well as its complete absence in otherwise healthy individuals, it becomes difficult to ascertain a particular role for this CTLR in TB infection. Moreover, the conflicting results from the genetic studies carried out with different populations suggest that MBL may not be directly involved pathogenesis of TB.

Membrane-bound CTLRs

Transmembrane PRRs are present on the cells of the immune system and play an important role in modulating the innate immune response to pathogens. While among the CTL receptors MR, DC-SIGN, and complement receptor 3 (CR3) have long been known to recognize Mtb [116–118], some new receptors have emerged in the last decade which have been shown to be of direct importance in Mtb-mediated immune response (Fig. 1). In humans, the genes encoding for these CTLs are located on chromosome 10, in the so-called Dectin-1 and Dectin-2 clusters of genes coding for Dectin-1, Dectin-2, Mincle, and MCL, among others [32, 119].

Mannose receptor

The mannose receptor, MR (synonym CD206), is abundantly expressed on AMs, monocyte-derived DCs (MDCs), and non-vascular endothelium (Table 1). It is a type I transmembrane protein with an extracellular N-terminal consisting of three domains: a cysteine-rich domain, a fibronectin type II domain, and eight CTLDs, followed by a transmembrane domain and a tyrosine-based motif in the cytoplasmic tail involved in ligand internalization [87, 120, 121]. MR can recognize a number of endogenous and exogenous ligands and is so involved in both maintaining homeostasis and acting as a PRR. Only CTLD4 seems to be able to bind to carbohydrate ligands such as terminal mannose-containing glycoconjugates, fucose, and GlcNAc [121]. The signaling pathway downstream MR is poorly understood. It may require aid from another receptor to initiate phagocytosis [122]. It may also undergo proteolytic cleavage, forming soluble sMR, and modulate the immune response by competing with the membrane-bound form [121]. MR serves as an endocytic receptor that is involved in the internalization of ligands and antigen presentation via MHCII and CD1b [123]. MR can recognize ManLAM, higher phosphatidylinositol mannosides (PIMs), LM, and other mannosylated proteins on the Mtb cell wall (Table 1) [124–126]. MR aids in adherence of virulent Mtb strains to human MDMs [116]. In addition, some reports have shown that phagocytosis of mannosylated beads by MR, as well as MR–ManLAM engagement, interferes with phagosome maturation, which may contribute to the intracellular survival of mycobacteria [67, 127, 128]. ManLAM from both BCG and Mtb, on cross-linking with MR, can

inhibit the TLR2-induced production of IL-12 by human DCs [129]. This was supported later by a study showing that ManLAM–MR engagement induced the production of anti-inflammatory factors IL-10, IL-1R antagonist, and IL-1R type II, and suppressed IL-12 secretion by human DCs [130]. Since Mtb has a plethora of ligands for different CTLRs, cross talk between these receptors is very likely. Indeed, MR together with DC-SIGN interferes with the Dectin-1-induced Th17 response and instead enhances the production of IFNγ by CD4+ cells favoring Th1 generation in the presence of Mtb-challenged human DCs [131]. Monocytes differentiated in the presence of irradiated Mtb had a low-DC-SIGN/low-MR profile associated with the loss of phagocytosis of irradiated Mtb [132]. MR was also shown to induce the production of matrix metalloproteinase-9 (MMP-9) by THP-1 cells in response to Mtb indicating a contribution to lung tissue damage during TB [133]. Together, these studies point to the fact that MR might favor Mtb in establishing its niche inside the infected phagocytes. However, in murine in vivo infection models with Mtb, MR was not involved in survival or disease progression [134].

Human MR is expressed by the MRC1 gene on chromosome 10. Only a couple of recent investigations carried out by Zhang et al. in Chinese populations focus on the detection of SNPs within MRC1 and its role in TB susceptibility. They concluded that a non-synonymous SNP, rs34039386 glycine to serine, in exon 7, coding for CTLD2 was associated with risk or protection in different groups of the Chinese population, albeit with low significance (Table 2) [135, 136]. The molecular mechanisms linked to the effect of this SNP on receptor function have not been deduced, but the authors suggest that it might affect the MR–ligand interaction [136].

