

SARS-CoV-2 Spike Protein Cleavage and Fusion

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Last update: February 4, 2021

This sequence of events was described by Jason McLellan TWiV 714 [1].

1. You can get cleavage at S1/S2 site (see Figure 1) while spike is being produced in the infected cell since there is furin present. Here the spike trimer is in the prefusion conformation.
2. In this case on the surface of an infectious virion the spike protein has already been cleaved at S1/S2.

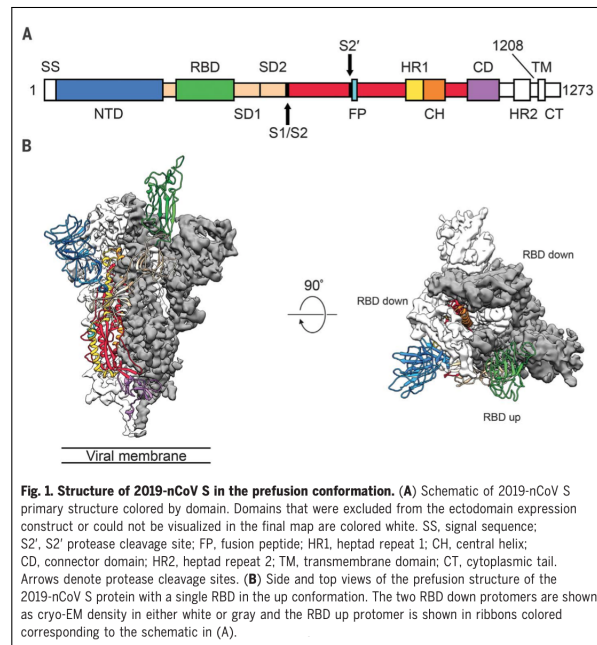


Figure 1: SARS-CoV-2 Spike Prefusion Confirmation [2]

3. Next S1 binds to ACE2 binding at the Receptor Binding Domains (RBDs), locking one, two or three of the RBDs in the "up" confirmation¹ which is a thermodynamically unfavorable state.
4. The binding of S1 to ACE2 destabilizes the spike and causes S1 to shed and fall off S2. S1 can be thought of as a "fusion suppressive cap" (like GP120, HA1), which prevents the fusion machinery, the spring-loaded S2, from firing.
5. S2 then undergoes a conformational change and starts rearranging from its spring loaded state, extending towards the host cell membrane.
6. Cleavage at S2', usually by TMPRSS2 on the host cell surface or by cathepsin L in an endosome (see Figure 2), liberates the fusion peptide from the new N-terminal domain of S2. This allows the S2 now is anchored in the host cell membrane and in the viral membrane.

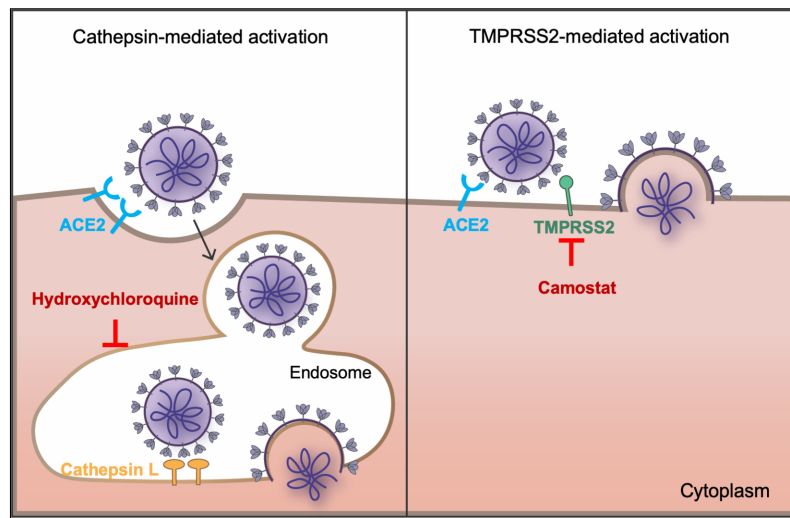


Figure 2: SARS-CoV-1 and SARS-CoV-2 fusion and cell entry can be activated by either or both of two pathways [3]

7. S2 bends around and brings the host cell membrane into contact with the viral membrane. This is the post fusion state.

¹The RBDs are locked in the "up" confirmation when bound by ACE2.

References

- [1] TWiV 714: The shape of spike with Jason McLellan. <https://www.microbe.tv/twiv/twiv-714>, 2021. [Online; accessed 01-February-2021].
- [2] Daniel Wrapp et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7164637/pdf/367_1260.pdf, 2021. [Online; accessed 01-February-2021].
- [3] Tianling Ou et al. Hydroxychloroquine-mediated inhibition of SARS-CoV-2 entry is attenuated by TMPRSS2. <https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1009212>, 2021. [Online; accessed 04-February-2021].