

## Review Article



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### Conflict of Interest

The authors declare no potential conflicts of interest.

### Abbreviations

ATG, autophagy-related gene; APC, antigen-presenting cell; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; cGAS-STING, cyclic GMP-AMP synthase-stimulator of interferon genes; DC, dendritic cell; erm, erythromycin ribosome

# Host-Pathogen Interactions Operative during *Mycobacteroides abscessus* Infection

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## ABSTRACT

*Mycobacteroides abscessus* (previously *Mycobacterium abscessus*; Mabc), one of rapidly growing nontuberculous mycobacteria (NTM), is an important pathogen of NTM pulmonary diseases (NTM-PDs) in both immunocompetent and immunocompromised individuals. Mabc infection is chronic and often challenging to treat due to drug resistance, motivating the development of new therapeutics. Despite this, there is a lack of understanding of the relationship between Mabc and the immune system. This review highlights recent progress in the molecular architecture of Mabc and host interactions. We discuss several microbial components that take advantage of host immune defenses, host defense pathways that can overcome Mabc pathogenesis, and how host-pathogen interactions determine the outcomes of Mabc infection. Understanding the molecular mechanisms underlying host-pathogen interactions during Mabc infection will enable the identification of biomarkers and/or drugs to control immune pathogenesis and protect against NTM infection.

**Keywords:** *Mycobacteroides abscessus*; Nontuberculous mycobacteria; Infections; Host-pathogen interactions

## INTRODUCTION

Nontuberculous mycobacteria (NTM) are emerging and ubiquitous microorganisms found in environments such as water and soil (1). Among NTM strains, the rapidly growing *Mycobacteroides abscessus* complex includes *M. abscessus* subsp. *bolletii*, *M. abscessus* subsp. *massiliense* (Mmass), and *M. abscessus* subsp. *abscessus* (Mabc) (2-4). *M. abscessus* complex members cause pulmonary infections (3,5), particularly in patients with cystic fibrosis (CF) and other underlying diseases (6-9). Mabc is thought to be the most pathogenic *M. abscessus* complex member due to natural and acquired antibiotic resistance (1,10,11). Although they primarily cause opportunistic infection in immunocompromised subjects, *M. abscessus* complex members can induce pathogenic infection in the immunocompetent people (12). In addition, there are considerable differences in the clinical and epidemiological characteristics of NTM diseases depending on race/ethnicity and geographical distribution (13). Treatment of NTM diseases is hampered by multidrug resistance. The *M. abscessus* complex is resistant to all first-line drugs against tuberculosis (1,2,14). According to the current CF Foundation

methyltransferase; Esp, ESAT6 secretion-1 secretion-associated proteins; ESX, ESAT6 secretion; GPL, glycopeptidolipid; HMG2, high-mobility group nucleosomal-binding domain 2; IRF, interferon regulatory factor; LAP, LC3-associated phagocytosis; Mabc, *Mycobacteroides abscessus* subsp. *abscessus*; MAC, *M. avium-intracellulare* complex; MaRg, Mabc rough variant; MaSm, Mabc smooth variant; Mmass, *M. abscessus* subsp. *massiliense*; miRNA, micro RNA; Mtb, *Mycobacterium tuberculosis*; mtDNA, mitochondrial DNA; MmpL, mycobacterial membrane protein large; NLR, nucleotide-binding leucine-rich repeat-containing receptor; NLRP3, nucleotide-binding and oligomerization domain-like receptor family pyrin domain containing 3; NO, nitric oxide; NOD, nucleotide-binding oligomerization domain; NTM, nontuberculous mycobacteria; NTM-PD, nontuberculous mycobacterial pulmonary disease; PAMP, pathogen-associated molecular pattern; PE, proline-glutamate; PLC, phospholipase C; Pmt, protein-O-mannosyltransferase; PPAR $\alpha$ , peroxisome proliferator-activated receptor- $\alpha$ ; PPE, proline-proline-glutamate; PRR, pattern recognition receptor; RGM, rapidly growing mycobacteria; SIRT3, sirtuin 3; TDM, trehalose dimycolate; Ulk1/2, Unc-51 like autophagy activating kinase.

#### Author Contributions

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Clinical Care Guidelines, amikacin, cefoxitin, and clarithromycin are the leading drugs for treating *M. abscessus* infection (15). However, these regimens show a low cure rate (29%–58%), as well as toxic side-effects because of prolonged treatment durations, thus reducing compliance with regimens (16). Therefore, new host-directed therapeutics against NTM diseases are needed. However, our understanding of the host factors that influence protective immune responses in NTM infections is inadequate.

In this review, we discuss recent progress in crosstalk between Mabc and the host innate and adaptive immune systems during infection. Specifically, we focus on the microbial components and host factors/pathways by which host cells regulate protective immunity and pathological inflammation. Finally, we review candidate host-directed therapeutics against Mabc infection. Understanding the mechanisms underlying host-pathogen interactions during Mabc infection will facilitate the development of host-targeted immunotherapeutics against drug-resistant refractory Mabc infection.

## OVERVIEW OF Mabc INFECTION

Over 190 species of NTM have been identified and several species cause diseases in immunocompromised and immunocompetent individuals. NTMs are typically present in soil, water networks, showerheads, tap water, and swimming pools, making human–pathogen contact likely (1,2). Among them, the *Mycobacterium avium-intracellulare* complex (MAC) and *M. abscessus* complex are clinically significant pathogens (17,18). *M. abscessus* complex members are rapidly growing mycobacteria (RGM) classified into 3 subspecies: Mabc, *M. bolletii*, and Mmass (2–4,18). Mabc causes various diseases, including pulmonary, extra-pulmonary, cutaneous, and systemic infections (18,19). *M. abscessus* complex members are the agent of pulmonary disease (PD) driven by RGM, accounting for 3%–13% of all NTM-PD (2,5). In South Korea the 6-, 10-, and 14-year cumulative mortality rates of patients infected with NTM increase over time (13.7%, 19.2%, and 22.9%, respectively) (20). Mabc pulmonary infection is often severe, requires prolonged treatment, and is one of the most antibiotic-resistant mycobacteria (2,14,18,21). Long-term macrolide therapy in CF patients promoted the emergence of Mabc infection (10,22). Exposure of CF patients to the macrolide clarithromycin increases the expression of the erythromycin ribosome methyltransferase (*erm*)(41) gene in Mabc and *M. bolletii*, indicating inducible macrolide resistance (23,24). However, the *erm*(41) gene in Mmass is in a short form of about 270 bp, likely because Mmass lacks inducible resistance to macrolides (2,23,24). In addition, Mabc can survive in water distribution systems and exhibits several virulence characteristics, such as biofilm formation, disinfectant resistance, and adherence to surfaces. The Mabc variants, smooth (MaSm) and rough (MaRg), have distinct colony morphologies, depending on the presence of cell wall glycopeptidolipids (GPLs) (1,8,18). MaSm variants have GPL in their cell wall, which is absent in MaRg. Although both variants induce biofilms to resist mechanical clearance from the lungs, MaRg biofilms are stiffer than those of MaSm (25).