Overall, the role of MR in phagocytosis of Mtb seems to be redundant as many other PRRs and complement receptors can aid in bacterial internalization. In contrast, results acquired from human cells suggest its negative immunomodulatory role by avoiding the intracellular killing of Mtb. However, to further enlighten the significance of this receptor for TB disease pathology, dedicated genetic and functional studies are required.

Dendritic cell-specific ICAM-grabbing non-integrin (DC-SIGN)

Dendritic cell-specific ICAM-grabbing non-integrin, DC-SIGN (synonym CD209), is a type II transmembrane receptor expressed mainly on myeloid DCs and some macrophage subsets including AMs [89] and also activated B cells (Table 1) [137]. The N-terminal makes the cytoplasmic tail and is endowed with three different motifs: a tyrosine-based motif, a dileucine motif, and a triacidic amino acid motif, all of which are thought to be mainly involved in endocytosis and phagocytosis. The transmembrane region consists of tandem repeats of 23 amino acids, which stabilize the tetrameric form of DC-SIGN that enhances its ligand-binding efficiency, while the extracellular C-terminus contains CTLD with an EPN motif and ligand-binding sites [89, 138]. DC-SIGN can bind to high mannose- and fucose-containing ligands and is able to bind to Mtb, as well as a variety of other pathogens. It has also been shown to bind to endogenous molecules of the human host-like intracellular adhesion molecules (ICAMs) and carcinoembryonic cell adhesion molecules CEACAM1, which is helpful in processes like DC migration, interaction with neutrophils, T cell activation, and antigen presentation [139, 140]. It can also serve as a signaling receptor. However, DC-SIGN triggering alone does not seem to initiate a response by DCs and a prior activation of NFκB by TLR signaling is required for its modulatory function [27, 55, 138, 141]. There is an evidence of TLR-independent signaling, as well [142]. It has been observed that different kinds of ligands can induce different kinds of signaling through DC-SIGN [55, 141]. Mannose-containing ligand engagement (e.g., mycobacterial ManLAM) leads to phosphorylation of Raf-1 and subsequent phosphorylation of NFκB subunit p65, increasing the production of cytokines such as IL-12, IL-10, IL-6, and CXCL8, whereas fucosylated antigens, such as Lewis antigens in LPS from *H. pylori*, seem to signal the DCs to suppress the pro-inflammatory cytokines production [141, 143].

In two independent studies, Geijtenbeek et al. and Tailleux et al. showed that mycobacteria directly bind to DC-SIGN to gain entry into human DCs. DC-SIGN was shown to enhance the internalization of both *M. bovis* BCG and Mtb [64, 117]. ManLAM–DC-SIGN binding inhibited LPS and *M. bovis*-induced DC maturation as well as increased IL-10 and decreased IL-12 production by LPS-activated DCs [64]. Moreover, DC-SIGN has been shown to be expressed on human lung DCs and is induced on AMs on Mtb infection [117, 144]. Further studies have demonstrated that, apart from ManLAM, DC-SIGN can also bind to other mannosylated ligands, PIMs, α-glucan on Mtb surface (Table 1) which may also contribute to host–pathogen interaction significantly [145–148]. Indeed, phagocytosis of BCG by DC-SIGN-lacking DCs [149] and the inability of mannose-dependent CLR inhibitor to inhibit Mtb infection in mice [150] suggest that the bacilli also use other modes of establishing intracellular niches and infection. Similar to MR, DC-SIGN co-stimulation also inhibits Dectin-1-induced Th17 response by Mtb-challenged DCs [131]. A transgenic mice expressing human DC-SIGN displayed higher survival rate and reduced tissue damage on high-dose infection with H37Rv advocating that DC-SIGN–Mtb interaction in vivo may in fact be beneficial to

the host [151]. Also, the results obtained by knockout (KO) mice studies, which express eight different DC-SIGN homologues (SIGNR1-8), suggest that SIGNR3 (the closest human DC-SIGN orthologue)-deficient mice have impaired resistance to early Mtb infection in lungs [89, 152, 153].

