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REVIEW

MmpL transporter-mediated export of cell-wall associated lipids and siderophores in mycobacteria

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SUMMARY

Mycobacteria produce a large variety of surface-exposed lipids with unusual structures. Some of these compounds are ubiquitously present in mycobacteria and play an important role in the structural organization of the cell envelope, while others are species-specific. The biosynthesis of most of these lipids requires modular polyketide synthases (PKS) or non-ribosomal peptide synthetases (NRPS) that are intracellular, suggesting that the assembly of these compounds takes place in the cytosolic compartment or near the inner leaflet of the plasma membrane. The molecular mechanisms that mediate the export of these lipid components across the cell envelope remain poorly understood. Mycobacterial membrane protein Large (MmpL) transporters, a subclass of Resistance-Nodulation-Cell Division (RND) transporters, appear to play a major role in this process, acting as scaffold proteins that couple lipid synthesis and transport. Recent studies have shown that this family of transporters also contributes to siderophore secretion in *Mycobacterium tuberculosis*. The goal of this review is to provide the most recent advances in our understanding of the molecular mechanisms involved in lipid and siderophore transport mediated by MmpL transporters.

Contents

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1. Introduction

One characteristic feature of the mycobacterial cell envelope is its high lipid content which represents up to 60% of the dry weight of the bacteria [1]. This structure is composed of a plasma membrane, a cell wall consisting of a covalently linked complex of peptidoglycan, arabinogalactan and mycolic acids associated with a large variety of atypical non-covalently linked lipids, and a capsule rich in polysaccharides that surrounds the cell [2–4] (Figure 1). Mycolic acids bound to arabinogalactan and non-covalently linked lipids, also known as extractable lipids, interact to form an atypical outer membrane called the mycomembrane [5,6] (Figure 1). Some extractable lipids play an important role in the organization of the envelope and/or contribute to the virulence of pathogenic mycobacterium species. This topic has been extensively reviewed elsewhere and is beyond the scope of this review [2–4,7,8].

Several families of cell-wall associated lipids contain long methyl-branched or polyunsaturated fatty acids [2,4]. The development of tools for the genetic manipulation of mycobacteria, in conjunction with rapid progress in bacterial whole genome sequencing, has greatly contributed to the characterization of the metabolic pathways involved in the formation of these substances. These approaches have shown that the assembly of the fatty-acyl components of these compounds requires the concerted action of polyketide synthases (PKS), fatty acyl-AMP or fatty acyl-CoA ligases, polyketide-associated protein (Pap)-type acyltransferases, and serine hydrolase enzymes [4,9,10].

The first group of polyketide-derived lipids includes various families of trehalose-containing glycolipids. Among these, trehalose monomycolates (TMM), and trehalose dimycolates (TDM), also called cord factor, are essential and abundant components of the mycobacterial cell envelope and play a crucial role in cell wall function and host–pathogen interactions [4] (Figure 2). This group also contains diverse species-specific trehalose esters, such as di- and poly-acyltrehaloses (DAT, PAT), sulfolipids (SL), also known as sulfatides, trehalose polyphleates (TPP), and lipooligosacharides (LOS) (Figure 2). DAT, PAT, and SL are restricted to the human pathogen *Mycobacterium tuberculosis* whereas TPP, a family of glycolipids originally described in *Mycobacterium phlei*, are produced by a wide range of nontuberculous mycobacteria including *Mycobacterium smegmatis* and the opportunistic pathogens *Mycobacterium abscessus* and *M. avium* [4,11–13]. LOS have been isolated from fast- and slow-growing *Mycobacterium* species including *M. kansasii*, *M. smegmatis*, and *M. canettii*, but have not been detected in the classical species of the *M. tuberculosis* complex. A second group of polyketide-derived lipids comprises two structurally related families of lipids, the phthiocerol dimycocerosates (DIM) and the glycosylated phenolphthiocerol dimycocerosates, also called phenolglycolipids (PGL) (Figure 2). These molecules are found in slow-growing pathogenic species such as *M. leprae*, *M. ulcerans*, *Mycobacterium marinum*, and in members of the *M. tuberculosis* complex [4].