Recent studies suggest a model for the stepwise pathogenic evolution of Mabc from horizontal gene acquisition by environmental clones, allopatric (or geographic) within host adaptation, constrained (or forced) transmission via the environment, and opportunities for direct transmission of emergent mycobacteria among populations (26,27). However, cohabiting patients with NTM-PDs have distinct genetic profiles, suggesting minimal patient-to-patient transmission (28). More data are needed to evaluate the person-to-person transmission of NTM diseases.

**Table 1.** Mabc components interacting with the host system

Category	Name	Role	Required for	Ref.
Mabc lipids	GPL	Surface components	<ul style="list-style-type: none"> <li>Masking the bacterial surface to prevent recognition by host immune systems</li> <li>The initial colonization at the lung alveoli</li> <li>Inhibition of host macrophage apoptosis</li> </ul>	(1,30,31)
	TDM		<ul style="list-style-type: none"> <li>Invasive infection by cord formation</li> </ul>	(8)
ESX systems	ESX-3	Secretion system	<ul style="list-style-type: none"> <li>Activation of proinflammatory responses during infections</li> </ul>	(40)
	ESX-4	Secretion system	<ul style="list-style-type: none"> <li>Intracellular survival</li> <li>Blockade of phagosomal acidification during infection</li> </ul>	(41)
Membrane proteins and enzymes	MmpL4	Membrane protein	<ul style="list-style-type: none"> <li>Transport and assembly of GPL at the bacterial surface</li> </ul>	(42)
	MmpL8	Membrane protein	<ul style="list-style-type: none"> <li>Adhesion to host macrophages</li> <li>Phagosome membrane rupture</li> </ul>	(43)
	PLC	Hydrolase	<ul style="list-style-type: none"> <li>Intracellular survival of Mabc</li> <li>The detrimental effect on murine macrophage</li> </ul>	(44)
	Pmt	Glycosylation	<ul style="list-style-type: none"> <li>Intracellular survival of Mabc</li> </ul>	(45)
Mabc protein antigens	MAB1843	Unknown	<ul style="list-style-type: none"> <li>Maturation of DCs</li> <li>Increment of the T cell proliferation and Th1 polarization</li> </ul>	(46)
	MgtC	Unknown	<ul style="list-style-type: none"> <li>Intramacrophage survival</li> <li>Adaptation to Mg<sup>2+</sup> deprivation</li> </ul>	(47)
	MAB_4780	Dehydratase	<ul style="list-style-type: none"> <li>The escape of phagosomal fusion</li> </ul>	(48)

## Mabc COMPONENTS THAT INTERACT WITH THE HOST IMMUNE SYSTEM

Although Mabc infection has similarities with that of *M. tuberculosis* (Mtb), the antigens/components responsible for host defense and pathogenesis in Mabc infection are unclear. This section discusses the Mabc components and antigens responsible for virulence and/or interaction with the host immune system (Table 1).

### Mabc lipids: glycopeptidolipids (GPLs) and others

GPLs are a family of glycolipids found in several pathogenic and nonpathogenic NTM species. Therefore, considerable effort has focused on identifying GPL structure, function, and role in pathogenesis. GPLs mask the bacterial surface, thereby inhibiting recognition by the host immune system. Mabc colonies have distinct phenotypes depending on the presence or absence of GPL in the cell wall. MaSm, which produces GPLs, is responsible for the initial colonization of lung alveoli (1,8,18). Spontaneous *in vivo* conversion from MaSm to MaRg was detected using an *in vivo* fibrin plug model of Mabc infection (29). The transition from the MaSm to MaRg variant is associated with exacerbation and persistence of Mabc infection and increased intensive proinflammatory responses, and host lethality (29). The virulence of MaRg is mainly due to massive production of serpentine cords, which form clumps or loose aggregates (1,30). In addition, Mabc GPLs inhibit the host macrophage apoptosis induced by proapoptotic stimuli, by inhibiting ROS generation and maintaining the mitochondrial transmembrane potential (31). Mabc GPL-mediated inhibition of host cell apoptosis is important for controlling bacterial spread in the context of Mabc infection (31) because apoptosis induction during Mtb infection is implicated in host antimicrobial defense (32). Trehalose dimycolate (TDM) is a glycolipid intermediating the construction of mycobacterial cell wall, produced by MaRg, not by MaSm. The production of TDM by MaRg contributes to invasive infection by cord formation (8). In addition to GPL and TDM, multiple isolates of the same NTM species and multiple NTM species have differential infectivity, at least in part because of modified phospholipids that antagonize antibacterial protein LL-37 (33). Given the host-protective function of LL-37 in Mtb infection (34), it would be interesting to explore the role of LL-37 in Mabc infection. In addition, whether GPLs of Mabc affect the functions of other antimicrobial proteins during Mabc infection warrants further investigation.