A closely related CLR called L-SIGN, also known as DC-SIGNR/CD209L/CLEC4M, proposed to have originated by gene duplication of DC-SIGN has also been described [154]. L-SIGN also binds to high mannose ligands, but not fucose, and can recognize pathogens including Mtb. In fact, L-SIGN shows more than 70 % amino acid identity with DC-SIGN and has similar structure and binding properties (HIV-1 gp120, ManLAM, and ICAM-3) [155, 156]. It is expressed on a restricted set of endothelial cells. Both DC-SIGN and L-SIGN are found in a tetrameric form, with the transmembrane repeats forming the neck region to which the CRDs are flexibly attached on the extracellular part providing high-avidity binding to multivalent ligands [155, 157].

DC-SIGN and L-SIGN are expressed by the genes CD209 and CD-209L, respectively, in human chromosome 19 [158]. Association of DC-SIGN promoter polymorphisms −336A/G and −871A/G with TB has been studied in many populations (Table 2). However, the results have been contrasting. Functionally, −336G was shown to be associated with decreased expression of DC-SIGN [159]. A meta-analysis performed to compare fourteen of these studies concluded that these promoter variations were not associated with susceptibility to TB, although an analysis performed and based on ethnicity revealed an association of the 336GG genotype as a risk for developing TB in an Asian population [160]. Barreiro et al. [161] showed that the haplotype −871G/−336A conferred protection in Africans. In another study, Russian males carrying −336GG were found to be more susceptible to lethal consequences of infection with Mtb Beijing strain than non-Beijing strains [162]. Thus, not only the host, but also the genotype and characteristics of Mtb may be responsible for different pathogenicity patterns.

Polymorphisms in the neck region of L-SIGN that lead to a change in the number of repeats (ranging from four to ten) have been attributed to variations in the binding affinity to the pathogenic antigens and are associated with developing an infection. Indeed, these polymorphisms in L-SIGN have been associated with viral infections [155, 163–165]. With regard to TB, there have been conflicting results between the two studies conducted by Barreiro et al. and da Silva et al. in a South African and a Brazilian population, respectively. While, in the former, no association was found, in the Brazilian population the allele with nine repeats was related to susceptibility to develop TB, while the one with five repeats conferred protection. The authors hypothesize that low number of repeats may disrupt the

binding of the receptor to Mtb, restricting its entry into the cell [166, 167].

In conclusion, the results from mice models and human cells provide conflicting results about the function of DC-SIGN in TB pathology. Also, the genetic studies with DC-SIGN promoter SNPs add to the confusion as to whether this receptor is beneficial for the host or the pathogen. As DC-SIGN recognizes a number of ligands on the Mtb surface, more in vitro and in vivo studies are required that focus on the effects of binding of these ligands with the receptor and subsequent functional responses.

