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

One sentence summary: This review summarizes the complexity of the interactions between mycobacterial ligands and host receptors during infection and pathogenesis.

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Abbreviated terms are defined in the supplementary material (supplementary table 1).

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 presented herein on adhesins and
42 host receptors may serve 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
44 mycobacterial surface molecules highlighted in this review may also provide potential new therapeutic
45 targets, diagnostic markers, or vaccine candidates to combat these notoriously challenging and
46 persistent pathogens.

47

48 INTRODUCTION

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

57 Successful infection requires adhesion of the pathogen to host cell, colonization of tissues/organs,
58 bacterial multiplication and eventual dissemination to other tissues and/or persistence within the host.
59 Bacteria exploit adhesins/invasins or other macromolecular complexes to trigger an intricate host-
60 pathogen crosstalk that leads to the subversion of cellular functions and establishment of disease.
61 Playing a role in this attachment, the mycobacterial cell envelope is composed of complex network of
62 glycopolymers, lipids, glycolipids, proteins, and of the mycolyl-arabinogalactan-peptidoglycan skeleton
63 (Dulberger, Rubin and Boutte 2020). Bacterial attachment to a substrate may be mediated by adhesins,
64 which are surface-localized molecules capable of binding specific host molecules (Kline *et al.* 2009). In
65 mycobacteria, these adhesins are comprised of a diverse range of glycopolymers, DNA, lipids and
66 proteins. Adhesion facilitates biofilm formation, an essential step for bacterial colonization of

67 environmental niches and for the establishment of infection, and endows bacteria with resistance to
68 immune effector mechanisms, bacteriolytic enzymes and antibiotics (Stones and Krachler 2016; Schulze
69 *et al.* 2021). The ubiquity of biofilm formation across most mycobacterial species, as has been seen in
70 fast-growing non-tuberculous mycobacteria adhering to household plumbing and shower heads
71 (Williams *et al.* 2009) and on clinical biomaterials by slow-growers, such as *M. tuberculosis* (Esteban and
72 García-Coca 2018), points to an advantageous mechanism during pathogenesis.

73 Following attachment, mycobacterial entry into host cells is mediated by two different membrane
74 receptor-dependent mechanisms: non-specific macropinocytosis and phagocytosis. Macropinocytosis is
75 characterized by an invagination of the membrane, forming an endosome, which then fuses with
76 microbicidal lysosome compartments to degrade the enclosed microorganisms. Though considered a
77 secondary pathway when phagocytosis receptors are already saturated, this process is also employed
78 by INF- γ -activated macrophages to clear bacteria (Bosedasgupta and Pieters 2014). Conversely, the
79 primary pathway engages multiple phagocytosis pattern recognition receptors (PRR) that recognize
80 specific pathogen-associated molecular patterns (PAMP) present on the surface of the bacilli (**Table S1,**
81 **Supporting Information**). PRR are PAMP-specific based on their location and include cellular receptors
82 (found in the plasma membrane, endosomal compartments, and the cytosol; reviewed in part I) and
83 the extracellular host matrix, including mucosal surfaces (reviewed in part II) (Vinod *et al.* 2020).
84 Recognition occurs in either a non-opsonic or opsonic fashion, the latter of which depends on bacteria
85 coated with complement proteins or immunoglobulins to enhance binding affinity with phagocytes *via*
86 complement receptors or Fc γ R immunoglobulin receptors, respectively. Non-opsonic phagocytosis
87 involves other classes of receptors, including Toll-like receptors (TLR) and C-type lectin receptors (CLR).
88 The interaction between PRR and PAMP triggers signaling cascades that lead to the restructuring of the
89 actin cytoskeleton. Depending on the receptor engaged, the plasma membrane subsequently remodels
90 in one of two ways: 1) invagination, or 2) the formation of membrane protrusions that encompass the
91 microorganism, known as pseudopods (Caron and Hall 1998).

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

101 tissues, their broader significance in both immune evasion and bacterial survival, and the features that
102 may contribute to reduced bacterial growth and pathogenicity.

103

104 RECEPTOR-MEDIATED RECOGNITION OF MYCOBACTERIA BY DIFFERENT CELL TYPES (Part I)

105 Innate immune receptors

106 The innate immune system, which comprises effector cells, antimicrobial peptides, soluble mediators
107 and cell receptors, represents the first line of defense against invading microbial pathogens. The
108 response is rapidly activated through the recognition of conserved PAMP by PRR (membrane-bound or
109 cytosolic). Each PRR is specific to a diverse set of PAMP, ensuring the appropriate downstream activation
110 of the adaptive immune response.

111

112 Toll-like receptors

113 TLR are type I transmembrane glycoproteins composed of extracellular, transmembrane and
114 intracellular signaling domains (Gay and Gangloff 2007). The extracellular domains contain repeated
115 modules of leucine-rich repeats (LRR) and are responsible for binding to PAMP (Medzhitov 2001). Each
116 PAMP type is engaged by different TLR. Di- and tri-acylated lipopeptides and lipoproteins are the defined
117 ligands of TLR2 (Jin and Lee 2008) while lipopolysaccharides (LPS) and microbial DNA are recognized by
118 TLR4 and TLR9, respectively (Uematsu and Akira 2008). Ligand-induced dimerization of TLR triggers the
119 recruitment of adaptor proteins to the intracellular Toll/Interleukin-1 receptor (TIR) domains to initiate
120 signaling (O'Neill and Bowie 2007). Signaling cascades *via* TIR domains are mediated by specific adaptor
121 molecules such as MyD88 (O'Neill and Bowie 2007). MyD88 is essential for TLR signaling (Medzhitov,
122 Preston-Hurlburt and Janeway 1997) and, with the exception of TLR3 and TLR4 (its signaling is composed
123 of at least two distinct pathways, a MyD88- and TRIF-dependent pathway), all TLR require MyD88 for
124 downstream signaling (Kawai *et al.* 1999; Kawai and Akira 2010). The MyD88 adaptor protein mediates
125 many biologically important signal transduction pathways in innate immunity (Warner and Núñez 2013)
126 and is important in the regulation of inflammation during bacterial infection (Wang *et al.* 2014).
127 Mutations in MyD88 are associated with immunodeficiencies that predispose patients to recurrent life-
128 threatening bacterial infections, as observed in MyD88-deficient mice susceptible to a variety of
129 pathogens (von Bernuth *et al.* 2008, 2012). *M. tuberculosis* infection in these mice is lethal as MyD88
130 signaling is required to elicit an adequate innate and acquired immune response (Fremond *et al.* 2004;
131 Hölscher *et al.* 2008; Berod *et al.* 2014). Phagocytosis, in turn, is essential for an optimal response to
132 MyD88-dependent bacteria (Ip *et al.* 2010). In addition to playing a central role in phagocytosis, MyD88
133 is crucial for downstream TLR activation and signaling that occurs after bacterial degradation in the
134 phagosome of human monocytes (Cervantes *et al.* 2013) and murine macrophages (Ip *et al.* 2010).
135 Bacteria must be phagocytosed and it is in the acidic environment of the phagosome that endosomal

136 TLR recognize their bacterial ligands. Once the bacterial ligands are released, a TLR-dependent response
137 can be initiated from the phagosome (Ip *et al.* 2010; Kagan and Iwasaki 2012; Cervantes *et al.* 2014).
138 Furthermore, MyD88 signaling in DCs and macrophages is essential to control the mycobacterial burden
139 and prevent their persistence (Scanga *et al.* 2004; Berod *et al.* 2014). MyD88-KO mice infected with *M.*
140 *tuberculosis* develop granulomatous lung lesions with enhanced neutrophil infiltration as compared to
141 wild-type mice (Sugawara *et al.* 2003). These massive cellular infiltrations accompanied by extensive
142 granuloma necrosis lead to high susceptibility of MyD88-KO mice to TB infection (Hölscher *et al.* 2008).
143 Consequently, higher bacterial loads in the lungs and spleen are found in MyD88-KO mice (Sugawara *et*
144 *al.* 2003; Hölscher *et al.* 2008). Furthermore, an aberrant inflammatory response ensues when MyD88
145 is absent, due to the fact that MyD88 acts as a negative signaling factor to stop NF- κ B activation (Burns
146 *et al.* 2003), a mechanism necessary to prevent excessive inflammation and return to homeostasis
147 (Ruland 2011). In the following section, we will discuss the current knowledge about TLR, focusing on
148 their role in mycobacterial infections.

149

150 TLR2

151 Establishment of an effective immune response against intracellular mycobacteria depends on
152 the rapid detection of the invading pathogen by the innate immune system and the coordinated
153 activation of the adaptive immune response. TLR are adept at detecting and restricting infection by
154 pathogenic microorganisms, including mycobacteria. The interaction is complex and involves distinct
155 mycobacterial cell wall components and multiple members of the TLR family. Numerous studies have
156 shown that TLR2, acting alone or in concert with other TLR, can recognize several secreted or surface-
157 associated mycobacterial components and help mounting an effective defensive response against *M.*
158 *tuberculosis*. In macrophages, recognition of the *M. tuberculosis* 19-kDa glycolipoprotein (LpqH) by TLR2
159 induces apoptosis *via* the caspase-8 pathway, limiting intracellular proliferation of the bacilli (**Figure 1**)
160 (López *et al.* 2003). Since lipoproteins/lipopeptides are detected by TLR2 at physiological picomolar
161 concentrations, the activity of other putative bacterial compounds reported in the literature as TLR2
162 agonists may, eventually, be due to the presence of highly active natural lipoproteins and/or
163 lipopeptides. It remains possible that recombinant proteins other than *bona fide* TLR2 ligands described
164 in some studies interact with activating lipopeptides, which may explain their observed effects
165 (Zähringer *et al.* 2008). Based on co-structure studies described in the literature (TLR2 in complex with
166 lipoproteins and lipopeptides), further studies reporting various mycobacterial proteins, such as Rv0350
167 or Rv0577, interacting with TLR2 should be cautiously considered as structural evidence is not yet
168 available. TLR2 is also found in other cell types, including human endothelial cells, where it has been
169 shown to activate the key immune regulatory NF- κ B pathway when interacting with *M. tuberculosis'*
170 Hsp70 (Rv0350) protein (Bulut *et al.* 2005). In DC, TLR2 seems to recognize the secreted Rv0577 protein,

171 involved in the methylglyoxal detoxification pathway, to induce pro-inflammatory cytokines, including
172 TNF- α , IL-1 β , IL-6 and IL-12p70 in a MyD88-dependent manner, as well as mitogen-activated protein
173 (MAP) kinases and NF- κ B (**Figure 1**). It has been shown that Rv0577-treated DC have the capacity to
174 activate naïve T cells, polarize CD4⁺ and CD8⁺ T cells to secrete IFN- γ and IL-2, and induce T cell
175 proliferation. Moreover, this mechanism has been observed to induce the proliferation of memory CD4⁺
176 and CD8⁺ CD44^{high}CD62L^{low} T cells in the spleen of *M. tuberculosis*-infected mice. Collectively, these
177 observations suggest the close association of TLR2 and Rv0577 in the protective regulation of both the
178 innate and adaptive immune responses to *M. tuberculosis* infection (Byun *et al.* 2012). Conversely, TLR2
179 may also play a harmful role in IL-10-producing B cells. Upon the interaction of TLR2 and *M. tuberculosis*'
180 mannose-capped lipoarabinomannan (ManLAM), the MyD88/PI3K/AKT/Ap-1 and NF- κ B signaling
181 pathways stimulate both B cell proliferation and their IL-10 production, causing the excessive cytokines
182 to diminish immune cell activity and increase infection susceptibility (**Figure 2**) (Yuan *et al.* 2019). While
183 there are many analyses that point to the role of TLR2 in *in vitro* model systems, investigations into the
184 importance of TLR2 in aerosolized *M. tuberculosis* infection of mice *in vivo* have yielded contradictory
185 results. In this context, some reports have found no individual role for TLR2 in establishing effective
186 immunity to growth-limiting *M. tuberculosis* after low- or high-dose aerosol infections (Reiling *et al.*
187 2002; Bafica *et al.* 2005). Another study, conversely, suggested TLR2 to play a non-redundant role in
188 providing protective immunity during long-term infection. Indeed, TLR2-deficient mice show reduced
189 bacterial clearance, a defective granulomatous response, and the development of chronic pneumonia,
190 causing them to prematurely succumb to infection within 5 months. The range of interactions of TLR2
191 with diverse ligands highlights its critical role in immune regulation, particularly as its absence yields an
192 exaggerated inflammatory response (Drennan *et al.* 2004). The underlying reasons for these
193 discrepancies are not known but may be explained by the loss of functionality of a single TLR in *M.*
194 *tuberculosis* aerosol infection models having a negligible effect on the development of the immune
195 response *in vivo* and is easily compensated by other receptors. However, seminal studies performed
196 after *M. tuberculosis* infection in TLR2/4/9- and MyD88-deficient mice, showed that only the latter
197 succumbed rapidly to uncontrolled mycobacterial growth, while the former controlled the infection
198 (Fremond *et al.* 2004, 2007; Scanga *et al.* 2004; Hölscher *et al.* 2008). This demonstrates that only
199 MyD88, but not TLR2, TLR4 and TLR9, is essential for triggering the macrophage effector mechanisms
200 that are central to anti-mycobacterial defense.

