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C-type lectins in immunity to *Mycobacterium tuberculosis*

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1. ABSTRACT

Tuberculosis (TB) remains one of the leading causes of death due to a single infectious agent, *Mycobacterium tuberculosis*, with nearly 2 million deaths per year (1). Most individuals exposed to the bacillus develop a nonpathological form, latent TB, with only a small minority (5 to 10%) developing active disease. It is estimated that one third of the human population worldwide may have latent *M. tuberculosis* infection. Latent TB is characterized by an efficient immune response that contains the infection in a nonpathological and noncontagious state, within a specific, dynamic structure called the granuloma. Interactions between *M. tuberculosis* and the immune system play a crucial role in determining the outcome of the disease, and are mediated by various pattern recognition receptors (PRRs) expressed in cells of the innate immune system and in nonimmune cells. These interactions may modulate the immune response in favor of the bacillus, by allowing it to persist within host phagocytes. They may also favor the host, by inducing immune defenses, such as autophagy, phagosome maturation, apoptosis and various bactericidal mechanisms.

2. INTRODUCTION

M. tuberculosis interacts with a diverse range of pattern recognition receptors (PRRs). Some of these interactions regulate endocytosis and signaling events. Endocytosis may require opsonization of the bacillus (e.g. by immunoglobulins, complement molecules, the mannose-binding lectin (MBL) or other members of the collectin family), or may occur through direct recognition of the bacterium by transmembrane receptors. These receptors include the type 3 complement receptor (CR3), several scavenger receptors (SR) and various membrane-associated C-type lectins (CTL). These CTLs, in addition to carrying out endocytosis, can also act with the PRRs of the Toll-like receptor (TLR) and nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) families to modulate the immune response and regulate the activation and maturation status of infected cells. These receptors control important cellular pathways regulating the secretion of various cytokines, chemokines and growth factors influencing the course of infection.