### ESAT6 secretion (ESX) system of Mabc

Most bacteria possess extracellular protein secretion systems that transport proteins across the cell wall. Mycobacterial cell envelopes contain several complex secretion systems (35). ESX system, also known as the Type VII secretion system, is conserved in high G+C Actinobacteria and is crucial for mycobacterial virulence and physiology, such as nutrient uptake (36). The first Type VII secretion system was discovered in Mtb. To date, 5 types of ESX system have been identified in mycobacteria, and the number of ESX systems differs among mycobacterial species. Tuberculosis-causing mycobacteria have ESX-1-5; *M. leprae* has ESX-1, -3, and -5; *M. smegmatis* has ESX-1-4; and Mabc has only ESX-3 and ESX-4, the fewest of any mycobacterial species (37). Mycobacterial Type VII secretion system substrates are divided into 3 types. First, ESX-1 secretion-associated proteins (Esp) are secreted via ESX-1, including EspA, EspB, and EspC. Next, as a proline-glutamate (PE) and proline-proline-glutamate (PPE) substrate, 2 proteins exist as heterodimers. PE and PPE motifs are conserved in the N-terminal domain, respectively, and comprise a helix-turn-helix motif (38). Finally, Esx substrates, typically of fewer than 100 amino acids, are represented by EsxA (early secretory antigenic target; ESAT-6) and EsxB (culture filtrate protein; CFP-10) of Mtb. Homologs of *esxA* and *esxB* are present in the gene cluster comprising the 5 ESX systems, and are widespread in mycobacteria other than tuberculosis (37,39). Compared to Mtb, ESX systems of Mabc have not been thoroughly investigated. Mabc ESX-3 induces a host immunopathological response during infection. In addition, ESX-3 contains the EsxH and EsxG substrates, matching EsxA and EsxB of Mtb, respectively. Recombinant EsxG and EsxH increase inflammatory cytokine generation in a dose-dependent manner in macrophages infected with an Mabc  $\Delta esx3$  deletion mutant strain (40). The ESX-4 system locus encompasses a cluster of 7 genes, including homologs encoding the Esx substrates. Mabc EccB4, a core structural component of ESX-4, is required for intracellular survival and blockade of phagosomal acidification during infection (41). Notably, Mabc  $\Delta eccB4$  cannot disrupt phagosomes, thereby inhibiting phagosome-to-cytosol contacts (41). The Mabc ESX-4 system may replace the function of the ESX-1 system in other mycobacteria based on 3 findings: the absence of an ESX-1 system in Mabc, in contrast to its presence in most other RGM (35); the Mabc ESX-4 locus harbors *eccE4*, which is implicated in host-pathogen communication and is depleted in all the other mycobacteria (35,41); and ESX-4 blocks phagosomal acidification and rupture during infection (41).

### Membrane proteins and enzymes

The mycobacterial membrane protein large (MmpL) family transporters translocate substrates and lipids (such as PDIM, sulfoglycolipid, and diacyltrehaloses) across the cell membrane via proton motive force. MmpL proteins are involved in drug resistance in both NTM and tuberculous mycobacteria. Mabc harbors 31 putative MmpL transporters, compared to 13 in Mtb (42). However, most MmpL transporters of Mabc are not characterized. Mabc MmpL4, which is implicated in GPL assembly and transport, was reported to be involved in Mabc virulence, suggesting that GPL produced by MmpL4 regulates the fate of Mabc within macrophages (30). Mabc *mmpL8* was identified in an investigation of the phylogenetic relationships between MmpL proteins of Mabc and Mtb. MmpL8 is essential in Mabc intracellular survival and virulence in both murine macrophages and zebrafish, mediating adhesion to host macrophages and phagosome membrane rupture (43). In addition, bacterial phospholipase C (PLC) is a hydrolase associated with surface molecules, such as phospholipids, required for Mabc pathogenicity. Purified recombinant protein PLC of Mabc exhibits strong cytotoxicity for murine macrophages, presumably due to decomposition of membrane phospholipids (44). Protein-O-mannosyltransferase (Pmt), involved in O-glycosylation, increases cell wall rigidity by glycosylating endogenous Mabc lipoproteins.

Deletion of Mabc *pmt* increases cell wall permeability and suppresses intracellular survival because of a cell wall defect of glycosylation (45). However, it has yet to be determined how Mabc Pmt escapes from host immune defenses.

### Mabc protein antigens

Mabc MAB1843 promotes dendritic cell (DC) maturation via TLR4 signaling, and MAB1843-treated DCs increased T cell proliferation and Th1 polarization (46). These data indicate that specific Mabc antigens, including MAB1843, potentiate innate and adaptive protective immune responses against Mabc, thus showing promise for the development of vaccines and therapeutic candidates (46). Although there is no effect of MgtC *in vitro*, blockade of MgtC, a virulence factor encoded by MAB\_3593, protects against Mabc infection in CF ( $\Delta$ F508 FVB) mice (47). Furthermore, MAB\_4780, encoding a dehydratase implicated in the metabolism of mycolic acids, is involved in escape from phagosomal fusion, which favors intracellular growth of Mabc (48).

Mycobacteria use various strategies to escape from host immune and effector mechanisms, establishing long-lasting infection within host cells (12,14,49). However, the immunomodulatory effects of Mabc components during infection are unclear, as are the signaling pathways activated by those components in innate and adaptive immune cells. Therefore, understanding the molecular mechanisms by which the host immune system interacts with mycobacteria and their components would facilitate the development of host-directed therapeutics against drug-resistant mycobacterial species, including Mtb and NTMs. **Table 1** lists the Mabc components that interact with the host immune system.

## CROSSTALK BETWEEN THE HOST INNATE IMMUNE SYSTEM AND Mabc

Several components of the innate immune system—such as pattern recognition receptors (PRRs), cytokines, and autophagy—play critical roles in protective and pathological responses to Mabc infection. The following 2 sections discuss the roles of various host innate and autophagic pathways in host-Mabc interaction. Knowledge of the interaction between Mabc antigens and host innate factors will enable identification of therapeutic targets and candidate vaccine antigens.