201 As described above, TLR2 plays a crucial role in the recognition of mycobacteria by their cell wall
202 components. These agonists activate macrophages by initiating NF- κ B through TLR2 ligation. However,
203 prolonged TLR2 signaling could help *M. tuberculosis* escape immune surveillance. For example, extended
204 exposure of macrophages to LpqH, LprG, LprA, LM and PIM results in the expression of IL-10, IL-4 and
205 TGF- β , which inhibits macrophage activation (Saraav, Singh and Sharma 2014). Furthermore, prolonged

206 TLR2 signaling activated by LpqH and LprG inhibits the expression of MHC class II molecules and the
207 processing of exogenous antigens for presentation to CD4⁺ T cells, providing a basis for *M. tuberculosis*
208 immune evasion (Hu and Spaink 2022).

209

210 **TLR heterodimers**

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

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

240

241 TLR4

242 In addition to TLR1/2/9, TLR4-mediated signaling also contributes to the protective response
243 against *M. tuberculosis*. TLR4 is the key receptor involved in LPS recognition and signal initiation (Soares
244 *et al.* 2010). In fact, LPS induces dimerization of the TLR4-MD-2 complex (Park and Lee 2013). A
245 hydrophobic pocket of MD-2 houses most of the lipid portion of LPS, however, one of the six acyl chains
246 of LPS is left outside the pocket and interacts with the ectodomain of a neighboring TLR4 molecule
247 (Płóciennikowska *et al.* 2015). Viable and attenuated strains of *M. tuberculosis* have been shown to
248 activate murine macrophages that overexpress TLR4 (Means *et al.* 1999). In contrast, expression of a
249 dominant negative TLR4 protein in macrophages partially blocked *M. tuberculosis*-induced NF- κ B
250 activation (Means *et al.* 2001). Interestingly, the lipid A antagonist E5531 specifically inhibited *M.*
251 *tuberculosis*-induced TNF- α production in macrophages and, thus, apoptosis (Means *et al.* 2001). As
252 agonists, several mycobacterial proteins, including Hsp65 and Hsp70, interact with TLR4 and stimulate
253 the NF- κ B cascade in human endothelial cells (Bulut *et al.* 2005). In DC, TLR4 recognizes the ribosomal
254 protein Rv0652, which induces cellular maturation and the pro-inflammatory cytokines TNF- α , IL-1 β and
255 IL-6 following activation of the MyD88 and TRIF signaling pathways (**Figure 1**) (Lee *et al.* 2014). These
256 newly activated DC in turn activate naïve T cells and efficiently polarize CD4⁺ and CD8⁺ to secrete IFN γ
257 and induce cell-mediated cytotoxicity to eliminate infected cells (Lee *et al.* 2014). The peptidoglycan
258 hydrolase RipA activates the NF- κ B signaling pathway and triggers the production of the pro-
259 inflammatory cytokines TNF- α , IL-6, and IL-12 through ligation to TLR4. Homology modelling, docking
260 and MD simulations suggest that the C-terminal globular domain of RipA monomers inserts into the
261 ligand binding pocket of the TLR4 dimer (Shariq *et al.* 2021). Unlike other mycobacterial ligands
262 interacting with TLR4, RipA activates the PI3K-AKT-mTORC1 signaling cascade, ultimately resulting in
263 inhibition of the autophagy-initiating kinase ULK1 (**Figure 2**) (Shariq *et al.*, 2021). This inhibition results
264 in efficient intracellular survival of recombinant *M. smegmatis* expressing *M. tuberculosis* RipA in
265 macrophages (Shariq *et al.*, 2021). RipA also targets host cell mitochondria and inhibits the production
266 of oxidative phosphorylation enzymes to promote mycobacterial replication in macrophages (**Figure 2**).
267 In addition, RipA also inhibits caspase-dependent programmed cell death in macrophages, thereby
268 preventing an effective innate antibacterial response (**Figure 2**) (Shariq *et al.*, 2021). Collectively, RipA
269 contributes to the creation of a permissive replication niche in host cells by altering autophagy and
270 apoptosis. In addition to proteins, the tetra-acylated LM-containing fraction from *M. bovis* BCG activates
271 macrophages in a MyD88-dependent manner through TLR4 (Doz *et al.* 2007) while PIMs induce TLR2-
272 and TLR4-dependent signaling, thus possibly influencing protective immunity (Abel *et al.* 2002).
273 However, the use of bacterial expression systems and the resulting protein agonists may contribute in
274 minute amounts (pico- to nanogram) of LPS, which are sufficient to induce the activation of phagocytes.
275 Resolution of co-structures are needed to definitively validate the described interactions between TLR4

276 with its different bacterial substrates. The role of TLR4 in host resistance to *M. tuberculosis* was also
277 evaluated in C3H/HeJ mice (harboring a point mutation within the coding region of the *tlr4* gene) after
278 aerosol infection (Qureshi *et al.* 1999). C3H/HeJ mice showed a reduced ability to clear mycobacteria
279 from the lungs, favoring the spread of the infection in the spleen and liver and accelerating mortality
280 (Abel *et al.* 2002). The lungs of these animals showed signs of chronic pneumonia and deficits in
281 pulmonary production of TNF- α , IL-12p40 and chemoattractant protein-1 (Abel *et al.* 2002). However,
282 careful interpretation is required when using the C3H/HeJ strain as a model of TLR4-deficient mice as
283 there are significant allelic differences between C3H/HeJ and other C3H mouse substrains. Taken with
284 caution, the data suggest that TLR4 may not be sufficient for optimal immunity against *M. tuberculosis*
285 (Kamath *et al.* 2003). It is likely that TLR4 signaling does not contribute to the initiation of protective
286 responses against low-dose airborne infection to *M. tuberculosis* (Reiling *et al.* 2002; Shim, Turner and
287 Orme 2003). These divergent results may indicate that subtle, but as yet unknown differences in
288 experimental conditions (including the type of mice used, the respective microbiome of these mice and
289 the different specific pathogen-free standards in the animal houses) may be instrumental in determining
290 whether TLR4 functionality is of significance in *M. tuberculosis* infection.

291

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

293 C-type lectin receptors (CLR) are Ca²⁺-dependent glycan-binding proteins, which adopt a C-type lectin
294 fold structure with a highly variable primary protein sequence and possess similarities in the primary
295 and secondary structures of their carbohydrate-recognition domain (CRD). CLR are widely expressed in
296 living organisms (Drickamer 1999) and are made up of a diverse components, including phagocytic
297 receptors and proteoglycans. Adopting both secreted, soluble forms and anchored forms in the plasma
298 membrane, they frequently oligomerize into homodimers, homotrimers and higher ordered oligomers.
299 These structures lend to the interaction with multivalent ligands and recognition of diverse glycans,
300 owing to the unique carbohydrate composition and structure found on the surface of pathogens (Hsu,
301 Pilobello and Mahal 2006). Functionally, CLR can act as adhesion molecules or phagocytic and/or
302 signaling receptors in the innate immune response to microbes and have been highly conserved
303 throughout evolution (Cummings and McEver 2015). Understanding of CLR family-mycobacterial ligand
304 interactions has expanded in recent years and will be discussed below.

305

306 **Collectins**

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

311 The CLR, including human pulmonary surfactant protein A (SP-A, a member of the collectin family
312 produced by lung epithelial cells of the distal and proximal air spaces), have been identified as key
313 players in the early recognition of invading pathogens and initiation of host defense responses. SP-A
314 decorates the surface of *M. tuberculosis* to enhance macrophage adhesion (**Figure 3**) (Ferguson *et al.*
315 1999). Although ManLAM is considered as the ligand of several CLR including DC-SIGN, MR and CR3, the
316 Apa glycoprotein has also been shown to interact with SP-A in a calcium-dependent fashion (Ragas *et al.*
317 2007). Through the interaction with cell wall-associated mycobacterial components, the human lung SP-
318 A acts as an effective opsonin to facilitate attachment of bacilli to macrophages. The surfactant protein
319 D (SP-D) is another collectin produced in the distal airspaces of the lungs. Capable of recognizing
320 carbohydrates through its CRD, SP-D regulates interactions between *M. tuberculosis* and macrophages
321 through the recognition of mannosylated compounds, such as ManLAM (Ferguson *et al.* 1999). Specific
322 binding of SP-D to *M. tuberculosis* causes bacterial agglutination, reduces adhesion to macrophages and
323 decreases its intracellular growth (**Figure 3**) (Ferguson *et al.* 1999; Carlson *et al.* 2009). Together, these
324 observations reveal that SP-A and SP-D play opposite roles in the host innate response to *M. tuberculosis*
325 in the lungs.

326 Another member of the collectin family, the mannose-binding lectin (MBL, produced by the liver
327 and circulating throughout the body) recognizes various slow-growing mycobacteria (e.g., *M.*
328 *tuberculosis*, *M. bovis*, *M. kansasii*, and *M. goodii*) as well as *M. smegmatis*. The molecular
329 recognition of ManLAM and the antigen 85 complex (Ag85) leads to activation of the lectin pathway of
330 the complement system and increases phagocytosis (**Figure 3**) (Bartłomiejczyk *et al.*, 2014, Świerżko
331 *et al.*, 2016). Given MBL's ability to bind fibronectin, it may play an additional role in the interaction of the
332 Ag85 complex with the extracellular matrix. Finally, MBL binding could also favor the uptake of *M.*
333 *africanum* by macrophages, thereby promoting infection and TB-imposed natural selection that could
334 have fostered the spread of functional MBL-G57E variant in *M. africanum* endemic regions (Thye *et al.*
335 2011).

336 While extensive research focus has been given to the interaction of *M. tuberculosis* with
337 phagocytic cells, less is understood about the molecular basis underlying mycobacterial binding and
338 entry with non-phagocytic cells. Among the different cell types investigated, Chinese hamster ovary
339 (CHO) fibroblasts and primary porcine aortic endothelial cells were reported to successfully interact with
340 *M. tuberculosis in vitro*. Binding markedly increases in the presence of 10% to 20% human or bovine
341 serum, suggesting that the bacteria benefit from the coating of serum opsonins (Hoppe *et al.* 1997). Pre-
342 incubation with individual opsonins revealed that recombinant serum-derived human mannose-binding
343 protein (MBP, belonging to the collectin family, possessing one lectin domain and produced in the liver
344 during infection) also improved binding (**Figure 3**). Using PIM-specific antibodies to demonstrate a
345 partial blocking of *M. tuberculosis* and *M. smegmatis*, these surface molecules were found to play a role

346 in binding to CHO and endothelial cells (Hoppe *et al.* 1997). Furthermore, binding of PIM-coated beads
347 to CHO cells was significantly enhanced after addition of MBP-enriched serum (Hoppe *et al.* 1997). These
348 findings confirm that PIM can function as adhesins to bind to non-phagocytic cells both directly and after
349 opsonization with serum MBP.

