MULTIVALENT AND SUPERSELECTIVE BINDING BY BACTERIAL TOXINS

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AB_5 toxins, such as cholera toxin (CTx) and shiga toxin (STx), exploit multivalent interactions with cell surface glycans to gain entry into host cells. While glycolipid receptors like GM1 and Gb_3 have long been identified as key ligands for CTx and STx respectively [1], recent evidence implicates fucosylated glycans, such as Lewis^x, in CTx binding [2,3]. This suggests a broader role for non-glycolipid components of the glycocalyx in toxin recognition, but these interactions remain poorly characterized. To investigate these complex interactions, we have developed defined valency neoglycoproteins [4], and biomimetic glycocalyx models with mucin-like glycopolymers displayed on supported lipid bilayers (Figure) [5]. These glycoconjugates present defined densities of glycans, including GM1, Gb_3, and Lewis^x, on protein and polysaccharide backbones, with high control over glycan presentation. Using quartz crystal microbalance with dissipation monitoring and spectroscopic ellipsometry, we have quantified toxin binding processes in a tunable artificial glycocalyx environment. The non-toxic B-subunits of CTx andB and STx showed significantly enhanced binding to their respective ligands in the polymer-grafted glycocalyx, with super-linear ("superselective") responses to increasing glycan density, highlighting how the physical and chemical architecture of the glycocalyx modulates multivalent interactions. Together, these approaches allow us to dissect the rules governing multivalent toxin-glycan recognition and provide a modular platform for the design of glycan-based inhibitors and probes. Our results offer new insights into host-pathogen interactions and tools for glycocalyx engineering.

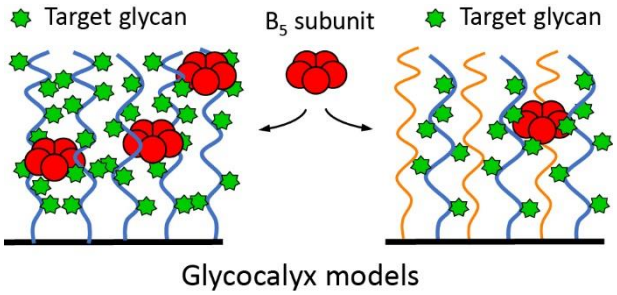

Figure 1. Biomimetic glycocalyx models binding to bacterial toxins [5].

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