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The molecular basis and downstream immune consequences of mycobacteria–host cell interactions

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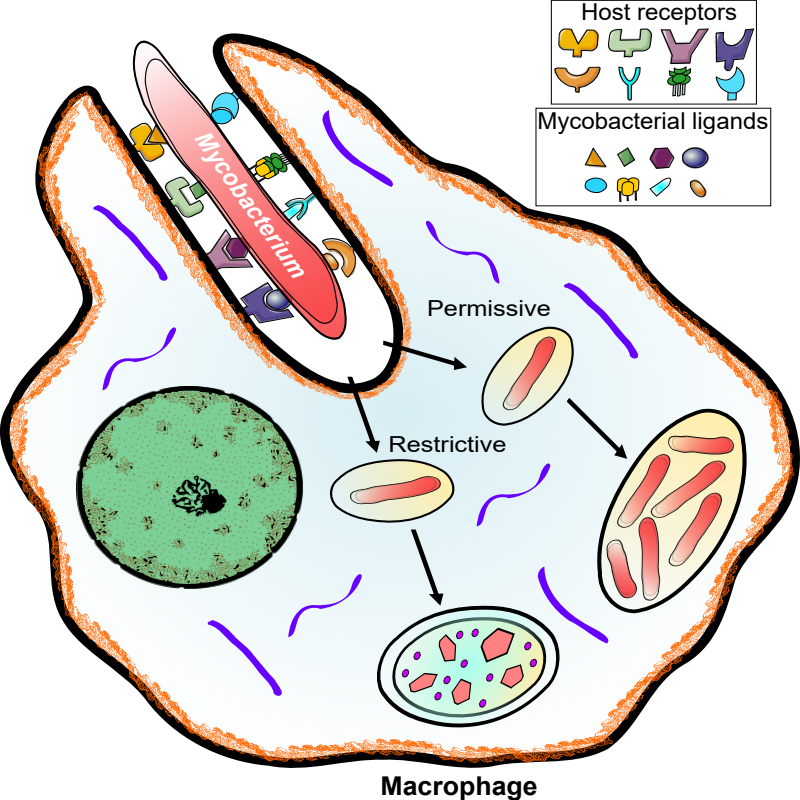
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32 ABSTRACT

33 Pathogenic mycobacteria gain entry to their hosts by inhalation or ingestion where they adhere to
34 different cell types and are subsequently internalized by professional phagocytic cells, such as
35 macrophages or dendritic cells. Multiple pathogen-associated molecular patterns present on the
36 mycobacterial surface are recognized by and interact with a diverse panel of phagocytic pattern
37 recognition receptors, representing the first step of the infection process. This review summarizes the
38 current knowledge on the numerous host cell receptors and their associated mycobacterial ligands or
39 adhesins. It further discusses the downstream molecular and cellular events resulting from the
40 engagement of the various receptor-mediated pathways, leading to either intracellular survival of
41 mycobacteria or to activation of host immune defenses. The content contained herein on adhesins and
42 host receptors may act as a resource for those developing novel therapeutic approaches, e.g., in the
43 design of anti-adhesin molecules to prevent bacterial attachment and infection. The collection of surface
44 molecules highlighted in this review may also serve as potential new therapeutic targets, diagnostic
45 markers, or vaccine design candidates to combat these notoriously challenging, persistent pathogens.

46

47 INTRODUCTION

48 *Mycobacterium* is a genus of the Actinobacteria phylum of over 190 species, comprised mostly of non-
49 pathogenic species, such as *Mycobacterium smegmatis*. Other species are opportunists or obligate
50 pathogens, including *Mycobacterium tuberculosis*, the causative agent of tuberculosis (TB) in humans
51 (Meehan *et al.* 2021). Inhalation or ingestion of bacilli are the most common modes of entry where after
52 the bacteria are engulfed by professional phagocytes at the site of infection, as seen in alveolar
53 macrophages for *M. tuberculosis*-infected lungs (Shim, Kim and Shin 2020) or intestinal macrophages
54 and dendritic cells (DCs) for *Mycobacterium avium* subsp. *paratuberculosis* (MAP)-infected animals
55 (Rees *et al.* 2020).

56 Successful establishment of infection by bacterial pathogens necessitates adhesion to host cells,
57 and, colonization of tissues, followed by intracellular multiplication, dissemination to other tissues or
58 persistence. Bacteria use adhesins/invasins or other macromolecular complexes to achieve a complex
59 host/pathogen molecular crosstalk that leads to subversion of cellular functions and establishment of
60 disease. Involved in the attachment, the mycobacterial cell envelope is composed of complex network
61 of glycopolymers, lipids, glycolipids, proteins, and of the mycolyl-arabinogalactan-peptidoglycan
62 skeleton (Dulberger, Rubin and Boutte 2020). Bacterial attachment to a substrate may be mediated by
63 adhesins, which are surface-localized molecules capable of binding specific host molecules (Kline *et al.*
64 2009). Mycobacterial adhesins include a broad range of diverse molecules, comprising glycopolymers,
65 lipids and proteins, which are embedded in the cell wall. Adhesion facilitates biofilm formation, an
66 essential step for bacterial colonization of environmental niches and for the establishment of infection,

67 and endows bacteria with resistance to immune effector mechanisms, bacteriolytic enzymes and
68 antibiotics (Stones and Krachler 2016; Schulze *et al.* 2021). In general, fast-growing emerging non-
69 tuberculous mycobacteria form and use biofilms to adhere to household plumbing and shower heads
70 (Williams *et al.* 2009). Similarly, slow-growing mycobacteria, such as *M. tuberculosis*, also develop
71 biofilms on clinical biomaterials (Esteban and García-Coca 2018).

72 Following attachment, mycobacterial entry into host cells is mediated by two different membrane
73 receptor-dependent mechanisms, non-specific macropinocytosis and phagocytosis. Macropinocytosis
74 is characterized by an invagination of the membrane, forming an endosome, which then fuses with
75 microbicidal lysosome compartments to degrade the enclosed microorganisms. Though considered a
76 secondary pathway when phagocytosis receptors are already saturated, this process is also employed
77 by INF- γ activated macrophages to clear bacteria (Bosedasgupta and Pieters 2014). Conversely, the
78 primary pathway engages multiple phagocytosis pattern recognition receptors (PRR) that recognize
79 specific pathogen-associated molecular patterns (PAMP) present on the surface of the bacilli. PRR are
80 PAMP-specific based on their location, which span cellular receptors (plasma membrane, endosomal
81 compartments, and the cytosol; reviewed in part I), but also the extracellular host matrix e.g. of the
82 mucosal surfaces (reviewed in part II) (Vinod *et al.* 2020). Recognition occurs in a non-opsonic or
83 opsonic fashion. The latter process depends on bacteria coated with complement proteins or
84 immunoglobulins to enhance binding affinity with phagocytes *via* complement receptors or Fc γ R
85 immunoglobulin receptors, respectively. Non-opsonic phagocytosis involves other classes of receptors,
86 including Toll-like receptors (TLR) and C-type lectin receptors (CLR). The interaction between PRR and
87 PAMP triggers signaling cascades that lead to the restructuring of the actin cytoskeleton. Depending
88 on the receptor engaged, the plasma membrane subsequently remodels in one of two ways:
89 invagination, or through the formation of membrane protrusions that encompass the microorganism,
90 known as pseudopods (Caron and Hall 1998) **(Table S1, Supporting Information)**.

91 Immune cells are central to mounting an adequate protective response, however they, with other
92 cells types, including pneumocytes, epithelial, endothelial, neuronal and intestinal cells, also provide a
93 favorable niche for mycobacterial multiplication and dissemination. Through the development of
94 adaptive mechanisms, mycobacteria transform these cells to enable colonization. Although it is known
95 that the fate of mycobacteria within host cells is largely dependent on the entry pathway, with some
96 enhancing host protection and others promoting infection and dissemination, the mechanisms
97 contributing to the latter are currently not fully understood. Unpacking the interaction between
98 mycobacteria and host cells during pathogenesis is of paramount importance to leverage into
99 improved and innovative therapeutic approaches. In this review, the processes employed by
100 mycobacteria to hijack host cells and tissues are discussed, as well as their broader significance in both

101 immune evasion and bacterial survival as well as features that may contribute to reduced bacterial
102 growth and pathogenicity.

103

104 RECEPTOR RECOGNITION OF MYCOBACTERIA BY DIFFERENT CELL TYPES

105 Innate immune receptors

106 The innate immune system, which includes physical barriers as well as effector cells, antimicrobial
107 peptides, soluble mediators and cell receptors, is considered the first line of defense against invading
108 microbial pathogens. Innate immune responses depend on a group of proteins and phagocytic cells that
109 recognize conserved features of pathogens and are rapidly activated to help destroy the invaders. One
110 of the four components of innate immunity, the receptors, exists in either membrane-bound or cytosolic
111 forms. Each receptor (PRR) recognize distinct microbial structures such as proteins, lipids, lipoproteins,
112 glycans and nucleic acids, referred to as PAMPs (Mishra *et al.* 2017). Recognition of PAMP by the PRR
113 triggers signaling cascades leading to the establishment of the inflammatory response and the
114 internalization and degradation of mycobacterial bacilli. Each PRR is specific to a diverse set of PAMP,
115 ensuring the appropriate selective downstream activation of the adaptive immune response.

116

117 Toll-like receptors

118 TLRs are type I transmembrane glycoproteins composed of extracellular, transmembrane and
119 intracellular signaling domains (Gay and Gangloff 2007). The extracellular domains contain repeated
120 modules of leucine-rich repeats (LRRs) and are responsible for binding so-called PAMPs (Medzhitov
121 2001). For example, di- and tri-acylated lipopeptides and lipoproteins represent the defined ligands of
122 TLR2 (Jin and Lee 2008), lipopolysaccharides are recognized by TLR4, and microbial DNAs are recognized
123 by TLR9 (Uematsu and Akira 2008). Ligand-induced dimerization of TLRs is thought to trigger the
124 recruitment of adaptor proteins to the intracellular Toll/interleukin-1 receptor (TIR) domains to initiate
125 signaling (O'Neill and Bowie 2007). Signaling cascades via TIR domains are mediated by specific adaptor
126 molecules such as MyD88 (O'Neill and Bowie 2007). MyD88 is essential for TLR signaling (Medzhitov,
127 Preston-Hurlburt and Janeway 1997) and, with the exception of TLR3, all TLRs require MyD88 for
128 downstream signaling (Kawai *et al.* 1999; Kawai and Akira 2010). The MyD88 adaptor protein mediates
129 many biologically important signal transduction pathways in innate immunity (Warner and Núñez 2013).
130 In addition, MyD88 signaling is important in the regulation of inflammation during bacterial infection
131 (Wang *et al.* 2014). Mutations in MyD88 are associated with immunodeficiencies that predispose
132 patients to recurrent life-threatening bacterial infections, as observed in MyD88-deficient mice that are
133 susceptible to a variety of pathogens (von Bernuth *et al.* 2008, 2012). *M. tuberculosis* infection in these
134 mice is lethal, as MyD88 signaling is required to elicit an adequate innate and acquired immune response
135 against *M. tuberculosis* (Fremond *et al.* 2004; Hölscher *et al.* 2008; Berod *et al.* 2014). Phagocytosis, in

136 turn, is essential for an optimal response to MyD88-dependent bacteria (Ip *et al.* 2010). In addition to
137 playing a central role in phagocytosis, MyD88 is crucial for downstream TLR activation and signaling that
138 occurs after bacterial degradation in the phagosome of human monocytes (Cervantes *et al.* 2013) and
139 murine macrophages (Ip *et al.* 2010). Bacteria must be phagocytosed and it is in the acidic environment
140 of the phagosome that endosomal TLR receptors can recognize their bacterial ligands. Once these
141 bacterial ligands have been released, a TLR-dependent response can be initiated from the phagosome
142 (Ip *et al.* 2010; Kagan and Iwasaki 2012; Cervantes *et al.* 2014). Furthermore, MyD88 signaling in DCs
143 and macrophages is essential to control mycobacterial load and prevent their persistence (Scanga *et al.*
144 2004; Berod *et al.* 2014). When MyD88-KO mice are infected with *M. tuberculosis*, they develop
145 granulomatous lung lesions with greater neutrophil infiltration than wild-type mice (Sugawara *et al.*
146 2003). These massive cellular infiltrations accompanied by extensive granuloma necrosis lead to a high
147 susceptibility of MyD88-KO mice to *M. tuberculosis* infection (Hölscher *et al.* 2008). Consequently, a
148 higher bacterial load in the lungs and spleen was detected in MyD88-KO mice 5 weeks after infection
149 (Sugawara *et al.* 2003; Hölscher *et al.* 2008). Furthermore, an aberrant inflammatory response ensues
150 when MyD88 is absent, because, MyD88 acts as a negative signaling factor to stop NF- κ B activation
151 (Burns *et al.* 2003), a mechanism necessary to prevent excessive inflammation and return to
152 homeostasis (Ruland 2011). In the following, we discuss current knowledge about TLRs, focusing on their
153 role in mycobacterial infections.

154

155 TLR2

156 Establishment of an effective immune response against intracellular mycobacteria depends on the
157 rapid detection of the invading pathogen by the innate immune system and the coordinated activation
158 of the adaptive immune response. TLR are adept at detecting and restricting infection by pathogenic
159 microorganisms, including mycobacteria. The interaction is complex and involves distinct
160 mycobacterial cell wall components and multiple members of the TLR family. Numerous studies have
161 shown that TLR2, acting alone or in concert with other TLR, can recognize several secreted or surface-
162 associated mycobacterial components and mount an effective defensive response against *M.*
163 *tuberculosis*. In macrophages, recognition of *M. tuberculosis*' 19-kDa glycolipoprotein (LpqH) by TLR2
164 induces apoptosis *via* the caspase-8 pathway, limiting intracellular proliferation of the bacilli (**Figure 1**)
165 (López *et al.* 2003). Since only lipoproteins/lipopeptides are detected at physiological concentrations
166 by TLR2 at picomolar levels. This finding implies that the activity of all other putative bacterial
167 compounds reported so far as TLR2 agonists was most likely due to the contamination of highly active
168 natural lipoproteins and/or lipopeptides. It could be that recombinant proteins other than bona fide
169 TLR2 ligands described in other studies have a high risk of contamination with activating lipopeptides,
170 which would often clearly explain their observed effects (Zähringer *et al.* 2008). Based on the co-

171 structure studies described in the literature (TLR2 in complex with lipoproteins and lipopeptides),
172 further studies reporting various mycobacterial proteins such as Rv0350, Rv0577 interacting with TLR2
173 should be taken with some caution as structural evidence is not yet available. TLR2 is also found in
174 other cell types, including human endothelial cells, where it has been shown to activate the key
175 immune regulatory NF- κ B pathway when interacting with *M. tuberculosis*' Hsp70 (Rv0350) protein
176 (Bulut *et al.* 2005). In dendritic cells (DC), TLR2 seems to recognize the secreted Rv0577 protein,
177 involved in the methylglyoxal detoxification pathway, to induce pro-inflammatory cytokines, including
178 TNF- α , IL-1 β , IL-6 and IL-12p70 in a MyD88-dependent manner, as well as mitogen-activated protein
179 kinases and NF- κ B (**Figure 1**). It has been shown that Rv0577-treated DC have the capacity to activate
180 naïve T cells, polarize CD4⁺ and CD8⁺ T cells to secrete IFN- γ and IL-2, and induce T cell proliferation.
181 Moreover, this mechanism has been observed to induce the proliferation of memory CD4⁺ and CD8⁺
182 CD44^{high}CD62L^{low} T cells in the spleen of *M. tuberculosis*-infected mice. Collectively, these observations
183 may suggest the close association of TLR2 and Rv0577 in the protective regulation of both the innate
184 and adaptive immune responses to *M. tuberculosis* infection (Byun *et al.* 2012). Conversely, TLR2 may
185 also play a harmful role in IL-10-producing B cells. Upon the interaction of TLR2 and *M. tuberculosis*'
186 mannose-capped lipoarabinomannan (ManLAM), the MyD88/PI3K/AKT/Ap-1 and NF- κ B signaling
187 pathways stimulate both B cell proliferation and their IL-10 production, causing the excessive cytokines
188 to diminish immune cell activity and increase infection susceptibility (**Figure 2**) (Yuan *et al.* 2019). While
189 there are many analyses that point to the important role of TLR2 in *in vitro* model systems,
190 investigations into the importance of TLR2 after aerosol infection of mice with *M. tuberculosis in vivo*
191 have yielded controversial results. In this context, some reports have found no individual role for TLR2
192 in establishing effective immunity to growth-limiting *M. tuberculosis* after low- or high-dose aerosol
193 infections (Reiling *et al.* 2002; Bafica *et al.* 2005). Another study shows that TLR2 may play a non-
194 redundant role in providing protective immunity during long-term infection. Indeed, TLR2-deficient
195 mice show reduced bacterial clearance, a defective granulomatous response, and the development of
196 chronic pneumonia, causing them to prematurely succumb to infection within 5 months. The range of
197 interactions of TLR2 with diverse ligands highlights its critical role in immune regulation, particularly as
198 its absence yields an exaggerated inflammatory response (Drennan *et al.* 2004). The underlying
199 reasons for these discrepancies are not known, but it could be explained by the fact that the loss of
200 functionality of a single TLR in *M. tuberculosis* aerosol infection models has a negligible effect on the
201 development of the immune response *in vivo* and is easily compensated by other receptors. However,
202 seminal tests performed after *M. tuberculosis* infection in TLR2/4/9- and MyD88-deficient mice,
203 showed that only the latter succumbed rapidly to uncontrolled mycobacterial growth, while the former
204 controlled the infection (Fremont *et al.* 2004, 2007; Scanga *et al.* 2004; Hölscher *et al.* 2008). These

205 results demonstrate that only MyD88, but not TLR2, TLR4 and TLR9, is essential for triggering the
206 macrophage effector mechanisms that are central to anti-mycobacterial defense.

207 As described above, TLR2 plays a crucial role in the recognition of mycobacteria by their cell
208 wall components. These ligands activate macrophages by activating NF- κ B through TLR2. However,
209 prolonged TLR2 signaling triggered by these ligands could help *M. tuberculosis* escape immune
210 surveillance. For example, prolonged exposure of macrophages to LpqH, LprG, LprA, LM and PIM
211 results in the expression of IL-10, IL-4 and TGF- β , which inhibits macrophage activation (Saraav, Singh
212 and Sharma 2014). Furthermore, it has been shown that prolonged TLR2 signaling activated by LpqH
213 and LprG inhibits the expression of MHC class II molecules and the processing of exogenous antigens
214 for presentation to CD4⁺ T cells, which may provide a basis for *M. tuberculosis* immune evasion (Hu
215 and Spaink 2022).

216

217 **TLR heterodimers**

218 Effective response to mycobacteria by heterodimeric TLR acting in concert has also been
219 described in the literature. In human monocytes at the innate immune level, stimulation of
220 TLR2/TLR1/CD14 by the LpqH lipoprotein triggers a cascade to induce the production of the
221 antimicrobial peptide cathelicidin. Cathelicidin paired with other components of the vitamin D
222 regulation pathway, including Cyp27b1 hydroxylase and AMP-activated protein kinase (AMPK) to
223 increase intracellular calcium concentration, and mitogen-activated protein kinase (MAPK) to induce
224 Cyp27b1 expression to trigger cellular autophagy (**Figure 1**) (Shin *et al.* 2010). Influencing adaptive
225 immune functions as well, the lipoproteins LprG and LpqH interact with TLR2/TLR1 heterodimers to
226 activate NF- κ B in primary human CD4⁺ T cells. Thus, these lipoproteins serve as important stimuli for
227 immune system regulation in both the innate, *via* cytokine and co-stimulatory molecule secretion, and
228 adaptive, *via* memory T cell activation, during *M. tuberculosis* infection (Lancioni *et al.* 2011). Another
229 study showed that LprG, ManLAM, and LM bind to TLR2 in the absence of TLR1. Nevertheless,
230 trimolecular interactions were revealed by binding of TLR2-LprG or TLR2-PIM₆ complexes to TLR1,
231 whereas binding of TLR2 to TLR1 was not detected in the absence of the lipoprotein or glycolipid. In
232 addition, ManLAM has a low affinity for TLR2 compared with PILAM, LM, and LprG, accounting for its
233 reduced ability to induce TLR2-mediated ERK signaling pathway activation and TNF- α secretion by
234 macrophages (Shukla *et al.* 2018). In contrast, LM from *Mycobacterium bovis* BCG induces both
235 macrophage activation and pro-inflammatory cytokine production through TLR2 ligation. This pro-
236 inflammatory activity has been attributed to the tri- and tetra-acylated forms of LM. Tri-acyl-LM, a
237 TLR2/TLR1 agonist, promotes IL-12p40 and NO secretion by macrophages through the adaptor proteins
238 MyD88 and TIRAP (**Figure 1**) (Doz *et al.* 2007).

