IDENTIFICATION OF RECEPTOR BINDING-DOMAIN OF BACTEROIDALES SECRETED ANTIMICROBIAL PROTEIN-3 (BSAP-3)

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Bacteroidales, a dominant order of Gram-negative bacteria, are highly efficient long-term colonizers of the human intestinal microbiota [1], playing a pivotal role in host physiology through their immunomodulatory and anti-inflammatory functions [2,3]. Their ability to persist and thrive in this competitive ecosystem is largely attributed to sophisticated antimicrobial strategies, including the production of Bacteroidales Secreted Antimicrobial Proteins (BSAPs) [4-6]. BSAPs represent a recently identified class of bactericidal pore-forming toxins with an unprecedented level of receptor specificity. Unlike other members of the membrane attack complex/perforin (MACPF) and cholesterol-dependent cytolysin (CDC) superfamily, BSAPs exhibit an extraordinary degree of selectivity, targeting only a single outer membrane β-barrel protein [7] or lipopolysaccharide [4-6], thus restricting their function predominantly to intra-species competition. This unique mechanism distinguishes BSAPs as the first known bacterial MACPF proteins with bactericidal activity. Their highly specific mode of action suggests significant potential as next-generation antimicrobial agents, offering precise bacterial targeting with minimal perturbation to the commensal microbiota and a lower propensity for inducing antibiotic resistance. Despite their therapeutic promise, the molecular determinants governing BSAP receptor specificity remain poorly understood.
In this study, we employed a structural biology approach to characterize the protein BSAP-3, aiming to delineate the specific domains responsible for receptor recognition and interaction. Our findings provide critical insights into the molecular basis of BSAP-3 specificity, advancing our understanding of bacterial mechanisms and paving the way for the potential development of BSAP-inspired antimicrobial therapeutics.

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