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Poster abstract submission

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Poster title

Structural basis for antibiotics murepavadin and thanatin targeting the lipopolysaccharide insertase LptD

Poster abstract

Gram-negative bacteria are shielded by an asymmetric outer membrane whose biogenesis depends on the lipopolysaccharide transport (Lpt) machinery. Therein, the essential membrane protein LptD mediates the final lipopolysaccharide insertion step, making it a prime target for antibiotics. Two peptide antibiotics targeting LptD are known, thanatin and murepavadin, but their mode of action has so far remined unresolved. Here, we determined five high-resolution cryo-electron microscopy structures of Escherichia coli and Pseudomonas aeruginosa LptDEM complexes bound with the peptide antibiotics murepavadin and thanatin, to address this question. The structures reveal that both compounds target the distal β-jellyroll edge of LptD, blocking the essential interaction with the periplasmic bridge protein LptA. Despite converging on the same binding region, thanatin and murepavadin engage LptD through distinct interaction modes: thanatin binds via β-sheet augmentation, whereas murepavadin binds through side chain interactions. These differences rationalize the broad-spectrum activity of thanatin compared to the species-specificity of murepavadin. Our results identify a structurally conserved, drug-accessible target site in LptD and provide a framework for the rational development of therapeutics targeting the outer membrane of Gram-negative bacteria.

Research topic Biological therapeutics