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Glycan binding properties of SARS-CoV-2 receptor binding domain variants of concern

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The ongoing COVID-19 global pandemic is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). SARS-CoV-2 spike (S) glycoprotein is responsible for binding to the primary host receptor (angiotensin-converting enzyme 2, ACE2) and mediates viral entry. Certain classes of host glycans such as heparan sulfates and sialic acid-containing glycolipids have been shown to serve as attachment factors and enhance cell binding and facilitate infection. Over the past two years, multiple emerging variants of concern, with increased transmissibility have emerged. The goal of the present work is to identify host glycans that are recognized by these variants.

The catch-and-release electrospray ionization mass spectrometry (CaR-ESI-MS) assay was used to screen both a defined library of 139 purified glycans (mostly mammalian), and natural N-glycan libraries produced from various human tissues against the SARS-CoV-2 receptor binding domain (RBD) of the S protein of Alpha (lineage B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2) variants. Next, we performed direct ESI-MS assay to quantify binding strengths of those RBDs with a small subset of glycan ligands. CaR-ESI-MS and direct binding measurements were be performed using an Ultra-High Mass Range and Classic Orbitrap mass spectrometers, respectively. Both instruments were equipped with a nanoflow ESI source.

CaR-ESI-MS screening of a defined library identified the ganglioside GM1 as the top hit for RBD in wild type, Alpha, Gamma and Delta strains. No hits were found for the Beta variant while Delta exhibits the most promiscuous glycan binding of all strains tested. Quantitative ESI-MS binding measurements performed on a subset of glycans revealed that GM1 is the highest affinity ligand for wild type, Alpha, Gamma and Delta strains. Interestingly, blood group A type antigens had same binding strength to Delta variant as GM1. The enhancement in the neutral glycans binding to Delta variant might correlate with its increased transmissibility. Future efforts will be directed to elucidating the specificities of the N-glycans ligands produced from human lung, intestine and brain tissues which can be recognized by these five strains. Future efforts will also be directed towards the latest Omicron variant to fully help understand why new variants of SARS-CoV-2 spread more rapidly.