DEVELOPMENT OF A MUCIN GLYCAN LIBRARY FOR STUDYING VIRULENCE ATTENUATION IN PATHOGENS

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The rise of antimicrobial resistance (AMR) calls for the urgent need for novel therapeutic approaches. Mucus is essential as a first line of defense against infections and influences the composition of our microbiome. Recent studies have demonstrated the ability of mucin glycoproteins and their associated O-glycans to downregulate the expression of virulence-associated genes in both bacterial and fungal pathogens, offering a promising avenue for the development of anti-virulence therapies. However, the structural diversity of native mucin glycans and the difficulties in isolating pure, well-defined individual structures in suitable amounts from natural sources has proven extremely challenging due to their similar physical and chemical characteristics. This has prevented the study of the virulence attenuating properties of individual glycan structures.

Therefore, to address this need and to elucidate which specific glycans are responsible for anti-virulence activity, we have been developing a scalable approach to produce a comprehensive library of structurally defined mucin O-glycans in sufficient quantity and quality (>30 mg of target glycan). This library includes core 1, core 2, core 3 & core 4-type structures, synthesized as methyl glycosides[1,2] that retain the natural stereochemistry of GalNAc-Ser/Thr linkage in mucins. Subsequent studies using this library have enabled the successful identification of discrete glycan structures responsible for virulence attenuation, for example, in fungal pathogen *Candida albicans*[3,4] and prominent Gram-negative bacterial pathogen *Vibrio cholerae*.[5] These findings offer new insights into how mucin O-glycans can influence pathogen behavior and provide a foundation for the development of anti-virulence therapeutics aimed at mitigating AMR.

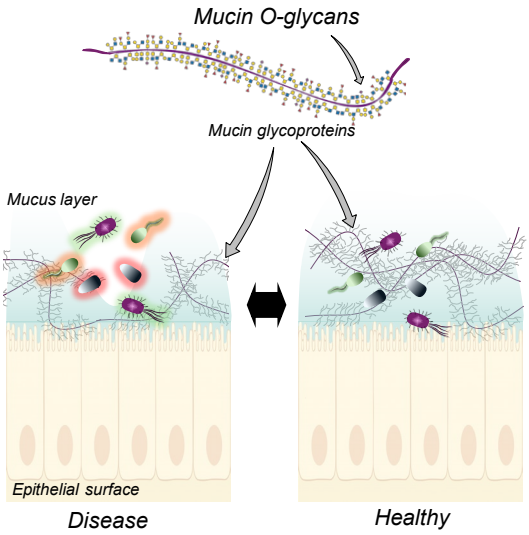

Figure 1.

By developing methods to further expand and produce a comprehensive library of mucin O-glycans in sufficient quantity and purity, we can assess the virulence attenuating capabilities of individual glycans and facilitate exploration of the molecular processes of pathogen virulence regulation, paving the way for subsequent development of novel anti-virulence therapeutics.

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