

## MINIREVIEW

# Macrophage Receptors for *Mycobacterium tuberculosis*

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### INTRODUCTION

The resurgence of concern about tuberculosis has resulted in the discovery that *Mycobacterium tuberculosis*, a facultative intracellular pathogen, has developed numerous mechanisms for entering human macrophages. In this regard *M. tuberculosis* differs from obligate extracellular pathogens, such as *Neisseria* species, which have evolved mechanisms for avoiding entry into phagocytes. This review summarizes recent studies of macrophage receptors involved in the uptake of *Mycobacterium tuberculosis* as well as the current state of knowledge of events that follow entry through a specific receptor-mediated pathway, including bacterial survival, phagosome trafficking, and activation of signal transduction pathways. In particular, it is meant to stimulate further efforts to determine why a pathogenic bacterium that can survive and replicate extracellularly has evolved multiple mechanisms to gain entry to the intracellular environment of the cells that are meant to kill it.

### COMPLEMENT RECEPTORS

Phagocyte complement receptors occur in two distinct structural forms. Complement receptor type 1 (CR1) is a monomeric transmembrane protein that binds C3b and C4b but not C3bi (1). CR1 possesses complement regulatory activity and can mediate phagocytosis of bound particles, but its capacity for signal transduction or cell activation has not been thoroughly characterized. CR3 and CR4 are heterodimeric proteins of the integrin superfamily. They are heterodimers that contain identical  $\beta$  subunits (CD18 or  $\beta_2$  integrin) and distinct  $\alpha$  subunits (CD11b or  $\alpha_M$  and CD11c or  $\alpha_X$ ). CR3 and CR4 bind C3bi, and CR3 also contains a glycan binding site (41). During maturation of blood monocytes to alveolar macrophages, expression of CR3 decreases while that of CR4 increases (2, 16).

Like many other bacteria and fungi, *M. tuberculosis* can activate the alternative pathway of complement activation, resulting in opsonization with C3b and C3bi (31). Bacteria that are sufficiently coated with these serum-derived ligands bind to CR1, CR3, and CR4 and are subsequently phagocytosed in membrane-bound phagosomes (16, 30, 31). Unlike other bacteria (*Staphylococcus aureus* and *Listeria monocytogenes*) or other intramacrophage pathogens, such as *Leishmania mexicana*, pathogenic mycobacteria, including *M. tuberculosis*, have developed an additional mechanism for acquiring opsonic C3 peptides. Pathogenic mycobacteria uniquely recruit the complement fragment C2a to form a C3 convertase and generate

opsonically active C3b in the absence of early activation components of the alternative or classical pathways (34). It appears that the predominant opsonin generated by scavenging C2a is C3b, rather than C3bi, as mycobacteria that are opsonized by this mechanism bind predominantly to CR1 rather than to CR3 or CR4.

