Mucus-derived glycans as a therapeutic strategy for cross-kingdom pathogens

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Glycans (*i.e.*, carbohydrates) are an important family of natural products which coat all cell surfaces and play essential roles in cell signaling 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 microbiome development and as a first line of defense. Although this has traditionally been attributed to its physicochemical properties, 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(s) of virulence attenuation, we identified the glycan component of mucins as responsible for this anti-virulence activity [1,2]. With mucins displaying several hundred distinct glycan structures, we next sought to identify the discrete 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-center collaborative effort (full list of contributors in [1-5]) we have been actively: (i) characterizing complex mucin O-glycan pools to identify structures most likely to have biological activity [1,2]; (ii) developing methods to produce individual mucin O-glycans in sufficient quantity and quality for functional analysis [3,4]; and (iii) assessing the virulence attenuating capabilities of individual glycans in diverse pathogens [1,2,5]. 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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[1] Takagi J, Aoki K, Turner BS, Lamont S, Lehoux S, Kavanaugh N, Gulati M, Valle Arevalo A, Lawrence TJ, Kim CY, Bakshi B, Ishihara M, Nobile CJ, Cummings RD, Wozniak DJ, Tiemeyer M, Hevey R*, Ribbeck K*. *Nat. Chem. Biol.* **2022**, *18*, 762-773.
[2] Wang BX, Takagi J, McShane A, Park JH, Aoki K, Griffin C, Teschler J, Kitts G, Minzer G, Tiemeyer M, Hevey R, Yildiz F, Ribbeck K. *EMBO J.* **2023**, *42*, e111562.
[3] Minzer G, Hevey R. *ChemistryOpen* **2023**, *12*, e202200134.
[4] Cori CR, Hevey R. *Helv. Chim. Acta.* **2024**, *107*, e202400026.
[5] Ribbeck K, Takagi J, Hevey R, "Mucin glycans as antifungal agents," US Patent Office, Application No. 18/189,190, filed March 23, 2023.