### Overview of host innate immune responses

The host immune response has innate and adaptive immune components (49,50). Innate immunity, the early and immediate immune response, recognizes various pathogenic stimuli via PRRs in innate immune cells (50,51). The sensing of pathogen-associated molecular patterns (PAMPs) by PRRs activates intracellular signals, leading to the production of antimicrobial effector molecules and eliminating intracellular bacteria (50,52). The PRRs include TLRs, nucleotide-binding leucine-rich repeat-containing receptors (NLRs), and scavenger receptors, all of which are primarily present in innate immune cells, particularly macrophages (50). These innate immune receptors are classified as membrane- and cytosolic receptors, recognize PAMPs during pathogenic infection, and are responsible for signal transduction in host cells, activating inflammatory and effector responses (50). The effector pathways include the production of inflammatory cytokines and antimicrobial peptides, generation of reactive oxygen and nitrogen species, autophagy, phagolysosomal fusion, and antigen presentation (49). The inflammatory signaling triggered by PRRs is transduced by

the formation of cooperative assemblies of multiple signaling molecules, including enzymes and adaptors, to activate transcription factors, including NF- $\kappa$ B and interferon regulatory factors (IRFs) (53). In the nucleus, NF- $\kappa$ B enhances the transcriptional activities of a variety of inflammatory mediators, including TNF- $\alpha$  and IL-6, whereas IRFs participate in the activation of type I IFNs and antiviral immune responses (53,54). The transcription factor IRF1 activates type I IFN gene expression (53). Interestingly, Mabc triggers both NF- $\kappa$ B and IFN signaling to differentially influence host innate immune responses during infection (55,56). Further studies are needed to clarify the mechanisms by which these 2 cytokine signaling pathways regulate host defense and pathology in Mabc infection.

Inflammasomes are multiprotein complexes that activate canonical caspase-1, noncanonical caspase-11 (or the equivalent caspase-4 and -5 in humans), or caspase-8 to induce secretion of the mature forms of IL-1 $\beta$  and IL-18, and pyroptotic cell death (57). Regulation of the nucleotide-binding and oligomerization domain-like receptor family pyrin domain containing 3 (NLRP3) inflammasome is important because it is implicated in the primary immune defense and pathophysiological responses of various immune and inflammatory diseases (57,58). Mabc infection induces NLRP3 inflammasome activation, leading to the production of IL-1 $\beta$  in human and murine macrophages (55,59). However, little is known of the roles of other inflammasome complexes in host defense or tissue damage during Mabc infection. Further studies are needed to clarify the mechanisms by which Mabc infection regulates inflammasome assembly to modulate host effector function.

#### **Innate immune receptors: TLR2, TLR4, nucleotide-binding oligomerization domain (NOD)2, and NLRP3**

TLR2 and TLR4 are essential for recognition of bacterial cell wall structures. TLR2 is critical for protection against infection with Mabc and Mmass. The TLR2-enriched fraction of MaRg is reported as vaccine and diagnostic candidate because antibodies from this fraction are found in infected samples from patients with CF (60). In addition, TLR2-deficient mice showed increased susceptibility to intravenous MaRg infection, at least in part because of failure of early inflammatory responses, recruitment of inflammatory cells into the bronchoalveolar space, and T cell activation (61). MaRg, but not MaSm, increases IL-8 activation and  $\beta$ -defensin 2 expression in airway epithelial cells via TLR2 (62). Moreover, IFN- $\beta$  is induced via the TLR2/TLR4-MyD88/TRIF-IRF3-dependent signaling pathway upon MaRg infection (63). TLR2-MyD88 is implicated in Mmass-induced macrophage activation (64). However, neither TLR4 nor dectin-1 is involved in Mmass-mediated innate immune responses *in vitro* (64). These data suggest that TLR2 signaling is crucial in Mabc- and Mmass-induced inflammatory responses in innate immune cells, such as macrophages and bronchial epithelial cells.

The NOD containing proteins (NOD1 and NOD2) are crucial for innate immunity as sensors of bacterial components. NOD2 is essential for protection against Mabc infection *in vivo*. NOD2-deficient mice infected intranasally with Mabc have increased pathological responses and exhibit defective microbial clearance in the lungs. Mechanistically, NOD2-mediated activation of nitric oxide (NO) and the expression of iNOS suppress intracellular Mabc growth (65). Mabc activates the NLRP3 inflammasome complex via the Dectin-1-mediated Syk signaling pathway (59). Mabc-mediated activation of the NLRP3 inflammasome contributes to antimicrobial responses against Mabc infection (59). The MaRg variant activates NLRP3 inflammasome-mediated IL-1 $\beta$  maturation in murine macrophages by increasing the production of mitochondrial ROS and cytosolic release of mitochondrial DNA (mtDNA) (55).

Mitochondrial ROS production and mtDNA translocation promote intracellular bacterial survival and replication in macrophages during MaRg infection (55). These data suggest that different variants of Mabc induce distinct innate immune responses during infection.

### Cystic fibrosis transmembrane conductance regulator (CFTR)

Mabc is frequently found as an opportunistic pathogen in patients with CF (6-9). CFTR gene variants, particularly Q1352H, are associated with increased susceptibility to NTM lung infections in the Korean population (66). The CFTR is an anion channel in the epithelial cell membrane and a member of the ATP-binding cassette transporter family. During Mabc infection, CFTR is vital for host protection according to a study in zebrafish (67). CFTR depletion impairs NADPH oxidase-dependent oxidative defenses, thus increasing susceptibility to Mabc infection. It also inhibits neutrophil chemotaxis, causes defective granuloma formation, and induces abscess formation during disease development (67). In one study, loss of CFTR increased susceptibility to and impaired host immunity in a zebrafish model during *M. fortuitum* infection (68). However, CF lungs have chronic inflammation and aging markers, and the sustained airway inflammation seen in CF accelerates the degradation of CFTR (69). Given the chronic neutrophilic inflammation and lung damage in CF lungs (70), more clinically relevant animal models of pathologies related to neutrophil infiltration during chronic NTM diseases are needed. Further studies should clarify the role of CFTR in regulating host immunity and inflammation during Mabc infection.