239 To evaluate the role of other TLR heterodimers, the independent function of TLR9 and cooperative
240 behavior with TLR2 in *M. tuberculosis* infection were elucidated through a knock-out murine study.
241 Infected *Tlr9*^{-/-} mice exhibited a defect in IL-12p40 and IFN γ production, whereas double knock-out *Tlr2*
242 ^{-/-}/*Tlr9*^{-/-} mice were markedly more susceptible to infection due to defects in pro-inflammatory cytokine
243 production and diminished *M. tuberculosis*-specific IFN γ responses, resulting in increased pulmonary
244 pathology (widespread inflammation and focal necrosis) (Bafica *et al.* 2005). *In vitro*, cooperation
245 between TLR9 and TLR2 was demonstrated by a reduced IL-12 response in the DC and macrophages of
246 the *Tlr2*^{-/-}/*Tlr9*^{-/-} mice compared to control cells. These findings reveal TLR9 plays a functional role both
247 independently and in tandem with other TLR members in the host resistance to mycobacterial infections
248 (Bafica *et al.* 2005).

249

250 TLR4

251 In addition to TLR1/2/9, TLR4-mediated signaling also contributes to the protective response against
252 *M. tuberculosis*. TLR4 is the key receptor involved in LPS recognition and signal initiation (Soares *et al.*
253 2010). In fact, LPS binding induces dimerization of the TLR4-MD-2 complex (Park and Lee 2013). A
254 hydrophobic pocket of MD-2 houses most of the lipid portion of LPS, however, one of the six acyl chains
255 of LPS is left outside the pocket and interacts with the ectodomain of a neighboring TLR4 molecule
256 (Płóciennikowska *et al.* 2015). Viable and attenuated strains of *M. tuberculosis* have been shown to
257 activate murine macrophages that overexpress TLR4 (Means *et al.* 1999). In contrast, expression of a
258 dominant negative TLR4 protein in macrophages partially blocked *M. tuberculosis*-induced NF-kappa
259 B activation (Means *et al.* 2001). Interestingly, the lipid A antagonist E5531 specifically inhibited *M.*
260 *tuberculosis*-induced TNF-alpha production in macrophages and thus apoptosis (Means *et al.* 2001). As
261 agonists, several mycobacterial proteins interact with TLR4, including Hsp65 and Hsp70, stimulating
262 the NF- κ B cascade in human endothelial cells (Bulut *et al.* 2005). In DC, TLR4 recognizes the ribosomal
263 protein Rv0652, which induces cellular maturation and pro-inflammatory cytokines TNF- α , IL-1 β and
264 IL-6 following the activation of the MyD88 and TRIF signaling pathways (**Figure 1**) (Lee *et al.* 2014).
265 These newly activated DC in turn activate naïve T cells and efficiently polarize CD4⁺ and CD8⁺ to secrete
266 IFN γ and induce cell-mediated cytotoxicity to eliminate infected cells. (Lee *et al.* 2014). The
267 peptidoglycan hydrolase RipA activates the NF- κ B signaling pathway and triggers the production of
268 pro-inflammatory cytokines, TNF- α , IL-6, and IL-12, by ligation to TLR4. Homology modelling, docking
269 and MD simulation studies suggested that the C-terminal globular domain of RipA monomers inserts
270 into the ligand binding pocket of the TLR4 dimer (Shariq *et al.* 2021a). Unlike other mycobacterial
271 ligands interacting with TLR4, RipA activates the PI3K-AKT-mTORC1 signaling cascade, ultimately
272 resulting in inhibition of the autophagy-initiating kinase ULK1 (**Figure 2**) (Shariq *et al.*, 2021). This
273 inhibition results in efficient intracellular survival of recombinant *M. smegmatis* expressing *M.*

274 *tuberculosis* RipA in macrophages (Shariq *et al.*, 2021). RipA also targets host cell mitochondria and
275 inhibits the production of oxidative phosphorylation enzymes to promote mycobacterial replication in
276 macrophages (**Figure 2**). In addition, RipA also inhibits caspase-dependent programmed cell death in
277 macrophages, thereby preventing an effective innate antibacterial response (**Figure 2**) (Shariq *et al.*,
278 2021). Collectively, the RipA endopeptidase contributes to the creation of a permissive replication
279 niche in host cells by inducing repression of autophagy and apoptosis. In addition to proteins, the tetra-
280 acylated LM-containing fraction from *M. bovis* BCG activates macrophages in a MyD88-dependent
281 manner through TLR4 (Doz *et al.* 2007) while PIMs induce TLR2- and TLR4-dependent signaling, thus
282 possibly influencing protective immunity (Abel *et al.* 2002). However, the use of bacterial expression
283 systems and the proteins produced which are then used as agonists carries a risk of contamination
284 with tiny amounts (pico- to nanogram) of lipopolysaccharide which are sufficient to induce the
285 activation of phagocytes such as macrophages. Future co-structure experiments are needed to
286 definitively validate the described interactions between TLR4 and its different bacterial substrates. The
287 role of TLR4 in host resistance to *M. tuberculosis* was also evaluated in C3H/HeJ (having a point
288 mutation within the coding region of the Tlr4 gene) mice (Qureshi *et al.* 1999) after aerosol infection.
289 C3H/HeJ mice showed a reduced ability to clear mycobacteria from the lungs, favoring the spread of
290 the infection in the spleen and liver and accelerating mortality (Abel *et al.* 2002). The lungs of these
291 animals showed signs of chronic pneumonia and deficits in pulmonary production of TNF- α , IL-12p40
292 and chemoattractant protein-1 (Abel *et al.* 2002). However, careful interpretation is required when
293 using the C3H/HeJ strain as a model for a TLR4-deficient mouse strain, as there are significant allelic
294 differences between C3H/HeJ and other C3H mouse substrains in response to *M. tuberculosis*
295 infection. With this caution, the data imply that TLR4 may not be sufficient for optimal immunity of
296 mice against *M. tuberculosis* (Kamath *et al.* 2003). It is likely that TLR4 signaling does not contribute to
297 the initiation of protective responses against naturally low-dose airborne infection to *M. tuberculosis*
298 (Reiling *et al.* 2002; Shim, Turner and Orme 2003). These divergent results may indicate that subtle,
299 but as yet unknown, differences in experimental conditions (including the type of mice used, the
300 respective microbiome of those mice used and the different specific pathogen-free standards in the
301 animal houses) may be instrumental in determining whether or not TLR4 functionality is of significance
302 in *M. tuberculosis* infection.

303

304 **Lectin domain-containing receptors and opsonins**

305 C-type lectin receptors (CLR) are Ca²⁺-dependent glycan-binding proteins, which adopt a C-type lectin
306 fold structure with a highly variable primary protein sequence and possess similarities in the primary
307 and secondary structures of their carbohydrate-recognition domain (CRD). CLR are widely expressed in
308 living organisms (Drickamer 1999) and are made up of a diverse members including phagocytic receptors

309 and proteoglycans. Adopting both secreted, soluble forms and anchored forms in the plasma
310 membrane, they frequently oligomerize into homodimers, homotrimers and higher order oligomers.
311 These structures lend to the interaction with multivalent ligands and recognition of diverse glycans,
312 owing to the unique carbohydrate composition and structure found on the surface of pathogens (Hsu,
313 Pilobello and Mahal 2006). Functionally, CLR can act as adhesion molecules or phagocytic and/or
314 signaling receptors in the innate immune response to microbes and have been highly conserved
315 throughout evolution (Cummings and McEver 2015). Understanding of CLR family-mycobacterial ligand
316 interactions has expanded in recent years and will be discussed below.

317

318 **Collectins**

319 Collectins are soluble PRR of the innate immune system. They belong to a group of collagenous
320 Ca²⁺-dependent defensive lectins found in animals and function to bind oligosaccharides or lipids
321 present on the surface of microorganisms. Following binding to collectins, microbes may be eliminated
322 through aggregation, complement activation, opsonization, phagocytosis activation, or growth
323 suppression.

324 The CLR of the innate immune system, including human pulmonary surfactant protein A (SP-A, a
325 member of the collectin family produced by lung epithelial cells of the distal and proximal air spaces),
326 have been identified as key players in the early recognition of invading pathogens and initiation of host
327 defense responses. SP-A decorates the surface of *M. tuberculosis* to enhance macrophage adhesion
328 **(Figure 3)** (Ferguson *et al.* 1999). Although ManLAM is considered as the primary target of several CLR
329 including DC-SIGN, MR, CR3, the Apa glycoprotein has also been shown to interact with SP-A in a calcium-
330 dependent fashion (Ragas *et al.* 2007). Through the interaction with cell wall-associated mycobacterial
331 components, the human lung SP-A acts as an effective opsonin to facilitate attachment of bacilli to
332 macrophages.

333 In addition to SP-A, the surfactant protein D (SP-D) is another collectin produced in the distal
334 airspaces of the lungs. Capable of recognizing carbohydrates through its CRD, SP-D regulates interactions
335 between *M. tuberculosis* and macrophages through the recognition of mannosylated components, such
336 as ManLAM (Ferguson *et al.* 1999). Also a calcium-dependent event, specific binding of SP-D to *M.*
337 *tuberculosis* causes bacterial agglutination, reduces adhesion to macrophages and decreases its
338 intracellular growth **(Figure 3)** (Ferguson *et al.* 1999; Carlson *et al.* 2009). Together, these observations
339 reveal that SP-A and SP-D play opposite roles in the host innate response to *M. tuberculosis* in the lungs.

340 Another member of the collectin family, the mannose-binding lectin (MBL, produced by the liver
341 and circulated throughout the body) recognizes various slow-growing mycobacteria (e.g., *M.*
342 *tuberculosis*, *M. bovis*, *M. kansasii*, and *M. goodnae*) as well as *M. smegmatis*. The molecular
343 recognition of ManLAM and the antigen 85 complex (Ag85) leads to activation of the lectin pathway of

344 the complement system and increases phagocytosis (**Figure 3**) (Bartłomiejczyk *et al.*, 2014, Świerzko *et al.*, 2016). Given MBL's ability to bind fibronectin, it may play an additional role in the interaction of the
345 Ag85 complex with the extracellular matrix. Finally, MBL binding could also favor the uptake of *M.*
346 *africanum* by macrophages, thereby promoting infection, and TB selection could have fostered the
347 spread of functional MBL-G57E variant in *M. africanum* endemic regions (Thye *et al.* 2011).

349 While extensive research focus has been given to the interaction of *M. tuberculosis* and phagocytic
350 cells, less is understood about the molecular basis underlying binding and entry with non-phagocytic
351 cells. Among the different cell types investigated, Chinese hamster ovary (CHO) fibroblasts and primary
352 porcine aortic endothelial cells were reported to successfully bind to *M. tuberculosis in vitro*. Binding
353 markedly increase in the presence of 10% to 20% human or bovine serum, suggesting that the bacteria
354 benefit from the coating of serum opsonins (Hoppe *et al.* 1997). Pre-incubation with individual opsonins
355 revealed that recombinant serum-derived human mannose-binding protein (MBP, belonging to the
356 collectin family, possessing one lectin domain and produced in the liver during infection) also improved
357 binding (**Figure 3**). Using PIM-specific antibodies to demonstrate a partial blocking of *M. tuberculosis*
358 and *M. smegmatis*, these surface molecules were found to play a role in binding to CHO and endothelial
359 cells (Hoppe *et al.* 1997). Furthermore, PIM-coated beads were observed to adhere to CHO cells with
360 significant enhancement through the addition of MBP-enriched serum and the presence of PIM
361 mannoses (Hoppe *et al.* 1997). These findings confirm PIM can function as adhesins to bind to non-
362 phagocytic cells both directly and after opsonization with serum MBP.

363

364 **Serum amyloid A-opsonin-dependent uptake**

365 Opsonization confers the coating of bacteria with various molecules, which are then recognized
366 by specific host receptors. Among these, the serum amyloid A1 (SAA1) protein belongs to the family of
367 apolipoproteins associated with high-density lipoproteins (HDL). These proteins play several roles,
368 including the transport of cholesterol to the liver for secretion into the bile, the recruitment of immune
369 cells to inflammatory sites and the induction of enzymes to degrade the extracellular matrix. The
370 interaction between *M. tuberculosis* and SAA1 occurs through the membrane effectors AtpA (Rv1308),
371 the ABC transporter (Rv2477c), the ESX-1 substrate EspB (Rv3881c), the antigen TB18.6 (Rv2140c), and
372 the phosphomethylpyrimidine synthase ThiC (Rv0423c) (**Figure 3**) (Kawka *et al.* 2021). Opsonization of
373 *M. tuberculosis* by SAA1 promotes bacterial entry into target phagocytes, stimulates intracellular growth
374 and survival (**Figure 3**), and upregulates two operons encoding mycobacterial transport systems,
375 MmpL5/MmpS5 (Rv0676c) and Rv1217c/Rv1218c (Kawka *et al.* 2021). Despite the protective opsonic
376 behavior of SAA1, the interaction with *M. tuberculosis* inadvertently promotes the infection of host
377 macrophages and modulates the functional response of the pathogen.

378

379 **Mincle and Dectin**

380 Mincle is principally expressed on myeloid cells, including macrophages and DC (Marakalala and
381 Ndlovu 2017). It is composed of a CRD, a transmembrane (TM) domain and a short cytoplasmic tail with
382 a positively-charged residue, which engages with the adaptor molecule FcRy to trigger intracellular
383 signaling *via* the Syk/CARD9 pathway (**Figure 1**) (Marakalala and Ndlovu 2017). Mincle is an essential
384 receptor for the glycolipid trehalose-6,6'-dimycolate (TDM, also known as cord factor) (Heitmann *et al.*
385 2013), which activates macrophages and downstream inflammatory cytokines and nitric oxide (**Figure**
386 **1**) (Ishikawa *et al.* 2009). It is also a known adjuvant for Th1/Th17 vaccination that activates Syk-Card9
387 signaling in antigen-presenting cells (APC). To confirm its role, genetic disruption experiments of Mincle
388 showed the complete elimination of TDM-induced macrophage activation and stimulation of T cell
389 immune responses to a TB vaccine (Ag85B-ESAT-6). Moreover, macrophages lacking Mincle or FcRy
390 exhibit impaired inflammatory responses to *M. bovis* BCG (Schoenen *et al.* 2010). In a murine study,
391 administration of TDM in wild-type mice triggered elevated inflammatory cytokine levels in sera and
392 lung inflammation associated with granuloma formation (Ishikawa *et al.* 2009), whereas Mincle-
393 deficient mice were still able to mount an effective granulomatous and protective immune response
394 after infection with both low and high doses of *M. tuberculosis* (Heitmann *et al.* 2013). These findings
395 suggest that the loss of Mincle *in vivo* can be fully compensated and a protective inflammatory immune
396 response still generated during *M. tuberculosis* infection. Mincle has been shown to further induce an
397 immune response in mice following interaction with other mycobacterial ligands, such as trehalose-
398 monomycolate (TMM), glucose-monomycolate (GMM) and arabinose-monomycolate (AraMM).
399 Stimulation with these ligands activate bone marrow-derived DC to produce IL-6, TNF- α and reactive
400 oxygen species (ROS) and stimulate the NLRP3 inflammasome to promote Th1 and Th17 responses (Tima
401 *et al.* 2017). The murine bone marrow-derived DC may also be activated through Mincle signaling after
402 exposure to *M. tuberculosis*' immunogenic β -gentiobiosyl diacylglycerides (Richardson *et al.* 2015).
403 Lastly, unique to the human immune response, Mincle interplays with glycerol-monomycolate (GroMM)
404 to stimulate macrophages for inflammatory cytokines production (Hattori *et al.* 2014).

405 Signaling through Dectin receptors activates the Syk/CARD9/BCL-10/MALT1 cascade (**Figure 1**),
406 resulting in the production of pro-inflammatory cytokines and the induction of T cell-mediated immunity
407 (Marakalala and Ndlovu 2017). Adopting several forms, Dectin-1, Dectin-2 and Dectin-3 have been linked
408 to antimycobacterial immunity. Dectin-1 is a glycosylated TM protein with an extracellular CRD and a
409 cytoplasmic immunoreceptor tyrosine-based activation motif (ITAM)-like domain that supports
410 intracellular signaling (**Figure 1**) (Marakalala and Ndlovu 2017). Dectin-1 is primarily expressed on
411 macrophages, DC, neutrophils and a subset of T cells, recognizing *M. tuberculosis* and less virulent
412 mycobacterial species, despite the mycobacterial ligand(s) remaining largely unknown. Dectin-1-
413 dependent infection of BMDM, DC, A549 cells, PBMC, MDC, neutrophils or monocytes with varied

414 mycobacterial species leads to the production of antimicrobial peptides, ROS and cytokines, such as TNF-
415 α , IL-6, G-CSF, RANTES, IL-12p40, IL-17A, IL-1 β , and IL-23 (**Figure 1**) (Yadav and Schorey 2006; Rothfuchs
416 *et al.* 2007; Lee *et al.* 2009; Zenaro, Donini and Dusi 2009; van de Veerdonk *et al.* 2010; Romero *et al.*
417 2016; Bisiaux *et al.* 2017). Furthermore, DC activated by a Dectin-1 agonist stimulates naïve CD4⁺ T cells
418 to upregulated IFN γ and IL-17 (Zenaro, Donini and Dusi 2009). During a *Dectin-1*-KO study, mice had
419 significantly decreased lung bacillary loads but developed histological signs of pneumonia (Marakalala
420 *et al.* 2011). Additionally, the loss of Dectin-1 did not result in any significant variations across the
421 pulmonary cytokine expression profiles when compared to control mice (Marakalala *et al.* 2011). Thus,
422 Dectin-1 does not appear to play a major role in immunity against *M. tuberculosis in vivo*, understanding
423 limited applicability due to the use of a murine model. Conversely, the structure of Dectin-2 consists of
424 a CRD, a TM and a short cytoplasmic tail and is mainly expressed on macrophages, certain subsets of DC
425 and peripheral blood monocytes (Marakalala and Ndlovu 2017). BMDC surface-associated Dectin-2
426 specifically recognizes ManLAM, resulting in the production of pro- and anti-inflammatory cytokines
427 (**Figure 1**), effects that are reversed in *Dectin-2*^{-/-} BMDC (Yonekawa *et al.* 2014). Upon mycobacterial
428 infection, *Dectin-2*^{-/-} mice exhibit increased lung pathology, demonstrating that this receptor is a key
429 factor in host immunity against mycobacterial infection. The remaining type, Dectin-3, recognizes TDM,
430 stimulates Mincle expression through the CARD9-Bcl10-MALT1 complex, and NF- κ B binding to the
431 Mincle promoter enhances host immunity to mycobacterial infection. Consistent with these findings,
432 Dectin-3- or CARD9-deficient mice produce significantly less pro-inflammatory cytokines and KLH-
433 specific antibodies after immunization with a TDM-containing adjuvant (Zhao *et al.* 2014).

434

435 **Dendritic cell immune activating receptor**

436 The DC immune activation receptor (DCAR) is expressed on peritoneal macrophages and
437 monocyte-derived inflammatory cells in the lungs and spleen. It lacks an immunoreceptor tyrosine-
438 based inhibitory motif (ITIM) in its intracellular domain (Toyonaga *et al.* 2016; Omahdi *et al.* 2020),
439 however, possesses a positively-charged amino acid in its TM, allowing protein-protein interactions with
440 FcR γ , which supplies the immunoreceptor tyrosine-based activation motif (ITAM) required for DCAR-
441 dependent signaling (Omahdi *et al.* 2020). Macrophages and monocytes produce the MCP-1 chemokine
442 upon exposure to PIMs, a function that is modulated through DCAR, which interacts directly with
443 acylated PIMs (Ac₁PIM₁, AcPIM₂ and Ac₂PIM₂) (Toyonaga *et al.* 2016; Arai *et al.* 2020). In the absence of
444 DCAR or FcR γ MCP-1 production is halted, as was observed in DCAR-deficient mice (Toyonaga *et al.*
445 2016). Upon mycobacterial infection, mice showed reduced numbers of monocyte-derived
446 inflammatory cells at the site of infection, decreased IFN γ production by T cells and increased bacterial
447 loads. For adequate T cell response against mycobacteria, DCAR is an essential receptor (Toyonaga *et al.*
448 2016).

