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Drug resistance mechanism and therapeutic strategies in *Mycobacterium abscessus*

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Abstract

Considering its resistance mechanisms, *Mycobacterium abscessus* (Mab) is a major threat to current therapeutic techniques since it is one of the primary causes of serious respiratory infections in immunocompromised persons. The chemotherapeutic choices for infections triggered by *Mycobacterium abscessus* have become scarce due to its innate and acquired resistance to regularly administered antibiotics. Therefore, for efficient therapy, it is imperative to understand both intrinsic and acquired resistant to antibiotics in Mab. In this current review, we provide recent updates on the mechanisms of both intrinsic and acquired resistant to antibiotics and treatment efficacy in Mab. Thus, a thorough comprehension of the mechanisms underlying drug resistance and the therapeutic effectiveness of antibiotics against Mab can yield novel suggestions for enhancing treatment results, lowering mortality, averting drug resistance, and stopping Mab transmission. Furthermore, it will aid in the development of new antibiotics for Mab as well as quick molecular diagnostic tools.

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Introduction

Globally, the nontuberculous mycobacteria (NTM)-caused infections are becoming an increasingly serious health issue, especially when it comes to lung-related diseases. Few species, such as Mycobacterium abscessus, are responsible for serious and frequently opportunistic infections in humans despite the diversity and ubiquity of NTM in the environment. *Mycobacterium abscessus* (Mab), one of the NTM, is a significant opportunistic respiratory infection in individuals with underlying lung illness. (Cowman *et al.*, 2019). Mab was initially identified as *Mycobacterium chelonae* subsp. abscessus when it was isolated from a knee abscess in a 63-year-old lady in 1952 by Moore and Frerichs (Moore and Frerichs, 1953). Severe infections in the skin, soft tissues, joints, and surgical sites are among the other body areas where *Mab* has been connected to infections. Mab-caused pulmonary infections can be especially harmful to people with cystic fibrosis because they can hasten the advancement of end-stage lung disease, transmit from person to person, and potentially compromise the outcome of a lung transplant (Qvist *et al.*, 2016; Ruis *et al.*, 2021; Leard *et al.*, 2021; Mudde *et al.*, 2022). The bacterial resistance to numerous widely used antibiotics is broad and intrinsic, making treatment of these diseases challenging. We have few treatment options because it is frequently considered to be one of the mycobacteria that is most resistant to antibiotics.

There are very few potent antibiotics that are effective against Mab due to intrinsic drug resistance. A combination of oral and injectable antibiotics, together with surgical lung incision in patients with localized but resistant lung illness, is frequently used to treat severe Mab lung infections (Abdelaal *et al.*, 2022). Presently, a multidrug regimen of clarithromycin is used to treat Mab infections; however, with repeated exposure to the antibiotic, certain Mab subspecies develop resistance. Because of this, there are few therapeutic alternatives that may be used, which might result in infections that persist, repeated infections, or even death in certain situations. There is a medical emergency to identify compounds that are clarithromycin potentiators for the purpose to safely reinstate clarithromycin effectiveness against Mab, since clarithromycin is the cornerstone of NTM therapies and right now the only extremely successful oral antibiotic for treating Mab infections.

However, our understanding remains limited about the intrinsic or acquired resistance to antibiotic against Mab. Therefore, it is essential to clarify the resistance mechanisms Mab uses against current antibiotics in addition to the ongoing efforts to find novel alternative drugs for Mab treatment. This project offers insightful information for the creation of novel compounds in addition to helping to improve the efficacy of currently available antibiotics in overcoming these resistance obstacles. The aim of this review is to provide a thorough overview of the state of knowledge on antibiotic resistance mechanisms and treatment efficacy in Mab.

Mycobacterium abscessus: a nightmare bacterium

Moore and Frerichs discovered Mab bacteria for the first time in 1953. The mycobacteria known as MABSC, which grow quickly and are resistant to a variety of antibiotics, are present in soil and water (Brown-Elliott and Wallace, 2002). According to Griffith *et al.* (2007), this complex can result in post-procedural and post-surgical infections because it is also resistant to standard disinfectants. As such, the infection brought on by this disease is challenging to treat. NTM species of great importance are Mab and *M. avium*.