As if it were not enough for *M. tuberculosis* to acquire opsonic C3 peptides by at least two distinct mechanisms, *M. tuberculosis* can bind to CR3 at two distinct sites on the receptor. Opsonized *M. tuberculosis* binds CR3 at its C3bi binding domain, and nonopsonized *M. tuberculosis* uses its endogenous capsular polysaccharides to interact with the  $\beta$ -glucan binding site near the C terminus of CD11b (9, 10). Experiments using human monocytes and murine macrophages had strongly implied that there is more than one mode of interaction between *M. tuberculosis* and CR3 (31, 37), but unambiguous evidence that nonopsonic (i.e., C3bi-independent) interactions occur was obtained in studies in which CR3 was expressed in a nonmacrophage background, so that endogenous synthesis of C3 by macrophages could not interfere. Chinese hamster ovary (CHO) cells stably transfected with CD18 and CD11b bind a strain of *M. tuberculosis* H37Rv ("CC") in a serum-independent manner, and binding of this strain is not enhanced by fresh human or bovine serum (9). A monoclonal antibody that blocks the C3bi binding site in the I domain of CD11b does not block binding of H37Rv-CC to transfected CHO cells, whereas an antibody to an alternative site within the I domain and an antibody to the C-terminal domain do block binding to CR3 expressed on CHO cells. Further analysis has revealed that distinct strains and substrains of *M. tuberculosis* vary in their predominant mode of interaction with CR3. For example, H37Rv-CC, *M. tuberculosis* Erdman, and four of five clinical isolates examined bind purely or predominantly by a C3bi-independent mechanism, while a distinct H37Rv substrain, H37Rv-HH, and one of five clinical isolates examined binds CR3 only after opsonization with C3bi (10). Nonopsonic binding of *M. tuberculosis* to CR3 is inhibited by laminarin (a seaweed-derived  $\beta$ -glucan), by *N*-acetyl-D-glucosamine, or by purified *M. tuberculosis* capsular glucan or mannan but not by capsular arabinomannan or yeast mannan. Moreover, mild mechanical extraction of capsular polysaccharides or treatment with amyloglucosidase markedly reduces nonopsonic binding, implying that the bacterial ligands for this domain of CR3 are peripherally located capsular carbohydrate residues. These studies clearly show that individual strains of *M. tuberculosis* can vary in their modes of interaction with CR3 and that they interact with distinct domains of the receptor. These results are consistent with the results of studies of the polysaccharide specificity of the  $\beta$ -glucan binding site(s) of CR3 (41). Whether binding to one site on CR3 or the other is advantageous to the bacteria remains to be determined, but engagement of both

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domains of CR3 on neutrophils or NK cells results in activation of cellular responses, while engagement of the C3bi binding alone does not (42). In summary, *M. tuberculosis* can exploit complement receptors through multiple mechanisms to bind to and enter macrophages. The mechanism and consequences that predominate in vivo may be determined by features of the individual bacterial strain (complement dependent or independent), the environment of the macrophage (such as the availability of complement proteins), and the state of differentiation or activation of the macrophage.

Currently, little is known about the trafficking of phagosomes that contain bacteria or model particles ingested by macrophages through complement receptors. As the understanding of phagosome trafficking and maturation expands, it will be of interest to determine whether the kinetics, order, and extent of phagosome interactions with the endocytic and exocytic pathways are distinct for phagocytosis mediated by complement receptors compared to that by other phagocytic receptors.

### MANNANOSE RECEPTOR

The macrophage mannose receptor is a monomeric transmembrane protein, with an extracellular domain containing eight carbohydrate-recognition domains characteristic of C-type (calcium-dependent) lectins (39). CHO cells transfected with mannose receptor cDNA acquire the ability to phagocytose unopsonized yeast, zymosan, or *Pneumocystis carinii* but only when mannose receptors are expressed at high copy numbers per cell (14). Mannose receptors are expressed on mature macrophages but not on fresh monocytes. Since assays of mannose receptors have utilized labeled ligands rather than monoclonal antibodies, it is not clear how the quantitative expression of mannose receptors compares to that of other macrophage receptors. The sequence of the cytoplasmic domain of the mannose receptor does not reveal an obvious means for interaction with well-characterized signalling molecules, although the mannose receptor is said to be able to mediate production of reactive oxygen intermediates by macrophages (14). Additional characterization of the molecular and cellular events that follow mannose receptor-mediated phagocytosis will be valuable in assessing whether mannose receptors direct target particles to distinct fates within macrophages.