449

450 DC-SIGN and its murine homologs

451 Interactions between DCs and the *M. tuberculosis* complex play a key role in anti-mycobacterial
452 immunity. *M. tuberculosis* gains entry to DC through the interaction between DC-SIGN and ManLAM or
453 LAM (Maeda *et al.* 2003; Tailleux *et al.* 2003), with the acyl chains of the ManLAM's
454 mannosylphosphatidylinositol anchor and the manooligosaccharide caps acting as the primary
455 interface (Maeda *et al.* 2003). Although mannose-capped LAM molecules are present across
456 mycobacterial species, DC-SIGN discriminates between these permutations and selectively recognizes
457 *M. tuberculosis*. For instance, *M. smegmatis*-derived LAM, capped with phosphatidylinositol (PILAM),
458 has a limited ability to preferentially bind DC-SIGN in the presence of *M. tuberculosis*. Furthermore, DC-
459 SIGN interacts poorly with PILAM and with the uncapped AraLAM molecules from *M. fortuitum* or *M.*
460 *chelonae*, respectively, or with *M. avium*'s single mannose residue-capped ManLAM (Maeda *et al.* 2003).
461 Despite this, the removal of the mannose caps in a $\Delta pimE$ mutant (PimE/Rv1159 catalyzes the transfer
462 of the fifth mannose to PIM₄ to generate PIM₅) fails to reduce the interaction of whole mycobacteria
463 with DC-SIGN (Driessen *et al.* 2009), suggesting that the receptor is likely to interact with additional
464 ligands. Indeed, DC-SIGN has also a strong affinity for hexamannosylated PIM₆ (**Figure 2**) (Driessen *et al.*
465 2009; Ehlers 2010). Generation of *M. bovis* BCG mutants deficient in PIM₆ (single mutant) or PIM₆ and
466 mannose capping on LAM (double mutant) (Driessen *et al.* 2009) still show similarly binding affinity to
467 DC-SIGN and DC and induce comparable levels of IL-10 and IL-12p40 as the wild-type strain.
468 Furthermore, infection studies with these strains have established that the ManLAM/PIM-DC-SIGN
469 interaction was not critical for protective immunity in mice (Ehlers 2010), strengthening the view that
470 while ManLAM and PIM₆ are true ligands of DC-SIGN, additional ligands are likely to govern the
471 interaction between mycobacteria and DC *in vivo*. This notion is further supported by other studies
472 reporting the binding of multiple ligands to DC-SIGN, including LM, PIM₂, α -glucan (a dominant capsular
473 polysaccharide) (**Figure 2**), and the 19-kDa or the 45-kDa mannosylated Apa glycoproteins (Pitarque *et al.*
474 2005; Torrelles, Azad and Schlesinger 2006; Geurtsen *et al.* 2009; Sawettanai *et al.* 2019).

475 The consequences of the DC-SIGN-mediated interactions between mycobacterial ligands and DC are
476 multifold. *M. tuberculosis* and *M. bovis* BCG (through ManLAM) bind to DC-SIGN, halting DC maturation,
477 impeding IL-12 release and inducing IL-10 secretion (Geijtenbeek *et al.* 2003; Gagliardi *et al.* 2005; Wu
478 *et al.* 2011). Similarly, binding of the *M. tuberculosis* α -glucan to DC-SIGN stimulates immunosuppressive
479 IL-10 production by DCs (**Figure 2**) (Geurtsen *et al.* 2009). This behavior is mirrored during ManLAM or
480 PIM₆ interactions with DC-SIGN in immature DC and macrophages, impairing DC maturation and
481 modulating cytokine secretion by phagocytes and DC, leading to overall suppressed protective immunity
482 to TB (Ehlers 2010). Furthermore, IFN γ levels have been showed to be significantly downregulated in the
483 supernatants of naïve T cells after co-culture ManLAM-primed DC (Wu *et al.* 2011). The same phenotype

484 was described in a clinical study reporting that overexpression of DC-SIGN in TB patients decreased DC
485 activation, elevated secretion of IL-10 by DCs, decreased induction of T cell proliferation and impaired
486 the immune response (Zhang, Guo and Luo 2009). Nevertheless, *M. tuberculosis* infection of human DC-
487 SIGN-transgenic mice for revealed that DC-SIGN can promote host protection by limiting tissue
488 pathology (Ehlers 2010). DC can also target and eliminate *M. tuberculosis*-infected apoptotic neutrophils
489 following the association between neutrophil Mac-1 protein (CD11b/CD18) and DC-SIGN, thereby
490 reducing inflammation (Hedlund *et al.* 2010). Inflammation reduction was further shown in an *in vivo*
491 experiment exposing DC to synthetic mannodendrimers mimicking the ManLAM of *M. tuberculosis*,
492 revealing the cells' pro-inflammatory cytokine production to be inhibited in a DC-SIGN-dependent
493 manner, limiting acute neutrophil influx in mice lungs (Blattes *et al.* 2013).

494 In *M. leprae*, the etiological agent of leprosy, infection severity is a function of DC-SIGN expression
495 levels and the interaction with ManLAM. When treated with *M. leprae*-specific ManLAM, DC upregulate
496 DC-SIGN expression, resulting in an increased nuclear intrusion of NF- κ B leading to potent production of
497 IL-10. This promotes an immunosuppressive environment during leprosy progression, creating an
498 optimal niche for bacterial persistence in the host (Kumar *et al.* 2013a). Overall, pathogenic
499 mycobacteria capitalize on the DC-SIGN-ManLAM interaction through the prevention of DC maturation
500 and induction of the immunosuppressive cytokine IL-10, permitting enhanced survival and persistence
501 **(Figure 2)**.

502 To further understand the function of DC-SIGN in anti-TB immunity, parallel murine studies were
503 undertaken. Among the eight murine homologs (SIGNR1-8), SIGNR1 and SIGNR3 are the closest analogs
504 to DC-SIGN. SIGNR1 is expressed by macrophages only, yet still interacts with *M. tuberculosis* through
505 ManLAM, similar to DC-SIGN (Koppel *et al.* 2004; Wieland *et al.* 2007). Peritoneal macrophages from
506 *Signr1*-KO mice produce less IL-10 upon stimulation with ManLAM than those from wild-type mice,
507 suggesting that the interaction of ManLAM with SIGNR1 may result in similar immunosuppression
508 observed in the human equivalent (Wieland *et al.* 2007). Another *in vivo* study showed that SIGNR1
509 upregulates SOCS1 expression during *M. tuberculosis* infection, impairs IL-12 production and promotes
510 *M. tuberculosis* survival (Srivastava *et al.* 2009). Moreover, upon stimulation of murine DC with C-type
511 lectin ligand LAM, SIGNR1 significantly suppresses NF- κ B activation as well as TNF α , IL-6 and IL-12p40
512 production (Ohtani *et al.* 2012). In contrast to the observations in the *Signr1*-KO mice, the *Signr3*-KO
513 mice were the only group to display dampened resistance to *M. tuberculosis*. SIGNR3 is expressed by
514 lung phagocytes during infection and interacts with *M. tuberculosis* surface glycoconjugates to induce
515 secretion of inflammatory cytokines critical for host defense, including TNF and IL-6, confirming the
516 protective role of murine SIGNR3 during the infection (Tanne *et al.* 2009; Tanne and Neyrolles 2010).

517

518 **Mannose receptor**

519 The mannose receptor (MR) is an eight lectin-domain transmembrane protein capable of binding
520 carbohydrate ligands including terminal mannose-containing glycoconjugates, fucose and GlcNAc
521 (Martinez-Pomares 2012). MR recognizes mycobacterial surface ManLAM (**Figure 2**), LAM, AraLAM,
522 acylated PIMs, LM, glycosylated and acylated 19-kDa antigen and PstS-1 (a 38-kDa mannosylated
523 glycolipoprotein) (Schlesinger, Hull and Kaufman 1994; Diaz-Silvestre *et al.* 2005; Torrelles, Azad and
524 Schlesinger 2006; Esparza *et al.* 2015). Its role facilitates the adhesion of *M. tuberculosis* strains to
525 human monocyte-derived macrophages (MDM). Playing a role in adhesion, MR facilitates non-opsonic
526 phagocytosis by binding surface glycopeptidolipids (GPL) on *M. smegmatis* (**Figure 2**) (Schlesinger 1993;
527 Villeneuve *et al.* 2005), and additionally was recently shown to internalize fluorescent beads coated with
528 the triglycosylated form of GPL (GPL-3) through the internal and external rhamnose residues linked to
529 the alaninol residue (Daher *et al.* 2022). After phagocytosis, maturation of the phagosome (**Figure 2**)
530 only takes place at the point of fusion with the lysosomal Hck compartment (a Src family tyrosine kinase
531 used as a marker of lysosome-phagosome fusion in human cells), providing an opportunity for
532 mycobacteria to inhibit this process through the MR-ManLAM interaction (**Figure 2**) (Astarie-Dequeker
533 *et al.* 1999; Kang *et al.* 2005). Specifically, it is the ManLAM mannose cap structures that prevent the
534 phagosome-lysosome fusion, and experimentally, it has been shown that the fully intact ManLAM
535 molecule is required to maintain this phenotype (Kang *et al.* 2005). The arrest of phagosome-lysosome
536 fusion has also been observed in *M. avium* serovar 4 through the GPL-MR interaction (**Figure 2**) (Shimada
537 *et al.* 2006), causing downstream suppression of EEA1 and Ca²⁺/calmodulin kinase II recruitment in THP-
538 1 cells (Shimada *et al.* 2006). Internalization *via* the MR not only inhibits phagosome-lysosome fusion
539 but blocks the production of cytokines that target mycobacteria. ManLAM, after cross-linking with MR,
540 inhibits TLR2-induced IL-12 production in human DC (Nigou *et al.* 2001). A subsequent study confirmed
541 the ManLAM-MR engagement reduces inflammation by both inducing the production of anti-
542 inflammatory factors IL-10 (IL-1R antagonist) and IL-1R type II, and suppressing IL-12 secretion by human
543 DCs (Chieppa *et al.* 2003). In THP-1 cells, the induction of matrix metalloproteinase-9 (MMP-9)
544 production by MR in response to *M. tuberculosis* and LAM is also a contributing factor to lung tissue
545 damage during TB infection (Rivera-Marrero *et al.* 2002). Overall, these studies demonstrate that MR
546 plays a multi-faceted role in promoting a favorable mycobacterial infection niche in phagocytes.

547

548 **Complement receptor type 3 (CR3)**

549 CR3 is a heterodimeric surface receptor that belongs to the integrin superfamily, comprising
550 CD11b and CD18 (**Figure 4**). It has multiple binding sites locate on the C-terminal lectin domain, which
551 can mediate both opsonic and non-opsonic phagocytosis (Velasco-Velázquez *et al.* 2003). Several studies
552 have evaluated the role of CR3 in mycobacterial infections, highlighting its involvement in initial binding
553 (**Figure 4**) (Stokes, Thorson and Speert 1998; Velasco-Velázquez *et al.* 2003). Monoclonal antibodies

554 against CR3 have been shown to inhibit adhesion and phagocytosis of virulent *M. tuberculosis* by human
555 monocytes in fresh, non-immune serum. Thermally inactivated serum similarly reduced *M. tuberculosis*
556 adhesion, and replenishment of component C3 or factor B (part of the alternative complement pathway,
557 cleaved by factor D to yield a protease that associates with C3b to form the C3 convertase) increased
558 adhesion (Schlesinger *et al.* 1990; Schlesinger 1993). This was also observed *in vivo* in *Itgam*^{-/-} (CR3
559 negative) mice where non-opsonic binding and serum-mediated opsonic attachment of *M. tuberculosis*
560 to resident macrophages was significantly reduced (Melo *et al.* 2000; Rooyakkers and Stokes 2005).
561 Downstream of internalization, *M. tuberculosis* survival and replication in infected macrophages and
562 mice were not significantly affected by the absence of ITGAM/CD11b, suggesting that CR3-mediated
563 uptake is not a major factor contributing to intracellular survival (Hu *et al.* 2000; Melo *et al.* 2000).
564 Consistently, MDM exhibit enhanced adherence of BCG and *M. leprae* and the attachment process is
565 CR3 and/or serum dependent (requiring thermolabile serum components) (Schlesinger and Horwitz
566 1990, 1991; Launois *et al.* 1992). Mechanistically, the C-terminal lectin domain of CR3 recognizes LAM,
567 PIM₂ and polar GPL (**Figure 4**) (Villeneuve *et al.* 2005). In addition, the 85C antigen promotes the uptake
568 of BCG and *M. tuberculosis* by monocytes through ligation to CR3 (**Figure 4**) (Hetland and Wiker 1994).
569 Furthermore, Rv0180c promotes the infection initiation in the lungs of mice and facilitates entry into
570 macrophages through CR3 (Payros *et al.* 2021). The cooperation between CR3 and TLR2 appears
571 fundamental to inhibit the release of peroxidase by eosinophils, which in turn modulate the innate
572 immune response to mycobacteria (Driss *et al.* 2012). Thus, CR3 is important in mycobacterial uptake
573 but is not needed for the induction of the microbicidal machinery and thus favors the survival of
574 intracellular bacteria.

575

576 **Oxidized low-density lipoprotein receptor-1 (LOX-1)**

577 The LOX-1 receptor is a TM protein that structurally belongs to the C-type lectin family (Zeya,
578 Arjuman and Chandra 2016). GroEL2, often found associated with the mycobacterial cell wall, has been
579 identified as a potential ligand for the macrophage LOX-1 receptor (**Figure 4**) based on the decreased
580 uptake of GroEL2-coated latex beads by macrophages following treatment with the LOX-1 inhibitor
581 polyinosinic acid (Vinod *et al.* 2021). This remains only a putative interaction, but may contribute to the
582 internalization of bacteria in macrophages.

583

584 **Galectin receptors**

585 Galectins are a large class of proteins serving multiple cellular roles including signaling and
586 adhesion. They are considered S-type lectins due to the presence of disulfide bonds, which function to
587 provide stability and the binding of carbohydrates, including nitrogen- or oxygen-linked β -galactoside
588 sugars. Found in a variety of species, there are 15 mammal-specific galectins, which are further

589 subdivided into three forms: chimera, tandem, and dimeric. Though most lectins exist as membrane-
590 bound proteins, galectins are unique in their soluble state. Tandem galectins, such as Galectin-9, possess
591 two distinct CRD whereas the chimeric Galectin-3 exists as a monomer or a multivalent form. Galectin-
592 3's multifunctionality lends itself to be found both primarily in the cytoplasm and additionally on the cell
593 surface of immune cells. At the surface, it is known to recognize mycolic acids (MA), the major lipid of
594 the mycobacterial cell envelope, yet the nature of this interaction is still not fully understood (Barboni,
595 Coade and Fiori 2005). More has been discovered concerning the biological role of Galectin-9,
596 particularly with its physical interaction with the essential cell wall polysaccharide, arabinogalactan (AG),
597 during mycobacterial infection (**Figure 2**). Structural-functional relationship analyses indicate that the
598 high-affinity interaction between AG and Galectin-9's CRD2 causes the latter to associate with
599 transforming growth factor β -activated kinase 1 (TAK1) to trigger the activation of extracellular signal-
600 regulated kinase (ERK) and the induction of matrix metalloproteinases (MMP) expression (**Figure 2**) (Wu
601 *et al.* 2021). These pathways contribute to AG-induced damage in the lungs and have been shown to
602 aggravate the *M. tuberculosis* infection in mice by promoting bacilli survival (**Figure 2**) (Wu *et al.* 2021).
603 The interaction between AG/Galectin-9 interaction may, therefore, serve as a viable target for
604 therapeutic development to reduce the severity of the TB pathology in mice (Wu *et al.* 2021).

605

606 **Other receptors**

607 **Nucleotide-binding oligomerization domain-like receptors**

608 Following internalization, mycobacteria typically inhabit the phagosomal compartment, however,
609 sporadic escape into the cytoplasm (Houben *et al.* 2012) exposes the bacteria to intracellular receptors,
610 including the nucleotide-binding oligomerization domain (NOD)-like receptors (NLR). The NLR member
611 NOD2 detects the N-glycolyl-muramyl dipeptide (MDP) component of peptidoglycan in the
612 mycobacterial cell wall (**Figure 1**) (Coulombe *et al.* 2009). More specifically, NOD2 is stimulated by the
613 N-acetyl muramic acid hydroxylase, NamH, which converts MDP into a N-glycolylated form (Coulombe
614 *et al.* 2009). Accordingly, disruption of *namH* in *M. smegmatis* and *M. tuberculosis* abrogates NOD2-
615 mediated TNF- α secretion in macrophages (Coulombe *et al.* 2009; Hansen *et al.* 2014) and NOD2-
616 dependent immune responses were confirmed to be contingent on the presence of NamH in a murine
617 study (Coulombe *et al.* 2009). Further still, N-glycolyl MDP promotes the secretion of pro-inflammatory
618 cytokines (TNF- α , IL-1 β , IL-6) (**Figure 1**) and induces T-cell immunity in a NOD2-dependent manner
619 (Coulombe *et al.* 2009; Juárez *et al.* 2012). During *M. tuberculosis* infection, NOD2 induces expression of
620 the antimicrobial peptide LL37, recruits the autophagy proteins IRGM, LC3, and ATG16L1 to the bacteria-
621 containing autophagosome (**Figure 1**) (Juárez *et al.* 2012), and increases NO production upon NF- κ B
622 activation (**Figure 1**) (Landes *et al.* 2015). Synergistic effect of MDP combined to Hsp70 increases IL-6,
623 IL-12p40, and TNF- α production in BMDC, enhances DC maturation and promotes T cell IFN γ production,

624 while accordingly these effects were diminished in NOD2-deficient BMDC (Kim *et al.* 2015).
625 Experimentally, it was demonstrated that, in mice, intraperitoneal injection of MDP together with Hsp70
626 increased the production of IL-6, CXCL-1, and CCL2 in serum (Kim *et al.* 2015), suggesting these combined
627 proteins could be harnessed for an effective vaccination strategy. NOD2 has also been identified in the
628 pathogenesis of other mycobacterial infections, including *M. leprae*, where the induction of IL-32 and
629 differentiation of monocytes into DC in the innate immune response occurs in a NOD2-dependent
630 manner (Schenk *et al.* 2016). Similarly, new insights into the potential roles of NOD2 during the innate
631 immune activation against *M. abscessus* lung infections have recently emerged. The production of pro-
632 inflammatory cytokines and NO to limit intracellular growth, eliminate bacteria and ultimately
633 ameliorate lung pathology in *M. abscessus*-infected mice has been shown to hinge on the presence of
634 NOD2 (Lee *et al.* 2017). These collective data demonstrate that NLR, and frequently NOD2, are central
635 to the host defense and reduction of mycobacterial survival.

636

637 **The cyclic GMP-AMP synthase (cGAS) receptor**

638 The recognition of microbial components in the cytosol is critical for initiating an innate immune
639 response against intracellular pathogens. The cytosolic DNA sensor cyclic GMP-AMP synthase (cGAS) is
640 essential for triggering STING-dependent signaling and initiating type I interferons (IFN-I) IFN- α and IFN-
641 β as central messengers in the host response against bacterial infections. Cyclic GAMP (cGAMP)
642 synthesis is triggered by the association of cGAS with *M. tuberculosis* DNA in the cytosol (**Figure 1**)
643 (Wassermann *et al.* 2015). The ESX-1 mycobacterial secretion system is required for the cytosolic
644 surveillance pathways to be activated during *M. tuberculosis* infection, which results in the generation
645 of IFN *via* the STING/TBK1/IRF3 pathway (**Figure 1**) and to interleukin-1 β (IL-1 β) synthesis (Wassermann
646 *et al.* 2015; Watson *et al.* 2015). In this way, cGAS promotes autophagic targeting and clearance of *M.*
647 *tuberculosis* (Watson *et al.* 2015). Similarly, in DC, type I IFN and its cognate receptor (IFNAR), in concert
648 with the cGAS signaling pathway, act against *M. bovis* infection by promoting phenotypic maturation
649 and functional activation of DC and also by increasing CD4⁺ T cell proliferation with DC (Li *et al.* 2019).
650 However, not all mycobacteria species stimulate the cGAS pathway to trigger IFN production. In
651 comparison to *M. smegmatis*-infected macrophages, those with *M. avium sbsp. paratuberculosis* (MAP)
652 infection produce much less IFN- β (Ruangkiattikul *et al.* 2017). This could be explained by the fact that
653 TBK1 is phosphorylated at higher rates in *M. smegmatis* and that there is more extracellular bacterial
654 DNA present in the cytosol (most likely as a result of bacterial autolysis, which releases more DNA
655 needed to effectively activate the cGAS/STING cascade). This is also true in a mouse model, where *M.*
656 *smegmatis*-induced high IFN- β production and bacterial clearance are correlated. But MAP only slightly
657 increases IFN- β expression, which is associated with bacterial persistence and enhanced hepatic
658 granuloma formation (Ruangkiattikul *et al.* 2017). As predicted, *M. smegmatis* survival was increased in

659 mice lacking IFNAR, although MAP survival was equivalent in *Ifnar*^{-/-} and wild-type mice (Ruangkiattikul
660 *et al.* 2017). Overall, cGAS is as an innate sensor of mycobacteria and contributes to the elimination of
661 the bacilli.

662

663 **CD43 receptor**

664 Found on the surface of all hematopoietic cells, CD43/SPN (sialophorin) is a large sialylated
665 glycoprotein essential in the general immune response to mycobacteria and the optimal uptake by
666 macrophages. *M. tuberculosis* engages various chaperones, Cpn60.2/Hsp65/GroEL and to a lesser extent
667 DnaK/Hsp70, as bacterial adhesins that bind to CD43 on the surface of human macrophages (**Figure 1**)
668 (Hickey *et al.* 2010). Both demonstrate *in vitro* and *in vivo*, CD43 is required for optimal uptake and
669 inhibition of *M. tuberculosis* growth. Mechanistically, binding of Cpn60.2 to CD43 stimulates
670 macrophages to produce TNF- α , IL-12, and IL-6 to control *M. tuberculosis* infection (**Figure 1**)
671 (Randhawa, Ziltener and Stokes 2008; Torres-Huerta *et al.* 2017). The signaling pathway leading to TNF-
672 α production upon interaction with Cpn60.2 necessitates the Src family kinases, the phospholipase C- γ
673 (PLC- γ), the phosphatidylinositol 3-kinase (PI3K), p38, and the Jun N-terminal protein kinase (JNK), in
674 both BMM and THP-1 cells (**Figure 1**) (Torres-Huerta *et al.* 2017). Furthermore, CD43 is involved in the
675 inflammatory response to *M. tuberculosis* and, through the induction of pro-inflammatory mediators,
676 regulates apoptosis to control intracellular bacterial growth (Randhawa, Ziltener and Stokes 2008).
677 Similarly, the absence of CD43 in *M. tuberculosis*-infected mice (*Spn*^{-/-}) increases the bacterial loads
678 during the acute and chronic phases of infection and the rapid development of granulomas (Randhawa
679 *et al.* 2005). Furthermore, macrophage CD43 is required for optimal induction of TNF- α production by
680 *M. avium* (Fratuzzi *et al.* 2000). This emphasizes the importance of CD43 in promoting a stable
681 interaction of mycobacteria with host cells allowing the host to respond primarily through TNF- α
682 production.