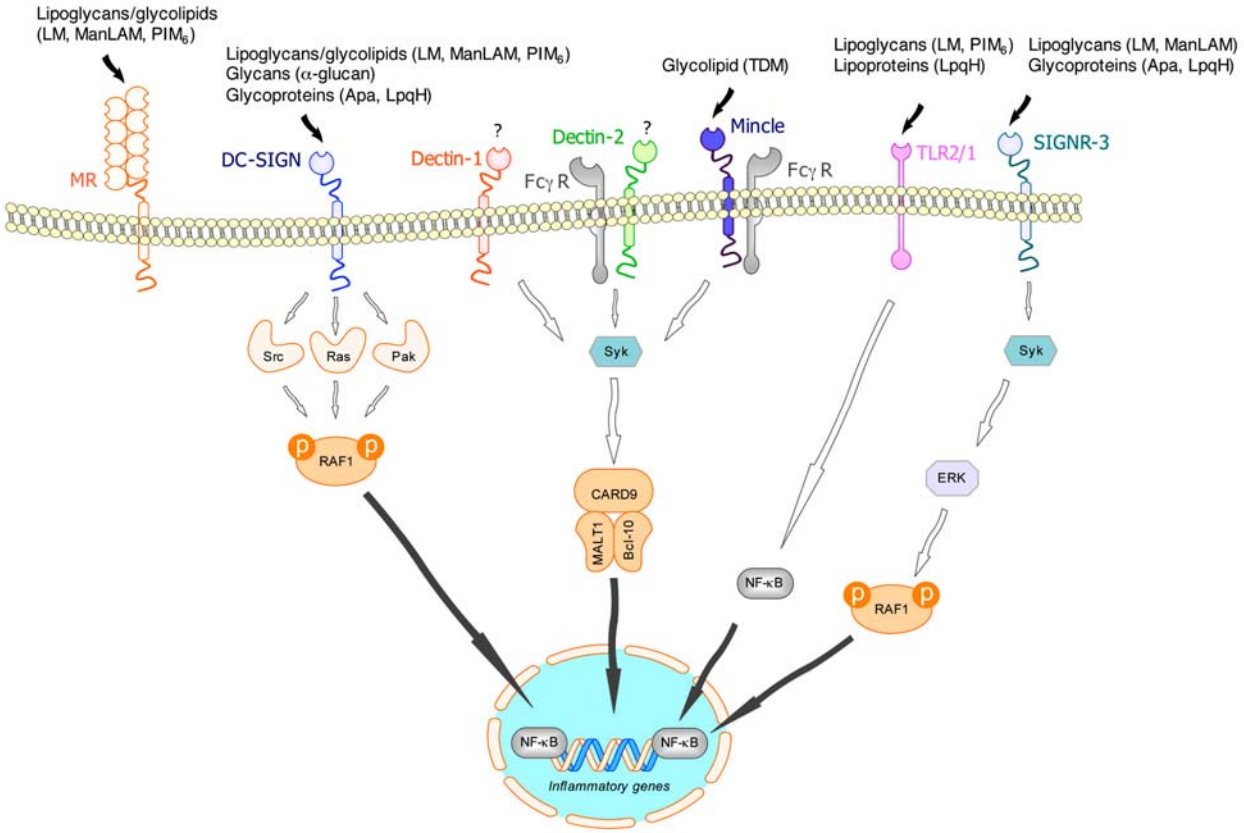

Figure 1. *M. tuberculosis* recognition by membrane-bound C-type lectins. Several members of the CTL family have been reported to recognize *M. tuberculosis* and/or mycobacterial ligands, namely the mannose receptor (MR), the dendritic cell-specific intercellular adhesion molecule-3 grabbing nonintegrin (DC-SIGN), the glucan receptors Dectins 1 and 2, the macrophage inducible C-type lectin (Mincle), and the DC-SIGN-related mouse homologs SIGNR1 and SIGNR3. These receptors recognize mycobacterial lipoglycans, such as mannosylated lipoarabinomannan (ManLAM) and lipomannan (LM) and glycolipids, such as phosphatidylinositol mannosides-6 (PIM_6) and trehalose dimycolate (TDM), as well as surface glucans and glyco- and lipo-proteins, such as LpqH and Apa. The mycobacterial ligands for Dectins 1 and 2 remain unknown to date. Ligand recognition can transduce intracellular signals, either directly, such as for DC-SIGN and SIGNR3, or through collaboration with other receptors, such as the Fcγ-receptor (FcγR) in the case of Dectin-2 and Mincle, which leads to the activation of the tyrosine kinase Syk, and the recruitment of the CARD9-MALT1-Bcl-10 complex. The signalosome recruited through DC-SIGN activation induces a RAF1-dependent signaling cascade that leads to acetylation of the NF-κB p65 subunit. The SIGNR3-dependent signal relies on Syk, ERK, RAF1 and NF-κB. The figure has been adapated from several publications cited in the text.

TLRs are the PRRs most extensively studied over the last 20 years. Early studies *in vitro* and *in vivo* in the mouse model suggested that TLR2 and TLR4 are involved in immunity to TB (2-8). *In vitro*, these TLRs recognize mycobacterial molecules and mediate the secretion of pro-inflammatory cytokines known to play a key role in the anti-mycobacterial immune response (9-11). However, the role of these receptors *in vivo* is less clear, and recent studies have shown that inactivation of the genes encoding TLR2, TLR4 and TLR9, either individually or together, has no significant effect on susceptibility to *M. tuberculosis*, at least in the mouse model (7, 8, 12). Conflicting results have been reported concerning the role of TLRs in controlling bacterial infections in humans. One such report, based on the study of patients with inherited MyD88 deficiency, concluded that TLRs may have redundant functions in immunity to most infectious agents (13). Other studies have identified single nucleotide polymorphisms (SNP) associated with differential susceptibility to TB in TLR-encoding genes (14-19). Collectively, these findings suggest that the role of TLRs in antimicrobial immunity may be highly dependent on the pathogen and human population considered, and further investigations of these aspects are required.

The *M. tuberculosis* cell envelope is particularly rich in glycosylated molecules, such as glycolipids (e.g. phosphatidyl-*myo*-inositol mannosides (PIMs), trehalose dimycolate (TDM)), lipoglycans (e.g. lipomannan (LM) and lipoarabinomannan (LAM)), polysaccharides (the α-glucan) and glycoproteins, including the 19 kDa, 45 kDa and 38 kDa antigens (20, 21). TLRs, such as TLR2 (for the 19 kDa antigen and LM for instance), recognize these molecules through their lipid moieties (9, 10, 22). In addition, these molecules may also interact with CTLs via their sugar moieties.

In addition to TLRs, *M. tuberculosis* can also interact with intracellular receptors of the NLR family (23). These receptors recognize a broad range of microbial ligands and mediate inflammatory and apoptotic mechanisms. In particular the muramyl dipeptide recognition NLR NOD2 can synergize with TLR2 to induce an inflammatory response to *M. tuberculosis* in human and mouse myeloid cells although NOD2-deificient mice were found as resistant to *M. tuberculosis* infection, as their wild-type counterparts (24-25). Another NLR, namely NLRP3, can recognize secreted mycobacterial components and promote inflammasome activation and the secretion of interleukin (IL)-1β (26). However, as in the case of NOD2-deificient mice, NLRP3-deficient animals are not more susceptible to *M. tuberculosis* than wild-type animals (27). These results suggest that a large degree of redundancy and/or cooperation exists between the different PRRs in the context of mycobacterial recognition and clearance, which largely remains to be explored. In particular, relevant to the context of this review, the cross-talk between NLRs, such as NOD2, and CTLs has yet to be fully understood.

3. *M. Tuberculosis* recognition by c-type lectins (CTL)

C-type lectins (CTL) are Ca^{2+}-dependent glycan-binding proteins displaying similarities in the primary and secondary structures of their carbohydrate-recognition domains (CRD). These proteins have a C-type lectin fold, a structure with a highly variable protein sequence that is also present in many proteins that do not bind carbohydrates (C-type lectin domain [CTLD]-containing proteins). CTL and CTLD-containing proteins are found in all organisms (28). The CTL family contains a large number of proteins, including collectins, selectins, endocytic receptors and proteoglycans. Some of these proteins are secreted, whereas others are transmembrane proteins. They often oligomerize into homodimers, homotrimers, and higher-order oligomers, which have a higher avidity for multivalent ligands. CTLs may be structurally similar, but they differ significantly in the types of glycans that they recognize with high affinity. These proteins function as adhesion, internalisation and signaling receptors in many immune functions, including inflammation and immunity to tumors and microbes (29).

There are at least 17 groups of CTLD-containing proteins, defined on the basis of their domain architecture. In most of these groups, the proteins have a single CTLD, but the macrophage mannose receptor (group VI) has eight such domains. Groups VII (e.g. Reg), IX (e.g. tetranectin), XI (e.g. attractin), XIII (e.g. DGCR2), XV (e.g. BIMLEC), and XVII (e.g. CBCP) have no known glycan ligands. The sugars exposed on the surfaces of host cells and pathogens are generally different. Segregation on the basis of sugar composition is therefore an effective way for the innate immune system to recognize foreign organisms. CTLs are thus key receptors of the innate immune response and have been strongly conserved throughout evolution. We now know more about the interactions between mycobacterial ligands and collectins (e.g. SPA, SPD and MBL) and myeloid transmembrane lectins (e.g. MR, Dectins 1 and 2, Mincle, CR3, DC-SIGN).