350

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

352 The serum amyloid A1 (SAA1) protein belongs to the family of apolipoproteins associated with
353 high-density lipoproteins (HDL). These proteins play several roles, including the transport of cholesterol
354 to the liver for secretion into the bile, the recruitment of immune cells to inflammatory sites and the
355 induction of enzymes to degrade the extracellular matrix. The interaction between *M. tuberculosis* and
356 SAA1 occurs through the membrane effectors AtpA (Rv1308), the ABC transporter (Rv2477c), the ESX-1
357 substrate EspB (Rv3881c), the antigen TB18.6 (Rv2140c), and the phosphomethylpyrimidine synthase
358 ThiC (Rv0423c) (**Figure 3**) (Kawka *et al.* 2021). Opsonization of *M. tuberculosis* by SAA1 promotes
359 bacterial entry into phagocytes, stimulates intracellular growth and survival (**Figure 3**) (Kawka *et al.*
360 2021). Despite the protective opsonic behavior of SAA1, the interaction with *M. tuberculosis*
361 inadvertently promotes the infection of host macrophages and modulates the functional response of
362 the pathogen.

363

364 **Mincle and Dectin**

365 Mincle is principally expressed on myeloid cells, including macrophages and DC (Marakalala and
366 Ndlovu 2017). It is composed of a CRD, a transmembrane (TM) domain and a short cytoplasmic tail with
367 a positively-charged residue, which engages with the adaptor molecule FcRγ to trigger intracellular
368 signaling *via* the Syk/CARD9 pathway (**Figure 1**) (Marakalala and Ndlovu 2017). Mincle is an essential
369 receptor for the glycolipid trehalose-6,6'-dimycolate (TDM, also known as cord factor) (Heitmann *et al.*
370 2013), which activates macrophages and downstream inflammatory cytokines and NO (**Figure 1**)
371 (Ishikawa *et al.* 2009). It is also a known adjuvant for Th1/Th17 vaccination that activates Syk-Card9
372 signaling in antigen-presenting cells (APC). Experimental genetic disruption of Mincle showed the
373 complete elimination of TDM-induced macrophage activation and stimulation of T cell immune
374 responses to a TB vaccine (Ag85B-ESAT-6). Moreover, macrophages lacking Mincle or FcRγ exhibit
375 impaired inflammatory responses to *M. bovis* BCG (Schoenen *et al.* 2010). Administration of TDM in
376 wild-type mice triggered elevated inflammatory cytokine levels in sera and lung inflammation associated
377 with granuloma formation (Ishikawa *et al.* 2009), whereas Mincle-deficient mice were still able to mount
378 an effective granulomatous and protective immune response after infection with both low and high
379 doses of *M. tuberculosis* (Heitmann *et al.* 2013). These findings suggest that the loss of Mincle *in vivo*
380 can be fully compensated and a protective inflammatory immune response remained during *M.*

381 *tuberculosis* infection. Mincle has been shown to further induce an immune response in mice following
382 interaction with other mycobacterial ligands, such as trehalose-monomycolate (TMM), glucose-
383 monomycolate (GMM) and arabinose-monomycolate (AraMM). Stimulation with these ligands activate
384 bone marrow-derived DC to produce IL-6, TNF- α and reactive oxygen species (ROS) and stimulate the
385 NLRP3 inflammasome to promote Th1 and Th17 responses (Tima *et al.* 2017). The murine bone marrow-
386 derived DC may also be activated through Mincle signaling after exposure to *M. tuberculosis*'
387 immunogenic β -gentiobiosyl diacylglycerides (Richardson *et al.* 2015). Lastly, unique to the human
388 immune response, Mincle interplays with glycerol-monomycolate (GroMM) to stimulate macrophages
389 for inflammatory cytokines production (Hattori *et al.* 2014).

390 Signaling through Dectin receptors activates the Syk/CARD9/BCL-10/MALT1 cascade (**Figure 1**),
391 resulting in the production of pro-inflammatory cytokines and the induction of T cell-mediated immunity
392 (Marakalala and Ndlovu 2017). Adopting several forms, Dectin-1, Dectin-2 and Dectin-3 have been linked
393 to antimycobacterial immunity. Dectin-1 is a glycosylated TM protein with an extracellular CRD and a
394 cytoplasmic immunoreceptor tyrosine-based activation motif (ITAM)-like domain that supports
395 intracellular signaling (**Figure 1**) (Marakalala and Ndlovu 2017). Dectin-1 is primarily expressed on
396 macrophages, DC, neutrophils and a subset of T cells. Dectin-1 recognizes *M. tuberculosis* and less
397 virulent mycobacterial species, although its mycobacterial ligand(s) remaining largely unknown. Dectin-
398 1-dependent infection of BMDM, DC, A549 cells, PBMC, MDC, neutrophils or monocytes with varied
399 mycobacterial species leads to the production of antimicrobial peptides, ROS and cytokines, such as TNF-
400 α , IL-6, G-CSF, RANTES, IL-12p40, IL-17A, IL-1 β , and IL-23 (**Figure 1**) (Yadav and Schorey 2006; Rothfuchs
401 *et al.* 2007; Lee *et al.* 2009; Zenaro, Donini and Dusi 2009; van de Veerdonk *et al.* 2010; Romero *et al.*
402 2016; Bisiaux *et al.* 2017). Furthermore, DC activated by a Dectin-1 agonist stimulates naïve CD4⁺ T cells
403 to upregulated IFN γ and IL-17 (Zenaro, Donini and Dusi 2009). *Dectin-1*-KO mice infected with *M.*
404 *tuberculosis* had a significantly decreased lung bacillary loads but developed histological signs of
405 pneumonia (Marakalala *et al.* 2011). Additionally, the loss of Dectin-1 did not result in any significant
406 variations across the pulmonary cytokine expression profiles when compared to control mice
407 (Marakalala *et al.* 2011). Thus, Dectin-1 does not appear to play a major role in immunity against *M.*
408 *tuberculosis in vivo*, understanding limited applicability due to the use of a murine model. The structure
409 of Dectin-2 consists of a CRD, a TM and a short cytoplasmic tail and is mainly expressed on macrophages,
410 certain subsets of DC and peripheral blood monocytes (Marakalala and Ndlovu 2017). Surface-
411 associated Dectin-2 specifically recognizes ManLAM in BMDC, resulting in the production of pro- and
412 anti-inflammatory cytokines (**Figure 1**), and these effects are reversed in *Dectin-2*^{-/-} BMDC (Yonekawa *et al.*
413 *et al.* 2014). Upon mycobacterial infection, *Dectin-2*^{-/-} mice exhibit increased lung pathology,
414 demonstrating that this receptor is a key factor in host immunity against mycobacterial infection, at
415 least in the mouse model. The remaining type of Dectin, Dectin-3, recognizes TDM, stimulates Mincle

416 expression through the CARD9-Bcl10-MALT1 complex, and binding of NF- κ B to the Mincle promoter
417 enhances host immunity to mycobacterial infection. Consistent with these findings, Dectin-3- or CARD9-
418 deficient mice produce significantly less pro-inflammatory cytokines and KLH-specific antibodies after
419 immunization with a TDM-containing adjuvant (Zhao *et al.* 2014).

420

421 **Dendritic cell immune activating receptor**

422 DC immune activation receptor (DCAR) is expressed on peritoneal macrophages and monocyte-
423 derived inflammatory cells in the lungs and spleen. It lacks an immunoreceptor tyrosine-based inhibitory
424 motif (ITIM) in its intracellular domain (Toyonaga *et al.* 2016; Omahdi *et al.* 2020). However, it possesses
425 a positively-charged amino acid in its TM, allowing protein-protein interactions with FcR γ , which supplies
426 the immunoreceptor tyrosine-based activation motif (ITAM) required for DCAR-dependent signaling
427 (Omahdi *et al.* 2020). Macrophages and monocytes produce the MCP-1 chemokine upon exposure to
428 PIM, a function that is modulated through DCAR, which interacts directly with acylated PIM (Ac₁PIM₁,
429 AcPIM₂ and Ac₂PIM₂) (Toyonaga *et al.* 2016; Arai *et al.* 2020). In the absence of DCAR or FcR γ , MCP-1
430 production is halted, as was observed in DCAR-deficient mice (Toyonaga *et al.* 2016). Upon
431 mycobacterial infection, *Dcar*-KO mice showed reduced numbers of monocyte-derived inflammatory
432 cells at the site of infection, decreased IFN γ production by T cells and increased bacterial loads, thus
433 revealing that an adequate T cell response against mycobacteria requires DCAR (Toyonaga *et al.* 2016).

434

435 **DC-SIGN and its murine homologs**

436 Interactions between DC and the *M. tuberculosis* complex play a key role in anti-mycobacterial
437 immunity. *M. tuberculosis* gains entry to DC through the interaction between DC-SIGN and ManLAM or
438 LAM (Maeda *et al.* 2003; Tailleux *et al.* 2003), with the acyl chains of the ManLAM's
439 mannosylphosphatidylinositol anchor and the manooligosaccharide caps acting as the primary
440 interface (Maeda *et al.* 2003). Although mannose-capped LAM molecules are present across
441 mycobacterial species, DC-SIGN discriminates between these permutations and selectively recognizes
442 *M. tuberculosis*. For instance, *M. smegmatis*-derived LAM, capped with phosphatidylinositol (PILAM),
443 has a limited ability to bind DC-SIGN in the presence of *M. tuberculosis*. Furthermore, DC-SIGN interacts
444 poorly with PILAM and with the uncapped AraLAM molecules from *M. fortuitum* or *M. chelonae*,
445 respectively, or with *M. avium* single mannose residue-capped ManLAM (Maeda *et al.* 2003). Despite
446 this, the removal of the mannose caps in a Δ *pimE* mutant (PimE/Rv1159 catalyzes the transfer of the
447 fifth mannose to PIM₄ to generate PIM₅) fails to reduce the interaction of whole mycobacteria with DC-
448 SIGN (Driessen *et al.* 2009), suggesting that the receptor is likely to interact with additional ligands.
449 Indeed, DC-SIGN has also a strong affinity for hexamannosylated PIM₆ (**Figure 2**) (Driessen *et al.* 2009;
450 Ehlers 2010). *M. bovis* BCG mutants lacking PIM₆ (single mutant) or PIM₆ and mannose capping on LAM

451 (double mutant) (Driessen *et al.* 2009) still show similar binding affinity to DC-SIGN and DC and induce
452 comparable levels of IL-10 and IL-12p40 as the wild-type strain. Furthermore, infection studies with
453 these strains have established that the ManLAM/PIM-DC-SIGN interaction was not critical for protective
454 immunity in mice (Ehlers 2010), strengthening the view that while ManLAM and PIM₆ are true ligands
455 of DC-SIGN, additional ligands are likely to govern the interaction between mycobacteria and DC *in vivo*.
456 This notion is further supported by other studies reporting the binding of multiple ligands to DC-SIGN,
457 including LM, PIM₂, α -glucan (a dominant capsular polysaccharide), the 19-kDa or the 45-kDa
458 mannosylated Apa glycoproteins (**Figure 2**) (Pitarque *et al.* 2005; Torrelles, Azad and Schlesinger 2006;
459 Geurtsen *et al.* 2009; Sawettanai *et al.* 2019).