683

684 **Scavenger receptors**

685 Scavenger receptors (SR) are a diverse group of cell surface receptors. They are involved in a
686 variety of processes, including pathogen clearance. SR are mainly found on myeloid cells and are
687 organized into several different classes. Class A receptors, such as MARCO, are mainly expressed on
688 macrophages and bind to ligands *via* their collagen-like domain. Macrophages expressing MARCO
689 receptors secrete pro-inflammatory cytokines in response to TDM by cooperation between MARCO and
690 TLR2/CD14 (**Figure 1**). Indeed, MARCO is used to tether TDM to the macrophage and to activate the
691 TLR2 signaling pathway that also requires CD14 (**Figure 1**) (Bowdish *et al.* 2009). As expected,
692 macrophages from *Marco*^{-/-} mice are defective in the activation of extracellular signal-related kinase 1/2
693 (ERK1/2) and subsequent production of pro-inflammatory cytokines in response to TDM or *M.*

694 *tuberculosis* infection (**Figure 1**) (Bowdish *et al.* 2009). In diabetic mice, the expression level of MARCO
695 is reduced, which restricts *M. tuberculosis* internalization by macrophages and indirectly contributes to
696 a defective sentinel function of alveolar macrophages, promoting susceptibility to TB in diabetic mice
697 (Martinez *et al.* 2016).

698 CD36 is classified as a scavenger B receptor (SR-B) and possesses two TM domains with an
699 extracellular loop. CD36 recognizes mycobacterial ligands such as LprA (Drage *et al.* 2009) or diglycerides
700 (Martin *et al.* 2011) and serves as a co-receptor for TLR2 by enhancing the recognition of specific
701 bacterial-derived diacylglycerides (Jimenez-Dalmaroni *et al.* 2009). In contrast to MARCO, CD36 plays a
702 permissive function to mycobacterial infection and may enhance mycobacterial uptake (Philips, Rubin
703 and Perrimon 2005). CD36 interacts with the surfactant lipid (composed of 90% lipids, particularly
704 phospholipids, and 10% proteins) to mediate uptake by human macrophages and, therefore, *M.*
705 *tuberculosis* exploits this function for its growth (**Figure 2**) (Dodd *et al.* 2016). In addition, treatment of
706 macrophage with ManLAM and its deacylated form promotes TNF- α production and inhibits NO
707 secretion by engaging CD36 (**Figure 2**) (Józefowski *et al.* 2011). *In vivo*, CD36 plays a critical role in cellular
708 events involved in granuloma formation that promote early bacterial expansion and dissemination. In
709 *Cd36*^{-/-} mice, mycobacterial loads are reduced in the liver and spleen and infection is associated with
710 reduced granuloma density and decreased levels of circulating TNF- α (Hawkes *et al.* 2010). However,
711 these observations were countered by another study demonstrating the functional redundancy
712 between SR other PRR, which may cooperate in a coordinated response to support the complete
713 immune control of *M. tuberculosis* infection. Therefore, dual deficiency of SR-A/CD204 and CD36 had a
714 limited effect on mycobacterial uptake by macrophages, TNF response, and long-term control of *M.*
715 *tuberculosis* infection (Court *et al.* 2010).

716

717 **Fc γ receptors**

718 Fc γ receptors (Fc γ R) belong to the immunoglobulin superfamily and are known to induce
719 phagocytosis of opsonized pathogens. This family includes several members, Fc γ RI (CD64), Fc γ RIIA
720 (CD32A), Fc γ RIIB (CD32B), Fc γ RIIIA (CD16a), Fc γ RIIIB (CD16b), which differ in their affinity to antibodies.
721 The role of Fc γ R in mycobacterial infections is not completely elucidated but a few studies showed either
722 a restrictive or a permissive impact on bacilli survival. As a restrictive example, during the chronic phase
723 of TB, PPD-specific IgG1 antibodies (which bind to Fc γ R) are upregulated and contribute significantly to
724 increased pro-inflammatory cytokine secretion by monocytes (Hussain *et al.* 2001). In addition,
725 antibodies opsonized against live *M. tuberculosis* have been shown to induce an elevated intracellular
726 calcium, which promotes maturation and acidification of bacilli-containing phagosomes, reducing the
727 intracellular viability of *M. tuberculosis* (**Figure 1**) (Malik, Denning and Kusner 2000). Therefore, both
728 studies indicate that Fc γ receptor expression provides control of infections caused by pathogenic

729 mycobacteria. In contrast, CD32B engagement attenuates the Th1 response, IL-12 production, APC
730 activation, and increases susceptibility to *M. tuberculosis* infection (**Figure 2**). Upon *M. tuberculosis*
731 infection, CD32B-deficient C57BL/6 mice exhibited enhanced mycobacterial clearance and reduced
732 immunopathology compared with wild-type controls. These outcomes are consistent with increased
733 pulmonary Th1 responses and production of large amount of IL-12 (Maglione *et al.* 2008). The CD32B-
734 induced signaling pathway also interferes with those of Mincle and FcγR and consequently causes a delay
735 in phagosome maturation, thereby promoting mycobacterial survival in host macrophages (Patin *et al.*
736 2017).

737

738 **TREM2 receptor**

739 The TREM2 receptor is a TM protein that possesses an extracellular region (also called
740 ectodomain). The ectodomain of TREM2 can bind to glycoproteins and lipids. The intracellular
741 component of TREM2 does not contain any signaling ability on its own but rather works in tandem with
742 the activator proteins 10 and 12 (DAP10, DAP12) to elicit a downstream signal (**Figure 2**). TREM2 is found
743 in myeloid cells, such as macrophages, monocytes and DC. Mycobacteria use mycolic acids (MA) to
744 control host immunity *via* TREM2. Indeed, macrophages respond to glycosylated MA in a
745 Mincle/FcRγ/CARD9-dependent manner to produce inflammatory cytokines and recruit inducible nitric
746 oxide synthase (iNOS)-positive mycobacterial macrophages to clear the mycobacterial infection (**Figure**
747 **2**) (Iizasa *et al.* 2021). To counteract this effect, macrophages respond to non-glycosylated MA in a
748 TREM2/DAP12-dependent manner to recruit iNOS-negative macrophages (Iizasa *et al.* 2021). Therefore,
749 TREM2-DAP12 signaling counteracts Mincle-FcRγ-CARD9-mediated anti-mycobacterial immunity to
750 evade the immune response.

751

752 **CD14 receptor**

753 CD14, primarily produced by macrophages, helps detect bacteria by binding to various PAMP. In
754 mycobacteria, the LM or LAM lipid anchor and Cpn60.1 bind to CD14 (Yu *et al.* 1998; Lewthwaite *et al.*
755 2001; Ellass *et al.* 2007). Mycobacteria have developed strategies to exploit CD14 in order to evade the
756 host immune system. Among these, *M. tuberculosis*-derived PG and ManLAM expand a subset of CD14⁺
757 DC with a low capacity to produce IL-12p70 (Søndergaard *et al.* 2014). This process blocks the ability of
758 naïve CD4⁺ T cells to efficiently produce IFNγ, abrogates IL-12p70 production by *M. tuberculosis*-
759 challenged DC and disrupts the synergic action between *M. tuberculosis*-infected macrophages, IFN-γ-
760 producing CD4⁺ T cells and IL-12p70-producing DCs (Søndergaard *et al.* 2014). Through binding to PIM₁
761 or PIM₂, mycobacteria inhibit TNF release and host inflammatory responses in a CD14-dependent
762 manner (**Figure 2**) (Court *et al.* 2011). *M. tuberculosis* stimulates also CD14 monocytes to increase the
763 production of two hyaluronan and IL-10, which promote bacillary growth or modulate the immune

764 response (Shams *et al.* 2003; Dhiman *et al.* 2011). However, by acting with other receptors, CD14 plays
765 a restrictive role in the course of infection. Stimulation of TLR2/1/CD14 by the lipoprotein LpqH activates
766 antibacterial autophagy through activation of vitamin D receptor signaling and induction of cathelicidin
767 **(Figure 1)** (Shin *et al.* 2010). Furthermore, MARCO-expressing macrophages secrete pro-inflammatory
768 cytokines in response to TDM through cooperation between MARCO and TLR2/CD14 **(Figure 1)** (Bowdish
769 *et al.* 2009). Other studies suggest that LM from *M. chelonae* or *M. kansasii* induce TNF- α and IL-8
770 secretion through a CD14-TLR2-dependent mechanism (Vignat *et al.* 2003). AraLAM has the ability to
771 induce, in a CD14-dependent manner, monocyte chemotaxis that could be detrimental to mycobacteria
772 *in vivo* by maximizing the recruitment of additional alveolar macrophages or peripheral blood
773 monocytes to the infection site (Bernardo *et al.* 1998). Although a significant role for CD14 in
774 antimycobacterial protection *in vivo* has not been substantiated (Ehlers *et al.* 2001), CD14 contributes
775 to pulmonary inflammation and mortality during murine TB. During chronic infection, *Cd14*-KO mice are
776 protected from lethality due to a reduced inflammatory response (Wieland *et al.* 2008). This conclusion
777 is supported by another study indicating that LM may play a functional role in the immunopathology of
778 TB through CD14-dependent secretion of MMP-9, which is directly involved in tissue destruction in TB
779 patients (Elass *et al.* 2007). Additionally, CD14 facilitates also the internalization of the bacilli by host
780 cells **(Figure 4)**. In THP-1 and CHO cells, a cross-talk between CD14 and CR3 promotes phagocytosis of
781 mycobacteria (Sendide *et al.* 2005). In addition, *M. bovis* strain TMV 401 selectively infects alveolar
782 macrophages subpopulations, particularly in those expressing high levels of CD14 (Khanna *et al.* 1996).
783 CD14 may facilitate also the entry of *M. tuberculosis* into brain macrophages (Peterson *et al.* 1995).

784

785 **CD40 receptor**

786 CD40 is a member of the TNF-receptor superfamily found on antigen-presenting cells, including DC,
787 B cells, and macrophages. In macrophages, the primary signal for activation is IFN γ from Th1-type CD4⁺
788 T cells. The secondary signal is CD40L (CD154) on the Th1 cell, which binds to CD40 on the macrophage
789 cell surface. As a result, the macrophage expresses more CD40 and TNF receptors on its surface, which
790 contributes to the increased level of activation, high production of microbicidal substances, including
791 ROS and NO, and destruction of the ingested microbe. Specific to *M. tuberculosis* infection, mucosal T-
792 helper cells producing IFN γ (Th1) and IL-17 (Th17) are important for protecting against TB. To this end,
793 *M. tuberculosis* alters CD40 expression on DC and restricts Th1 and Th17 responses. As a result, CD40-
794 deficient DC are unable to induce antigen-specific IL-17 responses after infection (Sia *et al.* 2017).
795 Intratracheal instillation of *M. tuberculosis*-infected DC treated with CD40LT (a multimeric CD40 agonist)
796 significantly enhanced antigen-specific Th17 responses in mice (Sia *et al.* 2017). Furthermore, enhanced
797 CD40-CD40L interactions promote better control of lung bacterial loads after aerosol challenge with *M.*
798 *tuberculosis* (Sia *et al.* 2017). Thus, targeting the CD40-CD40L pathway represents a novel strategy to

799 improve adaptive immunity against TB. Another CD40-dependent pathway is also important for
800 combatting *M. tuberculosis* infections, based on the stimulation by CD40 and TLR-4 that induces DC to
801 increase their production of IL-12, IL-6, and TNF- α and to upsurge autophagy (Khan *et al.* 2016). Note
802 that *M. tuberculosis* Hsp70 elicits IL-12 and RANTES production by DC and serves as a ligand for CD40
803 **(Figure 1)** (Wang *et al.* 2001; Lazarevic *et al.* 2003). This stimulation is an effective host-directed therapy
804 against *M. tuberculosis* because it amplifies the pool of memory CD4⁺ T cells as well as CD8⁺ T cells and
805 effectively contributes to reducing the bacterial burden in the lungs **(Figure 1)** (Khan *et al.* 2016).
806 Moreover, CD40 stimulation of DC enhances immune responses to *M. tuberculosis* infection.
807 Importantly, BCG-infected DC stimulated with CD40 show an increased ability to release bioactive IL-12
808 and activate IFN γ -producing T cells *in vitro* (Méndez-Samperio, Ayala-Verdin and Trejo-Echeverria 1999;
809 Demangel *et al.* 2001). Additionally, when C57BL/6 mice are immunized with these DC and challenged
810 with aerosol *M. tuberculosis*, increased levels of IL-12, IL-18, and IFN γ transcripts were found in the
811 draining mediastinal lymph nodes (Demangel *et al.* 2001). As for *M. tuberculosis*, CD40 is also required
812 for optimal protective immunity against *M. avium* (Flórido *et al.* 2004) and *M. bovis* BCG (Méndez-
813 Samperio, Ayala-Verdin and Trejo-Echeverria 1999). Indeed, *Cd40*-KO mice are more susceptible to *M.*
814 *avium* infection due to the generation of a poorer IL-12 and IFN γ response (Flórido *et al.* 2004).
815 Nevertheless, bacilli are capable of countering the CD40-dependent immune response that jeopardizes
816 their survival. For example, MDM infected with *M. avium* subspecies *paratuberculosis* fails to upregulate
817 the expression of iNOS and IL-12 in response to CD40 stimulating pathway (Sommer *et al.* 2009). In
818 addition to CD40, its partner CD40L also helps to induce an antimicrobial response against several
819 species. CD40L and IFN γ have been shown to activate the vitamin D-dependent antimicrobial pathway
820 and to trigger antimicrobial activity, through upregulation of antimicrobial peptides and induction of
821 autophagy, against intracellular *M. tuberculosis*, contributing to human host defense against
822 intracellular infection **(Figure 1)** (Samten *et al.* 2000; Klug-Micu *et al.* 2013). Finally, MDM expressing
823 CD40L inhibit *M. avium* growth by stimulating IL-12 production (Hayashi *et al.* 1999). In conclusion, the
824 CD40-CD40L axis plays an important role in the host immune response against mycobacterial infections.

825

826 **Aldolase**

827 Aldolase catalyzes a reversible reaction that cleaves the aldol, fructose 1,6-bisphosphate, into
828 the triose phosphates dihydroxyacetone phosphate (DHAP) and glyceraldehyde 3-phosphate (G3P). The
829 fructose-bisphosphate aldolase occupies a central position in glycolysis and gluconeogenesis. Beyond its
830 role in central metabolism, the aldolase has been implicated in other functions and is exploited as a
831 receptor by pathogenic mycobacteria. In HEp-2 or A549 epithelial cells, the aldolase, present in the
832 membrane and cytosolic compartment, binds to the *M. avium* superoxide dismutase (SOD) (Reddy and
833 Suleman 2004). This interaction allows *M. avium* to adhere, interact with and multiply inside epithelial

834 cells (**Figure 4**). In addition, the pathway that allows *M. avium* to colonize the gastrointestinal tract of
835 patients infected with human immunodeficiency virus (HIV) has been identified. Studies on mouse
836 intestinal mucus identified fructose-1-6-bisphosphate aldolase B as a host receptor interacting with the
837 SOD and the heparin-binding hemagglutinin (HBHA) (**Figure 4**) (Reddy, Suleman and Hayworth 2004). In
838 conclusion, MAC binds to the intestinal mucus aldolase, plausibly facilitating intestinal colonization of
839 the organism.

840

841 **The extracellular matrix platform**

842 The extracellular matrix (ECM) is a three-dimensional network of macromolecules and minerals that
843 provides structural and biochemical support to surrounding cells. The composition of the ECM varies
844 among multicellular structures; however, cell adhesion, intercellular communication and differentiation
845 are common functions of the ECM. ECM components are produced intracellularly by resident cells and
846 secreted into the ECM by exocytosis. Once secreted, they aggregate to the existing matrix. The ECM is
847 composed of an interlocking meshwork of fibrous proteins and glycosaminoglycans (GAG) such as
848 proteoglycans, heparan sulfate, hyaluronic acid, collagen, fibronectin, and laminin. The ability of
849 pathogenic microorganisms to adhere to host cells and avoid removal by the host immune system is the
850 initial and the most decisive step leading to infection. Mycobacteria have developed different means to
851 attach to various host surface structures. One important strategy consists of adhering to the ECM
852 components that are abundant in connective tissue and basement membranes. Mycobacteria express
853 variable outer membrane adhesins to attach to these components and understanding the molecular
854 mechanisms of mycobacterial adhesion is a prerequisite for inhibiting these interactions using "anti-
855 ligand" strategies to prevent/reduce host colonization.

856

857 **Integrins**

858 Integrins are TM receptors that facilitate cell-cell and cell-ECM interactions. When bound to a
859 ligand, integrins activate signal transduction pathways that transmit various cellular signals. The roles of
860 integrins in mycobacterial infections is not yet fully elucidated but two functions are known to benefit
861 pathogenic mycobacteria. On the one hand, the peptidyl prolyl isomerase A (PPIA) interacts with the
862 integrin $\alpha 5 \beta 1$, aids in *M. tuberculosis* survival and disease progression by exploiting host-associated
863 factors, such as upregulation of multiple host matrix metalloproteinases (**Figure 2**) (Dubey *et al.* 2021).
864 While PPIA deletion compromises granuloma-like formation and promotes host cell death through
865 ferroptosis, its overexpression enhances the bacilli burden and exacerbates pulmonary pathology in
866 mice (Dubey *et al.* 2021). Host integrins also facilitate the attachment of *M. avium* subsp.
867 *paratuberculosis* to intestinal epithelial M cells. Internalization is primarily mediated by the formation
868 of a fibronectin (FN) bridge formed between FAP-P (fibronectin attachment protein homologue) of *M.*

869 *avium* subsp. *paratuberculosis* and integrins on M cells (**Figure 4**) (Secott, Lin and Wu 2004). Thus, host
870 integrins facilitate host-pathogen interactions and disease progression.

871

872 **Collagens**

873 Collagens are the most abundant proteins in the ECM, present as fibrillar proteins and providing
874 structural support to resident cells. Using a collagen-sepharose affinity chromatography approach, the
875 *M. bovis* BCG collagen-binding protein was characterized as a laminin-binding histone-like protein
876 (LBP/Hlp), a highly conserved protein associated with the mycobacterial cell wall (**Figure 4**) (Dias *et al.*
877 2012). Moreover, the C-terminal domain of *M. leprae* LBP/Hlp was found to bind to collagen I (Dias *et al.*
878 2012). Exogenous collagen I supplementation cross-linked *M. bovis* BCG to improve the interaction
879 with pneumocytes and macrophages (Dias *et al.* 2012).

880

881 **Plasmin(ogen)**

882 Plasmin is a serine protease that acts to dissolve fibrin blood clots. In addition to fibrinolysis,
883 plasmin cleaves various proteins of the ECM, including fibronectin and laminin. The ability of a pathogen
884 to interact with and infect host tissues directly determines the spread of infection. Adherence due to
885 host-pathogen interactions and depth traversal within infected organs are involved in the process. *M.*
886 *tuberculosis* surface-associated and secreted glyceraldehyde-3-phosphate dehydrogenase (GAPDH) not
887 only recruits and serves as a dual receptor for both plasminogen and plasmin, but it also gives bacilli the
888 ability to break down physical tissue barriers during systemic bacterial dissemination (**Figure 4**) (Gani *et al.*
889 2021). Soluble GAPDH can re-associate with bacilli to promote plasmin(ogen) recruitment and thus
890 improves bacterial adhesion and passage through lung epithelial cells, whereas (Gani *et al.* 2021).
891 GAPDH association with ECM proteins, together with its ability to recruit plasmin(ogen), may confer on
892 the bacilli the capacity for directed proteolytic activity, vital for tissue infection (Gani *et al.* 2021).

893

894 **Hyaluronic acid**

895 Hyaluronic acid (HA) is a polysaccharide consisting of alternating residues of D-glucuronic acid
896 and N-acetylglucosamine. HA present in the extracellular space endows the tissue with stability to resist
897 compression by providing an antagonistic turgor force by absorbing large amounts of water. The *M.*
898 *tuberculosis* protease Rv3194c (residues 91-110) functions as an adhesin by binding to HA present on
899 the surface of pneumocytes (**Figure 4**) (Zhao, Lin and Xu 2020). *M. smegmatis* overexpressing Rv3194c
900 leads to persistent infections and pulmonary lesions in mice (Zhao, Lin and Xu 2020). Subsequent
901 intratracheal treatment with the Rv3194c peptide 91-110 to infected mice showed a growth suppression
902 of *M. smegmatis* and reduced lung pathology, attributable to the unavailable HA binding sites once

903 saturated with the peptide 91-110 (Zhao, Lin and Xu 2020). As Rv3194c functions as a HA-binding
904 adhesin, the peptide 91-110 may offer possibilities to reduce or prevent mycobacterial infections.