3.1. *M. tuberculosis* recognition by collectins

Collectins are CTLs with a collagen-like domain; they usually assemble into large oligomeric complexes of nine to 27 subunits (30). Nine different collectins have been identified: mannose-binding protein (MBP), conglutinin, surfactant proteins A and D, and collectins CL-43, CL-46, CL-P1, CL-L1, and CL-K1. Some of these molecules — MBP, conglutinin, CL-43, CL-46, CL-K1, SP-A, and SP-D — are soluble, whereas CL-L1 and CL-P1 are membrane proteins. Some secreted collectins, such as MBP and SP-A, are organized into a "bouquet", whereas others, such as bovine conglutinin and SP-D, adopt a "cruciform" shape. MBP is one of the best-studied serum collectins. Collectins contribute to innate immunity and act before the induction of an antibody-mediated response. *In vitro,* they stimulate phagocytosis through the recognition of surface glycans on pathogens, promote chemotaxis, and stimulate the production of cytokines and reactive oxygen species by immune cells (29). Three members of the collectin family have been shown to be involved in *M. tuberculosis* recognition and immunity to TB: SP-A, SP-D and MBL.

3.1.1. Surfactant proteins A and D (SP-A, SP-D)

SP-A and SP-D are collectins produced by the respiratory epithelium (31). Together with SP-B and SP-C, these surfactant proteins play an important role in lung physiology. However, SP-A and SP-D are also known to be key innate immune receptors and to be involved in the maintenance of lung integrity (32). SP-A and SP-D were originally discovered in the lung, but they are also expressed in the intestine (29). Several studies have shown that surfactant proteins A and D modulate host–mycobacterial interaction in the lung (33-40). Multimerization of the 32 kDa SP-A and 43 kDa SP-D subunits results in the generation of decaoctameric and dodecameric pattern molecules, respectively. The CRD domains of collectins bind glycoconjugates on the surface of pathogens in a Ca^{2+}-dependent manner (41, 42). The interaction of these collectins with Gram-negative bacteria may alter the viability of the microbe (43-45).

SP-A and SP-D also influence the uptake and fate of microbes, such as mycobacteria, in alveolar macrophages (35-37, 46, 47). SP-A increases *M. tuberculosis*-macrophage interactions by both directly upregulating phagocytosis and serving as a bacterial opsonin, whereas SP-D induces *M. tuberculosis* aggregation (47). Both SP-A and SP-D bind to lipoarabinomannans in the mycobacterial cell wall (47, 48). SP-A also interacts with Apa, a serine- and proline-rich glycoprotein of the *M. tuberculosis* cell envelope (49). SP-D binding enhances phagolysosomal fusion in macrophages, thereby enhancing the intracellular killing of mycobacteria (35). The role of SP-A is less clear, but it has been shown that opsonisation by this collectin increases the uptake and killing of the attenuated strain *M. bovis* BCG, whereas, for *M. avium,* it increases uptake without affecting killing (40, 50, 51). The improvement in *M. tuberculosis* uptake observed with SP-A opsonization seems to involve upregulation of the macrophage mannose receptor (MR), possibly allowing the pathogen to multiply within the macrophages (52). SP-A also enhances the expression of

additional innate immune receptors involved in *M. tuberculosis* recognition, including the scavenger receptor SR-A and the complement receptor CR3 (53-54). Both SR-A and CR3 are involved in mycobacterial uptake by macrophages (55-57). The ability of SP-A and SP-D to modulate the expression and inflammatory activity of TLRs may influence the inflammatory response of macrophages to *M. tuberculosis* infection (58-60). Furthermore, the SP-A-mediated attachment of *M. tuberculosis* to macrophages is associated with a suppression of nitric oxide synthesis, suggesting that SP-A may decrease the mycobactericidal activities of alveolar macrophages *in vivo* (61). Consistent with this ability of SP-A to suppress immunity, this collectin has been shown to suppress the recall response to mycobacterial antigens in PBMCs from tuberculin-positive individuals. Binding to the SP-A receptor SP-R210 decreases IFNγ synthesis, thereby suppressing lymphocyte proliferation in response to mycobacterial cell wall antigens via a mechanism involving the anti-inflammatory cytokines IL-10 and TGF-β (62).

Thus, SP-A and SP-D, together with surfactants, lipids and other proteins, are key components of the immune response to *M. tuberculosis* infection in the lung, and participate in the maintenance of lung integrity (63). The phenotype of mice lacking SP-A and SP-D in the context of *M. tuberculosis* infection has yet to be reported, but GM-CSF-deficient mice, in which surfactant metabolism is highly impaired, are much more susceptible to *M. tuberculosis* infection than wild-type mice (64-65).

3.1.2. The mannose-binding lectin (MBL)

MBL is a collectin that forms a trimeric helical structure through interactions between the collagenous tails, stabilized by disulfide bonds in the cysteine-rich amino-terminal region (66). These trimers undergo further oligomerization to form a "bouquet" structure. This functional form of the protein interacts with glycans and activates complement on microbial surfaces (67, 68). MBL is a CTL displaying selective Ca^{2+}-dependent binding to the terminal sugars D-mannose, L-fucose and N-acetyl-D-glucosamine, but not to D-galactose or sialic acid (69, 70). Within the oligomeric structure, the spacing between the various CRDs provides has a regulatory function, controlling interactions with extended mannan-containing glycoconjugates, particularly those on bacteria, yeast, and parasites. MBL is synthesized principally by the liver and is found mostly as a circulating extracellular protein. However, it has also been detected in other body compartments, such as the synovial and amniotic fluids (66). It has also been described as an intracellular protein associated with specific subcellular compartments, namely in the endoplasmic reticulum (ER) and in COPII vesicles (71). The binding of MBL and other collectins to a target cell results in the direct activation of complement via the classical lectin pathway and generates opsonic C3b fragments that coat pathogens, targeting them for phagocytosis (66). For human MBL, this activation results from a novel type of C1-like serine protease, which complexes with MBL and initiates the complement cascade *in vivo* (66). MBL may also associate with other surface receptors, such as calreticulin, CD91 or CD93, to potentiate microbial phagocytosis (66). MBL has also been shown to act as a proinflammatory modulator in response to various pathogens and, more specifically, through interactions with TLR2 and TLR6 within the phagosome of cells infected with *S. aureus* (66, 72). Some individuals with MBL deficiency syndrome have mutations in the Gly-X-Y repeat encoded by exon 1 of the MBL gene (*MBL2*). Diverse mutations within exon 1 have been found in human populations; they inhibit the assembly of the MBL subunits, increasing the risk of microbial infections. Furthermore, several polymorphisms within the promoter region of *MBL2* are associated with MBL deficiency and greater susceptibility to infections. In various genetic association studies, *MBL2* polymorphisms have been shown to be associated with protection against several pathogens, including *S. aureus*, *P. aeruginosa*, and the herpes simplex and influenza viruses (66).

