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Using Neutron Reflectometry to Understand Antibiotic Resistance in Gram-negative Bacteria at the Outer Membrane

With bacteria increasingly becoming resistant to common antibiotics, we are currently heading for a post-antibiotic world, where treatable common aliments are suddenly untreatable. This means that there is now considerable research effort in understanding how antibiotic resistance arises, and in creating a new generation antibiotics. The outer membrane is the first line of defence against antibiotics for Gram-negative bacteria. Being able to penetrate the outer membrane is essential to designing effective antibiotics and antimicrobial peptides. The outer membrane is an asymmetric bilayer consisting of phospholipids on its lower leaflet and lipopolysaccharides on its environment-facing outer leaflet. This work will present on creating model outer membranes from Pseudomonas aeruginosa, a bacterium that is normally harmless, but infections from which can prove to be problematic for those that are immunocompromised. Worryingly, P. aeruginosa is showing increasing signs of becoming resistant to Polymixin B, an antibiotic of last resort. Certain biochemical modifications to lipid A (a component of lipopolysaccharides) can confer resistance to Polymixin B. Model P. aeruginosa outer membranes using lipid A with different modifications were created on silica surfaces using Langmuir-Blodgett and Langmuir-Schaeffer deposition techniques. Model outer membranes created this way are ideal tools for studying the binding antimicrobial peptides because: a) they reflect the lipid composition of the membrane, b) reflect the fluidity of the membrane, and c) maintain the asymmetric nature of the outer membrane. The nanoscale structures of the membranes were determined using neutron reflectometry and it was observed that Polymixin B was unable to penetrate into bilayers that consist of de-acylated lipid A. New drug targets Octapeptin A3 [1], and modified Polymixins FADDI-019 and FADDI-020 [2] were tested and found to disrupt membranes composed of modified lipid A which confer resistance to Polymixin B.
[1] M.-L. Han et al., ACS Infect. Dis. 3, 606 (2017)
[2] M.-L. Han et al., ACS Chem. Biol. 13, 121 (2018)

Topic

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