Human monocyte-derived macrophages bind and internalize virulent *M. tuberculosis* via mannose receptors (30). A quantitatively important role for mannose receptors in binding and phagocytosis of *M. tuberculosis* was demonstrated by competitive inhibition, downregulation of apical mannose receptors by adherence of macrophages to mannan-coated coverslips, and blocking with a polyclonal anti-mannose receptor antibody (30). Of note, mannose receptors bind the virulent Erdman and H37Rv strains but not the avirulent H37Ra strain. While it is currently unclear whether *M. tuberculosis* contains other ligands for mannose receptors, one well-characterized ligand is lipoarabinomannan (LAM), which is abundant and peripherally exposed and contains terminal mannose residues that interact with mannose receptors (32, 33). Multiple biological responses have been attributed to LAM, but is not clear whether these are mediated through mannose receptors, since LAM can also interact with other receptors on macrophages, including CD14 (see below). The expression of mannose receptors is downregulated by gamma interferon (35, 36); therefore, their role in ingestion of *M. tuberculosis* early in infection or in individuals with compromised cellular immunity may be more important than in established granulomas. In addition to

a role for mannose receptors in phagocytosis of whole bacteria, these receptors can mediate delivery of LAM to endocytic compartments that contain CD1b, thereby facilitating presentation of mycolic acid and lipoglycan antigens to CD4<sup>-</sup> CD8<sup>-</sup> T cells or CD8<sup>+</sup> T cells (27).

### Sp-A AND Sp-A RECEPTORS

Since distal airways and pulmonary alveoli are the sites of initial inoculation of *M. tuberculosis*, the effects of pulmonary surfactant and its predominant protein, surfactant protein A (Sp-A), are of interest. While specific receptors for Sp-A are present on macrophages, the number and specific molecular identity of Sp-A receptors are incompletely defined. Sp-A is a member of the collectin family of proteins, which includes serum mannose binding protein (MBP) and complement component C1q. Sp-A, like other collectins, possesses a collagen-like domain (including hydroxyproline) and has a domain resembling C-type lectins such as that in MBP. In most systems examined evidence indicates that Sp-A interaction with cell surface receptors is mediated through the collagen-like domain and that the corresponding domain in C1q and MBP may bind to the same receptors. At least three distinct candidate receptors for Sp-A have been identified. A 126-kDa protein termed C1qR<sub>p</sub> is expressed on monocytes, macrophages, neutrophils, and endothelial cells, and monoclonal antibodies that recognize this protein block cellular interactions of Sp-A, MBP, and C1q. The cDNA sequence of C1qR<sub>p</sub> predicts a type I membrane protein with a potential carbohydrate recognition domain, epidermal growth factor-like repeats, a putative transmembrane domain, and a cytoplasmic tail (24). In addition, CR1 (also known as CD35) binds C1q with high affinity and may thus also represent an alternative Sp-A receptor, although direct demonstration of an interaction with Sp-A has not been reported (18). Finally, a 210-kDa protein termed SPR210 that binds Sp-A but not C1q has been identified on type II pneumocytes and macrophages (6). The sequence of this molecule has not yet been reported.

Sp-A enhances macrophage binding and uptake of *M. tuberculosis*, although the mechanisms of these phenomena have not been fully elucidated (12). Purified Sp-A binds directly to *M. tuberculosis* H37Ra, and binding to the bacteria is dependent on calcium and on glycosylation of Sp-A (25). Trypsin treatment of *M. tuberculosis* decreases binding of Sp-A, and in membrane overlay experiments, Sp-A binds to a 60-kDa protein in crude cell wall extracts of *M. tuberculosis*. The specificity of this interaction remains to be established, as it is unclear whether the interaction with the 60-kDa protein is dependent on calcium or on Sp-A glycosylation, and a 60-kDa protein was the most abundant protein in the cell wall extract used in the overlay assay. While type V collagen blocks binding of *M. tuberculosis* to murine lung macrophages, it does not block binding of Sp-A to *M. tuberculosis*. This finding suggests that Sp-A can operate as an opsonin, binding to *M. tuberculosis* by the N-linked polysaccharides of Sp-A and to macrophages by the collagen-like domain. It will be interesting to learn the identity of the receptor(s) that mediates attachment of Sp-A-coated *M. tuberculosis* to murine alveolar macrophages.

