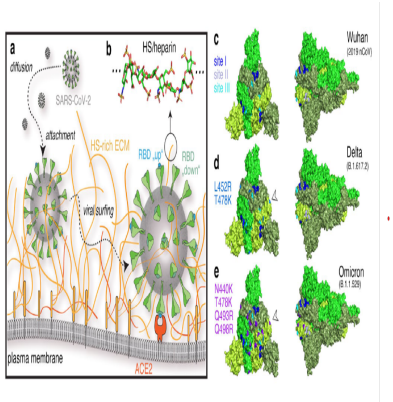

Evolution of SARS-CoV-2 spike trimers towards optimized heparan sulfate cross-linking and inter-chain mobility

Description

The heparan sulfate (HS) -rich extracellular matrix (ECM) serves as an initial interaction site for the homotrimeric spike (S) protein of SARS-CoV-2 to facilitate subsequent docking to angiotensin-converting enzyme 2 (ACE2) receptors and cellular infection. More recent variants, notably Omicron, have evolved by swapping several amino acids to positively charged residues to enhance the interaction of the S-protein trimer with the negatively charged HS. However, these enhanced interactions may reduce Omicron’s ability to move through the HS-rich ECM to effectively find ACE2 receptors and infect cells, raising the question of how to explain HS-associated viral movement mechanistically. This work shows that Omicron S proteins have evolved to balance HS interaction stability and dynamics, resulting in enhanced mobility on an HS-functionalized artificial matrix. This property is achieved by the ability of Omicron S-proteins to cross-link at least two HS chains, allowing direct S-protein switching between chains as a prerequisite for cell surface mobility. Optimized HS interactions can be targeted pharmaceutically, as an HS mimetic significantly suppressed surface binding and cellular infection, specifically of the Omicron variant. These findings suggest a robust way to interfere with SARS-CoV-2 Omicron infection and potentially future variants.

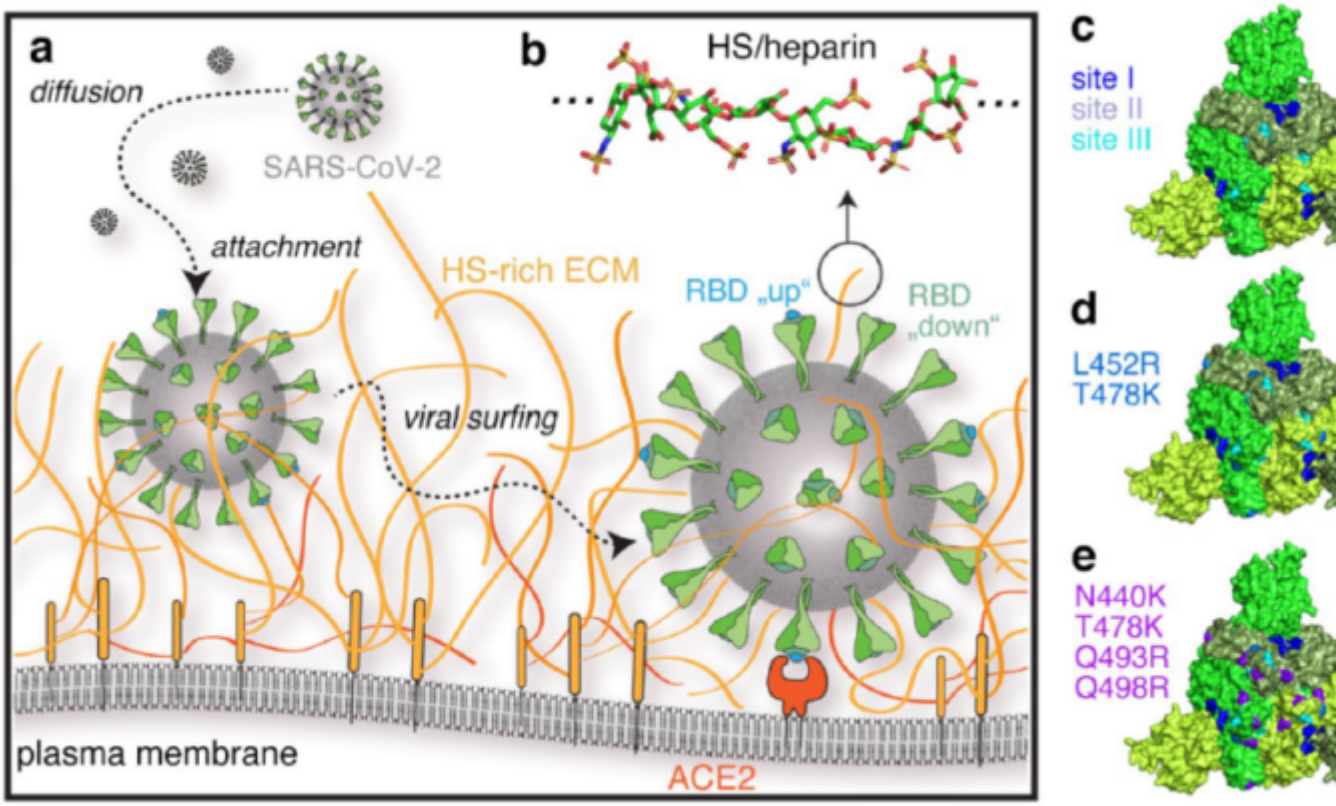

Figure . Schematic of SARS-CoV-2 host cell association and invasion

Category

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