### Cytokines and their receptors

Human genetic studies identified that patients with primary immunodeficiencies undergoing disseminated Mabc infection have IFNAR1 and IFNGR2 mutations. There are 3 groups of IFNs: type I (IFN- $\alpha$ , IFN- $\beta$ , IFN- $\kappa$ , IFN- $\epsilon$ , IFN- $\omega$ , and IFN- $\tau$ ), type II (IFN- $\gamma$ ), and type III (IFN- $\lambda$ 1, IFN- $\lambda$ 2, IFN- $\lambda$ 3, and IFN- $\lambda$ 4). Each group has a receptor (IFNAR, IFNGR, and IFNLR, respectively) and signaling pathway (71). Because IFNAR1 and IFNGR2 encode the signaling subunits for IFN- $\alpha$  and IFN- $\gamma$  receptors, respectively, these data strongly suggest a critical role of type I and II IFN signaling in protection against Mabc infection (71). Mabc-infected NTM-PD patients had lower IL-2-, TNF- $\alpha$ -, and IFN- $\gamma$ -positive polyfunctional T cell counts than controls and a colonization group (72). In addition, the IFN- $\gamma$  and IL-12 levels were significantly decreased, whereas that of TNF- $\alpha$  was increased in sera from Mabc-infected patients prior to antibiotic treatment compared to healthy control subjects (73). Human cytomegalovirus infection-induced IL-10 production abrogates host immune responses to Mmass infection (74). Further studies with larger populations are warranted to clarify whether cytokines could be used as biomarkers for diagnosis and/or treatment outcome prediction.

Mabc infection robustly activates the expression of type I IFNs in innate immune cells. An MaRg variant promotes type I IFN production in macrophages via the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) signaling pathway, thus contributing to virulence via cell-to-cell spreading (55). However, type I IFN responses might induce NO production and antimicrobial responses during Mabc infection (63). Although the discrepancy is apparent, further studies are warranted to clarify the role of type I IFN signaling during Mabc infection. In addition, gene and protein expression levels in the IFN-I signaling pathway significantly are increased in normal human bronchial epithelial cells and mouse lungs exposed to Mabc cell wall particles (75), although it is unclear the exact function of type I IFN in epithelial cells during Mabc infection.

**Table 2.** Host innate immune interaction with Mabc during infection

Innate immune components	Variants used	Observation/Mechanism	Model	Ref.
TLR2	R	<ul style="list-style-type: none"> <li>Detection of antibodies against TLR2eF in CF patients</li> <li>Partial protection by TLR2eF against Mabc infection in mice</li> </ul>	<i>In vivo</i> mice model, CF patients	(60)
TLR2	R	<ul style="list-style-type: none"> <li>Regulation of cytokine (IFN-<math>\gamma</math>, TNF-<math>\alpha</math> and IL-12p70) production, T cell activation, and recruitment of immune cells</li> </ul>	<i>Tlr2</i> <sup>-/-</sup> mice	(61)
TLR2	R and S	<ul style="list-style-type: none"> <li>Recognition of Mabc lacking GPL (R variant) by TLR2</li> <li>Increased expression of IL-8 and beta defensin 2 by variant lacking GPL (R variant)</li> </ul>	A549 cells	(62)
NOD2	R	<ul style="list-style-type: none"> <li>NOD-2 mediated production of cytokine and NO via p38 and JNK activation</li> </ul>	NOD2 <sup>-/-</sup> mice, BMDMs	(65)
NLRP3	-	<ul style="list-style-type: none"> <li>TLR2 mediated activation of NLRP3 inflammasome via Dectin-1-Syk signaling pathway</li> </ul>	Human MDMs	(59)
NLRP3/IFN-I	R and S	<ul style="list-style-type: none"> <li>Increased mitochondrial ROS and mtDNA leading to NLRP3 mediated IL-1b and cGAS-STING dependent IFN-I production</li> </ul>	J774A.1, RAW264.7 cells, BMDMs	(55)
CFTR	R and S	<ul style="list-style-type: none"> <li>Impaired NOX2/NADPH oxidase-dependent ROS production leading to increased growth of Mabc, decreased neutrophil recruitment, and defective granuloma formation during CFTR deficiency</li> </ul>	Zebrafish	(67)
IFNB	R and S	<ul style="list-style-type: none"> <li>Activation of TLR2-TLR4-IRF3 pathway for the production of IFNB (more during R variant infection as compared to S-variant) which is involved in NO production</li> </ul>	BMDMs	(63)
TNF/IL8	R and S	<ul style="list-style-type: none"> <li>Activation of TNF signaling leading to IL-8 release contributing to neutrophil recruitment and structured granuloma formation</li> </ul>	Zebrafish	(76)
TNF	R	<ul style="list-style-type: none"> <li>Increased level of <i>Tnf</i> and several proinflammatory cytokines in Mabc-infected mouse lung tissue correlated with increased bacterial burden</li> </ul>	BMDMs and <i>in vivo</i> mice model	(78)

TLR2eF, TLR2-enriched fraction; cGAS-STING, cyclic GMP-AMP synthase-stimulator of interferon genes; R, Mabc rough variant; S, Mabc smooth variant; MDM, monocyte-derived macrophage; BMDM, bone marrow-derived macrophage.

In a zebrafish model, TNFR signaling and downstream IL-8-dependent neutrophil recruitment are required for protective immunity to MaSm and MaRg infections (76). Given that anti-TNF therapy exacerbates NTM infection (77), these data suggest that TNF signaling is essential for host protection against Mabc infection. However, increased pathological inflammation with an upregulated TNF- $\alpha$  level in the lungs is detrimental to protection against MaRg infection *in vivo* (78). Therefore, TNF- $\alpha$  may be a double-edged sword, promoting both protective immunity and pathological inflammation. **Table 2** lists the innate immune components involved in host protection during Mabc infection.

## HOST AUTOPHAGY AND Mabc INFECTION

### Overview of autophagy/xenophagy

Autophagy is an intracellular homeostatic process that protects cells from stresses, including infection and other hazards (79,80). In addition, it is a central catabolic system by which intracellular cargos, including large protein aggregates and damaged organelles, are subjected to lysosomal degradation (80). It is a cell-autonomous defense system against a variety of infections, including mycobacterial ones (81). Canonical autophagy pathways are divided into macroautophagy, microautophagy, and chaperone-mediated autophagy (79). Macroautophagy (or widely known as autophagy) is a multistep process involving initiation, vesicle elongation, autophagosome maturation, lysosomal fusion, and degradation, and is orchestrated by numerous autophagy-related genes (ATGs) family of proteins (80). Autophagy is generally triggered by various stress signals including starvation, hypoxia, and microbial infections. The formation of double-membrane autophagosomes is regulated by mTOR, a master metabolic regulator. mTOR is a negative regulator of autophagy, so its dephosphorylation mediates the translocation of Unc-51 like autophagy activating kinase (Ulk1/2)-ATG13-FAK family-interacting protein (FIP200)-Atg101 complex to the endoplasmic reticulum, a process that also involves the class III PI3K complex (79). Elongation and closure of autophagosomes are conducted by the ATG5-ATG12-ATG16L complex and the ATG8 family composed of LC3 (80). The completed autophagosome fuses with a lysosome for the degradation of cytoplasmic cargo.



