Discovery & synthesis of mucosal glycans for attenuating virulence in pathogens

R. Hevey[1]

[1]Dept. Pharmaceutical Sciences, University of Basel

Glycans (i.e., carbohydrates) 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 structures, 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, recent reports indicate that mucin glycoproteins (the main protein component of mucus) and their associated glycans can regulate gene expression and are capable of attenuating virulence in diverse, cross-kingdom pathogens, including Gram-positive bacteria, Gram-negative bacteria, and fungi.

With mucins displaying several hundred distinct glycans, we sought to identify the discrete glycan structures responsible for this novel gene regulation. Individual mucin O-glycans 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 complex mucin O-glycan pools to identify structures most likely to display 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), and regulate pathogenicity in *Vibrio cholerae* (e.g., reduced cholera toxin production), with potency comparable to native mucin glycan pools.

[1] Julie Takagi, Kazuhiro Aoki, Bradley S Turner, Sabrina Lamont, Sylvain Lehoux, Nicole Kavanaugh, Megha Gulati, Ashley Valle Arevalo, Travis J Lawrence, Colin Y Kim, Bhavya Bakshi, Mayumi Ishihara, Clarissa J Nobile, Richard D Cummings, Daniel J Wozniak, Michael Tiemeyer, Rachel Hevey*, Katharina Ribbeck.* *Nature Chemical Biology*, **2022**, 18, 762-773.
[2] Giulietta Minzer, Rachel Hevey. *ChemistryOpen*, **2022**, e202200134.
[3] Benjamin X Wang, Julie Takagi, Abigail McShane, Jin Hwan Park, Kazuhiro Aoki, Catherine Griffin, Jennifer Teschler, Giordan Kitts, Giulietta Minzer, Michael Tiemeyer, Rachel Hevey, Fitnat Yildiz, Katharina Ribbeck. *The EMBO Journal*, **2023**, 42, e111562.