Epidemiology of Mab

The high prevalence of NTM in soil, dust, and water sources leads to frequent and recurring human–pathogen interaction. More than 200 species and subspecies are represented by NTM; some are regarded as opportunistic or strict pathogens (Cristancho-Rojas *et al.*, 2024). A NTM that grows quickly in the environment is called Mab (Strnad *et al.*, 2018). The earliest known case of its discovery was when Moore and Frerichs identified it from a knee infection in 1953 (Moore and Frerichs, 1953).

Often considered as one of the more prevalent antibiotic-resistant mycobacteria, Mab is the second most common pathogen associated with NTM pulmonary disease. The most common causing agents are the bacteria *M. avium* complex (MAC) and Mab, although the distribution of species varies by region and age group. Geographically, the prevalence of these diseases varies as well; in France, the isolation prevalence is 3.7%, but in the US, it is 13.9% (Zomer *et al.*, 2023). In 1992, Mab was recognized as a distinct species and split off from the *M. chelonae* group. Sub-species including *M. massiliense* and *M. bolletii* were later reported. According to recent research, a comparative genomic study divided the Mab complex into three subspecies: Mab subsp. abscessus, Mab subsp. massiliense, and Mab subsp. Bolletii (Victoria *et al.*, 2021).

Drug resistance mechanisms in Mab

Natural resistance

Many drugs, including tetracyclines, β-lactams, and rifamycin, are naturally ineffective against *M. abscessus*. The majority of the drugs utilized in the current treatment regimens are repurposed drugs meant to treat Mycobacterium TB infections, which makes them ineffective. The natural resistance of Mab to multiple drugs can be attributed to various reasons, such as its slow growth rate, impenetrable cell wall, efflux pump, and genetic variability in drugs target genes.

Mycobacterial cell wall envelope in drug resistance

Drug resistance and pathogenicity are significantly increased by the unique cell wall that Mab possesses. A thorough explanation of the role of the cell envelope in drug resistance has been provided. In 1990, Jarlier and Nikaido conducted research on the crucial function of the cell envelope in *M. chelonae*. The results of the investigation demonstrated a correlation between drug resistance and decreased permeability in the *M. chelonae* cell wall. The β-lactamase produced by bacteria renders β-lactams inactive. A similar poor permeability found in the cell membrane of Mab is important for aminoglycoside resistance. Furthermore, the cell membrane shields the cell from harmful extracellular substances and confers innate resistance to acids and alkalis on mycobacteria (Daffé and Draper, 1997). According to the study, cell envelope synergizes with "intrinsic resistance," an internal system that is induced by antibiotics, to eliminate the effects of the medications (Nguyen and Thompson, 2006). Efflux pumps, enzymes that change or inactivate antibiotics, enzymes that modulate targets and genes granting metal resistance make up the intrinsic resistance (Nessar *et al.*, 2012).

Antibiotic-modifying/inactivating enzymes mediated resistance

Mab exhibits a high level of antibiotic resistance due to the fact that its genome encodes numerous proteins/enzymes that may be involved in drug efflux systems. These proteins include members of the major facilitator family, ATP-binding cassette transporters (ABC transporters), and large proteins found on Mycobacterial membranes (MmpL proteins). These enzymes are in capable of modifying and degrading antibiotics so that their effects become inactive (Luthra *et al.*, 2018 .(Rifampicin (RIF) is a first-line antibiotic treatment for M. tuberculosis infections and it inhibits the bacterial transcription process by blocking the β-subunit of RNA polymerase, which is encoded by the rpoB gene. The reason for the rifampicin resistance in M. smegmatis is the existence of ADP-ribosyltransferase, an enzyme that modifies antibiotics. According to a recent publication by Rominski *et al.* (2017a), the Mab became vulnerable to RIF due to the deletion of the MAB_0591 gene, which codes for ADP-ribosyltransferase. According to Kohanski *et al.* (2010), aminoglycosides are the most widely utilized class of antibiotics used to treat bacterial infections because they prevent the translation of bacterial proteins. Although the 16S rRNA subunit of the 30S ribosomal subunit is the main target of all aminoglycosides, their precise binding site and manner of action may vary slightly based on their chemical makeup. Mutations in ribosomal protein genes, altered 16S rRNA, reduced cell permeability/efflux, and enzymatic drug modification