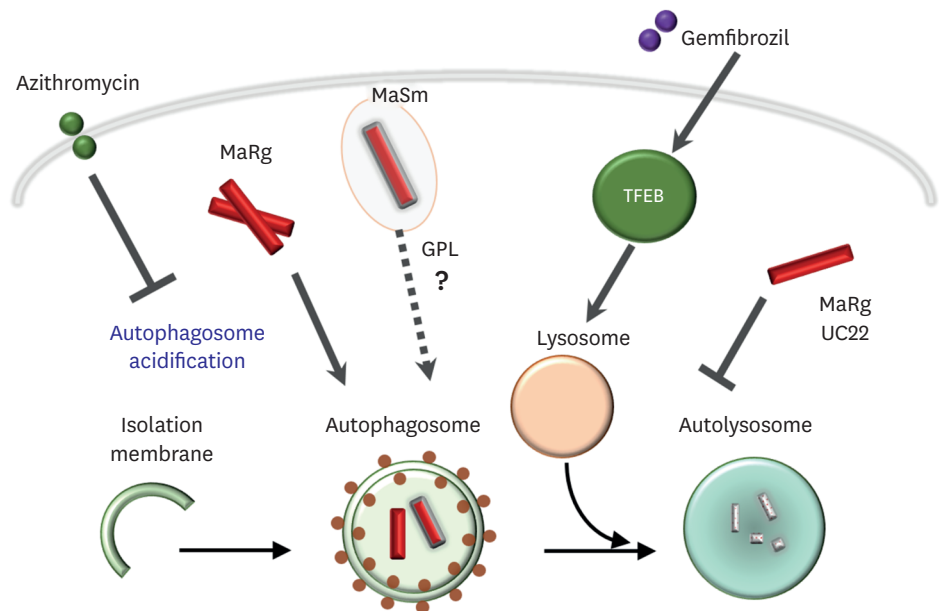
Noncanonical autophagy includes selective autophagy and LC3-associated phagocytosis (LAP) (82,83). Selective autophagy is triggered by a variety of stimuli, such as mitophagy for damaged mitochondria, lipophagy for lipids, and xenophagy for intracellular bacteria. During xenophagy, intracellular pathogens are directed to autophagic machineries through selective autophagic receptors for bacterial degradation (82,83). Because xenophagy activation during Mabc infection is unclear, we briefly discuss the regulation of xenophagy during Mtb infection before moving on to Mabc infection. Via the ESX-1 system, Mtb induces phagosomal permeabilization to activate ubiquitin-mediated/STING dependent xenophagy (82). Ubiquitinated bacterial phagosomes (by ubiquitin ligase, Parkin and Smurf1) interact with adaptors p62 and NDP52, thereby delivering Mtb phagosomes to autophagosomal structures (79). Additionally, TRIM16-galectin-3 cooperation is required for detection of damaged lysosomes and autophagic protection during Mtb infection (84). Furthermore, during Mtb infection, the surface protein Rv1468c of Mtb directly binds to ubiquitin to activate p62-mediated xenophagy and intracellular Mtb clearance (85). By sensing cytosolic Mtb DNA, the DNA sensor cGAS also triggers xenophagy (86).

Another noncanonical autophagic process, LAP, involves pattern PRR signaling-mediated direct recruitment of LC3 and Beclin-1 to the single-membrane phagosome, leading to phagosomal maturation and bacterial killing (82). The Rubicon complex, which is formed by Rubicon-BECN1-VPS34-UVRAG assembly and NOX2-dependent ROS, is essential for LAP activation (87). The detailed mechanisms and molecular importance of autophagy/xenophagy are reviewed elsewhere (79,81,82). However, whether noncanonical autophagy is activated in the context of Mabc infection and its regulation are unclear. Further studies are needed to elucidate the exact role of autophagy in defense against Mabc infection. Below we discuss recent findings on canonical autophagy in innate immune cells during Mabc infection.

### Crosstalk between host autophagy and Mabc infection

Host autophagy is implicated in infection with NTM bacteria, including Mabc (88,89). Among NTMs, *M. smegmatis* and *M. fortuitum* induce more robust autophagy compared to *M. kansasii* (90). Autophagy activation is independent of mTOR signaling in *M. smegmatis* infection (91). Mabc and *M. smegmatis* induce greater autophagosome formation than Mtb and MAC in THP-1 macrophages. These data suggest that different mycobacterial species elicit distinct functions in macrophages (56). Long-term use of azithromycin in CF patients inhibits bactericidal autophagy by preventing lysosomal acidification during Mabc infection (22). However, azithromycin treatment or autophagy modulation does not affect the mycobactericidal activity of neutrophils (92). Therefore, the role of autophagy in host defenses against Mabc infection might differ by cell type.

MaSm suppresses phagosomal acidification and fails to induce host apoptosis and autophagy (30,31). In contrast, MaRg induces more autophagy than MaSm, although the reason for this is unclear (30). Although these data suggest that GPLs of Mabc play a role in escape from host autophagy, it is unknown how Mabc and/or its components evade host autophagy. In addition, MaRg UC22, isolated from patients with the upper lobe fibrocavitary form of lung disease, leads to severe pulmonary inflammation in mice and increases the levels of cytokines in macrophages (93). This clinical Mabc strain markedly inhibits autophagic flux compared to MaSm (94), suggesting a unique ability to modulate host autophagic activity to promote virulence. Further work is needed to clarify the Mabc components that actively regulate host autophagy and to understand the modulation of autophagy by Mabc strains in the context of host immune defense during infection. Autophagy-restoring therapies enhance pathogen



**Figure 1.** Schematic of the interaction between Mabc and host autophagy during infection. MaRg upregulates autophagosome formation in host cells during infection, but MaSm blocks phagosomal acidification and fails to elicit autophagy. The clinical isolate MaRg UC22 inhibits autophagic flux. GPL of MaSm is a key component of MaSm that mediates escape from host autophagy. Although the autophagy-modulating effect of azithromycin differs by cell type, it inhibits host autophagy during Mabc infection. Gemfibrozil (a PPAR $\alpha$  activator) promotes host defense against Mabc infection by activating TFEB and lysosomal function. TFEB, transcription factor EB.

clearance and ameliorate lung inflammation, particularly in CF airways (95). The Mabc interaction with the host autophagy pathway is shown in **Fig. 1**. Given the essential function of autophagy in regulating immune responses and inflammation, autophagy-manipulating therapeutic strategies could promote immune defense and control pathologic inflammation during Mabc infection.