Dendritic cell-associated C-type lectin 1

Dendritic cell-associated C-type lectin 1, *Dectin-1* (synonym CLEC7A) was first discovered as a DC-specific receptor which binds to an unknown, probably proteinaceous, ligand on T cells increasing their proliferation and thereby acting as a co-stimulatory molecule [168]. Later, it was found to be a major receptor for β-1,3-glucans and expressed not only on DCs but also on monocytes, macrophages, neutrophils, and on eosinophils, B cells, and mast cells, lung epithelium in humans [55, 169–171]. Dectin-1 is one of the seven genes belonging to the Dectin-1 cluster in the natural killer gene complex (NKC) on chromosome 12 in humans. All the genes in this family are class V type II CLRs having a common structure consisting of an extracellular CTLD connected to the cell surface by a stalk, followed by a transmembrane region and a cytoplasmic domain having signaling motifs. Dectin-1 is one of the non-classical CLRs bearing a hemITAM, with only one YXXL motif, apart from a triacidic DED motif for signaling. Moreover, unlike many other CLRs, the β-glucan binding to Dectin-1 is Ca^{2+} independent [172]. Since it can bind to T cells, Dectin-1 has also been proposed to be a co-stimulatory molecule [168]. Dectin-1 can recognize Mtb, although the PAMP involved has yet to be determined. Because of its recognition of β-glucan signaling, mechanisms have been mostly studied in fungal infection models where ligand binding to Dectin-1 has been shown to induce a number of cellular processes, including the production of cytokines and chemokines, respiratory burst, ligand uptake through phagocytosis/endocytosis, and DC maturation [173]. Dectin-1-mediated signaling is complex, involving activation of various transcription factors like NFκB, MAPKs, NFAT, IRF1, IRF5, and NLRP3 inflammasome through Syk-dependent or Syk-independent pathways [174, 175]. The canonical subunits of NFκB are activated via CARD9-Bcl10-MALT1 complex formation through Syk interaction with PLCγ2 and PKCδ, leading to the production of IL-1β and IL-23 which are Th17 response-polarizing cytokines. It has also been shown to activate the non-canonical subunit NFκB RelB [27, 176–178]. A recent

study demonstrated that Dectin-1 induces pro-IL-1β processing by forming non-canonical caspase-8 inflammasome [179]. The triacidic motif is also involved in phagocytosis and synergistically increasing the production of NFκB-induced cytokines, as in the case of DC-SIGN, via activation of Raf-1, and leads to Th1-favoring cytokine production [55, 180].

Dectin-1 has been shown to collaborate with TLR2 in the recognition of some mycobacterial species to induce pro-inflammatory cytokine production (Table 1) [181–183]. The TLR2-mediated release of TNFα, IL-6, RANTES, and GM-CSF by mice bone-marrow-derived macrophages (BMDMs) infected with attenuated or non-pathogenic mycobacteria such as *M. smegmetis*, BCG, Mtb H37Ra required Dectin-1, but not in the case of Mtb H37Rv [181]. In another study, Mtb-induced IL-12p40 production in splenic DCs of TLR2$^{-/-}$ mice was reduced on blocking Dectin-1 with laminarin. The Mtb-triggered IL-12p40 production was also reduced in response to inhibition of Syk, suggesting that Dectin-1 might mediate Syk-dependent response independently in these cells [184]. In experiments with human cells, as well, there seems to be an interactive role of TLR2 and Dectin-1 in inducing Mtb-specific immune response. In human lung epithelial cells, Mtb induced Dectin-1 expression, Src kinase, and ROS activation via TLR2. Dectin-1 activation, in turn, also enhanced internalization of bacteria [66]. A recent study in human DCs additionally showed similar Mtb-induced ROS production in a Dectin-1–TLR2-dependent manner [185]. Mtb–Dectin-1 engagement induces adaptive Th1/Th17 response in human MDCs, and this effect seems to be inhibited by MR and DC-SIGN co-stimulation [131]. Mtb-mediated Th17 responses in human PBMCs were studied by van de Veerdonk and colleagues, who concluded that Dectin-1 and TLR4 were responsible for these responses and IL-17A response was IL-1 pathway dependent. TLR2 blocking had less effect on IL-17A production [186]. These Dectin-1-mediated responses may contribute to mycobacterial immunity, but KO studies in mice suggest a redundant role of this receptor in Mtb infection. Although the Dectin-1$^{-/-}$ mice had a low bacterial burden, it was not related to animal survival on Mtb challenge compared with wild type [187]. An early stop codon polymorphism Y238X which produces a truncated Dectin-1 has been studied in some fungal diseases [40, 41, 188, 189]. However, to date, no susceptibility studies focusing on the identification of SNPs in the CLEC7A gene have been carried out in patients with TB.