can all lead to bacterial resistance to aminoglycosides. Interestingly, the minimum inhibitory concentrations (MICs) of aminoglycosides decrease when the *M. abscessus* MAB_4395 gene, which codes for 2'0-N-acetyltransferase, is deleted (Rominski *et al.*, 2017b). It is interesting to note that Mab resistance to amikacin and clarithromycin is linked to the MAB_3508c gene, which encodes the WhiB7-like protein. Another an essential class of antibiotics for treating NTM infections is macrolides. In bacteria, the erythromycin ribosome methylase (erm) gene is linked to macrolide resistance. This enzyme inhibits the macrolide affinity for the ribosome exit tunnel and methylates the A2058 base of the 23S rRNA gene (Blair *et al.*, 2015).

Efflux pumps mediated resistance

Efflux pumps are among the elements that give mycobacteria their inherent resistance (Rossi *et al.*, 2006). Efflux pumps are crucial for the defense of bacteria because they export or efflux hazardous substances and metabolites into the external environment (Louw *et al.*, 2009). The genome of Mab has a significant number of ABC transporter families and mycobacterial membrane protein large (MmpL) proteins that encode genes (Ripoll *et al.*, 2009). According to Kerr *et al.* (2005), these transporters are divided into two groups: importers, which take up extracellular components, and exporters, which release the molecules into the extracellular environment. Nevertheless, nothing is known about the roles of ABC-transporters in M. abscessus. Lipids are transported to the cytoplasm membrane by the MmpL family of efflux transporters, which also encodes proteins involved in cell division, nodulation, and resistance. According to Paulsen *et al.* (1996), the RND proteins are a class of bacterial efflux pumps that identify and aid in the passage of several classes of substances, including metals, medications, and fatty acids, as well as cationic, anionic, and neutral chemicals. The MmpL transporter family of genes is encoded in the genome of Mab, yet nothing is known about their functional roles as of yet. The MmpL family with involvement in M. abscessus has not been extensively studied (Dupont *et al.*, 2016; Bernut *et al.*, 2016). According to a recent study by Richard *et al.* (2018), the MAB_2299c gene controls the expression of MmpS/MmpL membrane proteins. A mutation in the MAB_2299c gene can increase Mab resistance to bedaquiline (BDQ) and clofazimine (CFZ).

Mutation mediated by genetic polymorphism of target genes

Drug susceptibility within NTM is correlated with genotype due to variation in nucleotides within drug target genes (Alcaide *et al.*, 1997; Guillemin *et al.*, 1998). According to Alcaide *et al.* (1997), ethambutol (EMB) resistance increases as a result of a mutation in the *embB* ethambutol resistance-determining region (ERDR). At MICs > 64 mg/L, Mab exhibits inherent resistance to EMB. The substitution of leucine for methionine at position 304 (L304M) and isoleucine for glutamine at position 303 (I303Q) was discovered when the ERDRs of three NTM species, including Mab, *M. leprae*, and *M. chelonae*, which are sensitive to EMB, were aligned. Three NTM species became extremely resistant to EMB due to this mutation. In a similar vein, Guillemin *et al.* (1998) observed that Mab developed resistance to fluoroquinolones due to mutations in quinolone resistance-determining regions (QRDRs).