MBL has been shown to interact with mycobacteria and, in particular, to bind to the lipoarabinomannans (LAMs) of *M. tuberculosis*, *M. leprae* and *M. avium* (73, 74). *In vitro,* MBL enhances *M. tuberculosis* by facilitating the entry of mycobacteria into phagocytes, pathogen spread and the establishment of infection by this facultative intracellular pathogen (47, 75). Several genetic association studies have evaluated the relationship between certain *MBL2* genotypes and susceptibility to TB. However, no firm conclusions can yet be drawn concerning the role of MBL in TB (76-79). Indeed, the role of MBL in innate immunity remains a matter of debate, because *MBL2* deletion genotypes are present at high frequency in the population, and this is not consistent with strong selection operating on an essential gene (80). MBL seems to have a redundant function. In particular, it is absent or present in only small amounts in the lung, potentially accounting for its apparently minor role in the early phases of *M. tuberculosis* infection and its greater involvement in later phases of infection and extrapulmonary TB (81-83). The susceptibility of MBL-KO mice and of mice carrying MBL-deficient genotypes remains to be studied, to provide insight into the possible role of MBL in *M. tuberculosis* infection *in vivo* (72, 84).

3.2. *M. tuberculosis* recognition by transmembrane myeloid C-type lectins

Two types of transmembrane CTL have been reported to be involved in immune responses to pathogens: type 1 CTLs contain an extracellular CRD at their C-terminal end, whereas type 2 CTLs carry their CRD at the N-terminal end. The sugar specificity of a given CTL is determined by its amino-acid sequence and number of CRDs. The cytoplasmic tail of CTLs contains various amino-acid clusters mediating endocytosis, oligomerization, intracellular trafficking and signal transduction. Immunoreceptor tyrosine activation/inhibition motifs (ITAM/ITIM) are among the signaling determinants found in the cytoplasmic tails of several CTLs.

The myeloid CTLs reported to interact with *M. tuberculosis* or mycobacterial components include the mannose receptor (MR), Dectin 1 macrophage-inducible C-type lectin (Mincle) and dendritic cell-specific ICAM3-

grabbing nonintegrin (DC-SIGN/CD209) and its mouse counterparts SIGNR3 and SIGNR1 (85-96). Myeloid CTLs function as endocytic receptors. Ligands are internalized by clathrin-dependent pathways and delivered to early and then late endosomes. Receptors may be recycled or degraded, depending on the receptor and the type of ligand. At pH values below 5, CTLs typically lose Ca^{2+}, shifting the equilibrium toward ligand dissociation. The cytoplasmic domains of these receptors dictate their trafficking along the endocytic pathway. For instance, the tyrosine-based motif in the cytoplasmic domain of the mannose receptor promotes ligand delivery to early endosomes and receptor recycling to the cell surface (97). In addition to a tyrosine-based, coated pit sequence-uptake motif similar to that in the macrophage mannose receptor, DC-SIGN carries a dileucine motif essential for internalization, and a triacidic cluster essential for targeting to endosomes/lysosomes. Some CTLs also display signaling activities. For instance, the stimulation of Dectin-1 in myeloid cells leads to activation of the mitogen-activated protein kinase (MAPK) and NF-κB pathways, resulting in the upregulation of genes important for innate immune responses (98).

3.2.1. The mannose receptor (MR)

MR (CD207) is a type IV transmembrane CTL and a prototypic marker of alternatively activated macrophages. It is a 175 kDa type I protein with an N-terminal cysteine-rich domain, a single fibronectin type II domain, 8 CTLDs, a transmembrane region and a short cytoplasmic tail. Only one of its CTLDs seems to be dedicated to the recognition of terminal glycosylated motifs, such as D-mannose, L-fucose and N-acetyl-D-glucosamine (99-101). MR is widely expressed on tissue macrophages, such as alveolar macrophages, and on subsets of DCs mediating antigen uptake, enhancing the presentation of antigens to T cells (102). MR recognizes endogenous epitopes, such as L-selectin, in the cellular migration process, and is also involved in the clearance of endogenous molecules, such as lysosomal hydrolases, produced during inflammation. MR can bind to several autoantigens, including myeloperoxidase and collagen IV, and to glycosylated Igs (103-105). However, despite the ability of MR to recognize numerous pathogens, including *Candida albicans*, *Pneumocystis jiroveci*, *Klebsiella pneumoniae, Shistosoma mansoni, Cryptococcus neoformans* and dengue virus, no impairment of host responses to infections with *C. albicans*, *P. jiroveci*, or *Leishmania* is observed in mice lacking MR (106-111).