In summary, these studies suggest that Dectin-1 exerts a protective role by enhancing the pro-inflammatory immune response against Mtb, at least in experiments with human cells. Genetic studies investigating Dectin-1 SNPs associated with TB would provide further insights into the functional importance of this receptor in TB development.

Dendritic cell-associated C-type lectin 2

Dendritic cell-associated C-type lectin, *Dectin-2* (synonyms CLEC6A, CLECSF2), is a member of the Dectin-2 cluster in the NKC region on chromosome 12 consisting of six genes, all of which are type II transmembrane group II CTLRs. Believed to have originated by gene duplication, they share a common structure—an N-terminal cytoplasmic tail which is usually short and lacks a signaling motif, a transmembrane domain, a stalk, and a C-terminal extracellular domain with a Ca^{2+} binding and a CRD motif. The transmembrane domain bears a positively charged residue that aids in association with an ITAM-bearing adaptor molecule like FcRγ, DAP10, and DAP12 required for signaling [190–192]. In humans, Dectin-2 is expressed strongly in lungs, whereas weak expression is observed in spleen and lymph nodes. It is expressed on DC subsets, monocytes, tissue macrophages including AMs, and weakly on B cells (Table 1) [55, 192]. Its expression can be altered on peripheral blood cells by treatment with different stimuli, as has been observed in mice, as well as in humans [193, 194]. The EPN motif in CRD helps in the recognition of high mannose structures (albeit with low affinity) in a Ca^{2+}-dependent manner, as the ligand binding is completely inhibited in the presence of chelators [195]. Thereby, Dectin-1 acts as a PRR for mycobacterial ManLAM apart from many fungi [23]. Signaling has been mainly studied in fungal interactions, in particular with *C. albicans*. Ligand binding to Dectin-2 induces cellular activation, via FcRγ recruitment activating NFκB in a Syk-dependent manner, and is important in inducing a Th17 response, as well as other cytokines including TNF, IL-1RA, IL-6, IL-12, and IL-10 [191, 196–200]. Gringhuis et al. [199] showed that Dectin-2 induces Th17 immunity by Malt-1-mediated activation of c-Rel subunits of NFκB. Also, PLCγ has been shown to be important for the proper activation of Dectin-2-mediated NFκB and MAPKs [201]. Dectin-2 can also activate the NLRP3 inflammasome and induce allergic inflammation [202, 203]. Soluble recombinant Dectin-2 is able to bind with Mtb [195]. Yonekawa et al. [23] have recently demonstrated that Dectin-2 binds directly to ManLAM. They showed that the receptor could bind to Mtb and BCG and other slow-growing mycobacteria, but not to *M. abscessus* and *M. smegmatis* whose LAM lacks capped mannose, and mediated IL-6, TNF, MIP-2, IL-2, and IL-10 production by bone-marrow-derived DCs (BMDCs) in mice. Also, DC maturation and IL-17 production by activated T cells were all abrogated in Dectin-2-deficient Clec4n$^{-/-}$ mice [23]. Besides, the Clec4n$^{-/-}$ mice displayed augmented lung pathology on infection with *M.*

avium complex compared to WT. Moreover, IFNγ production in PBMCs from TB patients in response to mycobacterial antigenic peptides was enhanced on addition of Man-LAM and was significantly inhibited on treatment with anti-hDectin-2 Mab. However, whether this signaling was also Syk dependent was not tested [23].

Dectin-2 has been predominantly studied as a fungal receptor, and knowledge of its role in bacterial infections is still in its infancy. Nevertheless, recent results from in vitro human cell studies and KO mouse models suggest a protective function for it in TB infection. To date, the role of polymorphisms in this gene has not been studied in human TB infections and further studies focusing on this aspect may reveal the importance of this receptor in TB pathology.