460 The consequences of DC-SIGN-mediated interactions between mycobacterial ligands and DC are
461 multifold. *M. tuberculosis* and *M. bovis* BCG (through ManLAM) bind to DC-SIGN, halting DC maturation,
462 impeding IL-12 release and inducing IL-10 secretion (Geijtenbeek *et al.* 2003; Gagliardi *et al.* 2005; Wu
463 *et al.* 2011). Similarly, binding of the *M. tuberculosis* α -glucan to DC-SIGN stimulates immunosuppressive
464 IL-10 production by DC (**Figure 2**) (Geurtsen *et al.* 2009). This behavior is mirrored during ManLAM or
465 PIM₆ interactions with DC-SIGN in immature DC and macrophages, impairing DC maturation and
466 modulating cytokine secretion by phagocytes and DC, leading to overall suppressed protective immunity
467 to TB (Ehlers 2010). Furthermore, IFN γ levels have been showed to be significantly down-regulated in
468 the supernatants of naïve T cells after co-culture of ManLAM-primed DC (Wu *et al.* 2011). The same
469 phenotype was described in a clinical study reporting that overexpression of DC-SIGN in TB patients
470 decreased DC activation, elevated secretion of IL-10 by DC, decreased induction of T cell proliferation
471 and impaired the immune response (Zhang, Guo and Luo 2009). Nevertheless, *M. tuberculosis* infection
472 of human DC-SIGN-transgenic mice revealed that DC-SIGN can promote host protection by limiting
473 tissue pathology (Ehlers 2010). DC can also target and eliminate *M. tuberculosis*-infected apoptotic
474 neutrophils following the association between neutrophil Mac-1 protein (CD11b/CD18) and DC-SIGN,
475 thereby reducing inflammation (Hedlund *et al.* 2010). Reduced inflammation was further shown in an *in*
476 *vivo* experiment exposing DC to synthetic mannodendrimers mimicking the ManLAM of *M. tuberculosis*,
477 revealing the cells' pro-inflammatory cytokine production to be inhibited in a DC-SIGN-dependent
478 manner, limiting acute neutrophil influx in mice lungs (Blattes *et al.* 2013).

479 In *M. leprae*, the etiological agent of leprosy, infection severity is a function of DC-SIGN expression
480 levels and the interaction with ManLAM. When treated with *M. leprae*-specific ManLAM, DC upregulate
481 DC-SIGN expression, resulting in an increased nuclear translocation of NF- κ B and potent IL-10
482 production. This promotes an immunosuppressive environment during leprosy progression, creating an
483 optimal niche for bacterial persistence in the host (Kumar *et al.* 2013a). Overall, pathogenic
484 mycobacteria capitalize on the DC-SIGN-ManLAM interaction through the prevention of DC maturation
485 and induction of the immunosuppressive IL-10, permitting enhanced survival and persistence (**Figure 2**).

486 To further understand the function of DC-SIGN in anti-TB immunity, parallel murine studies were
487 undertaken. Among the eight murine homologs (SIGNR1-8), SIGNR1 and SIGNR3 are the closest analogs
488 to DC-SIGN. SIGNR1 is expressed by macrophages only, and interacts with *M. tuberculosis* through
489 ManLAM, similar to DC-SIGN (Koppel *et al.* 2004; Wieland *et al.* 2007). Peritoneal macrophages from
490 *Signr1*-KO mice produce less IL-10 upon stimulation with ManLAM than those from wild-type mice,
491 suggesting that the interaction of ManLAM with SIGNR1 may result in similar immunosuppression
492 observed in the human equivalent (Wieland *et al.* 2007). Another *in vivo* study showed that SIGNR1
493 upregulates SOCS1 expression during *M. tuberculosis* infection, impairs IL-12 production and promotes
494 *M. tuberculosis* survival (Srivastava *et al.* 2009). Moreover, upon stimulation of murine DC with C-type
495 lectin ligand LAM, SIGNR1 significantly suppresses NF- κ B activation as well as TNF α , IL-6 and IL-12p40
496 production (Ohtani *et al.* 2012). In contrast to the observations in *Signr1*-KO mice, *Signr3*-KO mice were
497 the only group to display dampened resistance to *M. tuberculosis*. SIGNR3 is expressed by lung
498 phagocytes during infection and interacts with *M. tuberculosis* surface glycoconjugates to induce, in
499 synergy with TLR2, the secretion of inflammatory cytokines critical for host defense, including TNF and
500 IL-6, confirming the protective role of murine SIGNR3 during the infection (Tanne *et al.* 2009; Tanne and
501 Neyrolles 2010).

502

503 **Mannose receptor**

504 The mannose receptor (MR) is an eight lectin-domain transmembrane protein capable of binding
505 carbohydrate ligands including terminal mannose-containing glycoconjugates, fucose and GlcNAc
506 (Martinez-Pomares 2012). MR recognizes mycobacterial surface ManLAM (**Figure 2**), LAM, AraLAM,
507 acylated PIMs, LM, glycosylated and acylated 19-kDa antigen and PstS-1 (a 38-kDa mannosylated
508 glycolipoprotein) (Schlesinger, Hull and Kaufman 1994; Diaz-Silvestre *et al.* 2005; Torrelles, Azad and
509 Schlesinger 2006; Esparza *et al.* 2015). The MR facilitates the adhesion of *M. tuberculosis* strains to
510 human MDM. Playing a role in adhesion, MR facilitates non-opsonic phagocytosis of *M. smegmatis* by
511 binding to surface glycopeptidolipids (GPL) (**Figure 2**) (Schlesinger 1993; Villeneuve *et al.* 2005). MR was
512 recently shown to internalize fluorescent beads coated with the triglycosylated form of GPL (GPL-3)
513 through the internal and external rhamnose residues linked to the alaninol residue (Daher *et al.* 2022).
514 After phagocytosis, maturation of the phagosome (**Figure 2**) only takes place at the point of fusion with
515 the lysosomal Hck compartment (a Src family tyrosine kinase used as a marker of lysosome-phagosome
516 fusion in human cells), providing an opportunity for mycobacteria to inhibit this process through MR-
517 ManLAM interaction (**Figure 2**) (Astarie-Dequeker *et al.* 1999; Kang *et al.* 2005). Specifically, it is the
518 ManLAM mannose cap structures that prevent the phagosome-lysosome fusion, and experimentally, it
519 has been shown that the fully intact ManLAM molecule is required to maintain this phenotype (Kang *et al.*
520 *et al.* 2005). The arrest of phagosome-lysosome fusion has also been observed in *M. avium* serovar 4

521 through the GPL-MR interaction (**Figure 2**) (Shimada *et al.* 2006), causing downstream suppression of
522 EEA1 and Ca²⁺/calmodulin kinase II recruitment in THP-1 cells (Shimada *et al.* 2006). Internalization *via*
523 the MR not only inhibits phagosome-lysosome fusion but also blocks the production of cytokines that
524 target mycobacteria. ManLAM, after cross-linking with MR, inhibits TLR2-induced IL-12 production in
525 human DC (Nigou *et al.* 2001). A subsequent study confirmed the ManLAM-MR engagement reduces
526 inflammation by both inducing the production of anti-inflammatory factors IL-10 (IL-1R antagonist) and
527 IL-1R type II, and suppressing IL-12 secretion by human DC (Chieppa *et al.* 2003). In THP-1 cells, the
528 induction of matrix metalloproteinase-9 (MMP-9) production by MR in response to *M. tuberculosis* and
529 LAM is also a contributing factor to lung tissue damage during *M. tuberculosis* infection (Rivera-Marrero
530 *et al.* 2002). Overall, these studies demonstrate that MR plays a multi-faceted role in promoting a
531 favorable mycobacterial infection niche in phagocytes.

532

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

534 CR3 is a heterodimeric surface receptor that belongs to the integrin superfamily, comprising
535 CD11b and CD18 (**Figure 4**). It has multiple binding sites located in the C-terminal lectin domain, which
536 can mediate both opsonic and non-opsonic phagocytosis (Velasco-Velázquez *et al.* 2003). Several studies
537 have evaluated the role of CR3 in mycobacterial infections, highlighting its involvement in early binding
538 events during infection (**Figure 4**) (Stokes, Thorson and Speert 1998; Velasco-Velázquez *et al.* 2003).
539 Monoclonal antibodies against CR3 inhibit adhesion and phagocytosis of virulent *M. tuberculosis* by
540 human monocytes. Thermally inactivated serum similarly reduced *M. tuberculosis* adhesion, and
541 replenishment of component C3 or factor B (part of the alternative complement pathway, cleaved by
542 factor D to yield a protease that associates with C3b to form the C3 convertase) increased adhesion
543 (Schlesinger *et al.* 1990; Schlesinger 1993). This was also observed *in vivo* in *Itgam*^{-/-} (CR3 negative) mice
544 where non-opsonic binding and serum-mediated opsonic attachment of *M. tuberculosis* to resident
545 macrophages was significantly reduced (Melo *et al.* 2000; Rooyackers and Stokes 2005). Downstream of
546 internalization, *M. tuberculosis* survival and replication in infected macrophages and mice were not
547 significantly affected by the absence of ITGAM/CD11b, suggesting that CR3-mediated uptake is not a
548 major factor contributing to intracellular survival (Hu *et al.* 2000; Melo *et al.* 2000). Consistently, MDM
549 exhibit enhanced adherence of BCG and *M. leprae* and the attachment process is CR3- and/or serum-
550 dependent, i.e. requiring thermolabile serum components (Schlesinger and Horwitz 1990, 1991; Launois
551 *et al.* 1992). Mechanistically, the C-terminal lectin domain of CR3 recognizes LAM, PIM₂ and polar GPL
552 (**Figure 4**) (Villeneuve *et al.* 2005). In addition, Ag85C promotes the uptake of BCG and *M. tuberculosis*
553 by monocytes through ligation to CR3 (**Figure 4**) (Hetland and Wiker 1994). Furthermore, Rv0180c
554 promotes the infection initiation in the lungs of mice and facilitates entry into macrophages through
555 CR3 (Payros *et al.* 2021). The cooperation between CR3 and TLR2 appears fundamental to inhibit the

556 release of peroxidase by eosinophils, which in turn modulate the innate immune response to
557 mycobacteria (Driss *et al.* 2012). Thus, CR3 is important in mycobacterial uptake but is not needed for
558 the induction of the microbicidal machinery and thus favors the survival of intracellular bacteria.

559

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

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

567

568 **Galectin receptors**

569 Galectins are a large class of proteins serving multiple cellular roles including signaling and
570 adhesion. They are considered S-type lectins due to the presence of disulfide bonds, which function to
571 provide stability and the binding of carbohydrates, including nitrogen- or oxygen-linked β -galactoside
572 sugars. Found in a variety of species, there are 15 mammal-specific galectins, which are further
573 subdivided into three forms: chimera, tandem, and dimeric. Although most lectins exist as membrane-
574 bound proteins, galectins are unique in their soluble state. Tandem galectins, such as Galectin-9, possess
575 two distinct CRD whereas the chimeric Galectin-3 exists as a monomer or a multivalent form. Galectin-
576 3's multifunctionality lends itself to be found both primarily in the cytoplasm and additionally on the cell
577 surface of immune cells. At the surface, it is known to recognize mycolic acids (MA), the major lipid of
578 the mycobacterial cell envelope, yet the nature of this interaction is still not fully understood (Barboni,
579 Coade and Fiori 2005). More has been discovered regarding the biological role of Galectin-9, particularly
580 with its physical interaction with the essential cell wall polysaccharide, arabinogalactan (AG), during
581 mycobacterial infection (**Figure 2**). Structural-functional relationship analyses indicate that the high-
582 affinity interaction between AG and Galectin-9's CRD2 causes the latter to associate with transforming
583 growth factor β -activated kinase 1 (TAK1) to trigger the activation of extracellular signal-regulated kinase
584 (ERK) and the induction of matrix metalloproteinases (MMP) expression (**Figure 2**) (Wu *et al.* 2021).
585 These pathways contribute to AG-induced damage in the lungs and have been shown to aggravate the
586 *M. tuberculosis* infection in mice by promoting bacilli survival (**Figure 2**) (Wu *et al.* 2021). Therefore,
587 interaction between AG and Galectin-9 may serve as a viable target for therapeutic development to
588 reduce the severity of TB pathology (Wu *et al.* 2021).