MR recognizes various glycosylated ligands in the *M. tuberculosis* envelope, including mannose-capped LAM, phosphatidylinositol mannosides (PIM) 5 and 6, arabinomannans, mannans and mannose-containing proteins (85, 86). MR activation induces the phagocytosis of virulent strains of the *M. tuberculosis* complex (85). MR has no known intracellular signaling motif, but it has been suggested that MR binding to selective ligands may orientate the antimycobacterial immune response toward an anti-inflammatory profile (112). For instance, the recognition of mannose-capped LAM by the MRs of dendritic cells and macrophages may inhibit TLR-mediated IL-12 production, in turn promoting a tolerogenic Th2 response rather than a protective Th1 response (87, 113, 114). The pathway by which MR may signal remains elusive, and it is possible that MR, like other CTLs of the Dectin-2 family (see below), may interact with ITAM/ITIM-containing coreceptors such as FcγR (115). However, the role of MR in immunity to TB has not yet been completely elucidated, and MR-deficient mice have no relevant phenotype during *M. tuberculosis* infection (57).

3.2.2. Dectin-1

Dectin-1 (CLEC7A) is a type II transmembrane receptor with a single extracellular CRD. It is expressed principally on myeloid cells, such as macrophages, dendritic cells, neutrophils and microglial cells, and, to a lesser extent, in subsets of T cells, B cells and epithelial cells (116). Dectin-1 is an atypical CTL, because it can interact with β(1-3) and (1-6) glucans in a Ca^{2+}-independent manner. Upon ligand binding, Dectin-1 mediates numerous cellular responses, including microbial uptake and killing and the production of several cytokines, chemokines and free radicals; this receptor thus directly couples the innate and adaptive immune responses (116-121). Dectin-1 has mostly been characterized as a key receptor for β-glucans capable of interacting with many epitopes on the surface of fungi (116, 122-124). This CTL has been shown both to transduce signals and to regulate immune functions, either alone or with co-receptors, such as TLRs and NLRs (116, 125-127). Furthermore, the ability to induce proinflammatory cytokines in a TLR-dependent or TLR-independent fashion seems to differ between myeloid cell types, such as macrophages and dendritic cells (125, 126). Dectin-1 may induce a signal transduction cascade through its intracellular ITAM-like motif YTQL. Once bound to its ligand, this motif can be phosphorylated by Src kinases for recruitment of the tyrosine-kinase Syk, leading to induction of the signal transduction cascade (128). The interactions between Syk and Dectin-1 are atypical and not well understood, but they seem to depend on dimerization of the lectin (129). This transduction pathway may induce the MAPK, NFAT and NF-κB pathways, through CARD9-BCL10 (125, 129-131). There is also evidence to suggest that Dectin-1 may signal through a Syk-independent pathway involving a Raf1-dependent cascade, to regulate NF-κB and cytokine secretion (116, 132).

Dectin-1 is a well characterized fungal β-glucan receptor. However, it may also recognize unidentified components of the mycobacterial envelope. Mycobacteria are not known to carry β-glucan in their envelopes, but their outer capsules contain α-glucan, a potentially good candidate ligand for Dectin-1 (133). Indeed, mycobacteria have been shown to bind directly to Dectin-1 in a process inhibited by laminarin (88, 89, 134). This demonstrates the presence of a specific Dectin-1 ligand in the mycobacterial envelope, potentially mimicking the carbohydrate structure present in the fungal envelope.

These interactions increase the binding and endocytosis of mycobacteria and may, in collaboration with

TLR2, modulate the proinflammatory response to mycobacterial infections (88, 89, 134). Mouse bone marrow-derived macrophages (BMMs) infected with mycobacteria other than *M. tuberculosis* (*M. avium*, *M. smegmatis*, *M. abscessus* or *M. bovis*) display Dectin-1-dependent production of crucial proinflammatory cytokines and chemokines, such as tumor necrosis factor-alpha (TNF-α), IL-6, RANTES and GCSF (88, 89, 134). Yadav and coworkers have shown that interactions between *M. tuberculosis* and Dectin-1 have less of an effect on modulation of the proinflammatory response in BMMs than interactions with non-tuberculous mycobacteria, potentially accounting for the lower immunogenicity of virulent mycobacteria (89). However, these results remain contentious, as other studies have failed to replicate this lower level of proinflammatory effector induction in response to virulent mycobacteria (135, 136). Studies of interactions between *M. tuberculosis* and splenic dendritic cells have shown that Dectin-1 triggers the synthesis of IL-12p40 and p70, thereby potentiating the pro-Th1 response and resulting in the TLR2-independent control of infection (88). However, the true function of Dectin-1 in anti-mycobacterial immunity remains unclear, and Lyakh and coworkers were unable to inhibit the synthesis of IL-12p40 and p70 by treating infected dendritic cells with laminarin (137). Studies of the interaction between Dectin-1 and *M. abscessus* have shown that interactions between Dectin-1 and TLR2 are required for phagocytosis in mouse macrophages and that these interactions trigger the Syk-dependent production of TNF-α, IL-6 and IL-12 (126, 134).

Lee and coworkers recently showed that Dectin-1 expression is not restricted to myeloid cells. Indeed, this CTL is expressed in endothelial cells, and the infection of keratinocytes with *M. ulcerans* induces the expression of Dectin-1 on the surface of these cells in a TLR2-dependent manner (138). These authors also showed that Dectin-1 is overexpressed on the surface of alveolar epithelial cells infected with mycobacteria (139). These cells are not professional phagocytes, but are known to be targeted by the TB bacillus *in vivo,* in the lungs. *In vitro*, interactions between Dectin-1 and TLR2 increase mycobacterial endocytosis, the secretion of key proinflamatory cytokines and the bactericidal activity of infected cells (139). Thus, the role of Dectin-1 expressed in myeloid and non-myeloid cells in anti-mycobacterial immunity *in vivo* remains to be fully deciphered.

