

Mucosal glycans as novel antimicrobial agents

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Carbohydrates (i.e., glycans) are an important family of natural products which coat all cell surfaces and play essential roles in cell signalling and function. Many diseases are characterized by changes in glycan composition, suggesting their potential utility as a therapeutic target.

The mucosal barrier is well-established to play an important role in microbiota development and as a first line of host defence. Although this has traditionally been attributed to the physicochemical properties of mucus, several recent publications indicate that mucin glycoproteins (the main protein component of mucus) can regulate gene expression and are capable of attenuating virulence in diverse, cross-kingdom pathogens, including Gram-negative bacteria, Gram-positive bacteria, and fungi.

In efforts to better understand the mechanism of virulence attenuation, non-reductive alkaline β -elimination was used to demonstrate that the glycan component of mucins is responsible for this antimicrobial activity [1]. With mucins displaying several hundred distinct glycan structures, we next sought to identify the discrete glycan structures responsible for this novel gene regulation. Individual mucin O-glycan structures are not commercially available, are not amenable to automated synthesis, and given their overlapping physical and chemical properties cannot be isolated as pure compounds from natural sources using current technologies.

Therefore, through a multi-centre collaborative effort (full list of contributors in [1-3]) we have been actively: (i) characterizing the complex mucin O-glycan pools to identify structures most likely to have biological activity; (ii) developing a synthetic approach to obtain individual mucin O-glycans in sufficient quantity for functional analysis [2]; and (iii) assessing the virulence attenuating capabilities of individual glycans in diverse pathogens [1,3]. Within this framework, we have successfully identified specific structures that suppress virulence phenotypes in the fungal pathogen *Candida albicans* (e.g., filamentation, biofilm formation, surface adhesion), and regulate pathogenicity in *Vibrio cholerae* (e.g., reduced cholera toxin production), with potency comparable to native mucin glycan pools.

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- [2] G. Minzer, R. Hevey. *ChemistryOpen*, **2022**, e202200134 (early view).
- [3] B.X. Wang, J. Takagi, A. McShane, J.H. Park, K. Aoki, C. Griffin, J. Teschler, G. Kitts, G. Minzer, M. Tiemeyer, R. Hevey, F. Yildiz, K. Ribbeck. *The EMBO Journal*, **2022**, e111562 (in press).