Contribution ID : **204** Type : **Oral**

Combating multidrug resistance. Structure of an endotoxin modifying enzyme

Friday, 25 November 2016 14:45 (15)

Multiple drug resistance (MDR) in Gram-negative bacteria represents one of the most intractable problems facing modern medicine. Colistin and polymyxin are cationic antimicrobial peptide antibiotics which permeabilise the bacterial outer membrane and have been used to treat infections. Resistance to these antibiotics is conferred by the modification of the lipid A headgroups with phosphoethanolamine (PEA) moieties resulting in a reduced negative charge of the bacterial surface and exclusion of the drug. This modification is carried out by the enzyme, lipid A PEA transferase (LptA). Recently a mobile colistin resistance determinant, mcr-1, encoding an LptA homologue was identified in MDR Escherichia coli. We have determined the crystal structure of a full-length LptA from Neisseria sp. to 2.75Å resolution. The structure reveals a previously uncharacterized helical membrane domain and a periplasmic facing soluble domain. The domains are linked by a single helix that runs along the membrane surface interacting with the phospholipid head groups. Two helical insertions containing conserved charged residues lie between two transmembrane helices and are implicated in substrate binding. Intrinsic fluorescence, limited proteolysis and molecular dynamics studies suggest that the protein may sample different conformational states to enable the binding of two very different sized lipid substrates. These results provide novel insights into the mechanism of endotoxin modification and will aid a structure-guided rational drug design approach to treat multidrug resistant bacterial infections.

Keywords or phrases (comma separated)

endotoxin modification, enzyme, Neisseria, multidrug resistance

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No

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No

Are you an ECR? (<5 yrs</br>since PhD/Masters)

No

What is your gender?

Female

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Session Classification : Concurrent Session 4: Structural Biology II - Sponosred by DECTRIS

Track Classification : Structural Biology