SARS-CoV-2 Spike Protein Cleavage and Fusion

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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 confirmation.
2. In this case on the surface of an infectous viron the spike protein has already been cleaved at S1/S2.

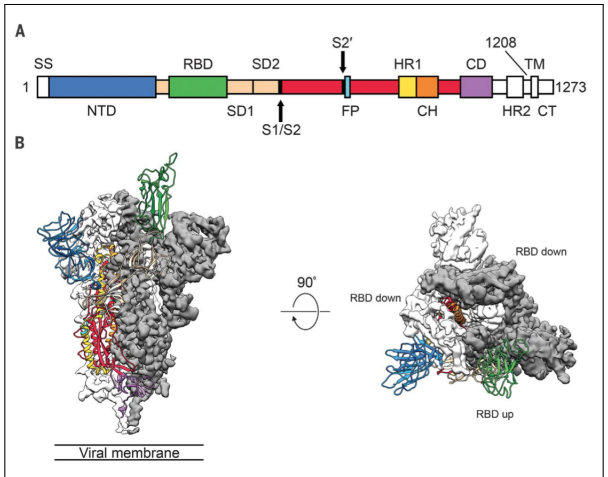

Fig. 1. Structure of 2019-nCoV S in the prefusion conformation. (**A**) Schematic of 2019-nCoV S primary structure colored by domain. Domains that were excluded from the ectodomain expression construct or could not be visualized in the final map are colored white. SS, signal sequence; S2', S2' protease cleavage site; FP, fusion peptide; HR1, heptad repeat 1; CH, central helix; CD, connector domain; HR2, heptad repeat 2; TM, transmembrane domain; CT, cytoplasmic tail. Arrows denote protease cleavage sites. (**B**) Side and top views of the prefusion structure of the 2019-nCoV S protein with a single RBD in the up conformation. The two RBD down protomers are shown as cryo-EM density in either white or gray and the RBD up protomer is shown in ribbons colored corresponding to the schematic in (A).

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" confirmation[1] 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 confirmational change and starts rearranging from its spring loaded state, extending towards the host cell membrane.

6. Cleavage at S2′ (usually by TMPRSS2) liberates the fusion peptide from the new N-terminal domain of S2. S2 now is anchored in the host cell membrane and in the viral membrane.

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

References

[1] TWiV 714: The shape of spike with Jason McLellan. `https://www.microbe.tv/twiv/twiv-714`, 2021. [Online; accessed 01-Feburary-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-Feburary-2021].

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