O-12.6 Short talk

Variant-Specific Interactions at the Plasma Membrane: Heparan Sulfate's Impact on SARS-CoV-2 Binding Kinetics

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Despite the high mutation rate in the receptor-binding spike protein (S) among SARS-CoV-2 variants, molecular studies have shown poor correlation between ACE2 affinity and SARS-CoV-2 infectivity. This suggests that the virus evolved to optimize entry by interacting with other plasma membrane components. We tested this hypothesis by exploring the virus interaction with the entire plasma membrane and directly addressing how avidity and membrane complexity affect attachment. Using single-particle tracking, we measured the virus binding kinetics to native supported lipid bilayers (nSLBs) derived from the plasma membrane of human pulmonary cells and observed a significant increase in avidity for Omicron BA.1 compared to earlier variants. Heparan sulfate (HS) emerged as the main driver of this variation. A 10-fold increase in the S affinity to HS for BA.1 was observed by single-molecule force spectroscopy, while enzymatic removal of HS from nSLBs increased virus binding for all variants but BA.1. These results indicate a shift in the role of HS from limiting ACE2 accessibility to becoming a key attachment factor. We speculate that the efficient use of HS, an abundant surface molecule, aids in the efficient infection of the upper airways observed for Omicron, providing possible molecular evidence for the origin of its tropism transition to higher transmissibility but milder symptoms.