TARGETING VIRAL GLYCANS TO STOP VIRAL INFECTIONS

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Viruses use glycans as an attachment factor during a viral docking to the host cell. Understanding and disrupting these binding processes could lead to new and desperately needed antiviral agents to counter the threat of viral outbreaks, especially those posed by enveloped viruses (EnV). In this contribution, we apply methods of molecular dynamics (MD) simulations to explain the mechanism how synthetic carbohydrate receptors (SCRs) - small molecules designed to bind carbohydrates - are able to bind selectively to EnV glycans and disrupt the viral docking.
First, the MD simulations of SCRs and *N*-glycans common to the surfaces of EnV reveal that SCRs would consistently bind to the trimannosylchitobiose core, the only conserved structural motif present in all *N*-glycans. Importantly, the binding affinity between SCRs and a specific glycan would depend on strength of interactions between the recognition element of the SCR and the *N*-glycan antennae. Systematic variations in the SCR and glycan composition helps to spell out the relationship to design more efficient SCRs which attain affinity and selectivity towards a chosen glycan target on a viral surface. Next, the MD techniques were used to investigate the binding of SCRs to the SARS-CoV-2 spike and NipaH Fusion glycoproteins. The simulations reveal that the SCRs associate on the glycan portion of the glycoprotein, and the resulting distribution of receptors on the protein surface depends on the type of SCRs and the glycan. The observed selectivity follows prediction made for free *N*-glycans. The reported simulations, in addition to experimental NMR, glycan microarray, *in vivo*, and animal studies, suggest that glycans can be selectively targeted by SCRs which could lead to reclassification of glycans from “undruggable” to a viable antiviral target and open new avenues for developing novel treatments, diagnostics and sensors.