3.2.3. The Dectin-2 family: Dectin-2 and Mincle

The Dectin-2 cluster consists of Dectin-2, DCIR, DCAR, BDCA-2, Mincle and Clecsf8, all belonging to the Group II C-type lectin family (140). They have a common structure, consisting of a single extracellular CRD, a stalk region of variable length, a transmembrane region, and a cytoplasmic domain. They have a type II transmembrane topology, with an extracellular C-terminus and an intracellular N-terminus. Dectin-2 and Mincle have been shown to bind sugar ligands, but several non carbohydrate ligands for these lectins, such as SAP130, an endogenous protein recognized by Mincle, have been identified. The members of this family generally have no consensus signaling motifs in their cytoplasmic domains. However, a positively charged residue in the transmembrane region of the receptor facilitates association with ITAM-containing adaptor molecules, such as the FcRγ chain. The physiological roles of most members of the Dectin-2 cluster remain poorly defined. Functions identified to date include fungal and viral pathogen recognition, the sensing of necrotic cell death, and the facilitation of antigen cross-presentation and control of the development of autoimmunity. Two members of the Dectin-2 cluster, Mincle and Dectin-2, have been identified as putative PRRs for *M. tuberculosis*.

Mincle was originally identified as a transcriptional target of nuclear factor (NF-)IL-6 in peritoneal macrophages, and Mincle gene expression is induced by the stimulation of macrophages with LPS, IFN-γ, IL-6 or TNF--α (141). Like Dectin-2, Mincle recognizes fungi and induces inflammatory signals. Initial microarray analyses of Mincle gene expression suggested that this gene was upregulated in BMMs exposed to *C. albicans.* A soluble Mincle protein was also found to bind to *C. albicans* and *S. cerevisiae in vitro* (142). However, Mincle is not a key phagocytic receptor for *C. albicans*, although it does mediate inflammatory responses to this yeast (142). Mincle-knockout mice with systemic *C. albicans* infection had significantly higher fungal burdens in the kidneys than wild-type mice, demonstrating the involvement of Mincle in pathogen clearance (142). Mincle has been shown to associate with the FcRγ chain (143). This interaction involves the positively charged arginine residue in the transmembrane region of Mincle and is essential for signaling through the receptor (143). This signaling follows the Syk and CARD9 pathway and is independent of MyD88 signaling, consistent with Mincle being able to induce cytokine production without the need for TLRs (143). Mincle also mediates inflammatory responses to necrotic cells (143). However, this role of Mincle seems to be independent of its CTL function, because mutation of the EPN motif in the CRD has no effect on cellular activation in response to dead cells, and the interactions are not Ca^{2+}-dependent (143). Indeed, Mincle recognizes a protein factor involved in necrosis, SAP130, which is released by necrotic cells and induces inflammation, cytokine production by macrophages and subsequent neutrophil infiltration into the damaged tissue. An association has also been reported between the Mincle gene complex and rheumatoid arthritis (144-146).

Mincle has recently been identified, by two independent groups, as a key CTL involved in *M. tuberculosis* recognition (91, 147). These two studies identified the myeloid cell receptor for a key immunomodulatory component of the mycobacterial envelope, trehalose dimycolate (TDM, also known as cord factor) (148). TDM is also recognized by the scavenger receptor MARCO, in a TLR-dependent and FcγR-dependent manner (149, 150). Ishikawa *et al.* have shown that Mincle recognizes mycobacteria, that this interaction depends on the integrity of the CRD of the CTL, and that such recognition, together with FcγR recruitment, may modulate the transcription program of activated cells in a

TLR-independent manner (91). These authors clearly identified TDM, from among the various lipid components of the mycobacterial envelope, as the main mycobacterial ligand for Mincle (91). They also showed that BMMs from Mincle-deficient mice displayed impaired production of inflammatory effectors, such as NO, TNF--α and MIP2, in response to stimulation with TDM (91). *In vivo*, Mincle-deficient mice developed no granulomatous response to TDM injection, and produced smaller amounts of cytokines in response to mycobacteria, demonstrating that Mincle is a key PRR regulating the anti-mycobacterial immune response in a TLR-independent manner (91). In parallel, Schoenen and coworkers also demonstrated the involvement of this CTL in innate immunity to *M. tuberculosis,* by showing that Mincle regulated the immunomodulatory function of TDM in a FcγR-, Syk-, and CARD9-dependent manner (147). These two studies identified the mechanism by which TDM stimulation modulates the Th1 and Th17 pathways and demonstrated, for the first time, the key role of a CTL, Mincle, in the well known adjuvant behavior of mycobacterial cell wall components (90, 91, 147). However, the susceptibility of the Mincle-deficient mice to *M. tuberculosis* remains to be evaluated.

Dectin-2 is a CTL expressed principally in dendritic cells. It recognizes mannosylated ligands in a Ca^{2+}-dependent manner. Unlike Dectin-1, Dectin-2 has no ITAM motif. However, it nonetheless plays a key immunomodulatory role in controlling fungal infection by interacting with the FcγR (151, 152). FcγR activation leads to recruitment of the Syk kinase and activation of the MAPK pathway through CARD9, inducing NF-κB independently of TLR, NLR and MyD88. Dectin-2 activation is a key regulator of the Th17 response to fungal infection (153).

However, the role of Dectin-2 in the control of *M. tuberculosis* infection is unknown. One study showed that a soluble form of the Dectin-2 CRD recognized *M. tuberculosis* envelope polysaccharides (154). This suggested a possible role for Dectin-2 as a key PRR in the development of, or protection against TB. However, an *in vitro* study of NFAT regulation through Dectin-2 and FcγR stimulation by mycobacteria identified no key immunomodulatory function for this CTL in response to infection and further studies are therefore required to determine the function of this CTL (91).