589

590

591 **Other receptors**

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

593 Following internalization, mycobacteria typically inhabit the phagosomal compartment, however,
594 sporadic escape into the cytoplasm (Houben *et al.* 2012) exposes the bacteria to intracellular receptors,
595 including the nucleotide-binding oligomerization domain (NOD)-like receptors (NLR). The NLR member
596 NOD2 detects the N-glycolyl-muramyl dipeptide (MDP) component of peptidoglycan in the
597 mycobacterial cell wall (**Figure 1**) (Coulombe *et al.* 2009). More specifically, NOD2 is stimulated by the
598 N-acetyl muramic acid hydroxylase, NamH, which converts MDP into a N-glycolylated form (Coulombe
599 *et al.* 2009). Accordingly, disruption of *namH* in *M. smegmatis* and *M. tuberculosis* abrogates NOD2-
600 mediated TNF- α secretion in macrophages (Coulombe *et al.* 2009; Hansen *et al.* 2014) and NOD2-
601 dependent immune responses were confirmed to be contingent on the presence of NamH in a murine
602 study (Coulombe *et al.* 2009). Further still, N-glycolyl MDP promotes the secretion of pro-inflammatory
603 cytokines (TNF- α , IL-1 β , IL-6) (**Figure 1**) and induces T-cell immunity in a NOD2-dependent manner
604 (Coulombe *et al.* 2009; Juárez *et al.* 2012). During *M. tuberculosis* infection, NOD2 induces expression of
605 the antimicrobial peptide LL37, recruits the autophagy proteins IRGM, LC3, and ATG16L1 to the bacteria-
606 containing autophagosome (**Figure 1**) (Juárez *et al.* 2012), and increases NO production upon NF- κ B
607 activation (**Figure 1**) (Landes *et al.* 2015). Synergistic effect of MDP combined to Hsp70 increases IL-6,
608 IL-12p40, and TNF- α production in BMDC, enhances DC maturation and promotes T cell IFN γ production,
609 while accordingly these effects were diminished in NOD2-deficient BMDC (Kim *et al.* 2015). In mice,
610 intraperitoneal injection of MDP together with Hsp70 increased the seric production of IL-6, CXCL-1, and
611 CCL2 (Kim *et al.* 2015), suggesting these combined proteins could be harnessed for an effective
612 vaccination strategy. NOD2 has also been identified in the pathogenesis of other mycobacterial
613 infections, including *M. leprae*, where the induction of IL-32 and differentiation of monocytes into DC in
614 the innate immune response occurs in a NOD2-dependent manner (Schenk *et al.* 2016). Similarly, new
615 insights into the potential roles of NOD2 during innate immune activation against *M. abscessus* lung
616 infections have recently emerged. The production of pro-inflammatory cytokines and NO to limit
617 intracellular growth, eliminate bacteria and ultimately ameliorate lung pathology in *M. abscessus*-
618 infected mice has been shown to hinge on the presence of NOD2 (Lee *et al.* 2017). These collective data
619 demonstrate that NLR, and frequently NOD2, are central to the host defense and reduction of
620 mycobacterial survival.

621

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

623 The recognition of microbial components in the cytosol is critical for initiating an innate immune
624 response against intracellular pathogens. The cytosolic DNA sensor cyclic GMP-AMP synthase (cGAS) is
625 essential for triggering STING-dependent signaling and initiating type I interferons (IFN-I) IFN- α and IFN-

626 β as central messengers in the host response against bacterial infections. Cyclic GAMP (cGAMP)
627 synthesis is stimulated by the association of cGAS with cytosolic *M. tuberculosis* DNA (**Figure 1**)
628 (Wassermann *et al.* 2015). The ESX-1 mycobacterial secretion system is required for the cytosolic
629 surveillance pathways to be activated during *M. tuberculosis* infection, which results in the generation
630 of IFN *via* the STING/TBK1/IRF3 pathway (**Figure 1**) and in interleukin-1 β (IL-1 β) synthesis (Wassermann
631 *et al.* 2015; Watson *et al.* 2015). In this way, cGAS promotes autophagic targeting and clearance of *M.*
632 *tuberculosis* (Watson *et al.* 2015). Similarly, in DC, type I IFN and its cognate receptor (IFNAR), in concert
633 with the cGAS signaling pathway, act against *M. bovis* infection by promoting phenotypic maturation
634 and functional activation of DC and also by increasing CD4⁺ T cell proliferation with DC (Li *et al.* 2019).
635 However, not all mycobacteria species stimulate the cGAS pathway to trigger IFN production. In
636 comparison to *M. smegmatis*-infected macrophages, those infected with *M. avium sbsp.*
637 *paratuberculosis* (MAP) produce much less IFN- β (Ruangkiattikul *et al.* 2017). This could be explained by
638 the fact that TBK1 is phosphorylated at higher rates in *M. smegmatis* and that there is more extracellular
639 bacterial DNA present in the cytosol (most likely as a result of bacterial autolysis, which releases more
640 DNA needed to effectively activate the cGAS/STING cascade). This is also true in a mouse model, where
641 *M. smegmatis*-induced high IFN- β production and bacterial clearance are correlated. But MAP only
642 slightly increases IFN- β expression, which is associated with bacterial persistence and enhanced hepatic
643 granuloma formation (Ruangkiattikul *et al.* 2017). As predicted, *M. smegmatis* survival was increased in
644 mice lacking IFNAR, although MAP survival was equivalent in *Ifnar*^{-/-} and wild-type mice (Ruangkiattikul
645 *et al.* 2017). Overall, cGAS is as an innate sensor of mycobacteria and contributes to the elimination of
646 the bacilli.

647

648 **CD43 receptor**

649 Found on the surface of all hematopoietic cells, CD43/SPN (sialophorin) is a large sialylated
650 glycoprotein essential in the general immune response to mycobacteria and the optimal uptake by
651 macrophages. *M. tuberculosis* engages various chaperones, Cpn60.2/Hsp65/GroEL and to a lesser extent
652 DnaK/Hsp70, as bacterial adhesins that bind to CD43 on the surface of human macrophages (**Figure 1**)
653 (Hickey *et al.* 2010). CD43 is required for optimal uptake and inhibition of *M. tuberculosis* growth both
654 *in vitro* and *in vivo*. Mechanistically, binding of Cpn60.2 to CD43 stimulates macrophages to produce
655 TNF- α , IL-12, and IL-6 to control *M. tuberculosis* infection (**Figure 1**) (Randhawa, Ziltener and Stokes
656 2008; Torres-Huerta *et al.* 2017). The signaling pathway leading to TNF- α production upon interaction
657 with Cpn60.2 necessitates the Src family kinases, phospholipase C- γ (PLC- γ), phosphatidylinositol 3-
658 kinase (PI3K), p38, and Jun N-terminal protein kinase (JNK) in both BMM and THP-1 cells (**Figure 1**)
659 (Torres-Huerta *et al.* 2017). Furthermore, CD43 is involved in the inflammatory response to *M.*
660 *tuberculosis* and, through the induction of pro-inflammatory mediators, regulates apoptosis to control

661 intracellular bacterial growth (Randhawa, Ziltener and Stokes 2008). Similarly, the absence of CD43 in
662 *M. tuberculosis*-infected mice (*Spn*^{-/-}) increases the bacterial loads during the acute and chronic phases
663 of infection and the rapid development of granulomas (Randhawa *et al.* 2005). Furthermore,
664 macrophage CD43 is required for optimal induction of TNF- α production by *M. avium* (Fratuzzi *et al.*
665 2000). This emphasizes the importance of CD43 in promoting a stable interaction of mycobacteria with
666 cells allowing the host to respond primarily through TNF- α production.

667

668 **Scavenger receptors**

669 Scavenger receptors (SR) are a diverse group of cell surface receptors. They are involved in a
670 variety of processes, including pathogen clearance. SR are mainly found on myeloid cells and are
671 organized into several different classes. Class A receptors, such as MARCO, are mainly expressed on
672 macrophages and bind to ligands *via* their collagen-like domain. Macrophages expressing MARCO
673 receptors secrete pro-inflammatory cytokines in response to TDM by cooperation between MARCO and
674 TLR2/CD14 (**Figure 1**). Indeed, MARCO is used to tether TDM to the macrophage and to activate the
675 TLR2 signaling pathway that also requires CD14 (**Figure 1**) (Bowdish *et al.* 2009). As expected,
676 macrophages from *Marco*^{-/-} mice are defective in the activation of extracellular signal-related kinase 1/2
677 (ERK1/2) and subsequent production of pro-inflammatory cytokines in response to TDM or *M.*
678 *tuberculosis* infection (**Figure 1**) (Bowdish *et al.* 2009). In diabetic mice, the expression level of MARCO
679 is reduced, which restricts *M. tuberculosis* internalization by macrophages and indirectly contributes to
680 a defective sentinel function of alveolar macrophages, promoting susceptibility to TB (Martinez *et al.*
681 2016).

682 CD36 is classified as a scavenger B receptor (SR-B) and possesses two TM domains with an
683 extracellular loop. CD36 recognizes mycobacterial ligands such as LprA (Drage *et al.* 2009) or diglycerides
684 (Martin *et al.* 2011) and serves as a co-receptor for TLR2 by enhancing the recognition of specific
685 bacterial-derived diacylglycerides (Jimenez-Dalmaroni *et al.* 2009). In contrast to MARCO, CD36 plays a
686 permissive function to mycobacterial infection and may enhance mycobacterial uptake (Philips, Rubin
687 and Perrimon 2005). CD36 interacts with the surfactant lipid (composed of 90% lipids, particularly
688 phospholipids, and 10% proteins) to mediate uptake by human macrophages and, therefore, *M.*
689 *tuberculosis* exploits this function for its growth (**Figure 2**) (Dodd *et al.* 2016). In addition, treatment of
690 macrophage with ManLAM and its deacylated form promotes TNF- α production and inhibits NO
691 secretion by engaging CD36 (**Figure 2**) (Józefowski *et al.* 2011). *In vivo*, CD36 plays a critical role in cellular
692 events involved in granuloma formation that promote early bacterial expansion and dissemination. In
693 *Cd36*^{-/-} mice, mycobacterial loads are reduced in the liver and spleen and infection is associated with
694 reduced granuloma density and decreased levels of circulating TNF- α (Hawkes *et al.* 2010). However,
695 these observations were countered by another study demonstrating the functional redundancy

696 between SR other PRR, which may cooperate in a coordinated response to support the complete
697 immune control of *M. tuberculosis* infection. Therefore, dual deficiency of SR-A/CD204 and CD36 had a
698 limited effect on mycobacterial uptake by macrophages, TNF response, and long-term control of *M.*
699 *tuberculosis* infection (Court *et al.* 2010).

700

701 **Fcγ receptors**

702 Fcγ receptors (FcγR) belong to the immunoglobulin superfamily and are known to induce
703 phagocytosis of opsonized pathogens. This family includes several members, FcγRI (CD64), FcγRIIA
704 (CD32A), FcγRIIB (CD32B), FcγRIIIA (CD16a), FcγRIIIB (CD16b), which differ in their affinity to antibodies.
705 The role of FcγR in mycobacterial infections is not completely elucidated but a few studies showed either
706 a restrictive or a permissive impact on bacilli survival. As an example of restriction, during the chronic
707 phase of TB, PPD-specific IgG1 antibodies (which bind to FcγR) are upregulated and contribute
708 significantly to increased pro-inflammatory cytokine secretion by monocytes (Hussain *et al.* 2001). In
709 addition, antibodies opsonized against live *M. tuberculosis* have been shown to induce elevated
710 intracellular calcium release, which promotes maturation and acidification of bacilli-containing
711 phagosomes, reducing the intracellular viability of *M. tuberculosis* (**Figure 1**) (Malik, Denning and Kusner
712 2000). Therefore, both studies indicate that Fcγ receptor expression provides control of infections
713 caused by pathogenic mycobacteria. In contrast, CD32B engagement attenuates the Th1 response, IL-
714 12 production, APC activation, and increases susceptibility to *M. tuberculosis* infection (**Figure 2**). Upon
715 *M. tuberculosis* infection, CD32B-deficient C57BL/6 mice exhibited enhanced mycobacterial clearance
716 and reduced immunopathology compared with wild-type controls. These outcomes are consistent with
717 increased pulmonary Th1 responses and production of large amounts of IL-12 (Maglione *et al.* 2008).
718 The CD32B-induced signaling pathway also interferes with those of Mincle and FcγR and, consequently,
719 causes a delay in phagosome maturation, thereby promoting mycobacterial survival in host
720 macrophages (Patin *et al.* 2017).