Acquired resistance

Acquired resistance is caused by genotypic alterations in clinical strains of mycobacterial species (Martin *et al.*, 1990). Chromosome gene function alterations are the main cause of acquired resistance in clinical isolates (Musser *et al.*, 1995). The infection brought on by multidrug-resistant (MDR) *M. tuberculosis* and NTM is treated using medications belonging to the 2-deoxystreptamine aminoglycosides class (Sander and Bottger, 1999). This family of medications targets the 16S rRNA gene (Shakil *et al.*, 2008). It has been demonstrated by Prammananan *et al.* (1998) that a single alteration in this gene causes Mab to be resistant to tobramycin, amikacin, and kanamycin. Predictably, macrolide medications are often recommended to treat NTM infections (Dautzenberg *et al.*, 1991). Macrolide drugs impede ribosomal translocation by targeting the rRNA operon

(Poehlsgaard *et al.*, 2003). The resistance of M. abscessus to clarithromycin and other macrolides is caused by the ribosome methylase erm(41) gene (Nash *et al.*, 2009).

Treatment of Mab infection

The second most frequent nontuberculous mycobacterial pathogen associated with lung disease is Mab. There are relatively few treatment options available for Mab infections, and the outcome is typically not good. Antibiotics such as macrolide antibiotics, amikacin, cefoxitin, and other drugs must be taken in combination to treat infections caused by Mab. On the other hand, the therapeutic prognosis is often dismal, with just a 25–58% cure rate (Chen *et al.*, 2019; Kwak *et al.*, 2019). As a result, Mab infections are frequently referred to as "antibiotic nightmares" (Nessar *et al.*, 2012). Thus, there is a pressing need for novel or repurposed drugs to resolve this therapeutic dilemma. Due to the high rate of inherent resistance to a wide range of antibiotics often used for bacterial infections, the prognosis for treating Mab pulmonary infections is extremely poor. Furthermore, anti-TB medication regimens are ineffective against this newly emerging disease; this trend led to the term "incurable nightmare" being used (Nessar *et al.*, 2012). As of right now, no efficient treatment plans have been suggested for Mab disease. Prior to drug delivery, in vitro drug susceptibility testing and subspecies identification are frequently performed (Ryu *et al.*, 2016). In the 1990s, ciprofloxacin was first used to treat Mab (Maxson *et al.*, 1994). A macrolide (clarithromycin or azithromycin) was administered orally to the patients throughout the first phase of treatment, in addition to intravenous antibiotics such as imipenem, tigecycline, and amikacin. Furthermore, amikacin and an oral macrolide combined with one oral antibiotic from the following list of options—co-trimoxazole, moxifloxacin, minocycline, linezolid, and clofazimine—are widely recommended for the treatment of the continuation phase (Haworth *et al.*, 2017). Even with long-term antibiotic therapy that is advised, Mab cannot completely be eradicated from the lungs, and recurrence is frequent following the conclusion of antibiotic regimens (Stout *et al.*, 2016). Finally it can be concluded that numerous specialists, including the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA), have advocated combination therapy consisting of intravenous amikacin combined with cefoxitin or imipenem and an oral macrolide (Griffith *et al.*, 2007; Colombo *et al.*, 2008). Regarding the clinical effectiveness of this combination antibiotic therapy for *Mab* lung disease, there are, nevertheless, surprisingly few data available in the literature. In particular, it is unclear what constitutes the best therapy regimens and how long treatments should last.

Conclusion and future perspective

Mab has emerged as a new pathogen, and more and more cases of the disease have been documented globally. These cases primarily affect those with weakened immune systems or chronic pulmonary conditions. It is logical to assume that there will be a rise in Mab infections in the next years due to the growing number of patients who have underlying health conditions that may be regarded as risk factors. Therefore, it is essential to clarify how resistance develops Mab uses against current antibiotics in addition to the ongoing efforts to find novel alternative drugs for Mab treatment. The goal of this study was to present a summary of the key antibiotic and disinfectant resistance pathways throughout various NTM infections. This project offers insightful information for the creation of novel compounds in addition to helping to improve the efficacy of currently available antibiotics in overcoming these resistance obstacles. In order to facilitate the creation of a Mab antibiotic pipeline and provide clarity on the molecular factors underlying the drug's notable resistance to chemotherapy, this paper attempts to provide a thorough overview of the state of the art regarding resistance to antibiotics strategies in Mab.

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