Macrophage-inducible C-type lectin

Macrophage-inducible C-type lectin, *Mincle* (synonym CLEC4E), is another member of the Dectin-2 cluster with a similar structure. It was first identified as a downstream target of NF-IL-6 transcription factor in murine macrophages and was inducible by treatment with inflammatory stimuli like LPS, IFNγ, IL-6, and TNFα, hence the name Mincle [204]. It is expressed on monocytes, macrophages, neutrophils, and myeloid DCs, and also some B cell subsets (Table 1) [205]. It binds mainly to mannose and fucose, but also shows some affinity for glucose, GlcNAc, galactose, and GalNAc [206]. Mincle also couples with ITAM-containing FcRγ and signals via the Syk-CARD9 pathway, inducing pro-inflammatory cytokine production [22, 207]. Mincle directly recognizes the mycobacterial cord factor [21] and many fungal species [35, 36]. Mycobacterial cord factor, TDM, is an important structural molecule in the cell wall of Mtb that functions as a PAMP. TDM has been shown to contribute to granuloma formation on Mtb infection in mice lungs [21]. The cord factor is also known to abrogate phagosome maturation and impairs the development of effective immune response enhancing the survival chances of the bacterium inside the cell and breaking the link between the innate and acquired arms of immunity, as the cell is unable to present the antigens to T cells [208–212]. TDM- and its synthetic analogue trehalose-6,6-dibehenate (TDB)-mediated adjuvanticity to induce Th1 and Th17 responses was lost in Mincle-deficient mice [22]. TDM-induced Mincle signaling in mice neutrophils leads to increased surface expression of CR3, ROS, and TNFα in synergy with TLR2 activation. Also, the Mincle$^{-/-}$ mice showed higher lung bacterial burden on Mtb infection [213]. However, Heitmann and colleagues reported that Mincle$^{-/-}$ mice were able to develop granuloma, generate Th1 and Th17 response, and control the infection similar to WT mice on aerosol infection with Mtb [214]. In line with this, Behler et al. [215] also obtained similar results

on intratracheal BCG infection of WT and Mincle$^{-/-}$ mice, but the KO mice were more susceptible to intravenous administration of BCG, developing high bacterial loads in the lung, as well as other tissues. Besides, Mincle was inducible in AMs of WT mice on BCG challenge and showed increased anti-mycobacterial immune response on a secondary BCG infection in vivo [215]. The group later also investigated the role of Mincle in systemic infection in KO mice and concluded that Mincle-expressing DCs elicit a Th1 response in spleen, but not in liver [216]. It may be noted that these studies involved different Mtb strains and/or administration methods which may contribute in part to the discrepancy in results. Mincle recognition of TDB has also been shown to activate the NLRP3 inflammasome via IL-1-dependent Myd88 pathway to induce a Th1 and Th17 response in mice BMDCs, and the adaptor ASC and caspase-1 were also required for this response [217–219], while in a recent work, Wook-bin Lee and colleagues demonstrated that Mincle–TDM engagement promotes nitric oxide (NO) production which in turn inhibits the inflammasome and that Mincle also has a stimulatory effect on TLR signaling [220]. Again, the results may be contrasting because of the type of cells used. Mincle shows low expression on resting macrophages, but is inducible on stimulation with TLR ligands in mice [204] and transcription factor C/EBPβ seems to play a role in the Myd88-dependent upregulation of Mincle, TDM/TDB responsiveness, and also HIF1α-mediated NO production [221, 222]. A recent study reported that human APCs respond similarly as the rodent cells to TDM/TDB, inducing cytokines like IL-6, IL-8, IL-1A, IL-1B, and G-CSF in a Syk-dependent manner [223]. Indeed, the CRDs of mice and human Mincle have been shown to have similar TDM-binding properties, but some differences have been observed with regard to other mycobacterial ligands, namely β-gentiobiosyldiacylglycerides and 2′S-stereoisomer of glycerol monomycolate (GroMM) [224–226]. TDM and BCG interaction with Mincle may also induce anti-inflammatory IL-10 cytokine production in mice BMDMs and modulate IL-12p40 production, as reported recently [227]. Besides its role as a PRR, Mincle can also recognize the damage-associated molecular patterns (DAMPs) like SAP130 released by damaged self-cells, suggesting its role in sensing necrosis [207]. More recently, cholesterol crystals have been reported as an endogenous ligand for Mincle in human monocyte-derived DCs upregulating pro-inflammatory cytokine and chemokine synthesis [228]. A recent study found no association of Mincle SNPs (Table 2) with TB in South African colored population [229].