3.2.4 Complement receptor type 3

CR3 (integrin αβ2, Mac 1) is a heterodimeric receptor (CD11b/CD18) of the integrin family (155, 156). It is expressed principally in immune cells, such as neutrophils, monocytes, natural killer cells and macrophages, including alveolar macrophages (155). CR3 is one of the receptors involved in the complement pathway for the binding of opsonized bacteria. The CD11b subunit (alpha chain) carries an integrin functional domain allowing it to interact with complement opsonins, which also interact with bacterial components, such as the 85C antigen of *M. tuberculosis* (157). Bacilli can interact with CR3 in a non specific manner to activate the alternative complement pathway through the C3b and iC3b components (55). Opsonized bacteria are recognized through CR1, CR3 and CR4, but their phagocytosis is mediated preferentially by CR3 (55). CR3 also interacts with the bacilli in an opsonin-independent manner, through its integrin domain, as for Ag85C, but also through its CTLD, which can bind mycobacterial oligosaccharides, such as LAM (158-160). This domain can recognize β–glucans as well as mannose, glucose an N-acetyl-D glucosamine residues and is inhibited by laminarin (a β–glucan competitor) (157, 158). CR3 can also bind mycobacterial PIMs (161). The direct interaction beween CR3 and *M. tuberculosis* has not yet been fully evaluated *in vivo,* because of the very low concentration of complement factors in the lungs (157). *In vitro,* the direct or opsonin-dependent activation of CR3 induces a phosphorylation cascade leading to the accumulation of free calcium ions and reorganization of the actin cytoskeleton for the induction of phagocytosis (157). CR3 seems to be more specific for pathogenic mycobacteria than for nonpathogenic species (157). However, the phagocytosis of the bacteria does not induce a bactericidal response, so the bacteria persist in the infected cells (157). The role of CR3 *in vivo* is difficult to evaluate, as CD11b-deficient mice display no relevant phenotype on *M. tuberculosis* infection (162). This suggests that CR3 may have a redundant function in interactions between the host and *M. tuberculosis* (163).

3.2.5. DC-SIGN and its murine homologs

DC-SIGN is a type II transmembrane mannose-binding CTL with a single extracellular CRD. It forms tetramers, the required structure for efficient ligand binding (164). Its intracellular region contains three motifs: a tyrosine-based internalization motif, a triacidic amino-acid cluster and a di-leucine motif, which are thought to be involved in phagocytosis, through interaction with clathrin, and in the intracellular trafficking of ligand particles ultimately destined for the phagolysosomes (47). DC-SIGN was initially identified as a receptor for the human immunodeficiency virus (HIV) glycoprotein-120 (GP120), and was thought to be specifically expressed in dendritic cells (165-167). With time, it became clear that DC-SIGN expression was not restricted to dendritic cells, this receptor also being expressed in other cell types, such as macrophages, including alveolar macrophages, and some lymphocyte populations (168-171). DC-SIGN can interact with a plethora of pathogens, including fungi, viruses and bacteria.

Early studies in our laboratory and elsewhere clearly demonstrated that DC-SIGN was a key receptor for *M. tuberculosis* in human dendritic cells (92, 93), and that it acted through the recognition of mannose-containing motifs, such as those in the LAM and 19 kDa antigen molecules (92, 172, 173). DC-SIGN has since been reported to recognize eight different purified components of the mycobacterial envelope: Man-LAM, LM, arabinomannan, glycol proteins (19 kDa, 38 kDa, 45 kDa), PIM-6 and α-glucan (92, 93, 172-175). We have also shown that DC-SIGN expression is induced in alveolar

macrophages in TB patients, again acting as a major receptor for the bacillus in these cells (169).

Studies of the interactions of DC-SIGN with *M. tuberculosis* ligands and whole mycobacteria in this model have shown DC-SIGN to be an endocytic/phagocytic receptor capable of potentiating TLR4 signaling to induce the secretion of various cytokines, including IL-10, IL-12 and TNF--α (176, 177). Cytokine induction through DC-SIGN is dependent on the recruitment of a specific signalosome to the cytoplasmic tail of the molecule, leading to kinase Raf1 activation and acetylation of the p65 subunit of nuclear factor NF-κB. This, in turn, stimulates the production of cytokines upon lipopolysaccharide (LPS) recognition by TLR4 (176). The early observation that DC-SIGN activation by mycobacterial components induces the pro-Th2 cytokine IL-10 and partial DC deactivation suggested that the TB bacillus might use DC-SIGN to evade immune defenses through immune deactivation (92). However, the use of LPS in these experiments may not accurately reflect the situation in mycobacterial infections, as, *in vitro* and *in vivo,* mycobacteria are potent activators of TLR2 but not of TLR4 (5, 178). Recent epidemiological and population genetics studies have shown that single nucleotide polymorphisms (SNPs) in the promoter of the DC-SIGN gene may be associated with differential susceptibility to the disease, further supporting a possible role for this CTL in immunity to TB (179, 180). The results of these two reports seem to conflict and could not be reproduced in two other studies, probably reflecting differences in the origin and genetic background of the studied populations (181, 182). This was extensively discussed by Ben-Ali *et al.*, and does not rule out a role for DC-SIGN in anti-mycobacterial immunity in humans (181). With a view to elucidating the role of DC-SIGN/CD209 in TB *in vivo*, *Ehlers* and colleagues used a humanized mouse model expressing the human DC-SIGN gene under the control of the CD11c promoter (183, 184). These mice died later than their littermate controls and had fewer physiopathological signs in their lungs after infection with *M. tuberculosis* (184). Thus, in this model, DC-SIGN seems to protect the host, by modulating the intensity of the immune response to the pathogen, by decreasing IL-12 production in particular.