905

906 **Syndecans**

907 Syndecans are single TM proteins carrying three to five chains of heparan sulfate and
908 chondroitin sulfate, *i.e.* they are proteoglycans, which allow interactions with a variety of ligands, such
909 as fibronectin. The mechanisms of attachment and internalization of *M. tuberculosis* to non-professional
910 phagocytes, like epithelial cells, remain incompletely understood. Syndecan 4 (Sdc4) has been identified
911 as a mycobacterial attachment receptor on alveolar epithelial cells interacting with the mycobacterial
912 HBHA (Zimmermann *et al.* 2016) (**Figure 4**). Sdc4 knockdown in alveolar epithelial cells or blocking with
913 an anti-Sdc4 antibody showed reduced mycobacterial attachment and internalization. *In vivo*, Sdc1/Sdc4
914 double-KO mice appeared more resistant to lung colonization by *M. tuberculosis* (Zimmermann *et al.*
915 2016), thus unraveling an important role for distinct Sdcs in promoting mycobacterial entry into alveolar
916 epithelial cells.

917

918 **Laminin**

919 Laminin, an extracellular matrix protein, is thought to play a role in the attachment, migration
920 and organization of cells in tissues during embryonic development by interacting with other components
921 of the extracellular matrix. The alpha, beta and gamma subunits are linked together by disulfide bonds
922 to form a cross-shaped molecule. The laminin-2 isoform on the Schwann cell-axon unit serves as the
923 initial neural receptor for *M. leprae* by interacting with ML-LBP21/Hlp (*M. leprae* laminin-binding protein
924 21-kDa/21-kDa histone-like protein) (Shimoji *et al.* 1999; de Melo Marques *et al.* 2000) (**Figure 4**). The
925 role of ML-LBP21 in Schwann cell adhesion and internalization was investigated using fluorescent
926 polystyrene beads coated with rML-LBP21. Although beads coated with rML-LBP21 alone specifically
927 adhered to and were ingested by primary Schwann cells, these processes were significantly enhanced
928 when the rML-LBP21-beads were pre-incubated with exogenous $\alpha 2$ laminins (most likely exogenous $\alpha 2$ -
929 laminins bridge rML-LBP21 to unoccupied laminin receptors on Schwann cells and subsequently
930 mediates the ingestion) (Shimoji *et al.* 1999). *M. smegmatis* produces a paralog, designated MS-LBP,
931 which is attached to the bacterial surface and, interacting with host laminin, is responsible for laminin-
932 mediated mycobacterial adhesion to human pneumocytes and macrophages (Pethe *et al.* 2001).
933 Deletion of the *hlp* gene fails to affect the capacity of mycobacteria to bind to neuronal cells, suggesting
934 that alternative adhesins and/or pathways are exploited by mycobacteria for adhesion to Schwann cells
935 (de Melo Marques *et al.* 2000). Testing malate synthase's (MS) (catalyzes the condensation of acetyl
936 coenzyme A and glyoxylate to form malate) involvement in bacilli entry into nerve cells, which uses this
937 enzyme to bind to host laminin and to interact with lung epithelial cells may help elucidate this process

938 (Kinhikar *et al.* 2006) **(Figure 4)**. Computational models suggest putative interactions between as yet
939 uncharacterized *M. tuberculosis* adhesins and laminin (Kumar *et al.* 2013b). Together, these studies
940 underscore the multiplicity of mycobacterial adhesins to interact with a single receptor. Overall, ML-
941 LBP21 functions as a critical surface adhesin that facilitates uptake of *M. leprae* into Schwann cells and
942 as a contributing factor to the pathogenesis of *M. leprae*-mediated nerve damage.

943

944 **Heparan sulfate**

945 Heparan sulfate (HS) is a linear polysaccharide in which two or three chains are attached in close
946 proximity to the cell surface or to ECM proteins. HS binds to a variety of ligands, regulates a wide array
947 of biological functions and serves as a cellular receptor for mycobacteria. Importantly, ML-LBP21/Hlp,
948 besides laminin, binds also to heparin and HS (Soares de Lima *et al.* 2005). The interaction between ML-
949 LBP21/Hlp with heparin is mainly driven by the C-terminal domain of the protein, also involved in
950 mediating bacterial binding to human Schwann cells (Soares de Lima *et al.* 2005) **(Figure 4)**. These
951 findings reinforce the participation of ML-LBP21/Hlp in mycobacterial infection and define its highly
952 positively charged C-terminal region as the major adhesive domain of this protein. Apart from LBP, the
953 Lys/Pro-rich C-terminal region of HBHA also binds to sulfated carbohydrates and functions as an adhesin
954 for epithelial cells (Menozzi *et al.* 1998; Pethe *et al.* 2000) **(Figure 4)**. Consequently, binding of HS chains
955 to HBHA promotes adhesion with epithelial cells and may be necessary for extrapulmonary
956 dissemination of *M. tuberculosis*. While HBHA induces a reorganization of the actin filament network in
957 confluent endothelial cells, it does not affect their tight junctions (Menozzi *et al.* 2006). In addition, the
958 transcellular migration of endocytic vacuoles containing HBHA-coated particles suggests that HBHA
959 induces epithelial transcytosis, representing a macrophage-independent mechanism of extrapulmonary
960 dissemination leading to systemic infection (Menozzi *et al.* 2006). Both LBP and HBHA are also
961 considered as major adhesins for the attachment of *M. leprae* to epithelial cells (Silva *et al.* 2013).

962

963 **Fibronectin**

964 Fibronectin (FN) is a high molecular weight glycoprotein of the ECM that binds to integrins. FN
965 also binds to other ECM proteins such as collagen, fibrin and HS proteoglycans, like syndecans. FN is
966 targeted by a large set of bacterial adhesins. A number of bacterial FN-binding proteins have been
967 reported as FN interactants playing diverse roles in bacterial colonization, virulence and bacterial-host
968 interactions. Studies have shown that mycobacteria attach to various FN-producing cells by engaging
969 various adhesins (Ratliff *et al.* 1993). The p55/FAP protein of *M. bovis* BCG and *Mycobacterium vaccae*
970 binds to FN and inhibits the attachment of the bacilli to host cells **(Figure 4)** (Ratliff *et al.* 1993).
971 Moreover, the *M. leprae* fibronectin attachment protein (FAP) adhesin binds to FN and significantly
972 enhances the attachment and ingestion of bacilli by epithelial and Schwann cells **(Figure 4)** (Schorey *et*

973 *al.* 1995), representing an important step in the initiation of *M. leprae* infection *in vivo*. The RWFV
974 sequence is required for the FN binding function of mycobacterial FAP proteins (Zhao *et al.* 1999).
975 Furthermore, MAC and *M. smegmatis* adhere to FN-containing epithelial cells *via* FAP (Middleton *et al.*
976 2000; Secott, Lin and Wu 2002). The other characterized ligand interacting with FN is the Ala/Pro rich
977 protein (Apa), a secreted antigen, which binds to the cell-binding domain of FN (**Figure 4**) (Kuo *et al.*
978 2019). In addition, the secreted Ag85 complex favors the attachment of mycobacteria in the lung or
979 during hematogenous spread by acting as a stress-sensitive adhesin (**Figure 4**) (Viljoen, Alsteens and
980 Dufrêne 2020). The C-terminal domain of the glycine-rich PE-PGRS proteins such as PE-PGRS81 of *M.*
981 *tuberculosis* exhibit FN binding properties (**Figure 4**) (Espitia *et al.* 1999). In this context, the cell wall-
982 localized MS of *M. tuberculosis* has adapted to function as an adhesin by binding to FN, enhancing
983 bacterial attachment to lung epithelial cells (**Figure 4**) (Kinhikar *et al.* 2006). Evidence of *in vivo*
984 expression of *M. tuberculosis* MS during active infection in humans show that a housekeeping enzyme
985 of *M. tuberculosis* contributes to its arsenal of virulence factors (Kinhikar *et al.* 2006). Moreover,
986 computational strategy using different algorithms has predicted putative bindings between human FN
987 with various *M. tuberculosis* adhesins (Rv2599, N-acetylmuramoyl-L-alanine amidase, L,D-
988 transpeptidase) (Kumar *et al.* 2013b). This approach, through further experimental investigations, could
989 expand the number of known *M. tuberculosis* adhesins. Lastly, binding and ingestion of *M. avium* subsp.
990 *paratuberculosis* (MAP) by host cells is dependent on both FN and the bacterial elongation factor Tu (EF-
991 Tu) (**Figure 4**) (Viale *et al.* 2014). This supports the view that human FN plays a primary role in the
992 internalization of several mycobacterial species and contributes to the infection process.

993

994 **DRP-2 and GAPDH**

995 MAP is the causative agent of Johne's disease, a chronic and fatal enteritis that affects ruminant
996 populations. Oral transmission of MAP occurs when young animals consume bacteria from infected
997 dams' colostrum and milk. Raw milk exposure has a dramatic effect on MAP, resulting in a more invasive
998 and virulent phenotype. Post-exposure, expression of the *MAP1203* gene is up-regulated more than 28-
999 fold and plays a role in increased binding and uptake by bovine MDBK epithelial cells during the early
1000 phase of infection (**Figure 4**) (Everman *et al.* 2018). Furthermore, MAP1203 is a MAP surface-exposed
1001 protein that interacts with the host proteins dihydropyrimidinase-related protein 2 (DRP-2) and GAPDH,
1002 both of which are found on the epithelial cell membrane (**Figure 4**) and are involved in cytoskeletal
1003 remodeling (Everman *et al.* 2018). Hence, MAP1203 plays a role in the initiation of MAP infection of
1004 bovine epithelial cells.

1005

1006 **MECHANISMS BEYOND PRR and ECM**

1007 Despite the identification of a large set of receptors interacting with bacterial surface glycolipids,
1008 a paucity of knowledge still exists around the host partners of certain mycobacterial ligands. A few
1009 bacterial adhesins play an important role in the internalization and pathogenesis of mycobacteria but
1010 the molecular mechanisms underlying these processes remain unknown. *M. leprae* is frequently
1011 encountered inside human microvascular endothelial cells (HMVEC) surrounding Schwann cells at the
1012 site of peripheral nerve damage in patients with lepromatous leprosy. Based on this observation, it was
1013 thought that *M. leprae* uses the nasal mucosa as an entry pathway and that HMVEC serves as an
1014 important reservoir for the bacteria before they interact with Schwann cells. An elegant study
1015 demonstrated that the first 72 amino acids of the Mce1A protein play an important role in *M. leprae*
1016 uptake by HMVEC and that antibodies against this region prevent the entry of *M. leprae* into HMVEC
1017 (Idris *et al.* 2019). In *M. tuberculosis* and *M. bovis* BCG, cell wall-associated PE/PE-PGRS proteins play an
1018 important role in establishing macrophage infectivity (Brennan *et al.* 2001). As a result, PE-PGRS proteins
1019 influence mycobacterial interactions with macrophages. Finally, the *M. tuberculosis* protein product
1020 encoded by the *Rv3312A* gene has been shown to be an adhesin/invasin of epithelial cells and
1021 macrophages, as well as an entry factor for *M. tuberculosis* (Ramsugit and Pillay 2014; Ramsugit, Pillay
1022 and Pillay 2016). *M. tuberculosis* strains lacking the *Rv3312A* gene showed a significant reduction in their
1023 ability to adhere to and interact with A549 pulmonary epithelial cells and THP-1 macrophages (Ramsugit
1024 and Pillay 2014; Ramsugit, Pillay and Pillay 2016).

1025 In a novel way, a new class of receptor named AhR has been identified and detects distinct
1026 bacterial ligands. The aryl hydrocarbon receptor (AhR) is a transcription factor that senses
1027 environmental toxins, among other substances, thereby modulating immune cell responses (Moura-
1028 Alves *et al.* 2014). Indeed, AhR recognizes pigmented bacterial virulence factors as ligands, namely
1029 naphthoquinone phthiocol from *M. tuberculosis* (Moura-Alves *et al.* 2014). After ligand binding, AhR
1030 activation leads to virulence factor degradation and regulated production of cytokines and
1031 chemokines. The importance of the AhR in host defense is underlined by the increased susceptibility
1032 of AhR-deficient mice to *M. tuberculosis* (Moura-Alves *et al.* 2014). Thus, the AhR senses bacterial
1033 pigments and controls antibacterial responses.

1034 Interestingly, host factors also facilitate phagocytosis of mycobacteria. In this context,
1035 sphingolipid biosynthesis inhibition has experimentally been shown to significantly reduce *M.*
1036 *tuberculosis* and *M. marinum* uptake by a panel of macrophages and DC (Niekamp *et al.* 2021).
1037 Microscopic analysis revealed that sphingolipid-deficient macrophages can recognize bacilli and
1038 assemble actin at the site of contact, but they are unable to remodel the actin cytoskeleton, which is
1039 required for complete internalization of the bacilli (**Figure 5**). Furthermore, sphingolipid-deficient
1040 macrophages failed to exclude the CD45 tyrosine phosphatase from the receptor-pathogen contact site
1041 or nascent phagosome, a critical step in phagocytosis progression (Niekamp *et al.* 2021). At the host-

1042 pathogen interaction sites, this impairment is accompanied by poor Rho-GTPase activation and a
1043 substantial reduction in phosphoinositide turnover (Niekamp *et al.* 2021). These observations highlight
1044 the importance of sphingolipid production in *M. tuberculosis* phagocytic uptake and identifies a possible
1045 target for future antimycobacterial treatments.

1046 Finally, very little is known about the dissemination of *M. tuberculosis* from the lungs, but it
1047 seems that specific adhesins are also involved in this biological process that leads to the infection of
1048 other organs in humans. Indeed, the dissemination of *M. tuberculosis* from the primary site of infection
1049 is critical to TB pathogenesis. While bacterial trafficking to regional lymph nodes is required for the
1050 development of a protective T cell-mediated immune response, entry into the circulatory system
1051 presents the risk of extrapulmonary dissemination, yielding some of the most lethal clinical
1052 consequences of TB. While the mechanism of exiting the lungs across the alveolar epithelium has yet to
1053 be fully characterized, some features have been identified (**Figure 6**). At the epithelial layer, *M.*
1054 *tuberculosis*' HBHA facilitates binding to sulphated glycoconjugates on epithelial cells. When HBHA is
1055 blocked, a marked decrease in dissemination from the lungs (**Figure 6**) to the spleen has been observed
1056 (Krishnan, Robertson and Thwaites 2010). Following attachment, the early secretory antigenic target 6-
1057 kDa (ESAT-6) and culture filtrate protein 10-kDa (CFP-10), encoded by the RD1 locus, have been linked
1058 to cell lysis and to internalization into the alveolar epithelium (**Figure 6**) (Krishnan, Robertson and
1059 Thwaites 2010). Work in embryonic zebrafish suggests that ESAT-6 may additionally contribute to early
1060 spreading of the bacteria by stimulating the trafficking of infected macrophages within granulomas,
1061 indicating that *M. tuberculosis* has evolved granuloma-dependent mechanisms for macrophage
1062 recruitment, infection, and subsequent bacterial dissemination (Krishnan, Robertson and Thwaites
1063 2010). In the absence of both ESAT-6 and HBHA, a notable reduction of bacterial migration across the
1064 alveolar barrier has been seen (Ryndak, Chandra and Laal 2016). Fully characterizing the behavior of
1065 these proteins and their interactions with host cells offers a potential for novel therapeutic targets.

1066

1067 **CONCLUDING REMARKS AND PERSPECTIVES**

1068 Adhesion molecules, found on the surface of most bacteria, facilitate the interaction with host cells, aid
1069 in colonization and uptake, and trigger the host's immunological response during infection. The precise
1070 interactions observed between pathogenic mycobacterial surface molecules and host receptors affirms
1071 the favorable and exploitable niche of the intracellular environment. The purpose of a multi-entry
1072 strategy may lie in the hijacking of macrophages and other host cells to cross the pulmonary and
1073 epithelial barriers. This is performed by macrophages that directly ingest inhaled mycobacteria or by
1074 monocytes, macrophages, and/or neutrophils that migrate to the initial infection site in response to
1075 chemokines secreted by infected macrophages. Bacterial entrance in macrophages alters transcriptional
1076 gene expression, permitting the stimulation genes that inadvertently support bacterial survival, growth,

1077 and intercellular spread. This is mirrored in the increased cytotoxicity to respiratory epithelial cells
1078 caused by *M. tuberculosis* emerged from intracellular environments *versus* those grown in cell-free
1079 media, suggesting that processes in the intracellular environment offer an advantage to aid in the
1080 breaching of epithelial barriers and spreading to distant sites (McDonough and Kress 1995).
1081 Furthermore, *M. avium* and *M. intracellulare* may spend time in macrophages to initiate specific
1082 virulence mechanisms (Bermudez, Parker and Goodman 1997; Cirillo *et al.* 1997). Additional work is still
1083 needed to fully understand the potential impact of the internalization pathway on intracellular
1084 trafficking of phagosomes and whether host cell responses differ according to the receptors engaged
1085 and mycobacterial species involved. Currently, mycobacterial interactions with both opsonic and non-
1086 opsonic receptors on host cells are complicated and remain poorly understood. Receptor studies are
1087 often performed in artificial *in vitro* systems, while more biologically representative *in vivo* results may
1088 only be cautiously interpreted due to their high variability across different experimental conditions.
1089 Despite best practices, inconsistencies in *Mycobacterium*-receptor function studies could be influenced
1090 by several technical conditions. Bacterial species, genetic diversity of strains of the *M. tuberculosis*
1091 complex (lineage 2 vs lineage 4 vs Lineage 1) (Brites and Gagneux 2017; Gisch *et al.* 2022; Zha *et al.*
1092 2022), population, host cell phenotype, infection site, individual culture conditions (the use of distinct
1093 detergents when culturing mycobacterial strains strongly affects the mycobacterial surface and thus
1094 adhesion of the bacteria and the interaction with the host) (Pietersen *et al.* 2020; Lim *et al.* 2022), and
1095 cell preparation are all considerations when controlling for features of the host-pathogen interactions.
1096 For this reason, approaching near-natural experimental conditions will yield the most physiologically-
1097 meaningful results. However, this is made more complicated by the nature of mycobacterial
1098 internalization by host cells *via* multiple receptor-mediated mechanisms. Experimentally, many of the
1099 receptors do not appear to be independently essential, suggesting compensatory alternatives.
1100 Furthermore, the synergism between the various receptor families and the impact on mycobacteria-
1101 caused diseases requires additional attention. The abundance of mycobacterial surface, ligands also
1102 contributes to this complexity, adopting several downstream permutations by binding receptors on
1103 diverse cell types, engaging multiple receptors in tandem or conversely blocking sufficient receptor
1104 clustering for cellular cross-talk and signaling. Currently well-established in the literature is that the type
1105 of interaction correlates to infection outcome. TLR signaling, for instance, promotes inflammatory and
1106 protective pathways, whereas C-type lectin signaling induces anti-inflammatory non-protective
1107 pathways. The LAM cap structure spans both ends of immunomodulation through PILAM as a pro-
1108 inflammatory molecule that stimulates the production of TNF- α and IL-12 and ManLAM as an anti-
1109 inflammatory molecule that stimulates the production of IL-10 while blocking the production of IL-12
1110 and TNF- α . These immunomodulatory processes will be influenced by a number of factors, including the
1111 expression and availability of certain receptors and their downstream responses.

1112 Better understanding the initial features of host-pathogen interactions *via* adhesion and
1113 internalization could reveal future targets for prophylactic strategies in preventing mycobacterial
1114 internalization. Current efforts are focused on unpacking the immunogenicity of surface-localized
1115 adhesins for application in vaccine development, as previously discussed for HBHA (Temmerman *et al.*
1116 2004). The synthesis of chemical scaffolds or peptides that mimic adhesin-receptor binding sites are also
1117 being pursued as alternative therapies to limit infection. Some success has been observed with anti-
1118 adhesion therapies against pathogenic mycobacteria and may prove to show improved outcomes when
1119 administered alone or with antibiotics (Ofek, Hasty and Sharon 2003). Finally, as additional
1120 mycobacterial adhesins continue to be identified, it is now more critical than ever to employ cutting-
1121 edge techniques such as super-resolution imaging or atomic force microscopy to clarify the intricacies
1122 of their functionality (Kreve and Reis 2021; Tabusi *et al.* 2021).