Another group of extractable lipids is formed by the glycopeptidolipids (GPL), a major class of glycolipids found in a number of nontuberculous mycobacterial species including *M. smegmatis*, *M. abscessus*, and *M. avium* [4] (Figure 2). Their biosynthesis requires the concerted action of two non-ribosomal peptide synthetases (NRPS) that condense specific amino acids to form the tripeptide-amino alcohol moiety of GPL (Figure 2) [14,15]. These compounds play important functions in colony morphology and biofilm formation in *M. smegmatis* and *M. abscessus*, and may contribute to the pathogenesis of mycobacterial infections [4,16].

As mentioned above, cell-wall associated lipids are important components of the outer membrane. Species-specific glycolipids, DIM/PGL, and GPL are also present in the outermost compartment of the capsule and are exposed on the cell surface, whereas TMM/TDM are found in deeper compartments of the capsule [17,18]. The cytoplasmic location of PKS and NRPS suggests that the assembly of these compounds takes place in the cytosolic compartment or near the inner leaflet of the plasma membrane of the bacteria. Their export toward the cell periphery envelope thus requires active transport systems for their correct localization in the cell.

Genes that encode the proteins involved in the production of polyketide-derived lipids and GPL are clustered on dedicated

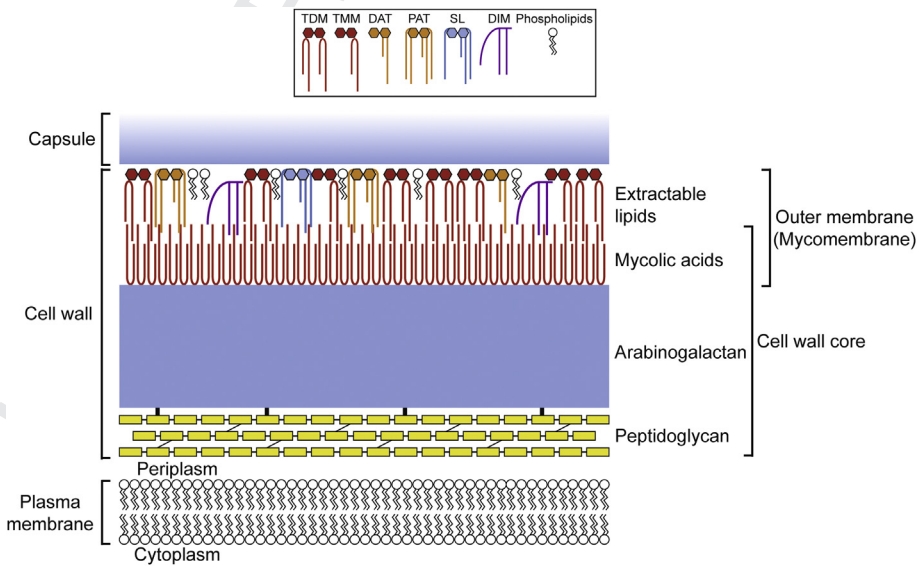

Figure 1. Schematic representation of the cell envelope of *M. tuberculosis*. The cell envelope is composed of a plasma membrane, a cell wall, and a capsule. The cell wall consists of a cell wall core made of peptidoglycan, arabinogalactan and mycolic acids, and a large variety of cell wall-associated lipids, known as extractable lipids, that interact with mycolic acids bound to arabinogalactan to form the outer membrane (mycomembrane). Extractable lipids are also found in the capsule (not shown). For the sake of clarity, phosphatidylinositol-derived lipoglycans (phosphatidyl-*myo*-inositol mannoside, lipomannan, and lipoarabinomannan), which are important structural constituents of the mycobacterial cell envelop [115], as well as proteins, have been omitted. Layers and chemical structures are not drawn at scale. A detailed description of the organization of the mycobacterial cell envelope is provided in recent reviews [2–4]. Abbreviations for extractable lipids are the same as those used in the text. Adapted from Angala et al. [2].

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