721

722 **TREM2 receptor**

723 The TREM2 receptor is a TM protein that possesses an extracellular region (also called
724 ectodomain). The ectodomain of TREM2 can bind to glycoproteins and lipids. The intracellular
725 component of TREM2 does not contain any signaling ability on its own but rather works in tandem with
726 the activator proteins 10 and 12 (DAP10, DAP12) to elicit a downstream signal (**Figure 2**). TREM2 is found
727 in myeloid cells, such as macrophages, monocytes and DC. Mycobacteria use mycolic acids (MA) to
728 control host immunity *via* TREM2. Indeed, macrophages respond to glycosylated MA in a
729 Mincle/Fcγ/CARD9-dependent manner to produce inflammatory cytokines and recruit inducible nitric
730 oxide synthase (iNOS)-positive mycobacterial macrophages to clear the mycobacterial infection (**Figure**

731 **2)** (Iizasa *et al.* 2021). To counteract this effect, macrophages respond to non-glycosylated MA in a
732 TREM2/DAP12-dependent manner to recruit iNOS-negative macrophages (Iizasa *et al.* 2021). Therefore,
733 TREM2-DAP12 signaling counteracts Mincle-FcRγ-CARD9-mediated anti-mycobacterial immunity to
734 evade the immune response.

735

736 **CD14 receptor**

737 CD14, primarily produced by macrophages, helps detect bacteria by binding to various PAMP. In
738 mycobacteria, the LM or LAM lipid anchor and Cpn60.1 bind to CD14 (Yu *et al.* 1998; Lewthwaite *et al.*
739 2001; Ellass *et al.* 2007). Mycobacteria have developed strategies to exploit CD14 in order to evade the
740 host immune system. Among these, *M. tuberculosis*-derived PG and ManLAM expand a subset of CD14⁺
741 DC with a low capacity to produce IL-12p70 (Søndergaard *et al.* 2014). This process blocks the ability of
742 naïve CD4⁺ T cells to efficiently produce IFN γ , abrogates IL-12p70 production by *M. tuberculosis*-
743 challenged DC and disrupts the synergic action between *M. tuberculosis*-infected macrophages, IFN- γ -
744 producing CD4⁺ T cells and IL-12p70-producing DC (Søndergaard *et al.* 2014). Through binding to PIM₁
745 or PIM₂, mycobacteria inhibit TNF release and host inflammatory responses in a CD14-dependent
746 manner (**Figure 2**) (Court *et al.* 2011). *M. tuberculosis* stimulates also CD14 monocytes to increase the
747 production of two hyaluronan and IL-10, which promote bacillary growth or modulate the immune
748 response (Shams *et al.* 2003; Dhiman *et al.* 2011). However, by acting with other receptors, CD14 plays
749 a restrictive role in the course of infection. Stimulation of TLR2/1/CD14 by the lipoprotein LpqH activates
750 antibacterial autophagy through activation of vitamin D receptor signaling and induction of cathelicidin
751 (**Figure 1**) (Shin *et al.* 2010). Furthermore, MARCO-expressing macrophages secrete pro-inflammatory
752 cytokines in response to TDM through cooperation between MARCO and TLR2/CD14 (**Figure 1**) (Bowdish
753 *et al.* 2009). Other studies suggest that LM from *M. chelonae* or *M. kansasii* induce TNF- α and IL-8
754 secretion through a CD14/TLR2-dependent mechanism (Vignal *et al.* 2003). AraLAM has the ability to
755 induce, in a CD14-dependent manner, monocyte chemotaxis that could be detrimental to mycobacteria
756 *in vivo* by maximizing the recruitment of additional alveolar macrophages or peripheral blood
757 monocytes to the infection site (Bernardo *et al.* 1998). Although a significant role for CD14 in
758 antimycobacterial protection *in vivo* has not been substantiated (Ehlers *et al.* 2001), CD14 contributes
759 to pulmonary inflammation and mortality during murine TB. During chronic infection, *Cd14*-KO mice are
760 protected from lethality due to a reduced inflammatory response (Wieland *et al.* 2008). This conclusion
761 is supported by another study indicating that LM may play a functional role in the immunopathology of
762 TB through CD14-dependent secretion of MMP-9, which is directly involved in tissue destruction in TB
763 patients (Elass *et al.* 2007). Additionally, CD14 facilitates also the internalization of the bacilli by host
764 cells (**Figure 4**). In THP-1 and CHO cells, a cross-talk between CD14 and CR3 promotes phagocytosis of
765 mycobacteria (Sendide *et al.* 2005). In addition, *M. bovis* strain TMV 401 selectively infects alveolar

766 macrophages subpopulations, particularly in those expressing high levels of CD14 (Khanna *et al.* 1996).
767 CD14 may facilitate also the entry of *M. tuberculosis* into brain macrophages (Peterson *et al.* 1995).

768

769 **CD40 receptor**

770 CD40 is a member of the TNF-receptor superfamily found on antigen-presenting cells, including DC,
771 B cells, and macrophages. In macrophages, the primary signal for activation is IFN γ from Th1-type CD4⁺
772 T cells. The secondary signal is CD40L (CD154) on the Th1 cell, which binds to CD40 on the macrophage
773 cell surface. As a result, the macrophage expresses more CD40 and TNF receptors on its surface, which
774 contributes to the increased level of activation, high production of microbicidal substances, including
775 ROS and NO, and destruction of the ingested microbe. Specific to *M. tuberculosis* infection, mucosal T-
776 helper cells producing IFN γ (Th1) and IL-17 (Th17) are important for protecting against TB. To this end,
777 *M. tuberculosis* alters CD40 expression on DC and restricts Th1 and Th17 responses. As a result, CD40-
778 deficient DC are unable to induce antigen-specific IL-17 responses after infection (Sia *et al.* 2017).
779 Intratracheal instillation of *M. tuberculosis*-infected DC treated with CD40LT (a multimeric CD40 agonist)
780 significantly enhanced antigen-specific Th17 responses in mice (Sia *et al.* 2017). Furthermore, enhanced
781 CD40-CD40L interactions promote better control of lung bacterial loads after aerosol challenge with *M.*
782 *tuberculosis* (Sia *et al.* 2017). Thus, targeting the CD40-CD40L pathway represents a novel strategy to
783 improve adaptive immunity against TB. Another CD40-dependent pathway is also important for
784 combatting *M. tuberculosis* infections, based on the stimulation by CD40 and TLR-4 that induces DC to
785 increase their production of IL-12, IL-6, and TNF- α and to upsurge autophagy (Khan *et al.* 2016). *M.*
786 *tuberculosis* Hsp70 elicits IL-12 and RANTES production by DC and serves as a ligand for CD40 (**Figure 1**)
787 (Wang *et al.* 2001; Lazarevic *et al.* 2003). This stimulation is an effective host-directed therapy against
788 *M. tuberculosis* because it amplifies the pool of memory CD4⁺ T cells as well as CD8⁺ T cells and effectively
789 contributes to reducing the bacterial burden in the lungs (**Figure 1**) (Khan *et al.* 2016). Moreover, CD40
790 stimulation of DC enhances immune responses to *M. tuberculosis* infection. Importantly, BCG-infected
791 DC stimulated with CD40 show an increased ability to release bioactive IL-12 and activate IFN γ -producing
792 T cells *in vitro* (Méndez-Samperio, Ayala-Verdin and Trejo-Echeverria 1999; Demangel *et al.* 2001).
793 Additionally, when C57BL/6 mice are immunized with these DC and challenged with aerosol containing
794 *M. tuberculosis*, increased levels of IL-12, IL-18, and IFN γ transcripts were found in the draining
795 mediastinal lymph nodes (Demangel *et al.* 2001). As for *M. tuberculosis*, CD40 is also required for optimal
796 protective immunity against *M. avium* (Flórido *et al.* 2004) and *M. bovis* BCG (Méndez-Samperio, Ayala-
797 Verdin and Trejo-Echeverria 1999). Indeed, *Cd40*-KO mice are more susceptible to *M. avium* infection
798 due to the generation of a poorer IL-12 and IFN γ response (Flórido *et al.* 2004). Nevertheless, bacilli are
799 capable of countering the CD40-dependent immune response that jeopardizes their survival. For
800 example, MDM infected with *M. avium* subspecies *paratuberculosis* fails to upregulate the expression

801 of iNOS and IL-12 in response to CD40 stimulating pathway (Sommer *et al.* 2009). In addition to CD40,
802 its partner CD40L also helps to induce an antimicrobial response against several species. CD40L and IFN γ
803 have been shown to activate the vitamin D-dependent antimicrobial pathway and to trigger
804 antimicrobial activity, through upregulation of antimicrobial peptides and induction of autophagy,
805 against intracellular *M. tuberculosis*, contributing to human host defense against intracellular infection
806 **(Figure 1)** (Samten *et al.* 2000; Klug-Micu *et al.* 2013). Finally, MDM expressing CD40L inhibit *M. avium*
807 growth by stimulating IL-12 production (Hayashi *et al.* 1999). In conclusion, the CD40-CD40L axis plays
808 an important role in the host immune response against mycobacterial infections.

809

810 **Aldolase**

811 The aldolase catalyzes a reversible reaction that cleaves the aldol, fructose 1,6-bisphosphate,
812 into the triose phosphates dihydroxyacetone phosphate (DHAP) and glyceraldehyde 3-phosphate (G3P).
813 The fructose-bisphosphate aldolase occupies a central position in glycolysis and gluconeogenesis.
814 Beyond its role in central metabolism, it appears also implicated in other biological functions and is
815 exploited as a receptor by pathogenic mycobacteria. In HEp-2 or A549 epithelial cells, the aldolase,
816 present in the membrane and cytosolic compartment, binds to the *M. avium* superoxide dismutase
817 (SOD) (Reddy and Suleman 2004). This interaction allows *M. avium* to adhere, gain entry and multiply
818 inside epithelial cells **(Figure 4)**. In addition, the pathway that allows *M. avium* to colonize the
819 gastrointestinal tract of patients has been identified. Studies on mouse intestinal mucus identified
820 fructose-1-6-bisphosphate aldolase B as a host receptor interacting with the SOD and the heparin-
821 binding hemagglutinin (HBHA) **(Figure 4)** (Reddy, Suleman and Hayworth 2004). In conclusion, MAC
822 binds to the intestinal mucus aldolase, plausibly facilitating intestinal colonization of the organism.

823

824 **THE EXTRACELLULAR MATRIX PLATFORM (Part II)**

825 The extracellular matrix (ECM) is a three-dimensional network of macromolecules and minerals that
826 provides structural and biochemical support to surrounding cells. The composition of the ECM varies
827 among multicellular structures; however, cell adhesion, intercellular communication and differentiation
828 are common functions of the ECM. ECM components are produced intracellularly by resident cells and
829 secreted into the ECM by exocytosis. Once secreted, they aggregate to the existing matrix. The ECM is
830 composed of an interlocking meshwork of fibrous proteins and glycosaminoglycans (GAG) such as
831 proteoglycans, heparan sulfate, hyaluronic acid, collagen, fibronectin, and laminin. The ability of
832 pathogenic microorganisms to adhere to host cells and avoid removal by the host immune system is the
833 initial and the most decisive step leading to infection. Mycobacteria have developed different means to
834 attach to various host surface structures. One important strategy consists of adhering to the ECM
835 components that are abundant in connective tissue and basement membranes. Mycobacteria express

836 variable outer membrane adhesins to attach to these components and understanding the molecular
837 mechanisms of mycobacterial adhesion is a prerequisite for inhibiting these interactions using "anti-
838 ligand" strategies to prevent/reduce host colonization.

