CHEMISTRY

Mechanistic Insights of Oligosaccharide Modulation at the Host-Pathogen Interface

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Human breast milk is the gold standard in infant nutrition. Human milk oligosaccharides (HMOs) are the third largest component of human breast milk and occur in high abundance. Originally discovered as a prebiotic factor in breast milk researchers have since demonstrated the vast health benefits these structurally diverse glycans confer. One such benefit of HMOs is their ability to modulate biofilm formation, a bacterial behavior that contributes to pathogenicity and antimicrobial resistance. Here, using *Acinetobacter baumannii*, a gram-negative, highly threatening, multidrug resistant pathogen, we demonstrate the impressive ability of HMOs to prevent and dismantle bacterial biofilms. We emphasized the applicability of these antiadhesive properties through an antibiotic adjuvant screen where HMOs significantly potentiate the efficacy of current antibiotics to this bacterium. This phenotype perpetuates in a murine model of infection, where we have showed significant reductions in bacterial colonization of respiratory organs when treated with HMOs in combination with an antibiotic compared to no treatment negative controls. Through a pan-omics approach we identified phenylacetic acid (PAA), a ubiquitous microbial signaling molecule, as a key mediator of these HMO-induced perturbations. We report here that PAA modulates bacterial biofilm formation in a Csu independent manner, contrary to literature precedence. This work includes one of the first published accounts of HMO perturbations of a known bacterial signaling molecule. Further, we establish HMOs as a viable therapeutic intervention in the treatment of *A. baumannii* infections. Taken together, this work affords greater insight into HMO-modulation of bacterial behaviors as a mechanism to combat infectious diseases.

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