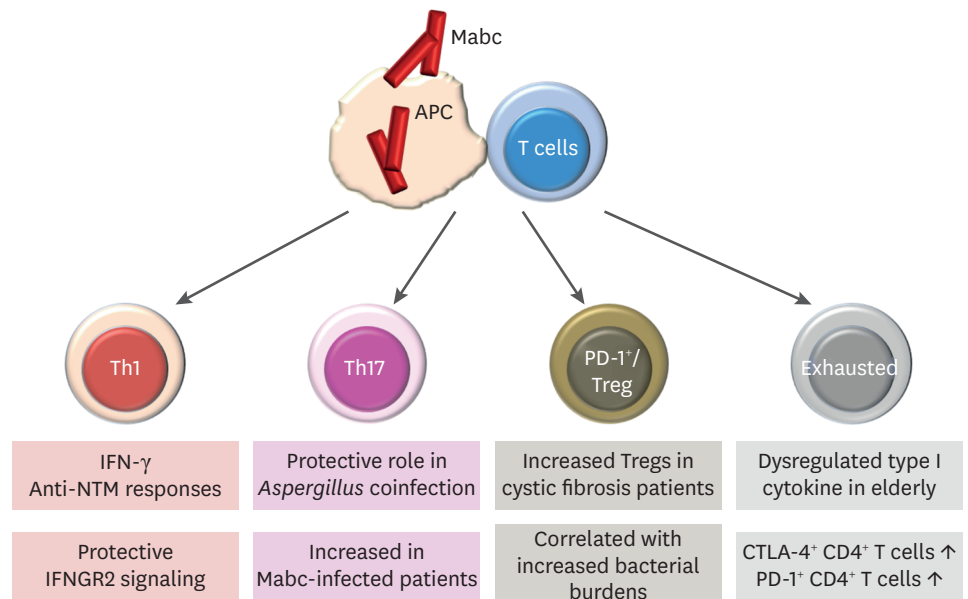
## ADAPTIVE IMMUNE SYSTEM DURING Mabc INFECTION

Innate immune cells, such as DCs and macrophages, function as antigen-presenting cells (APCs) to activate adaptive immune responses, i.e., humoral and cell-mediated immunity. Adaptive immunity is associated with tight regulation of the interplay between APCs and T cells. APCs express markers involved in APC-T cell interactions and antigen presentation, such as CD40, CD70, and PD-L2 (96-98). The adaptive immune system encompasses CD4<sup>+</sup> Th1 cells, Th2 cells, Th17 cells, and cytotoxic T cells. Th1 cells produce IFN- $\gamma$  to protect against intracellular microbes, including Mtb and NTMs, by activating the mononuclear phagocyte family, NK cells, and cytolytic T cells (14,49). The activation of bacteria-loaded macrophages caused by Th1 cells is crucial for intercellular interactions in Mtb infection. The IFNGR2 signaling pathway is critical for protective immune responses against Mabc infection (71). Because most studies have not focused on NTMs, further *in vitro* and *in vivo* works are needed to clarify the functions of adaptive immune components and cells in Mabc infection.

Distinct patterns of adaptive immune responses are related to protection and pathogenesis during NTM-PD. In patients with Mabc lung diseases, Th1- and Th2-related cytokine levels were significantly decreased, whereas IL-17-related cytokine levels were increased, in Mabc-

infected patients compared to controls (73). Interestingly, a recent study revealed that there were no differences in Th1- and Th2-related cytokine levels in PBMCs between Mabc-infected patients and controls and the IL-17-related cytokine level was lower in patients than in healthy controls (99). These discrepancies could be a result of different cell types, patients with different disease severities, or sample sizes, etc. Further comprehensive studies on larger populations are needed to clarify the distinct patterns of cytokine profiles in patients with *M. abscessus* infection at different clinical stages. By contrast, the level of IL-17 was reduced in patients with MAC PD compared to healthy subjects, implying MAC actively suppresses Th17 production in the disease sites during infection (100). BCG vaccination enhances cross-reactive T cell immunity to inhibit intracellular Mav and Mabc (101). These data highlight the potential of BCG-mediated NTM cross-reactive immunity to facilitate the development of a vaccine or immunotherapy for pulmonary NTM disease (101). The proportion of PD-1 levels on CD4<sup>+</sup> lymphocytes are upregulated in PBMC from the patients with MAC lung infection, but not in those with Mabc infection, compared to healthy controls (102). In patients with NTM lung disease, the level of PD-1<sup>+</sup>CD4<sup>+</sup> lymphocytes is correlated with radiographic progression (102). Therefore, IFN- $\gamma$ -producing protective T cell activity is associated with anti-NTM host defenses; however, it is unclear whether immunosuppressive PD-1 expression and Treg expansion are related to the pathogenesis of NTM-PD by different NTM strains. **Fig. 2** shows the roles of T cell types in the host adaptive immune response to Mabc infection.