839

840 **Integrins**

841 Integrins are TM receptors that facilitate cell-cell and cell-ECM interactions. When bound to a
842 ligand, integrins activate signal transduction pathways that transmit various cellular signals. The role of
843 integrins in mycobacterial infections is not yet fully elucidated but two functions are known to benefit
844 pathogenic mycobacteria. On the one hand, the peptidyl prolyl isomerase A (PPIA) interacts with the
845 integrin $\alpha 5\beta 1$, aids in *M. tuberculosis* survival and disease progression by exploiting host-associated
846 factors, such as upregulation of multiple host matrix metalloproteinases (**Figure 2**) (Dubey *et al.* 2021).
847 While PPIA deletion compromises granuloma-like formation and promotes host cell death through
848 ferroptosis, its overexpression enhances the bacilli burden and exacerbates pulmonary pathology in
849 mice (Dubey *et al.* 2021). On the other hand, host integrins also facilitate the attachment of *M. avium*
850 subsp. *paratuberculosis* to intestinal epithelial M cells. Internalization is primarily mediated by the
851 formation of a fibronectin (FN) bridge formed between FAP-P (fibronectin attachment protein
852 homologue) of *M. avium* subsp. *paratuberculosis* and integrins on M cells (**Figure 4**) (Secott, Lin and Wu
853 2004). Thus, host integrins facilitate host-pathogen interactions and disease progression.

854

855 **Collagens**

856 Collagens are the most abundant proteins in the ECM, present as fibrillar proteins and providing
857 structural support to resident cells. Using a collagen-sepharose affinity chromatography approach, the
858 *M. bovis* BCG collagen-binding protein was characterized as a laminin-binding histone-like protein
859 (LBP/Hlp), a highly conserved protein associated with the mycobacterial cell wall (**Figure 4**) (Dias *et al.*
860 2012). Moreover, the C-terminal domain of *M. leprae* LBP/Hlp was found to bind to collagen I (Dias *et al.*
861 2012). Exogenous collagen I supplementation cross-linked *M. bovis* BCG to improve the interaction
862 with pneumocytes and macrophages (Dias *et al.* 2012).

863

864 **Plasmin(ogen)**

865 Plasmin is a serine protease that acts to dissolve fibrin blood clots. In addition to fibrinolysis,
866 plasmin cleaves various proteins of the ECM, including fibronectin and laminin. The ability of a pathogen
867 to interact with and infect host tissues directly determines the spread of infection. Adherence due to
868 host-pathogen interactions and in-depth traversal within infected organs are involved in the process. *M.*
869 *tuberculosis* surface-associated and secreted glyceraldehyde-3-phosphate dehydrogenase (GAPDH) not
870 only recruits and serves as a dual receptor for both plasminogen and plasmin, but it also gives bacilli the

871 ability to break down physical tissue barriers during systemic bacterial dissemination (**Figure 4**) (Gani *et al.* 2021). Soluble GAPDH can re-associate with bacilli to promote plasmin(ogen) recruitment and thus
872 improves bacterial adhesion and passage through lung epithelial cells (Gani *et al.* 2021). GAPDH
873 association with ECM proteins, together with its ability to recruit plasmin(ogen), may confer capacity for
874 directed proteolytic activity by the bacilli, vital for tissue infection (Gani *et al.* 2021).
875

876

877 **Hyaluronic acid**

878 Hyaluronic acid (HA) is a polysaccharide consisting of alternating residues of D-glucuronic acid
879 and N-acetylglucosamine. HA present in the extracellular space endows the tissue with stability to resist
880 compression by providing an antagonistic turgor force by absorbing large amounts of water. The *M.*
881 *tuberculosis* protease Rv3194c (residues 91-110) functions as an adhesin by binding to HA present on
882 the surface of pneumocytes (**Figure 4**) (Zhao, Lin and Xu 2020). *M. smegmatis* overexpressing Rv3194c
883 leads to persistent infections and pulmonary lesions in mice (Zhao, Lin and Xu 2020). Subsequent
884 intratracheal treatment with the Rv3194c peptide 91-110 to infected mice showed a growth suppression
885 of *M. smegmatis* and reduced lung pathology, attributable to the unavailable HA binding sites once
886 saturated with the peptide 91-110 (Zhao, Lin and Xu 2020). As Rv3194c functions as a HA-binding
887 adhesin, the 91-110 peptide may offer possibilities to reduce or prevent mycobacterial infections.
888

888

889 **Syndecans**

890 Syndecans are single TM proteins carrying three to five chains of heparan sulfate and
891 chondroitin sulfate, *i.e.* they are proteoglycans, which allow interactions with a variety of ligands, such
892 as fibronectin. The mechanisms of attachment and internalization of *M. tuberculosis* to non-professional
893 phagocytes, like epithelial cells, remain incompletely understood. Syndecan 4 (Sdc4) has been identified
894 as a mycobacterial attachment receptor on alveolar epithelial cells interacting with the mycobacterial
895 HBHA (Zimmermann *et al.* 2016) (**Figure 4**). Sdc4 knockdown in alveolar epithelial cells or blocking with
896 an anti-Sdc4 antibody showed reduced mycobacterial attachment and internalization. *In vivo*, Sdc1/Sdc4
897 double-KO mice appeared more resistant to lung colonization by *M. tuberculosis* (Zimmermann *et al.*
898 2016), thus unraveling an important role for distinct Sdcs in promoting mycobacterial entry into alveolar
899 epithelial cells.
900

900

901 **Laminin**

902 Laminin, an extracellular matrix protein, is thought to play a role in the attachment, migration
903 and organization of cells in tissues during embryonic development by interacting with other components
904 of the extracellular matrix. The alpha, beta and gamma subunits are linked together by disulfide bonds
905 to form a cross-shaped molecule. The laminin-2 isoform on the Schwann cell-axon unit serves as the

906 initial neural receptor for *M. leprae* by interacting with ML-LBP21/Hlp (*M. leprae* laminin-binding protein
907 21-kDa/21-kDa histone-like protein) (Shimoji *et al.* 1999; de Melo Marques *et al.* 2000) (**Figure 4**). The
908 role of ML-LBP21 in Schwann cell adhesion and internalization was investigated using fluorescent
909 polystyrene beads coated with rML-LBP21. Although beads coated with rML-LBP21 alone specifically
910 adhered to and were ingested by primary Schwann cells, these processes were significantly enhanced
911 when the rML-LBP21-beads were pre-incubated with exogenous $\alpha 2$ laminins (most likely exogenous $\alpha 2$ -
912 laminins bridge rML-LBP21 to unoccupied laminin receptors on Schwann cells and subsequently
913 mediates the ingestion) (Shimoji *et al.* 1999). *M. smegmatis* produces a paralog, designated MS-LBP,
914 which is attached to the bacterial surface and, interacting with host laminin, is responsible for laminin-
915 mediated mycobacterial adhesion to human pneumocytes and macrophages (Pethe *et al.* 2001).
916 Deletion of the *hlp* gene fails to affect the capacity of mycobacteria to bind to neuronal cells, suggesting
917 that alternative adhesins and/or pathways are exploited by mycobacteria for adhesion to Schwann cells
918 (de Melo Marques *et al.* 2000). Verifying the involvement of malate synthase's (MS) (catalyzes the
919 condensation of acetyl coenzyme A and glyoxylate to form malate) in the entry of the bacilli into nerve
920 cells could help elucidate this process (Kinhikar *et al.* 2006) (**Figure 4**). Computational models suggest
921 putative interactions between as yet uncharacterized *M. tuberculosis* adhesins and laminin (Kumar *et*
922 *al.* 2013b). Together, these studies underscore the multiplicity of mycobacterial adhesins that interact
923 with a single receptor. Overall, ML-LBP21 functions as a critical surface adhesin that facilitates uptake of
924 *M. leprae* into Schwann cells and as a contributing factor to the pathogenesis of *M. leprae*-mediated
925 nerve damage.

926

927 **Heparan sulfate**

928 Heparan sulfate (HS) is a linear polysaccharide in which two or three chains are attached in close
929 proximity to the cell surface or to ECM proteins. HS binds to a variety of ligands, regulates a wide array
930 of biological functions and serves as a cellular receptor for mycobacteria. Importantly, ML-LBP21/Hlp,
931 besides laminin, binds also to heparin and HS (Soares de Lima *et al.* 2005). The interaction between ML-
932 LBP21/Hlp with heparin is mainly driven by the C-terminal domain of the protein, also involved in
933 mediating bacterial binding to human Schwann cells (Soares de Lima *et al.* 2005) (**Figure 4**). These
934 findings reinforce the participation of ML-LBP21/Hlp in mycobacterial infection and define its highly
935 positively charged C-terminal region as the major adhesive domain of this protein. Apart from LBP, the
936 Lys/Pro-rich C-terminal region of HBHA also binds to sulfated carbohydrates and functions as an adhesin
937 for epithelial cells (Menozzi *et al.* 1998; Pethe *et al.* 2000) (**Figure 4**). Consequently, binding of HS chains
938 to HBHA promotes adhesion to epithelial cells and may be necessary for extrapulmonary dissemination
939 of *M. tuberculosis*. While HBHA induces a reorganization of the actin filament network in confluent
940 endothelial cells, it does not affect their tight junctions (Menozzi *et al.* 2006). In addition, the

941 transcellular migration of endocytic vacuoles containing HBHA-coated particles suggests that HBHA
942 induces epithelial transcytosis, representing a macrophage-independent mechanism of extrapulmonary
943 dissemination leading to systemic infection (Menozi *et al.* 2006). Both LBP and HBHA are also
944 considered as major adhesins for the attachment of *M. leprae* to epithelial cells (Silva *et al.* 2013).

945

946 **Fibronectin**

947 Fibronectin (FN) is a high molecular weight glycoprotein of the ECM that binds to integrins. FN
948 also binds to other ECM proteins such as collagen, fibrin and HS proteoglycans, like syndecans. FN is
949 targeted by a large set of bacterial adhesins. A number of bacterial FN-binding proteins have been
950 reported as FN interactants playing diverse roles in bacterial colonization, virulence and bacterial-host
951 interactions. Studies have shown that mycobacteria attach to various FN-producing cells by engaging
952 various adhesins (Ratliff *et al.* 1993). The p55/FAP protein of *M. bovis* BCG and *Mycobacterium vaccae*
953 binds to FN and inhibits the attachment of the bacilli to host cells (**Figure 4**) (Ratliff *et al.* 1993).
954 Moreover, the *M. leprae* fibronectin attachment protein (FAP) adhesin binds to FN and significantly
955 enhances the attachment and ingestion of bacilli by epithelial and Schwann cells (**Figure 4**) (Schorey *et*
956 *al.* 1995), representing an important step in the initiation of *M. leprae* infection *in vivo*. The RWFV motif
957 is required for the FN binding function of mycobacterial FAP proteins (Zhao *et al.* 1999). Furthermore,
958 MAC and *M. smegmatis* adhere to FN-containing epithelial cells *via* FAP (Middleton *et al.* 2000; Secott,
959 Lin and Wu 2002). The other characterized ligand interacting with FN is the Ala/Pro rich protein (Apa), a
960 secreted antigen, which binds to the cell-binding domain of FN (**Figure 4**) (Kuo *et al.* 2019). In addition,
961 the secreted Ag85 complex favors the attachment of mycobacteria in the lung or during hematogenous
962 spread by acting as a stress-sensitive adhesin (**Figure 4**) (Viljoen, Alsteens and Dufrêne 2020). The C-
963 terminal domain of the glycine-rich PE-PGRS proteins such as PE-PGRS81 of *M. tuberculosis* exhibit FN
964 binding properties (**Figure 4**) (Espitia *et al.* 1999). In this context, the cell wall-localized MS of *M.*
965 *tuberculosis* has adapted to function as an adhesin by binding to FN, enhancing bacterial attachment to
966 lung epithelial cells (**Figure 4**) (Kinhikar *et al.* 2006). Evidence of *in vivo* expression of *M. tuberculosis* MS
967 during active infection in humans show that a housekeeping enzyme of *M. tuberculosis* contributes to
968 its arsenal of virulence factors (Kinhikar *et al.* 2006). Moreover, computational strategy using different
969 algorithms has predicted putative bindings between human FN with various *M. tuberculosis* adhesins
970 (Rv2599, N-acetylmuramoyl-L-alanine amidase, L,D-transpeptidase) (Kumar *et al.* 2013b). This approach,
971 through further experimental investigations, could expand the number of known *M. tuberculosis*
972 adhesins. Lastly, binding and ingestion of *M. avium* subsp. *paratuberculosis* (MAP) by host cells is
973 dependent on both FN and the bacterial elongation factor Tu (EF-Tu) (**Figure 4**) (Viale *et al.* 2014). This
974 supports the view that human FN plays a primary role in the internalization of several mycobacterial
975 species and contributes to the infection process.