1123

1124 **SUPPLEMENTARY DATA**

1125 Supplementary data are available at FEMSRE online.

1126

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1135

1136 **CONFLICT OF INTEREST**

1137 None declared.

1138

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Figure 1. Host receptors and signaling networks limiting mycobacterial survival in phagocytes. Toll-like receptors (TLR), CD14, C-type lectin receptors (CLR), NOD-like receptors (NLR), cGAS, CD43, MARCO, FcγR, and CD40-CD40L are expressed on the cell surface, in endosomes, or in the cytosol of different types of immune cells. Their activation through ligation to mycobacterial ligands causes cytokine gene expression and autophagy, production of antibacterial peptides and redox molecules (ROS and NO), activation of immune cells, and the induction of phagolysosomal fusion. The depicted pathways are important in limiting intracellular survival of mycobacteria. FADD: FAS-associated death domain protein; IRAK: Interleukin-1 receptor-associated kinases; TRAF6: TNF Receptor Associated Factor 6; NF-κB: Nuclear factor kappa B; Src: Proto-oncogene tyrosine-protein kinase; *PLC-γ*: Phospholipase C gamma; AMPK: AMP-activated protein kinase; MAPK: mitogen-activated protein kinase; CYP27b1: cytochrome P450 25-hydroxyvitamin D₃-1α-hydroxylase; 1,25D₃: 1,25-Dihydroxyvitamin D₃; RXR: Retinoid X Receptor; VDR: vitamin D receptor; DEFβ4: Defensin Beta 4; TIRAP: TIR Domain Containing Adaptor Protein; MYD88: Myeloid differentiation primary response 88; NO: nitric oxide; TRIF: TIR-domain-containing adapter-inducing interferon-β; TBK1: TANK Binding Kinase 1; IKKε: IκappaB kinase epsilon; IRF3: Interferon regulatory factor 3; ITAM: immunoreceptor tyrosine-based activation motif; SYK: spleen tyrosine kinase; PKCδ: Protein kinase C δ; CARD9: Caspase recruitment domain-containing protein 9; MALT1: Mucosa-associated lymphoid tissue lymphoma translocation protein 1; Bcl10: B-cell lymphoma/leukemia 10; ROS: Reactive oxygen species; ATG16L1: Autophagy Related 16 Like 1; IL-1β: interleukin-1β; CARD: Caspase-associated recruitment domains; NOD: nucleotide-binding and oligomerization domain; LRR: leucine-rich repeat; RIP2: Receptor Interacting Protein-2; TAK1: transforming growth factor-activated kinase 1; TAB2: TAK1-binding protein 2; TAB3: TAK1-binding protein 3; cGAS: cyclic GMP-AMP Synthase; ATP: adenosine triphosphate; GTP: Guanosine triphosphate; AMP: Adenosine monophosphate; GMP: Guanosine monophosphate; STING: Stimulator of interferon genes; ER: endoplasmic reticulum; RAF: rapidly accelerated fibrosarcoma kinases; MEK: Mitogen-activated protein kinase kinase; p38: mitogen-activated protein kinase; JNK: c-Jun NH₂-terminal kinase; AP-1: Activator protein 1; ERK: extracellular signal-regulated kinase.

Figure 2. Mycobacteria are recognized by receptors that are bacterial infection-friendly. Several kinds of receptors (TLR2, TLR4, DC-SIGN, MR, Galectin-9, CD36, CD32B, TREM2, CD14, and integrins) activate various pathways that increase mycobacteria intracellular survival by interacting with the bacterial adhesins depicted in panels A and B after infection. These pathways are involved in the generation of IL-10 and metalloproteinases, as well as the inhibition of specific cytokine responses, autophagy, oxidative stress, and immune cell activation. Furthermore, coronin-1a is recruited to the mycobacterial phagosome, causing calcium flux to be induced and calcineurin to be activated, preventing

phagosome-lysosome fusion. PI3K: Phosphoinositide 3-kinase; Akt/PKB: Protein kinase B; mTORC1: mTOR Complex 1; ULK1: unc-51-like kinase 1; OXPHOS: oxidative phosphorylation; Ras: Rat sarcoma virus; PAK: p21-activated kinase; DAG: diacylglycerol; IP₃: 1,4,5-trisphosphate; Th1: T helper cell type 1; DAP12: DNAX-activating protein of 12 kDa; CARD9: caspase recruitment domain family member 9.

Figure 3. Internalization of mycobacteria by opsonins. Opsonization and complement activation by C-type lectins. Soluble C-type lectins and other opsonins, such as SAA1, can interact directly with pathogens to promote opsonization of the microbe, which in turn will be phagocytosed. In addition, some C-type lectins can activate complement, leading to its deposition on the microbial surface and complement receptor-mediated phagocytosis (e.g., MBL-associated MASPs are activated upon binding with pathogens, which in turn cleave complement components and activate the complement system). To note, unlike SP-A, SP-D clumps bacteria and prevents them from being internalized. C4b2a/C3 convertase catalyzes the cleavage of C3 into C3a and C3b; C3a: is one of the proteins formed by the cleavage of complement component 3; C3b: is the larger of two elements formed by the cleavage of complement component 3; MASP: Mannan-binding lectin serine protease.

Figure 4. Mycobacteria attach to different cell types via multiple receptors and the extracellular matrix. An illustration of mycobacteria adhesins (surface proteins or wall glycolipids) that interact with specific receptors (CR3, LOX-1, CD14, Aldolase, GAPDH, DRP-2, heparan sulfate or syndecan receptor 4) or extracellular matrix components (collagen, plasmin, GAGs, laminin, fibronectin) to facilitate attachment prior to internalization. Importantly, fibronectin connects host integrins with mycobacterial FAP. Plasmin and plasminogen, which are exploited by bacterial GAPDH, promote attachment but also tissue invasion, a process related to their ability to digest tissue barriers, which can obstruct the progression of bacterial dissemination.

Figure 5. Host sphingolipid is central to internalization of the bacilli. F-actin remodeling during phagocytosis is depicted schematically. PRR clustering at the pathogen interaction site produces second messengers that promote local actin polymerization. Actin is actively polymerized to extend the phagosomal membrane while being remodeled at the phagocytic cup's base. Further actin polymerization and contractile activity result in membrane apposition and, eventually, phagosome formation. The absence of the sphingolipid does not interfere with the bacterium's recognition of the host cell but does affect the steps that follow, which are critical in surrounding the pathogen with the host membranes that will later give rise to the phagosomal membrane once the bacilli is completely internalized. CD45: receptor-linked protein tyrosine phosphatase.

Figure 6. Mycobacterial components involved in intra- and extrapulmonary dissemination. The HBHA invasin contributes to the dissemination of mycobacteria from the lung to other organs. In contrast, ESAT-6 and CFP-10 facilitate the spread of bacilli within the lung by facilitating the passage of bacteria from alveoli to lung macrophages and by promoting the infection of phagocytes at the level of lung granulomas. Migration of activated macrophages can propagate bacteria to other tissues such as the liver and lymph nodes.

Figure 1

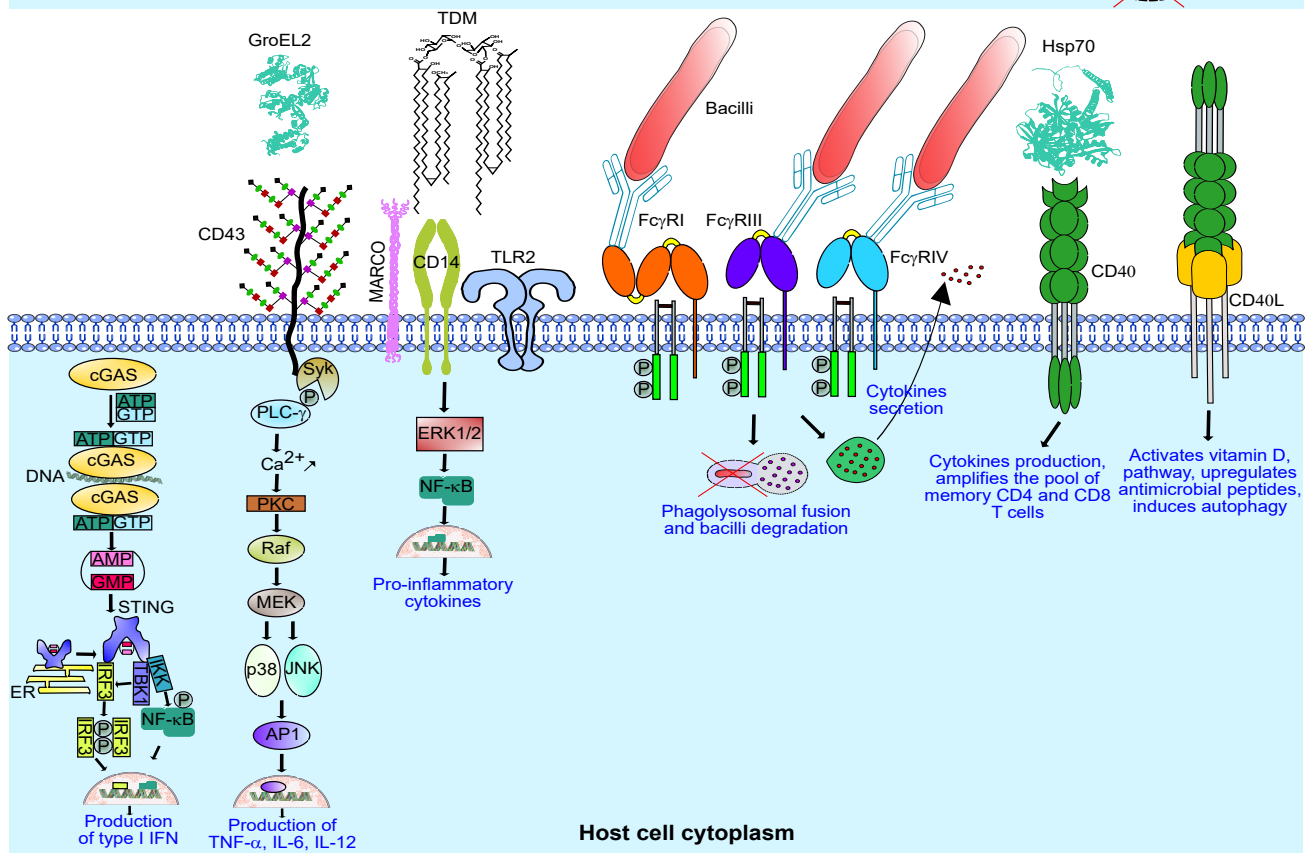
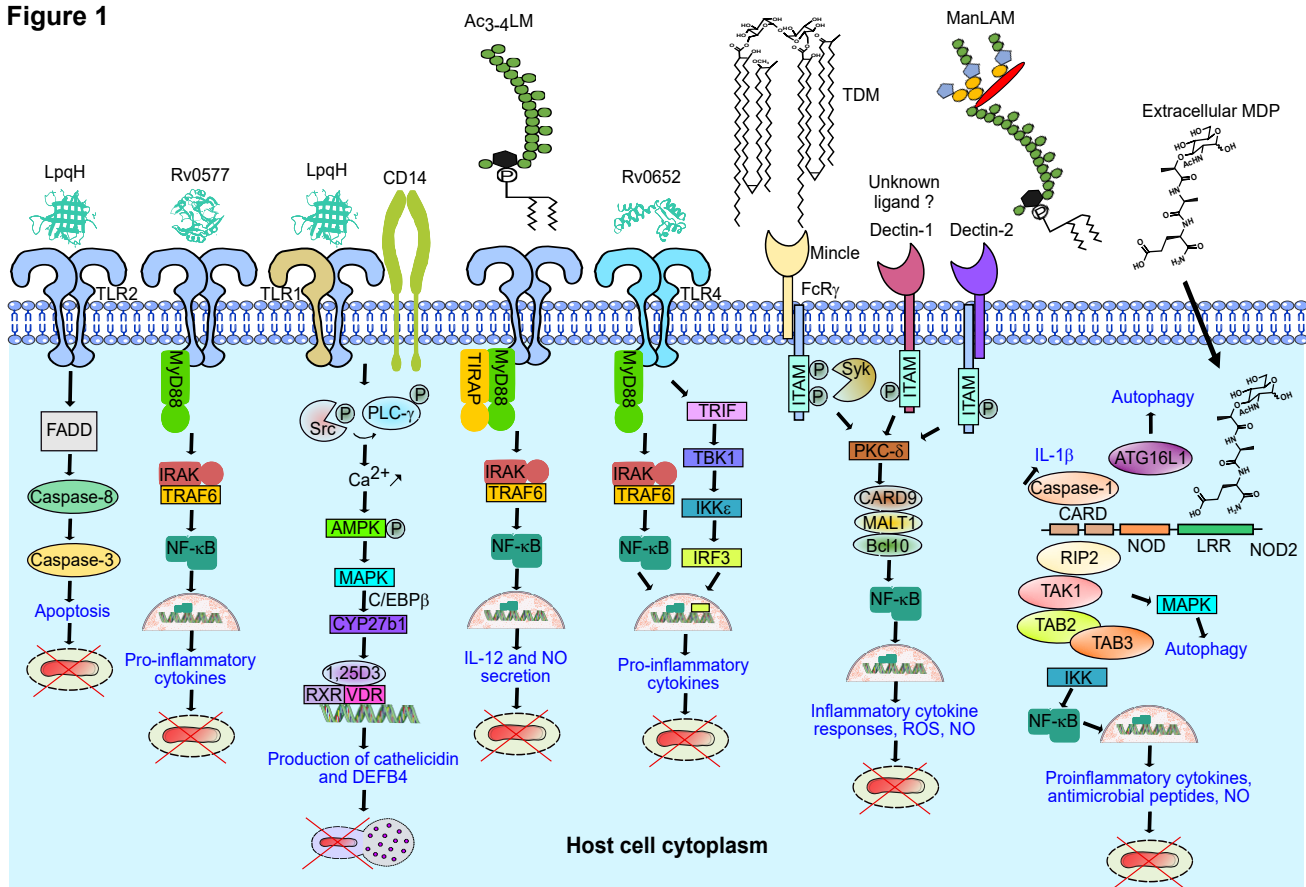


Figure 2

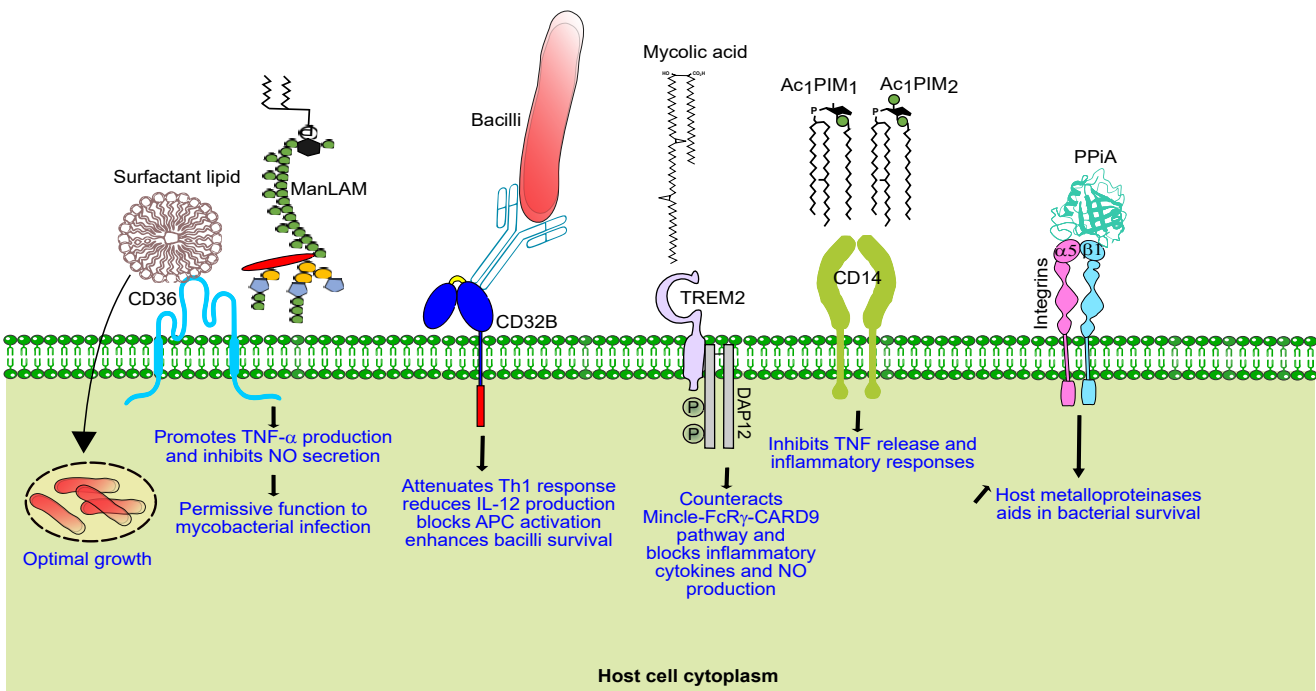
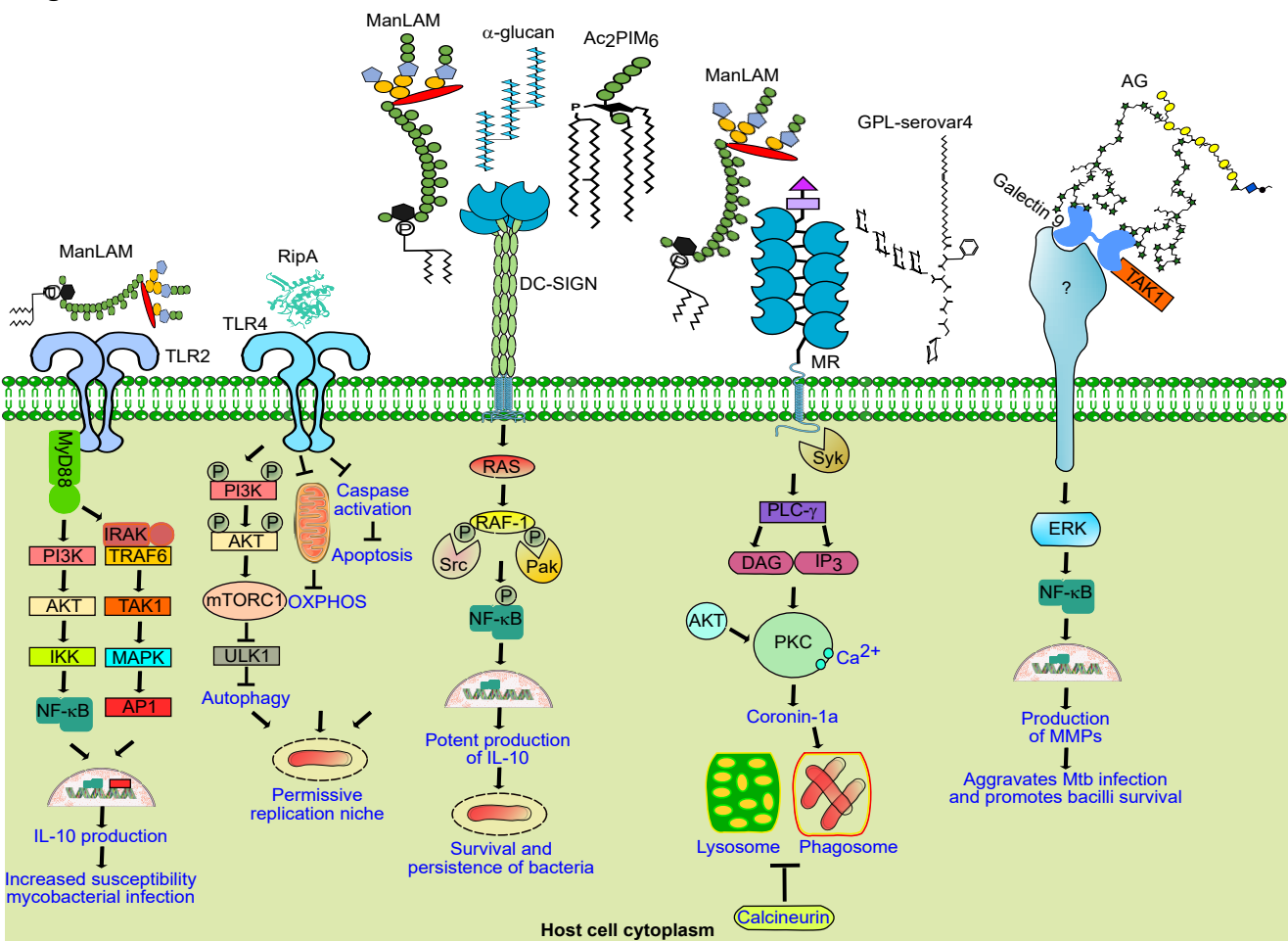