In experiments with human monocyte-derived macrophages and alveolar macrophages, different results have been obtained. In this system, Sp-A enhances binding and phagocytosis of *M. tuberculosis* (Erdman) to macrophages, but pretreatment of the macrophages followed by washing is as effective as simultaneous incubation of macrophages with *M. tuberculosis* and Sp-A (15). This finding suggests that Sp-A is not simply acting as an opsonin and may be modulating the activity of one

or more receptors that are responsible for directly binding *M. tuberculosis*. Mannose receptors account for some of this binding activity, as indicated by the ability of yeast mannan or a polyclonal antibody to the mannan receptor to abrogate the effects of Sp-A in enhancing *M. tuberculosis* binding. Sp-A also binds to *Mycobacterium bovis* BCG and enhances the binding and phagocytosis of BCG to rat pulmonary macrophages and human monocytes. A polyclonal antibody to the Sp-A receptor SPR210 blocks the binding of Sp-A-coated BCG to macrophages and monocytes (44).

While it is clear that Sp-A enhances interactions of *M. tuberculosis* and macrophages, the mechanisms and cognate receptors demand further study. At a minimum, Sp-A can act as an opsonin that allows recognition of mycobacteria, but the identities of macrophage receptors that account for this recognition remain incompletely defined. Monospecific blocking reagents and heterologous expression of C1qR<sub>p</sub> and SPR210 need to be applied to this problem, and CR1 (CD35) warrants further study as a candidate Sp-A receptor. In addition to serving as an opsonin, there is also evidence that Sp-A can enhance ingestion of particles including *M. tuberculosis* by other mechanisms. Attachment of macrophages to Sp-A-coated surfaces enhances phagocytosis by Fc and complement receptors (40) and probably by mannose receptors (15). That this mechanism extends to such structurally diverse receptors makes it improbable that Sp-A interacts physically with each of these receptors. It is more likely that this effect of Sp-A is exerted at a step in phagocytosis that is common to and downstream of various receptors, but a full understanding of this effect awaits directed mechanistic studies.

#### OTHER RECEPTORS

**CD14.** CD14, a phosphatidylinositol glycan-linked membrane protein, is best known and characterized as the high-affinity receptor for lipopolysaccharides of gram-negative bacteria. However, CD14 can also bind LAM of *M. tuberculosis* (H37Ra), and this binding induces macrophages to secrete interleukin-8 (28). The signal transduction pathway initiated by LAM binding to CD14 is not well characterized, but the pathway requires one or more components that are restricted to hematopoietic cells and are at least partially distinct from that initiated by binding of lipopolysaccharide to CD14 (29). Microglial cells are derived from monocyte precursors and exhibit many macrophage-like functions, including phagocytosis. These cells have been shown to utilize CD14 to recognize whole *M. tuberculosis* (H37Rv) (26). This recognition is followed by internalization of the bacteria by microglial cells, although since it is a lipid-anchored membrane protein without transmembrane and cytoplasmic domains, it is unclear whether CD14 is capable of mediating phagocytosis without the cooperation of another membrane protein.

**Scavenger receptors.** Macrophage scavenger receptors bind polyanionic macromolecules and particles, including lipopolysaccharides of gram-negative bacteria and lipoteichoic acid of gram-positive bacteria (13, 20). Experiments using competitive inhibitors have implicated class A scavenger receptors as quantitatively important receptors for *M. tuberculosis* (Erdman) on human monocyte-derived macrophages (46). Moreover, purified class A scavenger receptors bind *M. tuberculosis*, and sulfolipids (sulfatides) from *M. tuberculosis* compete with other ligands for class A scavenger receptor binding while LAM does not (17a). It is not yet known whether scavenger receptors can activate the cytoskeleton to internalize bacteria or, alternatively, whether scavenger receptors act to bind bacteria but phagocytosis is executed by other receptors.

