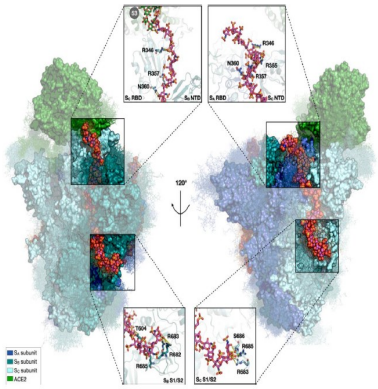
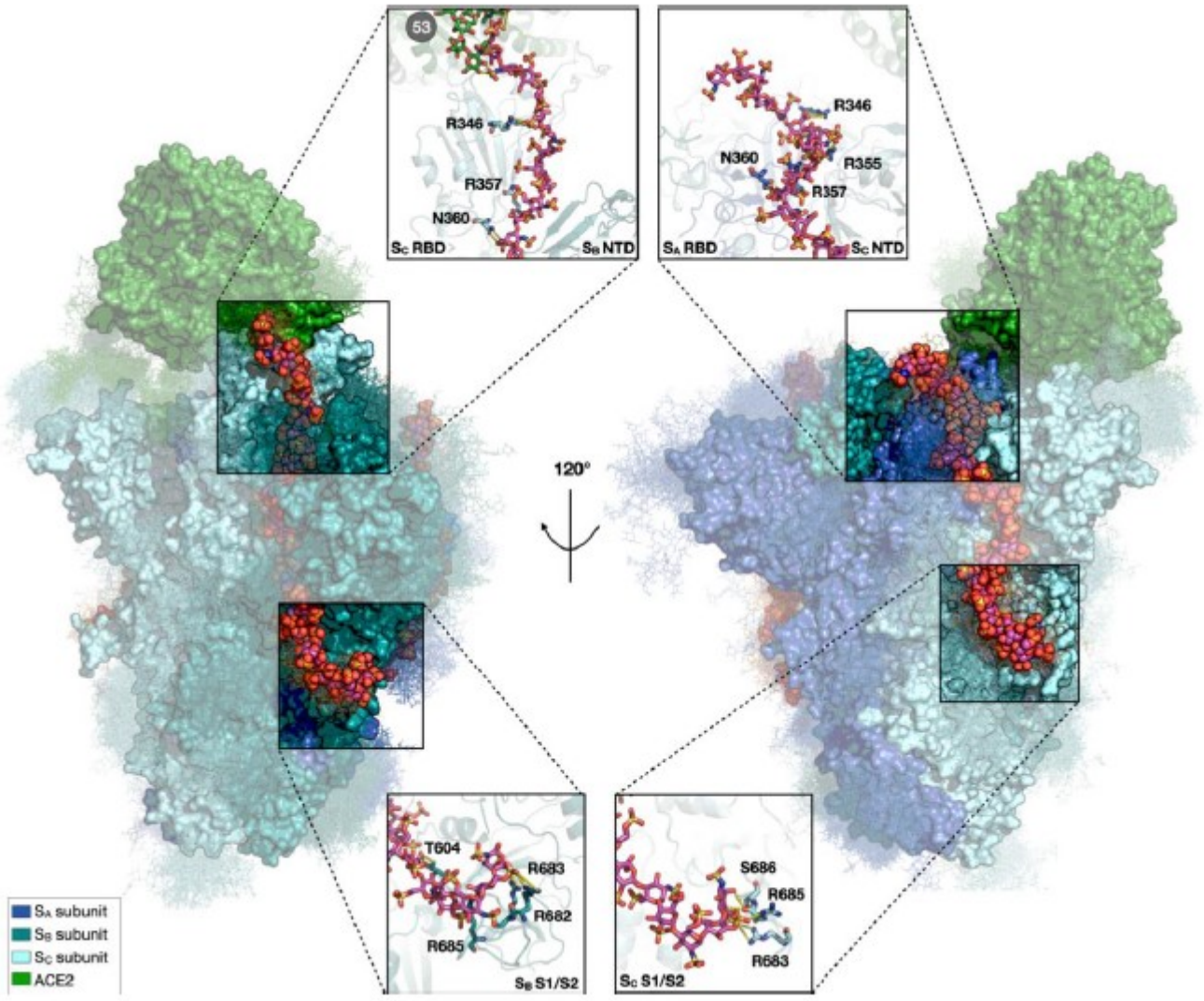


The accomplices: Heparan sulfates and N-glycans foster SARS-CoV-2 spike: ACE2 receptor binding and virus priming

Description

The SARS-CoV-2 spike glycoprotein mediates virus attachment to human host cells by binding angiotensin-converting enzyme 2 (ACE2) and heparan sulfate (HS) proteoglycans. To elucidate these interactionsâ?? structure, dynamics, and functional consequences, the authors carried out microsecond-long all-atom molecular dynamics simulations, followed by random acceleration molecular dynamics simulations, of the fully glycosylated spike: ACE2 complex with and without heparin chains bound.



Structural model of the complex of the open, active spike homotrimer, the ACE2 RBD and three heparin chains, showing stabilizing interactions of two heparin chains and N-glycans with spike and ACE2. *Two side views of a representative structure obtained from the last snapshot of one of the MD simulation replicas are shown. SA, SB, and SC subunits and ACE2 are shown as molecular surfaces in blue, teal, cyan, and green, respectively. N-glycans covalently attached to the spike and ACE2 are shown in line representation, coloured according to the subunit to which they are attached. 40 frames of the N-glycan structures collected at intervals of 25 ns from the simulation are shown. The 31mer heparin chains are depicted as spheres coloured by elements with magenta carbons. On the left, heparin2 spans from the SC up-RBD to the SB S1/S2 multifunctional domain. On the right, heparin3 follows a similar path, simultaneously binding the SA down-RBD and the SC NTD and S1/S2.*

Heparin, as a model for HS, promotes structural and energetic stabilization of the active conformation of the spike receptor binding domain (RBD) and reorientation of ACE2 toward the N-terminal domain in the same spike subunit as the RBD. Spike and ACE2 N-glycans exert synergistic effects, promoting better packing, strengthening the protein-protein interaction, and prolonging the residence time of the complex. ACE2 and heparin-binding trigger rearrangement of the S2 functional site through allosteric

interdomain communication. Thus, HS has a multifaceted role in facilitating SARS-CoV-2 infection.

Category

1. News