Overall, Mincle has been associated with pro-inflammatory responses in human cell models. The new reports about additional Mtb ligands for Mincle and the anti-inflammatory effects show that our understanding of the

role of this receptor is still incomplete. Further studies need to be carried out to investigate if potential SNPs in Mincle gene might contribute to the pathogenesis of TB.

Macrophage C-type lectin

Macrophage C-type lectin (MCL) (synonyms CLEC4D/ Clecsf8/Dectin-3) is another newly described member of Dectin-2 family. It was first described as macrophage-restricted CLR in mice [230]. Human MCL is a type II transmembrane receptor with an intracellular N-terminal lacking any signaling motif, a transmembrane domain, and extracellular C-terminal connected via stalk to the cell surface bearing a single CRD [231]. It is expressed by neutrophils, CD14$^+$ CD16$^-$ monocytes, and some DC subsets (Table 1). Although constitutively expressed on myeloid cells [232], monocyte differentiation into macrophages or DCs has been shown to downregulate MCL expression [233]. MCL has been proposed to have originated by Mincle duplication and, likewise, it can also recognize TDM and some fungi [45, 232], albeit with lower affinity, since the CRD of MCL lacks the conserved tripeptide motif required for carbohydrate recognition [231]. Arce et al. [231] reported that MCL lacks an intracellular positively charged residue for pairing with adaptors and that cross-linking of this receptor leads to its internalization, suggesting a role in antigen uptake, while later it was shown that it can also induce phagocytosis, respiratory burst, and cytokine production in a Syk-dependent manner [233]. More recently, MCL has been associated with Mincle-related responses. Here, MCL associates with FcRγ and is required for inducing Mincle expression on TDM stimulation. In addition, Clec4d$^{-/-}$ mice showed impaired TDM-induced responses, such as granuloma formation and cytokine production (TNF, MIP-2, IL-1β, IL-6) [24, 232]. Along this line, Lobato-Pascual also observed similar results for rat receptors expressed on HEK293T cells and proposed Mincle–MCL heterodimer to be a functional unit mediating Mincle-associated immune response [234]. It was later confirmed in mice and human cells that MCL indeed associates with Mincle through its stalk region [235]. Recent studies suggest that MCL expression is co-regulated with Mincle and can be induced in mice in a Myd88-dependent manner [222, 236]. However, Zhao and colleagues, in their experiments, negated any such association between MCL and Mincle to form dimers and suggested that the main function of MCL is to induce initial Mincle expression in response to TDM via CARD9/Bcl10/MALT1-dependent NFκB activation [24]. A resolution of these differing results has yet to be made. Wilson et al. [25] concluded that MCL is non-redundantly important for anti-mycobacterial immunity. Infection with BCG or

H37Rv leads to higher bacterial burdens, increased production of TNFα, IFN-γ, and G-CSF, as well as higher neutrophil infiltration in lungs of Clec4d$^{-/-}$ mice. Moreover, the in vitro studies showed that loss of MCL affects the bacterial binding to leukocytes and thus reduces phagocytosis [25].

Only a few data are available regarding the impact on SNPs in the MCL gene for TB susceptibility. A non-synonymous SNP Ser32Gly has been associated with pulmonary TB in an Indonesian cohort with the G allele associated with disease susceptibility in a dominant model (Table 2). The polymorphism causes a missense mutation in the transmembrane region of the protein affecting its association with adaptor Fcγ and influencing its surface expression [25].

In a nutshell, MCL has an important protective function in generating anti-mycobacterial immunity by enhancing Mincle expression, Mtb recognition, and internalization. The only genetic study has further supported its role in TB, and further studies would be interesting to more deeply understand its significance in mycobacterial infections.

