Molecular dynamics simulations to investigate the interactions of heparin with the Sars-CoV2 spike glycoprotein

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Heparin is polysaccharide administered intravenously as an anticoagulant to COVID-19 patients and via aerosol for the treatment of other lung diseases. Experiments indicate that heparin has antiviral activity against Sars-CoV2. It has been suggested that heparin inhibits infection by binding to the virus spike glycoprotein, which plays a key role in attachment and fusion with host cells by interacting with the host cell ACE2 receptor and heparan sulphate proteoglycans, structural analogues of heparin that act as co-receptors and may influence host susceptibility. In this presentation, we will describe the results of molecular dynamics simulations to investigate the role of heparan sulphate proteoglycans in Sars-CoV2 infection and the inhibitory activity of heparin. We modelled the homotrimeric head of the spike glycoprotein in active and inactive prefusion conformations with zero, one or three heparin oligosaccharides bound. We then performed several replica microsecond simulations of each system. Our models reveal long positively charged patches on the spike head that can accommodate the linear anionic polysaccharide chains of heparin or heparan sulphate proteoglycans. Heparin binds at these patches and interacts with some of the spike N-glycans, masking key functional sites on the protein, stabilizing it in its closed inactive conformation, and allosterically hampering the exposure of the host receptor binding site in the open active conformation. Our results provide a basis for understanding the antiviral effects of heparin and for the rational optimization of heparin derivatives for antiviral therapy.

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