Figure 3

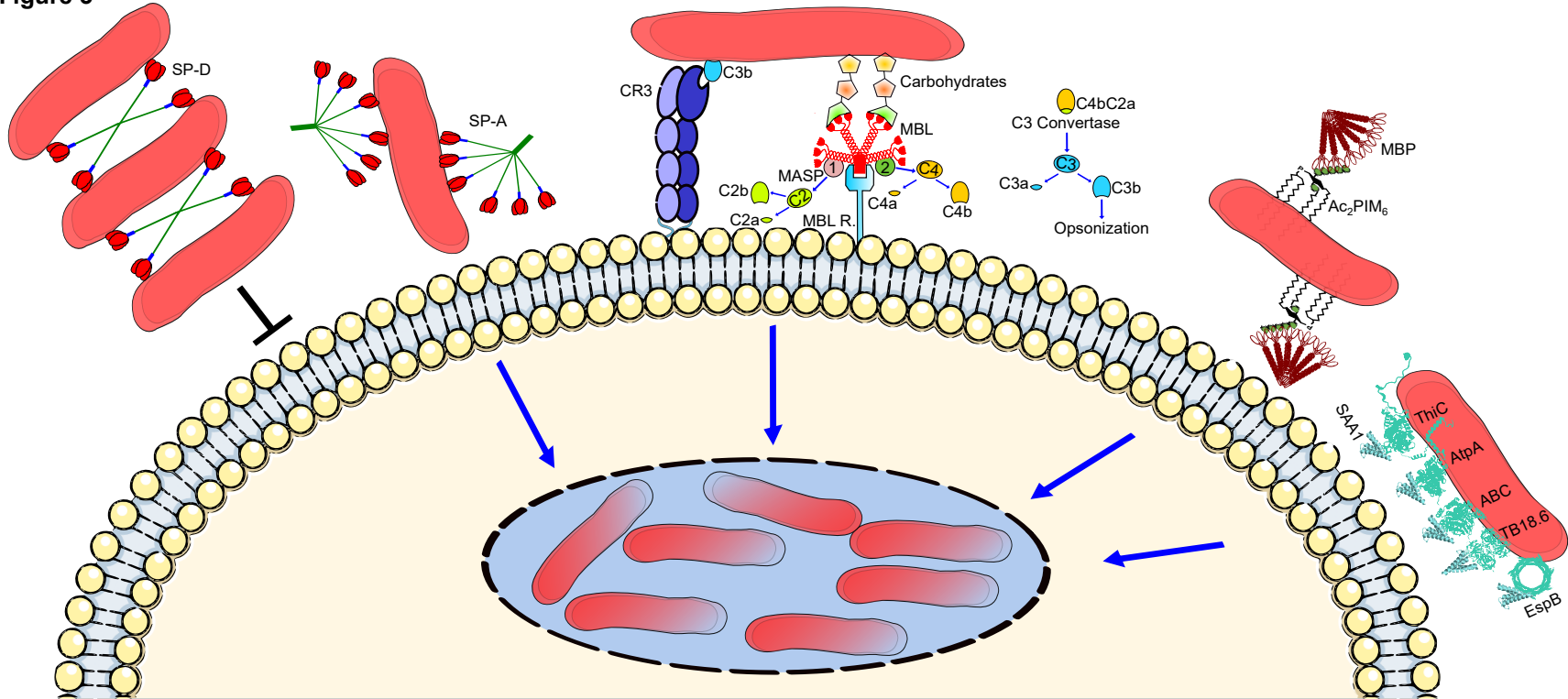


Figure 4

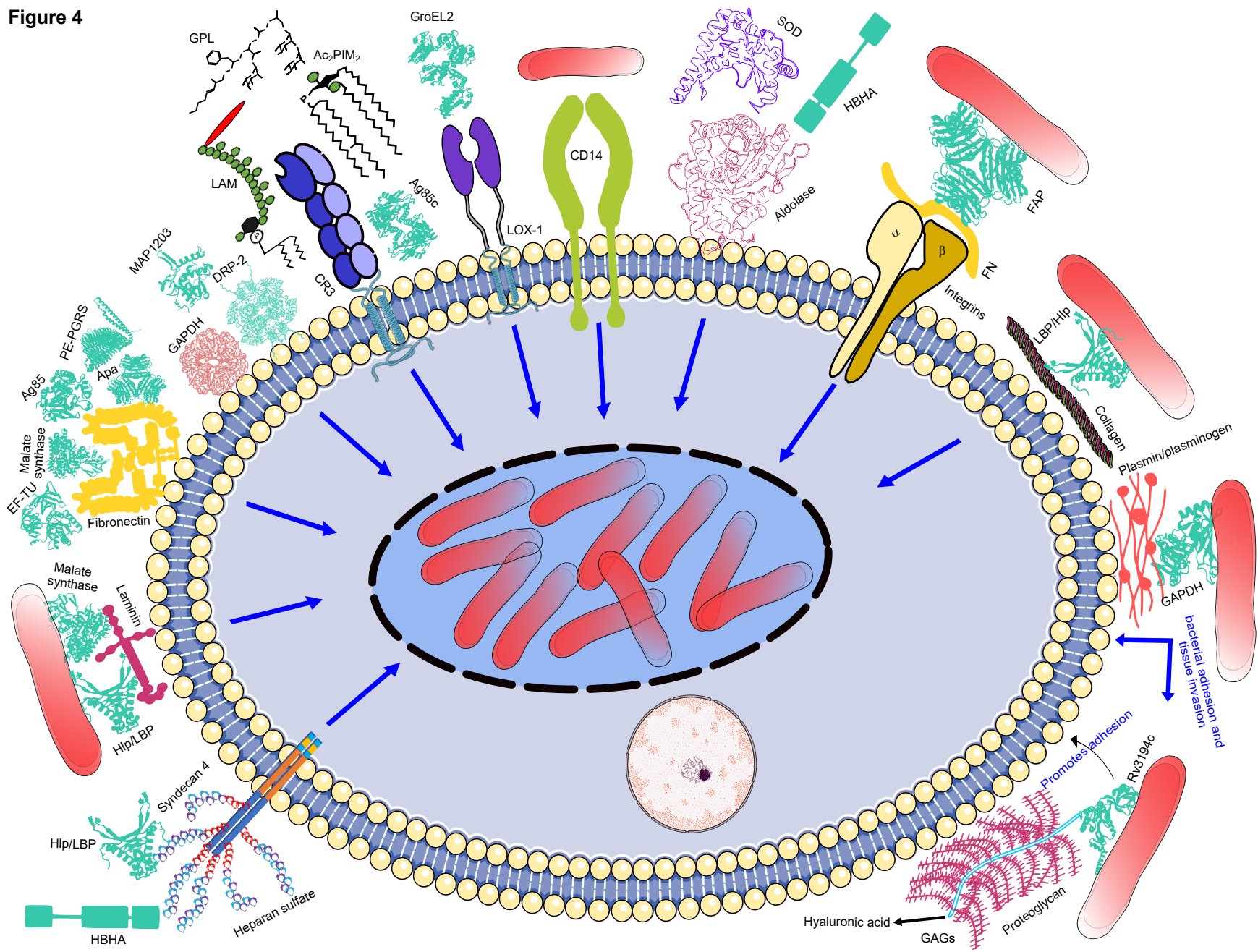


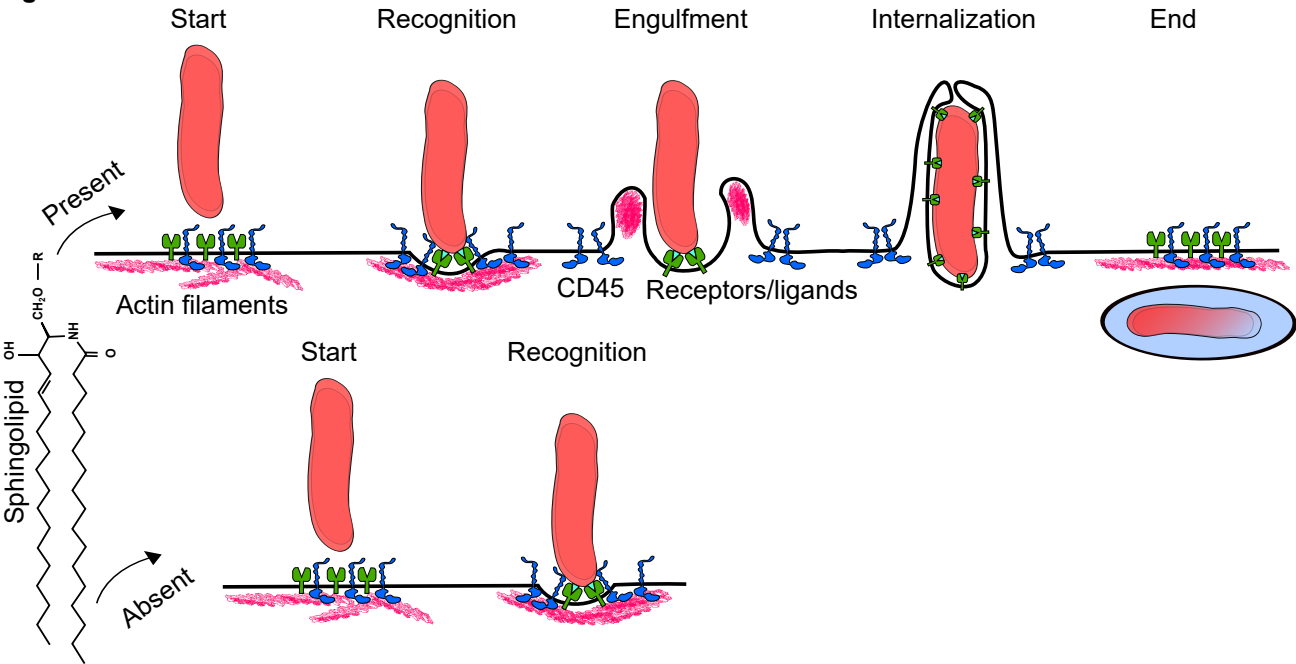
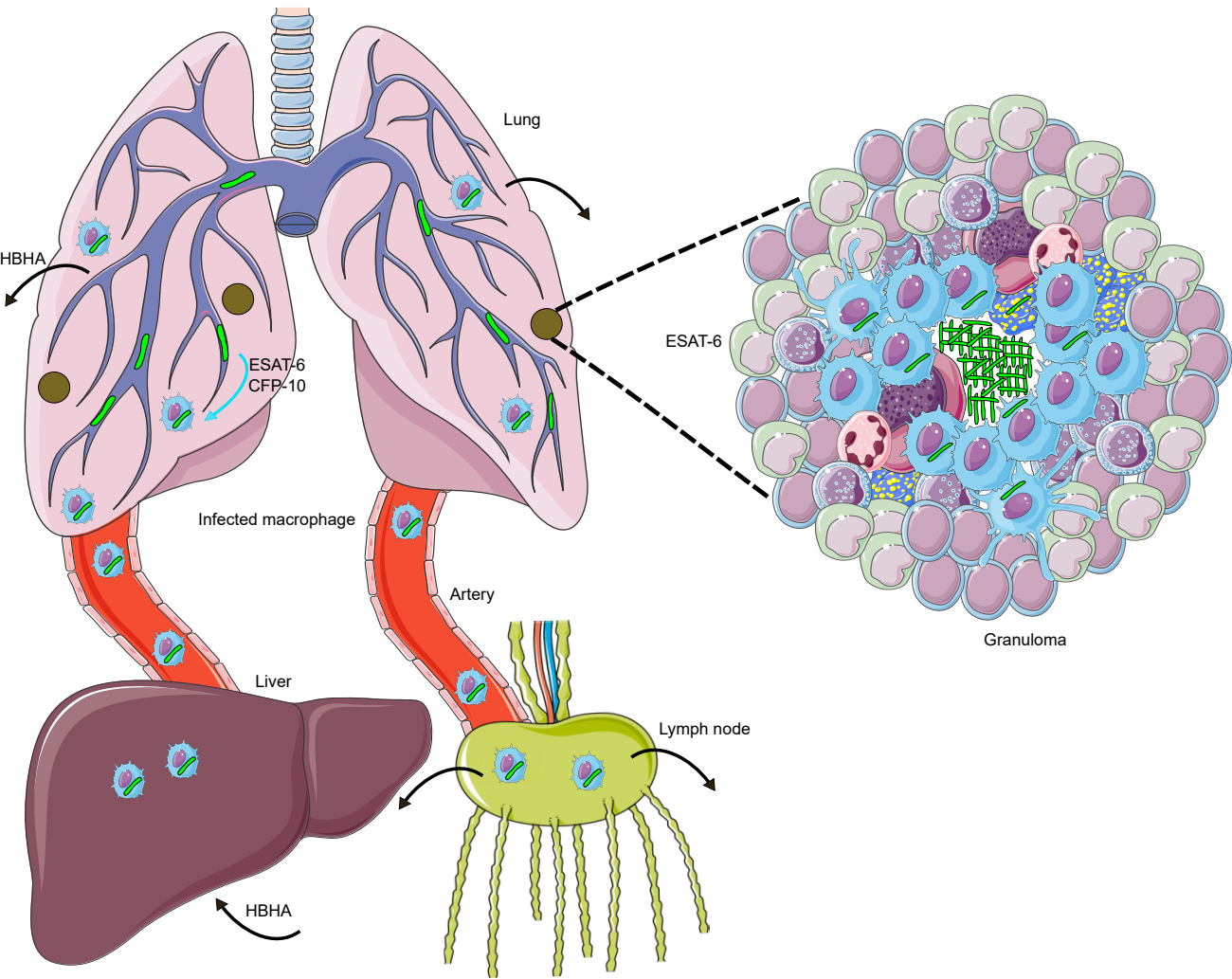
Figure 5

Figure 6



SUPPLEMENTARY DATA

The molecular basis and downstream immune consequences of mycobacteria host cell interactions

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Content

Supplementary Table S1: List of currently known mycobacterial adhesins and their corresponding host receptors: recognition and subsequent responses as observed in the host.

Table S1. List of currently known mycobacterial adhesins and their corresponding host receptors: recognition and subsequent responses as observed in the host.

PRR (Host receptor)	PAMP (Mycobacterial ligand)	<i>Mycobacterium</i> species	Type of phagocytosis	Type of cells	Significance/implication	Reference(s)
TLR2	Man-LAM, LAM, LM, PIMs, lipoproteins LpqH/19 kDa protein and LprG, Rv0577, Hsp70, PE-PGRS33	<i>M. tuberculosis</i>	Non-opsonic	Macrophages; CD4(+) T cells; dendritic cells ; B10 cells	Control of <i>M. tuberculosis</i> infection; induction of apoptosis, autophagy, DCs maturation and T-cell proliferation; production of pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6, and IL-12p70) via NF κ B; activation of naïve T cells to secrete IFN- γ and IL-2; Induces IL-10 production; inhibits CD4+ Th1 polarization; increases susceptibility to mycobacterial infection.	(López <i>et al.</i> 2003; Drennan <i>et al.</i> 2004; Bulut <i>et al.</i> 2005; Shin <i>et al.</i> 2010; Kleinnijenhuis <i>et al.</i> 2011; Lancioni <i>et al.</i> 2011; Byun <i>et al.</i> 2012; Stamm, Collins and Shiloh 2015; Shukla <i>et al.</i> 2018; Yuan <i>et al.</i> 2019)
TLR4	RipA (Rv1477)	<i>M. tuberculosis</i>	Non-opsonic	Macrophages	Activates the NF κ B signaling pathway and elicits the production of pro-inflammatory cytokines; inhibits autophagy and the production of oxidative phosphorylation enzymes; hinders an efficient innate antibacterial response	(Shariq <i>et al.</i> 2021)
TLR9	CpG DNA	<i>M. tuberculosis</i>	Non-opsonic	Macrophages; dendritic cells	Induction of IL-12 and IFN γ production to control <i>M. tuberculosis</i> infection	(Bafica <i>et al.</i> 2005)
SP-A	LAM, Apa glycoprotein	<i>M. tuberculosis</i>	Opsonic	Human alveolar macrophages	Enhances binding and phagocytosis of <i>M. tuberculosis</i>	(Ferguson <i>et al.</i> 1999; Ragas <i>et al.</i> 2007)
SP-D	LAM, LM, PILAM	<i>M. tuberculosis</i>	Opsonic	Human alveolar macrophages	Reduces phagocytic uptake; increases phagosome-lysosome fusion	(Ferguson <i>et al.</i> 1999; Carlson <i>et al.</i> 2009)
MBL	Man-LAM, Ag85	<i>M. tuberculosis</i> <i>M. africanum</i>	Opsonic	Macrophages	Activates lectin-pathway of complement; agglutinates bacteria and promotes their phagocytosis; influences the Ag85 interaction of mycobacterium with ECM	(Bartłomiejczyk <i>et al.</i> 2014; Świerzko <i>et al.</i> 2016; Thye <i>et al.</i> 2011)

Serum proteins (MBP)	PIM	<i>M. tuberculosis</i> <i>M. smegmatis</i>	Opsonic	Fibroblasts; aortic endothelial cells	Mediates opsonic binding to nonphagocytic mammalian cells	(Hoppe <i>et al.</i> 1997)
Serum amyloid A	AtpA, ABC, EspB and TB18.6	<i>M. tuberculosis</i>	Opsonic	Macrophages	Favors bacterial entry and enhances intracellular bacilli survival; modulates the functional response of the pathogen	(Kawka <i>et al.</i> 2021)
Mincle	TDM, GMM, GroMM, β -gentiobiosyldiacylglycerides	<i>M. tuberculosis</i> BCG	Non-opsonic	Macrophages; T cells; dendritic cells	Produces inflammatory cytokines and nitric oxide; induces a robust elevation of inflammatory cytokines in vivo; activates the production of pro-inflammatory and inflammatory cytokines and ROS; activates NLRP3 inflammasome; promotes Th1 and Th17 responses in mice	(Ishikawa <i>et al.</i> 2009; Schoenen <i>et al.</i> 2010; Heitmann <i>et al.</i> 2013; Hattori <i>et al.</i> 2014; Richardson <i>et al.</i> 2015; Tima <i>et al.</i> 2017)
Dectin-1	/	<i>M. tuberculosis</i> <i>M. smegmatis</i> BCG	Non-opsonic	Macrophages; dendritic cells; airway epithelial cells; T cells; neutrophils; monocytes	Promotes the production of TNF- α , IL-6, G-CSF, IL-12p40, IL-1 β , IL-17, IL-23, ROS, antimicrobial peptides, and RANTES; induces the maturation of monocyte-derived DCs; decreases pulmonary bacillary burdens	(Yadav and Schorey 2006; Rothfuchs <i>et al.</i> 2007; Lee <i>et al.</i> 2009; Zenaro, Donini and Dusi 2009; van de Veerdonk <i>et al.</i> 2010; Marakalala <i>et al.</i> 2011; Romero <i>et al.</i> 2016; Bisiaux <i>et al.</i> 2017)
Dectin-2	Man-LAM	<i>M. tuberculosis</i> BCG <i>M. intracellulare</i> <i>M. goodii</i>	Non-opsonic	Dendritic cells	Produces pro- and anti-inflammatory cytokines; attenuates lung pathology; contributes to host immunity against mycobacterial infection	(Yonekawa <i>et al.</i> 2014)
Dectin-3	TDM	<i>M. tuberculosis</i>	Non-opsonic	Macrophages	Activates the production of pro-inflammatory cytokines	(Zhao <i>et al.</i> 2014)
DCAR	AcPIM ₂ , Ac ₂ PIM ₂ , Ac ₁ PIM ₁	<i>M. tuberculosis</i>	Non-opsonic	Macrophages; monocytes	Produces MCP-1; increases the numbers of monocyte-derived inflammatory cells; enhances IFN production by T cells; decreases bacterial load	(Toyonaga <i>et al.</i> 2016; Arai <i>et al.</i> 2020)
DC-SIGN	Man-LAM, PIM ₂ , PIM ₆ , α -glucan, LAM, LM,	<i>M. tuberculosis</i> BCG	Non-opsonic	Dendritic cells; phagocytes	Blocks DC maturation and down-regulates DC-mediated immune responses; prevents IL-	(Geijtenbeek <i>et al.</i> 2003; Maeda <i>et al.</i> 2003; Tailleux <i>et al.</i> 2003;

	mannosylated 19-kDa and 45-kDa glycoproteins				12 and IFN γ secretion; induces IL-10 secretion; inhibits pro-inflammatory cytokines; limits <i>in vivo</i> tissue pathology	Gagliardi <i>et al.</i> 2005; Pitarque <i>et al.</i> 2005; Torrelles, Azad and Schlesinger 2006; Driessen <i>et al.</i> 2009; Geurtsen <i>et al.</i> 2009; Ehlers 2010; Wu <i>et al.</i> 2011; Blattes <i>et al.</i> 2013; Kumar <i>et al.</i> 2013a; Sawettanai <i>et al.</i> 2019)
SIGNR1	LAM, Man-LAM	<i>M. tuberculosis</i>	Non-opsonic	Macrophages; splenocytes; dendritic cells	Induces immunosuppression, production of IL-10 and higher SOCS1 expression; decreases T cell activity and both IL-12 and IFN γ production; suppresses activation of NF- κ B as well as production of TNF- α , IL-6 and IL-12p40; promotes <i>M. tuberculosis</i> survival	(Koppel <i>et al.</i> 2004; Wieland <i>et al.</i> 2007; Srivastava <i>et al.</i> 2009; Ohtani <i>et al.</i> 2012)
SIGNR3	LM, Man-LAM	<i>M. tuberculosis</i>	Non-opsonic	Lung phagocytes,	Contributes to protection of the host against <i>M. tuberculosis</i> through secretion of IL-6 and TNF	(Tanne <i>et al.</i> 2009; Tanne and Neyrolles 2010)
Mannose receptor	Higher PIMs, LAM, Man-LAM, GPL, glycosylated proteins (glycosylated and acylated 19-kDa protein, PstS1 glycoprotein)	<i>M. tuberculosis</i> <i>M. smegmatis</i> BCG	Non-opsonic	Macrophages; dendritic cells	Enhances adherence and aids in mycobacterial internalization; Interferes with phagosome-lysosome fusion, activation of NADPH oxidase and contributes to the intracellular survival of mycobacteria; induces DCs maturation, the production of MMP-9, anti-inflammatory factors and inhibits IL-12 secretion; dampens inflammation and inhibits the generation of Th1-polarized immune responses	(Schlesinger 1993; Schlesinger, Hull and Kaufman 1994; Astarie-Dequeker <i>et al.</i> 1999; Nigou <i>et al.</i> 2001; Rivera-Marrero <i>et al.</i> 2002; Chieppa <i>et al.</i> 2003; Diaz-Silvestre <i>et al.</i> 2005; Kang <i>et al.</i> 2005; Villeneuve <i>et al.</i> 2005; Shimada <i>et al.</i> 2006; Torrelles, Azad and Schlesinger 2006; Esparza <i>et al.</i> 2015; Daher <i>et al.</i> 2022)
CR1 (CR1+CD35)	Complement components	<i>M. tuberculosis</i> <i>M. leprae</i> BCG	Opsonic	Monocytes; macrophages	Mediates phagocytosis of mycobacteria	(Schlesinger and Horwitz 1990, 1991; Schlesinger <i>et al.</i> 1990; Launois <i>et al.</i> 1992; Schlesinger 1993)
CR3 (CD11b+CD18)	PIM ₂ , Man-LAM, LAM, Ag85C, Rv0180c, GPL,	<i>M. tuberculosis</i> <i>M. leprae</i> BCG	Non-opsonic and opsonic	Macrophages; monocytes; eosinophils	Favors internalization of mycobacteria; inhibits eosinophil peroxidase release	(Schlesinger and Horwitz 1990, 1991; Schlesinger <i>et al.</i> 1990; Launois <i>et al.</i> 1992; Schlesinger