Other *in vivo* models have been used to address these questions, including, in particular, mouse strains lacking the DC-SIGN homologs SIGNR1 and SIGNR3. There are eight putative *DC-SIGN* homologs, named *Signr1-8*, in the mouse genome (185, 186). The sequences of the CRD of the mouse homologs SIGNR1, SIGNR3 and SIGNR4 most closely match that of the CRD of human DC-SIGN (94, 186). Functional analysis of the interactions between these CTLs and various sugar motifs demonstrated that SIGNR1 and SIGNR3, like human DC-SIGN, interacted with mannosylated motifs, whereas SIGNR4 had no lectin activity, probably due to inactivation of one of the calcium-binding sites. Finally, only SIGNR3 was found to interact with both fucosylated and mannosylated complexes, an unusual feature common to human DC-SIGN, and SIGNR3 is thus considered the closest functional homolog for human DC-SIGN (186).

SIGNR1 and SIGNR3 interact with various glycosylated *M. tuberculosis* ligands, such as mannose-capped LAM (ManLAM), LM and the 19 kDa antigen (94-96, 187). Mouse lines in which SIGNR1 and SIGNR5 are inactivated display no particular phenotype upon *M. tuberculosis* infection in terms of survival, and lung and spleen bacterial loads (94, 96, 188). This finding has been reproduced by various groups and results, at least in part, from the inability of SIGNR5 to recognize mycobacterial ligands and the lack of SIGNR1 expression in the lungs. By contrast, *Signr3*-KO mice were found to have significantly larger numbers of bacteria in their lungs 21 and 42 days after infection, whereas the number of bacteria in the spleen did not increase (94). This suggests that SIGNR3 inactivation does not influence early mycobacterial dissemination, instead impairing immune control during the early phases of infection, between days 0 and 21. Finally, *Signr3*-KO animals managed to control the infection after day 21 and did not display more severe physiopathological lesions or die earlier than their wild-type controls. SIGNR3 function may thus be restricted to the early immune response to the pathogen. In naive mice, SIGNR3 is expressed in the spleen and lymph nodes, and is undetectable or present at only low levels in other organs (185). In *M. tuberculosis*-infected mice, we have shown that SIGNR3 expression, like that of DC-SIGN in humans, is induced soon after infection, in cells with a macrophage phenotype (expressing iNOS and F4/80). *In vitro* experiments have been carried out to obtain insight into the function of SIGNR3 in experimental *M. tuberculosis* infection in mice. The stimulation of SIGNR3 by ManLAM or whole mycobacteria was found to induce secretion of the proinflammatory cytokines IL-6 and TNF--α by macrophages, whereas IL-10 secretion was not affected. SIGNR3 signaling is dependent on a tyrosine motif in the intracellular fragment of the protein, and on the spleen tyrosine kinase Syk, the Raf1 kinase, and extracellular signal-regulated kinase (ERK) and NF-κB pathways (94).

Collectively, these studies in various mouse models, despite generating results that it is difficult to piece together, tend to suggest that DC-SIGN is involved in protection against TB, either at an early stage to promote bacterial control and granuloma formation, as shown for SIGNR3, or at later stages, by controlling inflammation and preserving the integrity of the lung tissue, like DC-SIGN in transgenic humanized mice. These two possibilities are not mutually exclusive; nevertheless, these results suggest that DC-SIGN is not used by *M. tuberculosis* as an immune evasion receptor (183, 187).

4. CONCLUSIONS AND PERSPECTIVES

The involvement of Syk and CARD9 seems to be strongly conserved in the signaling pathways associated with various members of the CTL family (128, 189, 190). Interestingly, it has recently been reported that CARD9–deficient mice are highly susceptible to *M. tuberculosis*. In particular, these mice develop exacerbated inflammation due to the impairment of IL-10 production by granulocytes, and die earlier than wild-type animals (191). This suggests that C-type lectins are key immune receptors for *M.*

tuberculosis in myeloid cells as well as possibly in other immune cell populations such as granulocytes (192). It also seems likely that future studies will identify additional other receptors for this major pathogen from this family of molecules. Various CTLs, such as DC-SIGN and MR, have been shown not only to allow bacilli to enter the host, but also to promote Th2 immune responses. This may favor immune escape and the persistence of the pathogen *in vivo* (193, 194). However, the induction of an anti-inflammatory response may help to protect sensitive organs and mucosa, such as the lung surface, and may therefore be essential for protection of the host against pathogens, such as mycobacteria.

Every year, new TLRs, NLRs and CTLs potentially capable of interacting with *M. tuberculosis* or purified mycobacterial components are discovered. It remains difficult to understand the roles of these multiple molecular partners, because no real consensus has emerged, due to differences in the experimental models used. Future studies should focus on this plethora of receptors and try to provide insight into their function as an integrated signaling system. Zenaro and coworkers have studied the function of Dectin-1, MR and DC-SIGN in regulation of the Th1 and Th17 responses to *M. tuberculosis* infection (195). They have shown that the stimulation of human dendritic cells by the bacillus induces a pro-Th17 phenotype through strong Dectin-1 stimulation, whereas the coactivation of MR and DC-SIGN reduces the pro-Th17 polarization and favors a pro-Th1 response. In this model, dendritic cell stimulation is independent of TLRs and there is no induction of a pro-Th2 cytokine profile, by contrast to other models (176). In a second study, van de Veerdonk and coworkers also demonstrated the key function of Dectin-1 as an inducer of Th17 responses, although in this case, TLR-4 dependence was reported (196). These models highlight the difficulties underlying any suggestion that MR, DC-SIGN or Dectin-1 is a potential innate immune escape receptor for *M. tuberculosis,* as Th17 and Th1 responses mostly control the infection efficiently (197). Much still remains to be done to decipher the innate immune response to *M. tuberculosis* as a system, and to determine the integrated roles of all the mycobacterial receptors in such a global network of signaling and regulation.

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