Antibiotic resistance re-visited

With the introduction of antibiotics at the beginning of the 20th century, the threat of bacterial infections was thought to over. Today, antibiotics are still used as the first, if not only, line of defense against bacterial infections. However, the excessive use and misuse of antibiotics has selected for bacteria that are resistant to single and multiple antibiotics. Finding new or alternative antibiotics has proven to be very difficult since the mechanisms that lead to antibiotic tolerance or resistance are still not fully understood. One method by which bacteria achieve antibiotic tolerance or resistance is the alteration of cellular structures on the surface of the bacterial envelope. This particular mechanism is important to understand since surface-acting antibiotics like Polymyxin B (PmB) and Colistin (Polymyxin E) have become important as the last line of defense for treatment of emerging multi-drug resistance Gram-negative bacteria, especially in critical care settings. A disturbing fact is that several pathogenic bacterial species are inherently resistant to polymyxins, including *Burkholderia*, *Pseudomonas*, *Proteus*, *Neisseria*, and *Brucella* species.

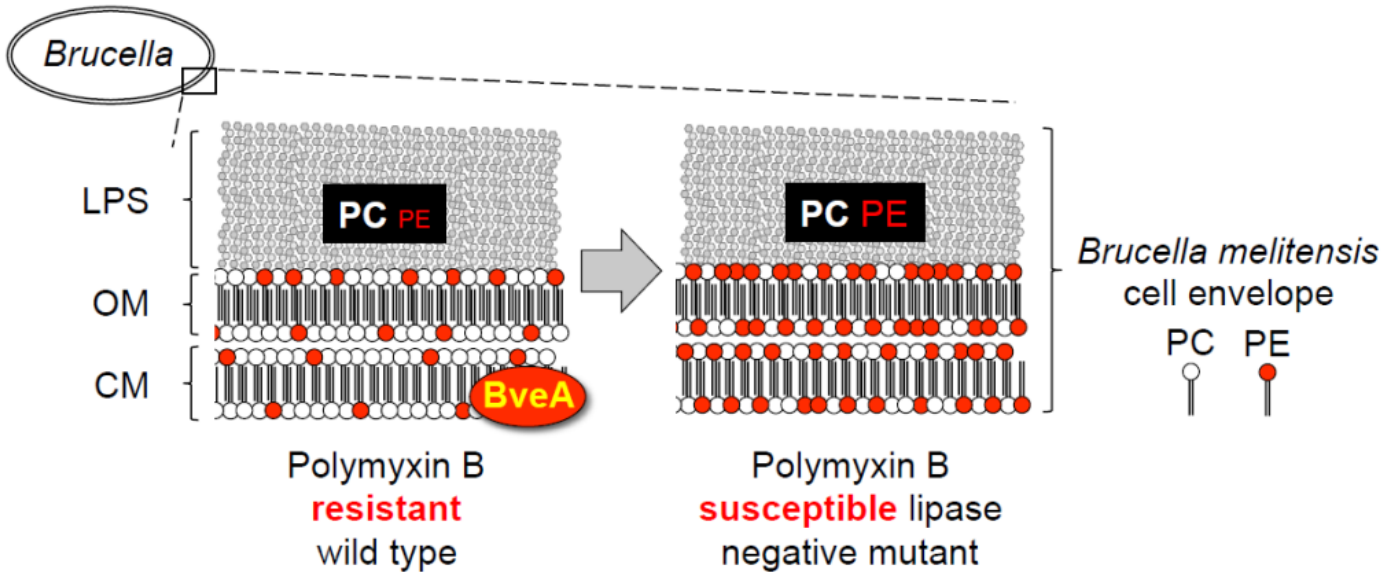

Fig. 1. Schematic representation of the cell envelope of Brucella melitensis antibiotic resistant and susceptible strains. Three major components comprise the cell envelope of Gram-positive bacteria: lipopolysaccharide (LPS), outer membrane (OM) and cellular membrane (CM). Human pathogenic Brucella melitensis strains exploit the lipase BveA to fine-tune the ratio of membrane lipids PE to PC to convey resistance to the antibiotic polymyxin B.

Although bacterial polymyxin resistance has been attributed primarily to modification of molecules that are embedded in the cell membrane (mainly lipopolysaccharides), we identified a new mechanism whereby the cell membrane itself is modified to convey antibiotic resistance. This novel mechanism contributes directly to high-level resistance against this class of drugs.

Our study revealed that the lipid composition of the cell membrane is actively fine-tuned by the highly polymyxin B resistant human pathogen, *Brucella melitensis.* The bacterium produces a lipase enzyme (BveA) that specifically cleaves the membrane lipid phosphotidylethanolamine (PE), thereby lowering the abundance of PE in the cell envelope. We could show that a strain lacking the BveA contains significantly higher amounts of the membrane lipid PE in its cell envelope and lost at the same time its resistance against polymyxin B antibiotic. Additionally, we were able to show that the bacterial pathogen *Brucella melitensis* depends on membrane fine-tuning as a resistance mechanism enabling the bacteria to cause infections in mammalian hosts. Our findings are supported by studies with artificially generated membranes that showed the ratio of PE to other membrane components, such as phosphatidylcholine (PC), directly contributed to the resistance of membranes against disrupting agents. This class of enzymes is evolutionarily interesting since they are encoded in the genomes of bacterial species that co-exist with polymyxin-producing bacteria in the rhizosphere, suggesting that maintaining a low PE content of the bacterial cell envelope may be a shared persistence strategy for association with plant and mammalian hosts.

Publication

Phospholipase A1 Modulates the Cell Envelope Phospholipid Content of Brucella melitensis, Contributing to Polymyxin Resistance and Pathogenicity.
Kerrinnes T, Young BM, Leon C, Roux CM, Tran L, Atluri VL, Winter MG, Tsolis RM
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