	Complement components					1993; Hetland and Wiker 1994; Stokes, Thorson and Speert 1998; Hu <i>et al.</i> 2000; Melo <i>et al.</i> 2000; Driss <i>et al.</i> 2012; Payros <i>et al.</i> 2021)
CR4 (CD11c+CD18)	Complement components	<i>M. tuberculosis</i> <i>M. leprae</i>	Opsonic	Macrophages	Facilitates phagocytosis of mycobacteria	(Schlesinger and Horwitz 1991; Schlesinger 1993)
LOX-1	GroEL2	<i>M. tuberculosis</i>	Non-opsonic	Macrophages	Contributes to <i>M. tuberculosis</i> internalization by macrophages	(Vinod <i>et al.</i> 2021)
Galectin3	Mycolic acid	<i>M. tuberculosis</i>	Non-opsonic	Dendritic cells	/	(Barboni, Coade and Fiori 2005)
Galectin9	AG	<i>M. tuberculosis</i> BCG <i>M. marinum</i>	Non-opsonic	Macrophages	Triggers activation of ERK signaling pathway and induces the expression of MMPs; induces pathological impairments in the lung and aggravates mycobacterial infections in hosts	(Wu <i>et al.</i> 2021)
NOD2	MDP	<i>M. tuberculosis</i> BCG <i>M. abscessus</i>	Non-opsonic	Macrophages; dendritic cells	Controls the intracellular growth of virulent <i>M. tuberculosis</i> and <i>Mab</i> ; induces the expression of host defence factors (LL37 and IRGM); stimulates production of NO; induces differentiation of monocytes into dendritic cells; activates proinflammatory cytokine secretion (IL-1 β , IL-6, IL-12, TNF- α); increases production of IL-6, IL-32, CXCL-1, CCL2 and IFN- γ	(Coulombe <i>et al.</i> 2009; Juárez <i>et al.</i> 2012; Hansen <i>et al.</i> 2014; Kim <i>et al.</i> 2015; Landes <i>et al.</i> 2015; Schenk <i>et al.</i> 2016; Lee <i>et al.</i> 2017)
cGAS	Cytosolic DNA	<i>M. tuberculosis</i> <i>M. bovis</i> <i>M. avium</i> <i>M. smegmatis</i>	Non-opsonic	Dendritic cells; macrophages	Promotes maturation and activation of DCs and CD4+ T cells' proliferation; enhances autophagic targeting of <i>M. tuberculosis</i> ; promotes IL-1 β production; induces IFN- β secretion leading to mycobacteria clearance	(Wassermann <i>et al.</i> 2015; Watson <i>et al.</i> 2015; Ruangkiattikul <i>et al.</i> 2017; Li <i>et al.</i> 2019)
CD43	Cpn60.2/Hsp65/GroEL	<i>M. tuberculosis</i> <i>M. avium</i> BCG	Non-opsonic	Macrophages	Contributes to mycobacteria binding to host cells; Induces the production of TNF- α , IL-6 and IL-12; regulates apoptosis of the host cell	(Fratuzzi <i>et al.</i> 2000; Randhawa <i>et al.</i> 2005; Randhawa, Ziltener and Stokes 2008; Hickey <i>et al.</i> 2010; Torres-Huerta <i>et al.</i> 2017)

					and restricts intracellular mycobacterial growth	
Scavenger receptor class A (MARCO)	TDM	<i>M. tuberculosis</i>	Non-opsonic	Macrophages	Facilitates <i>M. tuberculosis</i> phagocytosis; activates TLR2 signaling pathway; induces pro-inflammatory cytokines production; promotes tuberculosis resistance in hosts	(Bowdish <i>et al.</i> 2009; Martinez <i>et al.</i> 2016)
Scavenger receptor class B (SR-B1/CD36)	LM, Man-LAM, LprA, diglycerides lipoteichoic acid (LTA)	<i>M. tuberculosis</i> <i>M. fortuitum</i>	Non-opsonic	Macrophages; APCs; dendritic cells	Contributes in surfactant lipid uptake by macrophages and augments <i>M. tuberculosis</i> growth and burden; enhances TNF α production; promotes macrophage uptake of mycobacteria; activation of the immune response against pathogens	(Philips, Rubin and Perrimon 2005; Drage <i>et al.</i> 2009; Jimenez-Dalmaroni <i>et al.</i> 2009; Hawkes <i>et al.</i> 2010; Józefowski <i>et al.</i> 2011; Martin <i>et al.</i> 2011; Dodd <i>et al.</i> 2016)
Fcγ receptors	Human Fc fragment	<i>M. tuberculosis</i>	Opsonic	Macrophages; monocytes	Dampens Th1 responses and secretion of IFN γ and IL-12 cytokines; Enhances mycobacterial survival, increases immunopathology and susceptibility to <i>M. tuberculosis</i> infection; increases TNF α , IL-6 and IL-10 secretion; interferes with phagosome maturation	(Hussain <i>et al.</i> 2001; Maglione <i>et al.</i> 2008; Patin <i>et al.</i> 2017)
TREM2	Non-glycosylated Mycolic Acid	<i>M. tuberculosis</i>	Non-opsonic	Macrophages	Counteracts Mincle-FcR γ -CARD9-mediated anti-mycobacterial immunity; supports mycobacterial survival and immune evasion	(Iizasa <i>et al.</i> 2021)
CD14	PIM ₁ , PIM ₂ , LM, LAM, AraLAM, LpqH, Cpn 60.1	<i>M. tuberculosis</i> BCG <i>M. chelonae</i> <i>M. kansasii</i> <i>M. avium</i>	Non-opsonic	Macrophages; dendritic cells; monocytes; CHO; microglia	Promotes bacilli internalization; Expands a CD14+ DC subset with weak IL-12 producing capacity; prompts IL-17A producing ROR γ T+ and CD4+ T cells; inhibits TNF release; increases production of hyaluronan and IL-10 that promote growth of <i>M. tuberculosis</i> ; activates antibacterial autophagy and human PBMCs; stimulates pro-inflammatory cytokines secretion; reduces inflammatory response and protects mice from lethality; stimulates MMP-9, TNF- α and IL-8 secretion;	(Peterson <i>et al.</i> 1995; Khanna <i>et al.</i> 1996; Bernardo <i>et al.</i> 1998; Yu <i>et al.</i> 1998; Ehlers <i>et al.</i> 2001; Lewthwaite <i>et al.</i> 2001; Shams <i>et al.</i> 2003; Vignal <i>et al.</i> 2003; Ellass <i>et al.</i> 2005, 2007; Sendide <i>et al.</i> 2005; Wieland <i>et al.</i> 2008; Bowdish <i>et al.</i> 2009; Shin <i>et al.</i> 2010; Court <i>et al.</i> 2011; Dhiman <i>et al.</i> 2011; Søndergaard <i>et al.</i> 2014)

					induces rise in [Ca ²⁺]; promotes chemotaxis of phagocytes	
CD40	Hsp70	<i>M. tuberculosis</i> <i>M. avium</i> BCG	Non-opsonic	Dendritic cells; monocytes; macrophages	Generates IL-6, IL-8, IL-10, IL-12, IL-17, IL-18, TNF- α , IFN- γ , iNOS and RANTES responses; augments autophagy; amplifies the pool of memory CD4 T and CD8 T cells; controls bacterial burdens, activates antimicrobial response and develops protective immunity	(Hayashi <i>et al.</i> 1999; Méndez-Samperio, Ayala-Verdin and Trejo-Echeverria 1999; Samten <i>et al.</i> 2000; Demangel <i>et al.</i> 2001; Wang <i>et al.</i> 2001; Lazarevic <i>et al.</i> 2003; Flórido <i>et al.</i> 2004; Sommer <i>et al.</i> 2009; Klug-Micu <i>et al.</i> 2013; Khan <i>et al.</i> 2016; Sia <i>et al.</i> 2017)
Aldolase	SOD, heparin binding protein	<i>M. avium</i>	Non-opsonic	Epithelial cells (HEp-2 and A549); intestinal mucus	Promotes adherence to and invasion of epithelial cells; facilitates gastrointestinal colonization	(Reddy and Suleman 2004; Reddy, Suleman and Hayworth 2004)
Integrins	ppiA, bFAP-hFN	<i>M. tuberculosis</i> <i>M. avium</i>	Non-opsonic	Macrophages; M cells	Upregulates multiple MMPs; assists bacilli survival and aids in the disease progression; facilitates bacilli invasion	(Secott, Lin and Wu 2004; Dubey <i>et al.</i> 2021)
Collagen/ECM	Hlp	BCG <i>M. leprae</i>	Opsonic	Pneumocytes; macrophages	Facilitates bacilli attachment to host cells; cross-links bacilli to form clumps	(Dias <i>et al.</i> 2012)
Plasminogen, plasmin	GAPDH	<i>M. tuberculosis</i>	Opsonic	Lung epithelial cells (A549)	Enhances bacterial adherence to and traversal across lung epithelial cells	(Gani <i>et al.</i> 2021)
Hyaluronic acid	Rv3194c protease	<i>M. tuberculosis</i> <i>M. smegmatis</i>	Opsonic	Lung epithelial cells (A549)	Promotes bacilli adherence to host cells; contributes in the attachment of <i>rMsmeg</i> to A549 cells; enhances <i>Msmeg</i> persistence and induces lesions in the lungs	(Zhao, Lin and Xu 2020)
Syndecan 1 and 4	HBHA	<i>M. tuberculosis</i>	Non-opsonic	Alveolar epithelial cells	Enhances mycobacterial attachment and internalization; impacts on outcome of TB disease	(Zimmermann <i>et al.</i> 2016)
Laminin-2	LBP-21kDA/Hlp, MS-LBP, malate synthase, amidase, transpeptidase	<i>M. leprae</i> <i>M. smegmatis</i> <i>M. tuberculosis</i>	Opsonic	Schwann cells; pneumocytes; macrophages	Enhances the attachment of bacilli to host cells	(Shimoji <i>et al.</i> 1999; de Melo Marques <i>et al.</i> 2000; Pethe <i>et al.</i> 2001; Kinhikar <i>et al.</i> 2006; Kumar <i>et al.</i> 2013b)

Heparan sulfate glycosaminoglycans	HBHA, Hlp	<i>M. leprae</i> <i>M. avium</i> <i>M. intracellulare</i> <i>M. tuberculosis</i> BCG	Non-opsonic	Schwann cells; alveolar macrophages; epithelial cells; pneumocytes (A549); human laryngeal epithelial cells (HEp-2)	Promotes attachment of bacilli to host cells; induces epithelial transcytosis leading to systemic infection by <i>M. tuberculosis</i>	(Menozzi <i>et al.</i> 1998, 2006; Pethe <i>et al.</i> 2000; Soares de Lima <i>et al.</i> 2005; Silva <i>et al.</i> 2013; Lefrancois <i>et al.</i> 2020)
Fibronectin	p55, FAP, PE-PGRS81, malate synthase, amidase, transpeptidase, EF-TU, Apa, Ag85 complex proteins	<i>M. bovis</i> <i>M. vaccae</i> <i>M. leprae</i> <i>M. avium</i> <i>M. smegmatis</i> <i>M. avium subsp paratuberculosis</i> <i>M. tuberculosis</i> <i>M. abscessus</i>	Opsonic	Macrophages; epithelial cells (T-24, caco-2); schwann cells (JS1); human respiratory mucosa; A549	Promotes the attachment of bacilli to host cells; initiates mycobacterial infections <i>in vivo</i>	(Ratliff <i>et al.</i> 1993; Schorey <i>et al.</i> 1995; Espitia <i>et al.</i> 1999; Zhao <i>et al.</i> 1999; Middleton <i>et al.</i> 2000; Secott, Lin and Wu 2002; Kinhikar <i>et al.</i> 2006; Kumar <i>et al.</i> 2013b; Viale <i>et al.</i> 2014; Kuo <i>et al.</i> 2019; Viljoen, Alsteens and Dufrêne 2020)
DRP-2 and GAPDH	MAP1203	<i>M. avium subsp paratuberculosis</i>	Non-opsonic	bovine MDBK epithelial cells	Increases binding and invasion of bovine MDBK epithelial cells	(Everman <i>et al.</i> 2018)
GAPDH	SOD	<i>M. avium</i>	Non-opsonic	Epithelial cells (HEp-2 and A549)	Promotes adherence to and invasion of epithelial cells	(Reddy and Suleman 2004)
Cyclophilin-A	SOD	<i>M. avium</i>	Opsonic	Epithelial cells (HEp-2 and A549)	Promotes adherence to and invasion of epithelial cells	(Reddy and Suleman 2004)
AhR	Naphthoquinone phthiocol	<i>M. tuberculosis</i>	/	/	Degrades virulence factors; regulates production of cytokines and chemokines; increases resistance to <i>Mtb</i> infection, controls antibacterial responses.	(Maura-Alves <i>et al.</i> 2014)
/	ESAT6, CFP-10 and HBHA	<i>M. tuberculosis</i>	/	Alveolar epithelium and	Enable <i>M. tuberculosis</i> to invade and spread within the alveolar epithelium; stimulates the trafficking of infected macrophages within	(Krishnan, Robertson and Thwaites 2010; Ryndak, Chandra and Laal 2016)

				endothelial cells	granulomas; promotes the dissemination of bacteria through the alveolar barrier	
/	Mce1A	<i>M. leprae</i>	/	Human microvascular endothelial cells (HMVEC)	Promotes invasion of <i>M leprae</i> into HMVEC	(Idris <i>et al.</i> 2019)
/	PE-PGRS proteins	BCG <i>M. tuberculosis</i>	/	Macrophages	Influence interactions of mycobacteria with macrophages	(Brennan <i>et al.</i> 2001)
/	MTP	<i>M. tuberculosis</i>	/	Macrophages; A549	Plays a role in <i>M. tuberculosis</i> entry	(Ramsugit and Pillay 2014; Ramsugit, Pillay and Pillay 2016)

Abbreviations used: **TLR:** Toll-like receptor; **SP-D:** Surfactant protein D; **Mincle:** Macrophage inducible Ca²⁺-dependent lectin receptor; **Dectin:** dendritic cell-associated C-type lectin; **DCAR:** Dendritic cell immune-activating receptor; **SIGNR3:** specific intracellular adhesion molecule-3 grabbing non-integrin homolog-related 3; **NOD2:** nucleotide-binding and oligomerization domain containing protein 2; **cGAS:** DNA-sensing receptor cyclic GMP–AMP synthase; **CD43:** cluster of differentiation 43; **MARCO:** macrophage receptor with collagenous structure; **CD1:** cluster of differentiation 1; **CD40:** Cluster of Differentiation 40; **MBL:** mannose-binding lectin; **SIGNR1:** specific ICAM-3 grabbing nonintegrin-related 1; **DC-SIGN:** Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin; **CR3:** complement receptor 3; **TREM2:** triggering *receptor* expressed on myeloid cells 2; **FcγR:** fragment crystallizable gamma receptor; **SP-A:** Surfactant protein A; **LOX-1:** lectin-type oxidized LDL receptor 1; **CR1:** complement receptor type 1; **CR4:** complement-receptor type 4; **ECM:** extra-cellular matrix; **GAPDH:** glyceraldehyde 3-phosphate dehydrogenase; **MBP:** mannose-binding protein; **DRP-2:** dihydropyrimidinase related protein 2; **SR-B1:** Scavenger receptor class B type 1; **CD14:** cluster of differentiation 14; **LAM:** lipoarabinomannans; **LM:** lipomannans; **PIM:** phosphatidyl-myo-inositol mannoside; **LpQH:** 19-kDa secreted lipoglycoprotein; **LprG:** 24-kDa lipoprotein; **Hsp70:** heat shock protein 70; **PE-PGRS:** proline glutamic acid - polymorphic GC-rich repetitive sequence; **Man-LAM:** Mannose-capped lipoarabinomannan; **CpG DNA:** short, single-stranded oligodeoxynucleotides that contain a cytosine triphosphate deoxynucleotide linked by a phosphodiester to a guanine triphosphate deoxynucleotide; **PILAM:** phosphatidyl-myo-inositol capped lipoarabinomannan; **TDM:** trehalose-6,6'-dimycolate; **GMM:** glucose monomycolate; **GroMM:** glycerol monomycolate; **AcPIM₂:** acyl-phosphatidylinositol dimannoside; **Ac₂PIM₂:** diacylphosphatidylinositol dimannoside; **Ac₁PIM₁:** acyl phosphatidylinositol mannoside; **MDP:** muramyl dipeptide; **Cpn:** chaperonin; **Ac₂PIM₆:** diacylphosphatidylinositol hexamannoside; **Ag85:** antigen 85; **PIM₂:** phosphatidylinositol dimannoside; **PIM₆:** phosphatidylinositol hexamannoside;

GPL: glycopeptidolipid; **PstS1:** phosphate-specific transport substrate binding protein-1; **ppiA:** peptidyl prolyl isomerase A; **bFAP-hFN:** bacterial fibronectin attachment protein – human fibronectin; **AtpA:** ATP synthase subunit alpha; **ABC:** ATP-binding cassette; **EspB:** ESX-1 secretion-associated protein B; **Apa:** alanine- and proline-rich antigen; **Hlp:** histone-like protein; **LBP-21kDa:** laminin-binding protein of 21 kDa; **MS-LBP:** *M. smegmatis* laminin-binding protein; **p55:** 55 kDa protein; **FAP:** fibronectin attachment protein; **EF-Tu:** elongation factor Tu; **SOD:** superoxide dismutase; **HBHA:** Heparin-binding haemagglutinin antigen; **AGs:** arabinogalactans; **LprA:** a cell wall-associated lipoprotein with no homologs outside the slow-growing mycobacteria; **PIM₁:** phosphatidylinositol monomannoside; **AraLAM:** arabinosylated lipoarabinomannan; **ESAT6:** early secreted antigenic target of 6 kDa; **CFP-10:** culture filtrate protein of 10 kDa; **Mce1A:** mammalian cell entry protein 1A; **MTP:** *M. tuberculosis* pili; **BCG:** *Mycobacterium bovis* bacillus Calmette-Guérin; **CHO:** Chinese hamster ovary; **APC:** Antigen-presenting cells; **MDBK:** Madin-Darby Bovine Kidney Cells; **Caco:** human colon adenocarcinoma; **M:** Microfold cells; **DCs:** dendritic cells; **TNF:** tumor necrosis factor; **IL:** interleukin; **IFN:** interferon; **Th1:** T helper type 1; **Th17:** T helper 17 cells; **MCP-1:** Monocyte chemoattractant protein-1; **G-CSF:** granulocyte colony-stimulating factor; **ROS:** reactive oxygen species; **RANTES:** regulated upon activation, normal T cell expressed, and secreted; ***M. tuberculosis:*** *Mycobacterium tuberculosis*; **Mab:** *Mycobacterium abscessus*; **LL-37:** cathelicidin peptide starts with double leucine and consists of 37-amino acids; **IRGM:** Immunity-related GTPase family M protein ; **NO:** Nitric oxide; **CXCL-1:** C-X-C motif chemokine ligand 1; **CCL2:** C-C Motif Chemokine Ligand 2; **iNOS:** inducible nitric oxide synthase; **SOCS1:** Suppressor of cytokine signaling 1; **NF-κB:** nuclear factor kappa light chain enhancer of activated B cells; **NADPH:** nicotinamide adenine dinucleotide phosphate hydrogen; **MMP-9:** Matrix metalloproteinase 9; **CARD9:** caspase recruitment domain-containing protein 9; **TB:** tuberculosis; **ERK:** extracellular signal-regulated kinases; **rMsmeg:** recombinant *Mycobacterium smegmatis*; **RORγT:** retinoic acid-related orphan receptor gamma T cells; **PBMC:** Peripheral blood mononuclear cells; **AhR:** aryl hydrocarbon receptor.