In the increasing population of CF patients infected by NTMs, Mabc infection is often associated with coinfection with *Aspergillus fumigatus*, the most common filamentous fungus in CF, spores of which are usually inhaled into the airways (103). Control of Mabc infection is dependent on the Th1 and Th17 immune responses in *A. fumigatus*-coinfected mouse lung (104), suggesting a protective role for adaptive immunity against coinfection. In addition,



**Figure 2.** Role of the adaptive immune system during Mabc infection. APCs, including DCs and macrophages, present antigens to T cells, which mediate the adaptive immune response to Mabc infection. Th1 cells produce IFN- $\gamma$  to protect against Mabc. IFNGR2 signaling is crucial for the host immune response to Mabc infection. The Th17 immune response controls Mabc infection in *A. fumigatus*-coinfected mouse lungs. The levels of PD-1<sup>+</sup>CD4<sup>+</sup> lymphocytes and Tregs are related to the bacterial burden. Treg levels are increased in patients with CF. The exhausted T cell phenotype and dysregulated type I cytokine production is found in elderly individuals. CTLA-4, cytotoxic T lymphocyte antigen 4.

the T cell immune signature differs depending on host risk factors; i.e., CF and old age. In response to mitogens, CF patients have increased Tregs and defective TNF- $\alpha$  production, whereas elderly individuals have the exhausted T cell phenotype with dysregulated type I cytokine production (105). Further research with a larger population is needed to assess adaptive immune responses and investigate the therapeutic efficacy of blockade of immune checkpoint inhibitors, such as PD-1 and/or cytotoxic T lymphocyte antigen 4 antibody, for NTM infections.

## OTHER HOST FACTORS INVOLVED IN PROTECTIVE AND PATHOGENIC RESPONSES

### Sirtuin 3 (SIRT3), peroxisome proliferator-activated receptor- $\alpha$ (PPAR $\alpha$ ), and high-mobility group nucleosomal-binding domain 2 (HMGN2)

Several host factors are involved in antimicrobial defenses during Mabc infection. SIRT3 is central to biological metabolic processes and is localized to mitochondria (106). It is one of the main deacetylases which can control acetylation of mitochondrial proteins and enzymes involved in the mitochondrial functions (107). This enzyme belongs to a conserved class that requires NAD<sup>+</sup> for its activity (107). SIRT3 is also implicated in non-metabolic cells including immune cells. Our previous data represent that SIRT3 promotes host defense against Mabc pulmonary infection (78). SIRT3 regulates excessive inflammation and mitochondrial damage in the Mabc-infected lung (78). In addition, a SIRT3 agonist (resveratrol) promoted antimicrobial growth in mice and zebrafish, suggesting a critical role for SIRT3 in metazoan host defense (78).

The transcription factor PPAR $\alpha$  is crucial in several metabolic processes, such as carbohydrate and lipid metabolism and control of inflammation in diverse cell and tissue types (108). PPAR $\alpha$  promotes antimicrobial responses against Mabc in macrophages and *in vivo* via the transcription factor EB and the regulation of excessive inflammatory cytokine production (109). Notably, gemfibrozil, a PPAR $\alpha$  activator, reduces the lung Mabc load and pathological inflammatory responses in mice (109). Both compounds are shown in **Fig. 1** as lysosomal activators, although their functions in autophagy regulation are unclear.

Little is known about the host immune factors that promote Mabc infection. A case study showed that the heterozygous missense mutation of STAT3, associated with a gain of function, is responsible for chronic immunodeficiency and recurrent bronchopulmonary infections caused by Mabc (110). These data strongly suggest a role for STAT3 signaling in the pathogenesis of human Mabc infection.

HMGN2, a highly conserved nucleus-associated small protein, functions in bacterial clearance and various cellular processes, including regulation of gene transcription, chromatin structure, and DNA replication. HMGN2 is also induced during NTM infection (along with Mabc and *M. smegmatis*), suppresses antimicrobial responses in host cells by inhibiting NO synthesis and M1 macrophage polarization (111). These findings have improved our understanding of host factors with protective and/or detrimental functions during Mabc pulmonary infection.

### Micro RNAs (miRNAs)

The mRNAs and miRNAs in immune cells and body fluids have been investigated as biomarkers of NTM diseases. Post-transcriptional gene silencing is an attractive gene silencing mechanism moderated by miRNAs, which are widely distributed in eukaryotes (112). Each miRNA may negatively regulate multiple targets, and several miRNAs can control a single miRNA. miRNAs are a family of small non-coding RNAs of 18–25 nucleotides and participates in the fine-tuning of innate immune and inflammatory responses (112,113). Several miRNAs control the production of cytokines that are crucial in mycobacterial infection. NTM-PD patients infected with Mabc and Mmass showed increased miR-144-3p levels in PBMCs (114). Although the target of miR-144-3p has not been identified, the expression levels of proinflammatory cytokines/chemokines are strongly correlated with miR-144-3p levels in PBMCs (114). Combined with the finding that miR-144-3p favors intracellular mycobacterial growth, upregulation of miR-144-3p is involved in NTM-PD (114). NTM-PD patients exhibit significant differences in serum levels of multiple miRNAs compared to healthy controls (115). Four miRNAs (hsa-miR-484, hsa-miR-584-5p, hsa-miR-625-3p, and hsa-miR-4732-5p) are differentially expressed in sera between NTM-PD patients and controls, suggesting that differentially expressed miRNAs have potential as diagnostic biomarkers for NTM-PD (115). Although bioinformatics analysis suggested that the target genes of these miRNAs are involved in immune responses, the functions of the miRNAs are unknown (115). Further studies are warranted to clarify the roles and precise mechanisms by which these miRNAs regulate host defenses in NTM infections.

## CONCLUSION

In the last decade, research on pathogen-host interactions during Mabc infection has advanced considerably. Mabc manipulates host immune defenses via lipid and protein components. Mabc GPLs enable immune escape and survival in the host. However, MaRg lacks GPLs and, unlike MaSm, disrupts phagosomal structures and induces a robust inflammatory response and cell death. Further studies of bacterial factors are needed to gain insight into pathogenesis and host-protective responses. In addition, numerous host factors interact with Mabc to modulate protective and pathological responses during infection. Host antimicrobial defense mechanisms include PRRs, cytokines, autophagy, SIRT3, miRNAs, and the adaptive immune system, all of which determine the outcome of Mabc infection. Future studies should clarify the molecular mechanisms underlying the protective factors/pathways that achieve Mabc clearance from host cells. In addition, *in vivo* and translational studies will promote the design of novel host-directed therapeutics against drug-resistant Mabc infection.

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