STRUCTURAL AND CONFORMATIONAL INSIGHTS INTO BACTERIAL LECTIN RECOGNITION OF HOST RECEPTORS

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Lectins play a crucial role in bacterial colonization of host tissues and have emerged as promising therapeutic targets due to their involvement in host-pathogen interactions [1]. The increasing threat of antimicrobial resistance (AMR) is rendering standard antibiotics ineffective, necessitating the development of novel treatment strategies against multidrug-resistant pathogens, particularly Gram-negative ESKAPE pathogens. Targeting bacterial lectins, such as LecA and LecB in *Pseudomonas aeruginosa*, has been shown to effectively interfere with bacterial virulence and biofilm formation, offering a promising alternative to traditional antibiotics [2].

In this context, an orthologue of LecA, named EclA, has been identified in *Enterobacter cloacae*, a member of the human gut microbiota that can also act as an opportunistic pathogen in immunocompromised patients.

The crystal structure of EclA, in complex with methyl α-L-selenofucoside, revealed a unique two-domain architecture, consisting of a dimeric N-terminal LecA-like domain and a novel dimeric C-terminal carbohydrate-binding domain. This domain adopts an unprecedented intertwined β-sheet dimeric structure, suggesting a binding mode distinct from previously characterized bacterial lectins and indicating a potential role for EclA as a cross-linker for specific host glycans. Glycan array analysis demonstrated high specificity of EclA for fucosylated blood group antigens, particularly LewisA and H-type II [3], in contrast to LecA, which binds galactose-containing sugars.

Despite these findings, the molecular mechanisms underlying EclA's interaction with fucosylated ligands remained unresolved. To address this gap, a multidisciplinary approach was employed, using saturation transfer difference (STD) NMR to obtain ligand epitope mapping, trNOESY for the identification of the bioactive conformation, and computational studies to generate a three-dimensional model of the complexes. Additionally, isothermal titration calorimetry (ITC) was used to quantify binding thermodynamics and affinities, providing a comprehensive understanding of EclA-ligand interactions. These findings not only deepen insights into *E. cloacae* adhesion mechanisms but also lay the groundwork for developing anti-adhesion therapies targeting bacterial lectins in drug-resistant infections.

References:

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