**Fc $\gamma$  receptors.** Some infected individuals have circulating antibodies to *M. tuberculosis* (21), and one study has demonstrated that the intracellular trafficking of *M. tuberculosis* (H37Rv) opsonized with immune serum is distinct from that of nonopsonized bacteria. Immunoglobulin G (IgG)-coated mycobacteria were ingested by macrophages in vesicles that readily fused with ferritin-loaded lysosomes, whereas unopsonized mycobacteria resided in phagosomes that did not acquire ferritin from labeled lysosomes (3). Despite the fusion with labeled lysosomes, IgG-opsonized mycobacteria survived intracellularly at the same rate as did nonopsonized bacteria. This finding implies that entry through Fc $\gamma$  receptors may specify a distinct intracellular trafficking pathway for virulent *M. tuberculosis* but that this alteration of intracellular trafficking does not affect the intracellular growth of the bacteria. Perhaps this helps explain the lack of benefit conferred by passive transfer of immune serum in experimental tuberculosis.

#### RECEPTOR DIVERSITY AND RECEPTOR COOPERATION

A particulate target such as *M. tuberculosis* that displays numerous and diverse ligands on its surface is likely to engage multiple receptors of multiple types simultaneously. Therefore, in vivo, *M. tuberculosis* is probably not internalized by macrophages using a single receptor-mediated pathway. However, in some contexts, receptor utilization by *M. tuberculosis* may be biased by the state of differentiation or the state of activation of the macrophage. For example, during differentiation of monocytes to macrophages, CR3 decreases in abundance while CR4, mannose receptors, scavenger receptors, and SPR210 increase. Stimulation of macrophages with gamma interferon downregulates mannose receptor expression and increases expression of SPR210 (5). On the other hand, distinct types of receptors may cooperate to optimize binding and internalization of a target particle. Cooperation between CR1 and CR3 has been demonstrated for binding of model particles (38), and cooperation between phosphatidylinositol glycan-linked Fc $\gamma$  receptors and CR3 markedly facilitates phagocytosis of IgG-opsonized targets (19). Such cooperation may account for phagocytosis of particles bound to receptors that lack transmembrane and cytoplasmic domains, such as CD14.

#### DOES THE RECEPTOR-MEDIATED ROUTE OF ENTRY OF *M. TUBERCULOSIS* AFFECT SUBSEQUENT EVENTS?

Certain intramacrophage pathogens exploit specific macrophage receptors to ensure their own survival. *Leishmania major* activates the alternative complement pathway to deposit C3b on its surface (23). When opsonized metacyclic promastigotes bind to CR1, they survive and replicate intracellularly. When promastigotes (noninfective forms) enter macrophages through the lectin-like domain of CR3, they are killed (11). *Salmonella typhi* that enters murine macrophages through CR3 is phagocytosed in a vesicle that fuses with lysosomes, while entry via CR1 allows *S. typhi* to survive in a phagosome that does not acquire lysosomal markers (17). These observations suggest that one way that successful pathogens can survive within phagocytes is by entering by a receptor-mediated pathway that is not coupled to the activation of macrophage antimicrobial mechanisms such as production of reactive oxygen or nitrogen intermediates. So far, there has been only limited examination of whether *M. tuberculosis* uses such a mechanism to favor its survival in macrophages. By using monoclonal antibodies or competitive ligands to block CR1, CR3/4, mannose receptors, and class A scavenger receptors during initial