976 **DRP-2 and GAPDH**

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

987

988 **MECHANISMS BEYOND PRR and ECM (Part III)**

989 Despite the identification of a large set of receptors interacting with bacterial surface glycolipids, a
990 paucity of knowledge still exists around the host partners of certain mycobacterial ligands. A few
991 bacterial adhesins play an important role in the internalization and pathogenesis of mycobacteria but
992 the molecular mechanisms underlying these processes remain unknown. *M. leprae* is frequently
993 encountered inside human microvascular endothelial cells (HMVEC) surrounding Schwann cells at the
994 site of peripheral nerve damage in patients with lepromatous leprosy. Based on this observation, it was
995 thought that *M. leprae* uses the nasal mucosa as an entry pathway and that HMVEC serves as an
996 important reservoir for the bacteria before they interact with Schwann cells. An elegant study
997 demonstrated that the first 72 amino acids of the Mce1A protein play an important role in *M. leprae*
998 uptake by HMVEC and that antibodies against this region prevent the entry of *M. leprae* into HMVEC
999 (Idris *et al.* 2019). In *M. tuberculosis* and *M. bovis* BCG, cell wall-associated PE/PE-PGRS proteins play an
1000 important role in establishing macrophage infectivity (Brennan *et al.* 2001). As a result, PE-PGRS proteins
1001 influence mycobacterial interactions with macrophages. Finally, the *M. tuberculosis* protein product
1002 encoded by *Rv3312A* has been shown to be an adhesin/invasin of epithelial cells and macrophages, as
1003 well as an entry factor for *M. tuberculosis* (Ramsugit and Pillay 2014; Ramsugit, Pillay and Pillay 2016).
1004 *M. tuberculosis* strains lacking *Rv3312A* showed a significant reduction in their ability to adhere to and
1005 enter A549 pulmonary epithelial cells and THP-1 macrophages (Ramsugit and Pillay 2014; Ramsugit,
1006 Pillay and Pillay 2016).

1007 The aryl hydrocarbon receptor (AhR) is a transcription factor that senses environmental toxins,
1008 among other substances, thereby modulating immune cell responses (Moura-Alves *et al.* 2014). AhR
1009 recognizes pigmented bacterial virulence factors as ligands, namely naphthoquinone phthiocol from *M.*

1010 *tuberculosis* (Moura-Alves *et al.* 2014). After ligand binding, AhR activation leads to virulence factor
1011 degradation and regulates production of cytokines and chemokines. The importance of the AhR in host
1012 defense is underlined by the increased susceptibility of AhR-deficient mice to *M. tuberculosis* (Moura-
1013 Alves *et al.* 2014). Thus, the AhR is an intracellular PRR that senses bacterial pigments and controls
1014 antibacterial responses.

1015 Host factors can also facilitate phagocytosis of mycobacteria. In this context, sphingolipid
1016 biosynthesis inhibition has experimentally been shown to significantly reduce *M. tuberculosis* and *M.*
1017 *marinum* uptake by a panel of macrophages and DC (Niekamp *et al.* 2021). Microscopic analysis revealed
1018 that sphingolipid-deficient macrophages can recognize bacilli and assemble actin at the site of contact,
1019 but they are unable to remodel the actin cytoskeleton, which is required for complete internalization of
1020 the bacilli (**Figure 5**). Furthermore, sphingolipid-deficient macrophages failed to exclude the CD45
1021 tyrosine phosphatase from the receptor-pathogen contact site or nascent phagosome, a critical step in
1022 phagocytosis progression (Niekamp *et al.* 2021). At the host-pathogen interaction sites, this impairment
1023 is accompanied by poor Rho-GTPase activation and a substantial reduction in phosphoinositide turnover
1024 (Niekamp *et al.* 2021). These observations highlight the importance of sphingolipid production in *M.*
1025 *tuberculosis* phagocytic uptake and identifies a possible target for future antimycobacterial treatments.

1026 Finally, very little is known about the dissemination of *M. tuberculosis* from the lungs but it
1027 seems that specific adhesins are also involved in this process. Indeed, the dissemination of *M.*
1028 *tuberculosis* from the primary site of infection is critical to TB pathogenesis. While bacterial trafficking
1029 to regional lymph nodes is required for the development of a protective T cell-mediated immune
1030 response, entry into the circulatory system presents the risk of extrapulmonary dissemination, yielding
1031 some of the most lethal clinical consequences of TB. While the mechanism of exiting the lungs across
1032 the alveolar epithelium has yet to be fully characterized, some features have been identified (**Figure 6**).
1033 At the epithelial layer, *M. tuberculosis*' HBHA facilitates binding to sulphated glycoconjugates on
1034 epithelial cells. When HBHA is blocked, a marked decrease in dissemination from the lungs to the spleen
1035 has been observed (**Figure 6**) (Krishnan, Robertson and Thwaites 2010). Following attachment, the early
1036 secretory antigenic target 6-kDa (ESAT-6) and culture filtrate protein 10-kDa (CFP-10), encoded by the
1037 RD1 locus, have been linked to cell lysis and to internalization into the alveolar epithelium (**Figure 6**)
1038 (Krishnan, Robertson and Thwaites 2010). Work in embryonic zebrafish suggests that ESAT-6 may
1039 additionally contribute to early spreading of the bacteria by stimulating the trafficking of infected
1040 macrophages within granulomas, indicating that *M. tuberculosis* has evolved granuloma-dependent
1041 mechanisms for macrophage recruitment, infection, and subsequent bacterial dissemination (Krishnan,
1042 Robertson and Thwaites 2010). In the absence of both ESAT-6 and HBHA, a notable reduction of bacterial
1043 migration across the alveolar barrier has been observed (Ryndak, Chandra and Laal 2016). More

1044 complete characterization of these proteins and their interactions with host cells may offer a potential
1045 for novel therapeutic targets.

1046

1047 **CONCLUDING REMARKS AND PERSPECTIVES**

1048 Adhesion molecules, found on the surface of most bacteria, facilitate the interaction with host cells, aid
1049 in colonization and uptake, and trigger the host's immunological response during infection. The precise
1050 interactions observed between pathogenic mycobacterial surface molecules and host receptors affirms
1051 the favorable and exploitable niche of the intracellular environment. The purpose of a multi-entry
1052 strategy may lie in the hijacking of macrophages and other host cells to cross the pulmonary and
1053 epithelial barriers. This is performed by macrophages that directly ingest inhaled mycobacteria or by
1054 monocytes, macrophages, and/or neutrophils that migrate to the initial infection site in response to
1055 chemokines secreted by infected macrophages. Bacterial entrance in macrophages alters transcriptional
1056 gene expression, permitting the stimulation genes that inadvertently support bacterial survival, growth,
1057 and intercellular spread. This is mirrored in the increased cytotoxicity to respiratory epithelial cells
1058 caused by *M. tuberculosis* emerged from intracellular environments *versus* those grown in cell-free
1059 media, suggesting that processes in the intracellular environment offer an advantage to aid in the
1060 breaching of epithelial barriers and spreading to distant sites (McDonough and Kress 1995).
1061 Furthermore, *M. avium* and *M. intracellulare* may spend time in macrophages to initiate specific
1062 virulence mechanisms (Bermudez, Parker and Goodman 1997; Cirillo *et al.* 1997). Additional work is still
1063 needed to fully understand the potential impact of the internalization pathway on intracellular
1064 trafficking of phagosomes and whether host cell responses differ according to the receptors engaged
1065 and mycobacterial species involved. Mycobacterial interactions with both opsonic and non-opsonic
1066 receptors on host cells are complex and not yet fully understood. Receptor studies are often performed
1067 in artificial *in vitro* systems, while more biologically representative *in vivo* results may only be cautiously
1068 interpreted due to their high variability across different experimental conditions. Despite best practices,
1069 inconsistencies in *Mycobacterium*-receptor function studies can be influenced by several technical
1070 conditions. Bacterial species, genetic diversity of strains of the *M. tuberculosis* complex (lineage 2 vs
1071 lineage 4 vs Lineage 1, etc.) (Brites and Gagneux 2017; Gisch *et al.* 2022; Zha *et al.* 2022), genetic diversity
1072 in humans, host cell types, infection sites and cell preparation are all considerations to be taken into
1073 account when monitoring the characteristics of host-pathogen interactions. Mycobacteria culture
1074 conditions are also important aspects to consider. For instance, the use of detergents when culturing
1075 mycobacteria strongly affects the mycobacterial surface properties and, consequently, subsequent
1076 adhesion and interaction with the host (Pietersen *et al.* 2020; Lim *et al.* 2022). For these reasons,
1077 approaching near-natural experimental conditions will yield the most physiologically-meaningful results.
1078 However, this is made more complicated by the nature of mycobacterial internalization by host cells *via*

1079 multiple receptor-mediated mechanisms. Experimentally, many of the receptors do not appear to be
1080 independently essential, suggesting compensatory alternatives. Furthermore, synergism between the
1081 various receptor families and the impact on mycobacteria-caused diseases requires additional attention.
1082 The abundance of mycobacterial surface ligands also contributes to this complexity, adopting several
1083 downstream permutations by binding receptors on diverse cell types, engaging multiple receptors in
1084 tandem or conversely blocking sufficient receptor clustering for cellular cross-talk and signaling. It is
1085 currently well-established that the type of interaction correlates with infection outcome. The LAM cap
1086 structure spans both ends of immunomodulation through PILAM as a pro-inflammatory molecule that
1087 stimulates the production of TNF- α and IL-12 and ManLAM as an anti-inflammatory molecule that
1088 stimulates the production of IL-10 while blocking the production of IL-12 and TNF- α . These
1089 immunomodulatory processes will be influenced by a number of factors, including the expression and
1090 availability of certain receptors and their downstream responses.

1091 Better understanding the initial features of host-pathogen interactions *via* adhesion and
1092 internalization could reveal future targets for prophylactic strategies in preventing mycobacterial
1093 internalization. Current efforts are focused on unpacking the immunogenicity of surface-localized
1094 adhesins for application in vaccine development, as previously discussed for HBHA (Temmerman *et al.*
1095 2004). The synthesis of chemical scaffolds or peptides that mimic adhesin-receptor binding sites are also
1096 being pursued as alternative therapies to limit infection. Some success has been observed with anti-
1097 adhesion therapies against pathogenic mycobacteria and may show improved outcomes when
1098 administered alone or with antibiotics (Ofek, Hasty and Sharon 2003). Finally, as additional
1099 mycobacterial adhesins continue to be identified, it is now more critical than ever to employ cutting-
1100 edge techniques such as super-resolution imaging or atomic force microscopy to clarify the intricacies
1101 of their functionality (Kreve and Reis 2021; Tabusi *et al.* 2021).

1102

1103 **SUPPLEMENTARY DATA**

1104 Supplementary data are available at FEMSRE online.

1105

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1117

1118 **CONFLICT OF INTEREST**

1119 None declared.

1120

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