Enhanced Binding of SARS-CoV-2 Spike Protein to Receptor by Distal Polybasic Cleavage Sites

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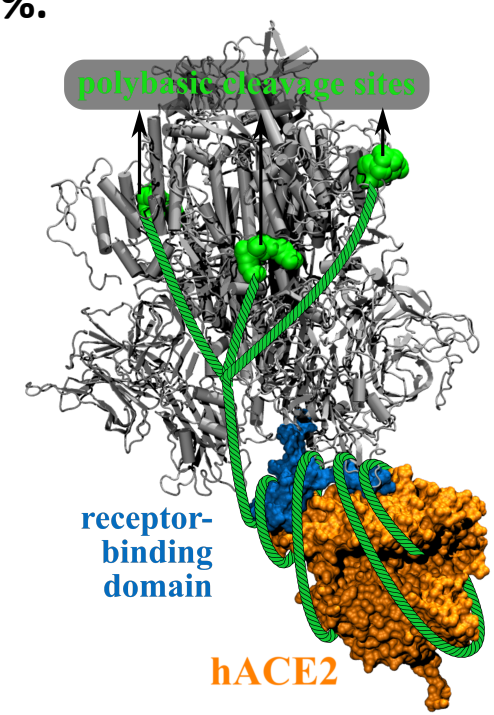
The polybasic cleavage sites of SARS-CoV-2 spike protein, located around 10 nm from the receptor-binding domain (RBD), was found to enhance the binding affinity between the SARS-CoV-2 RBD and the human cell receptor (hACE2). A peptide inhibitor was found to reduce the RBD-hACE2 binding by 34%.

Though being unique to SARS-CoV-2 compared to SARS-CoV and other lineage B coronavirus, the functions of the polybasic cleavage sites remain elusive. Multiscale simulations at all-atom and coarse-grained resolutions demonstrated that they can enhance the binding affinity between the SARS-CoV-2 spike protein RBD and hACE2. The long-range effects originate from Coulomb interactions and hydration effects.

A model tetrapeptide GluGluLeuGlu was thus designed to neutralize the SARS-CoV-2 polybasic cleavage sites. The SARS-CoV-2 RBD-hACE2 binding was remarkably weakened, shedding insights into the design of efficient therapeutic peptide inhibitors.



Polybasic cleavage sites tight (cartooned *via* green ropes) SARS-CoV-2 RBD-hACE2 binding.

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