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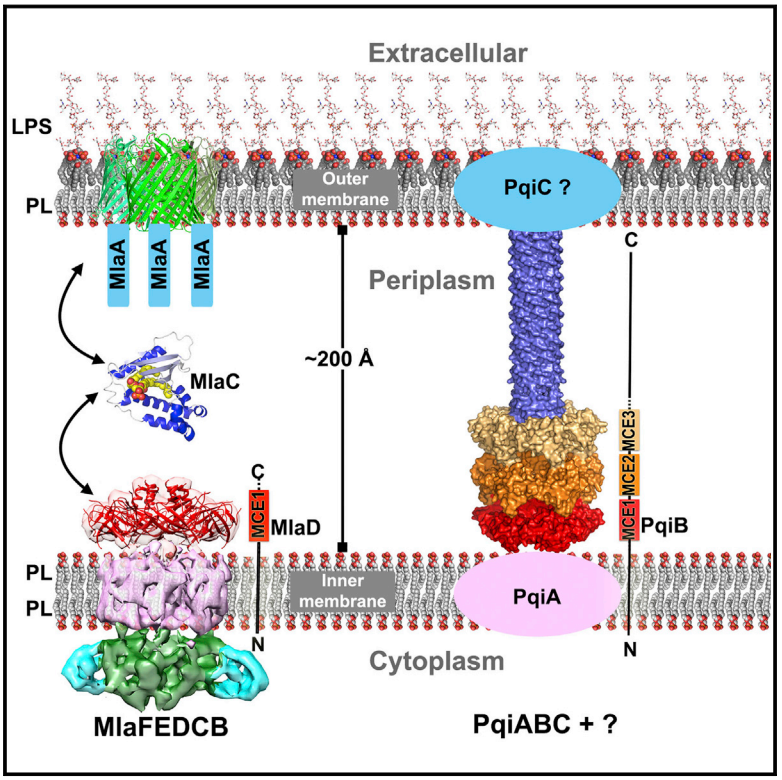
Architectures of Lipid Transport Systems for the Bacterial Outer Membrane

Graphical Abstract



Highlights

- MCE proteins adopt diverse architectures based on conserved hexameric ring modules
- Structures show how the Mla system is poised to shuttle lipids across the periplasm
- YebT and PqiB form tube- and syringe-like architectures with central channels

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In Brief

A conserved structural building block is used to create a wide range of periplasm-spanning architectures implicated in lipid trafficking between the inner membrane and outer membrane in bacteria.

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Architectures of Lipid Transport Systems for the Bacterial Outer Membrane

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SUMMARY

How phospholipids are trafficked between the bacterial inner and outer membranes through the hydrophilic space of the periplasm is not known. We report that members of the mammalian cell entry (MCE) protein family form hexameric assemblies with a central channel capable of mediating lipid transport. The *E. coli* MCE protein, MlaD, forms a ring associated with an ABC transporter complex in the inner membrane. A soluble lipid-binding protein, MlaC, ferries lipids between MlaD and an outer membrane protein complex. In contrast, EM structures of two other *E. coli* MCE proteins show that YebT forms an elongated tube consisting of seven stacked MCE rings, and PqiB adopts a syringe-like architecture. Both YebT and PqiB create channels of sufficient length to span the periplasmic space. This work reveals diverse architectures of highly conserved protein-based channels implicated in the transport of lipids between the membranes of bacteria and some eukaryotic organelles.

INTRODUCTION

The bacterial outer membrane (OM) is a critical barrier, restricting the traffic of small molecules such as antibiotics into the cell. Mutations that disrupt OM integrity reduce virulence in pathogenic bacterial species (Cox et al., 1999; Kong et al., 2012; Wang et al., 2007) and increase their susceptibility to antibiotics, suggesting that targeting pathways important for OM maintenance and biogenesis may be a fruitful approach for developing new therapies for bacterial disease.

The OM of most Gram-negative bacteria is asymmetric, with an outer leaflet rich in lipopolysaccharide (LPS) and an inner leaflet composed of phospholipids. Much research has uncovered a detailed, but still evolving, picture of how LPS is synthesized, trafficked, and inserted into the OM (May et al., 2015; Ruiz et al., 2009). Yet, the mechanisms and structural basis of how nascent phospholipids are trafficked between the inner membrane (IM) and OM and how asymmetry between the leaflets of the OM is maintained remain unclear.

Proteins of the MCE superfamily (originally thought to mediate mammalian cell entry in *M. tuberculosis* [Arruda et al., 1993]) are defined by the presence of one or more conserved MCE domains at the sequence level but have no similarity to other proteins of known structure or function. MCE proteins are ubiquitous among double-membraned bacteria (Casali and Riley, 2007) (Figure 1A) and eukaryotic chloroplasts (Awai et al., 2006), a double-membraned bacteria-derived organelle. In contrast, MCE proteins appear to be absent in bacteria bound by a single membrane. MCE proteins are important virulence factors for pathogenic bacteria (Carpenter et al., 2014; Gioffré et al., 2005; Nakamura et al., 2011; Pandey and Sassetti, 2008; Senaratne et al., 2008; Zhang et al., 2012) and have been implicated in the transport of lipids (Awai et al., 2006; Malinverni and Silhavy, 2009; Roston et al., 2011; Sutterlin et al., 2016; Xu et al., 2003, 2008), cholesterol and steroids (Klepp et al., 2012; Mohn et al., 2008; Pandey and Sassetti, 2008), and other hydrophobic molecules (Kim et al., 1998). MCE proteins from plants (Awai et al., 2006), and more recently from *V. parahaemolyticus* and *E. coli*, have been shown to bind phospholipids (Krachler et al., 2011; Thong et al., 2016). MCE systems are thought to drive the transport of hydrophobic molecules from the OM to the IM, although it has also been suggested that they may function as exporters to move molecules toward the OM and the outside of the cell (Kim et al., 1998).