Complement receptor 3

Complement receptor 3, CR3 [synonyms α$_M$β$_2$, CD11b/ CD18, macrophage-1 antigen (Mac-1)], is a heterodimeric membrane receptor belonging to the integrin superfamily. It is expressed on neutrophils, macrophages, natural killer cells, and monocytes (Table 1) [237]. The extracellular part of its α chain, which is a type I transmembrane protein, consists of an I domain for binding a variety of ligands like iC3b (making it a major complement receptor for opsonized tubercle bacteria), mycobacterial Ag85C, ICAM-1, and many bacterial components [238, 239], while the C domain having a lectin-like site can interact with sugars like β-glucan, glucose, GlcNAc, and mycobacterial oligosaccharides, including LAM and PIMs (Table 1) [238, 240]. Thus, CR3 is capable of inducing both opsonic and non-opsonic phagocytosis [238, 241]. Increased expression of CR3 was observed in the peripheral blood phagocytes and AMs in TB patients, suggesting its role in pathogenesis [242–244]. Studies with human BALF suggest that classical complement pathway activation leads to opsonization of pathogens like Mtb and may enhance their phagocytosis by AMs [245, 246]. However, it was shown that the absence of CR3 does not influence bacterial survival inside the cell as observed in CR3- and CD11b-deficient mice [118, 247, 248]. This suggests that, in the absence of CR3, mycobacteria can still be internalized by other receptors; thus, the role of CR3 in Mtb pathogenesis seems to be redundant. Besides, no SNP studies have been performed in humans to support its role in the development of TB.

Conclusion

CTLRs have gained attention in recent decades with respect to the increasing numbers of pathogens and endogenous ligands that are recognized by these PRRs, strengthening their significance in maintaining immunity and homeostasis. While some CTLRs with newly discovered roles in mycobacterial infections, such as MCL and Mincle, are important for inducing a specific immune response against the pathogen, there are others, such as CR3, MR, DC-SIGN, which may in fact contribute to immune evasion strategies of mycobacteria. The outcome may depend on various factors which include, but are not limited to the type of cells infected, surface expression of receptors, and interactions between them, the cell's gene expression profiles of receptors and adaptors involved in Mtb recognition, extracellular factors, and bacterial, as well as host genetics. Apart from this, standardization of the experimental procedures and practices, such as ensuring the purity of ligands used and minimizing the endotoxin contamination, is also crucially important to attain reliable results. Recent finding that MCL is indispensable for anti-mycobacterial response and that it also regulates the expression of Mincle suggests the importance of interactions between the receptors in defining a specific immune response. Genetic association studies offer further information on the relevance of a receptor and its function. However, in several genetic studies, polymorphisms are not investigated for their functional effect, and in others, the significance level for the association between the SNPs and TB is rather low. Additionally, while performing such studies, it is to be considered that complex diseases like TB do not follow the patterns of Mendelian diseases and are in fact polygenic, being largely affected by gene–gene interaction. Mtb is recognized by a number of PRRs and precise knowledge about cross talk between these receptors and their signaling, as well as the manipulation elicited by bacteria, in order to develop its niche would enable us to better understand the host–bacteria interaction and control the infection and also block further spread.

Elucidating the mechanisms of ligand recognition, adaptors involved in signaling cascades and signaling regulation by CTLRs, and other receptors involved in TB may be helpful in designing vaccine adjuvants that can specifically activate an adaptive response and help develop other protective strategies, such as targeting the key components in specific signaling pathways via immunomodulation. Along with this information, the host genetics profile data, including the SNPs in different genes involved in specific responses toward TB, should be further elucidated for their functional significance which will help in identifying prognostic markers and aid in the ambitious goal of tailoring individual specific therapies. As knowledge about the significance of Mtb-recognizing members of CTLRs is in preface, they serve as an important and promising group of receptors that have the potential to be further explored and more clearly define their roles in mycobacterial infections.

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