entry of *M. tuberculosis* into human macrophages, no apparent difference in the extent of survival or rate of intracellular growth of one virulent strain (Erdman) was observed (46). Thus, from examination of these crude endpoints, there was no evidence that *M. tuberculosis* selectively uses specific receptors to confer an intracellular survival advantage. It is possible that examination of other downstream events after entry of *M. tuberculosis* through specific pathways will reveal more discrete differences. For example, mannose receptors can deliver LAM to the endocytic compartment containing CD1b and thereby participate in loading LAM or mycolic acid onto CD1b for antigen presentation to T lymphocytes (27). Whether other receptors can perform this function has not been determined. *M. tuberculosis* occupies phagosomes that do not interact with the endocytic and exocytic networks in the same manner as phagosomes containing other particles. *M. tuberculosis* phagosomes do not acquire subunits of the vacuolar proton ATPase and do not acidify normally (45). In addition, *M. tuberculosis* phagosomes contain increased amounts of HLA class I and class II proteins, probably due to decreased vesicular traffic leaving the phagosome (8). The abnormal phagosome traffic may be due to retention of rab5 and lack of acquisition of rab7 by *M. tuberculosis*-containing phagosomes, since rab proteins are strongly implicated in controlling traffic in the endosomal pathway (43). The roles of distinct receptors in determining the qualitative, quantitative, or kinetic interactions of phagosomes with endosomes have not been examined.

It is also possible that distinct routes of entry of *M. tuberculosis* dictate activation of distinct cytokine secretion responses by macrophages. These responses may result in distinct outcomes that are important in vivo but would not have been detected in the aforementioned study that examined mycobacterial survival and replication in vitro.

#### A MYCOBACTERIAL RATIONALE FOR USE OF MULTIPLE RECEPTORS

From the evidence available, it appears that *M. tuberculosis* is quite eager to gain entry to macrophages. *M. tuberculosis* uses two distinct mechanisms for becoming opsonized with complement (the alternative pathway and capture of C2a), two distinct ligands for binding different domains of CR3, and a minimum of seven to nine distinct macrophage receptors for recognition (CR1, CR3, CR4, MR, scavenger receptors, CD14, and up to three different Sp-A receptors). These findings suggest that *M. tuberculosis* has found the intracellular environment of macrophages especially advantageous. What are the possible advantages to the bacterium that make it worth evolving multiple mechanisms for entering macrophages? One possibility suggested by the classic studies of Lurie is that macrophages promote dissemination of *M. tuberculosis* by assisting transport of bacteria across pulmonary epithelial barriers. This might be accomplished by the macrophages that directly ingested the inhaled mycobacteria or by monocytes, macrophages, and/or neutrophils that migrate to the site of initial infection in response to chemokines secreted by infected macrophages. Furthermore, studies in progress in several laboratories reveal that *M. tuberculosis* gene expression is altered by bacterial entry into macrophages. Some of the genes induced may play specific roles in survival, growth, and intercellular spread of bacteria. It is also possible that the bacteria benefit from host cell modification of surface proteins, carbohydrates, and/or lipids. While the specific mechanism has not been defined, *M. tuberculosis* harvested from murine macrophages is more cytotoxic to respiratory epithelial cells than that grown in cell-free media, suggesting that *M. tuberculosis* that has emerged

from the intracellular environment of macrophages may be more able to violate epithelial barriers and disseminate to distant sites (22). Another mycobacterium, *M. avium-intracellulare*, may also sojourn in macrophages in order to enhance specific virulence properties (4, 7).

In summary, *M. tuberculosis* has developed a large number of mechanisms to enter human macrophages. Evidence to date implies that individual entry pathways do not have a major influence on intracellular survival and growth of the bacteria, but distinct receptor-mediated pathways may dictate differences that will be revealed by careful examination of phagosome trafficking or that are only evident in vivo. On the other hand, *M. tuberculosis* may not care how it enters macrophages, only that it does. Distinguishing these possibilities should be examined in future studies. Further studies should also consider whether intracellular trafficking of *M. tuberculosis* phagosomes is affected by the route of entry and whether macrophage responses to *M. tuberculosis* are activated differently if the macrophages meet the bacteria through distinct receptors. Recent work has provided much information on initial *M. tuberculosis*-macrophage interactions. Considerable additional work will be required to understand the consequences of this complex interaction.

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