Mechanism of SARS-CoV-2 Cell Entry

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Introduction

- The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an RNA virus from the subfamily *Orthocoronovirinae* that is responsible for the ongoing COVID-19 pandemic.
- In order to control the spread of the coronavirus disease, understanding the molecular basis of its infection of human host cells is crucial.
- This would allow for the design of potential vaccines or therapies that target associated pathways, thereby preventing infection.

Spike protein

- The entry of the coronavirus into the host cell, which involves receptor attachment and membrane fusion, is mediated by the **spike (S) protein**.
- This is a glycoprotein that exists as a homotrimer.
- The viral membrane has many spike proteins implanted into it, giving the virus a crown-like appearance. This morphology gives the virus the name 'coronavirus'.
- The S protein has two subunits – **S1** and **S2**. These subunits interact non-covalently and are both present in fully mature viral particles.
- During viral replication, the cell machinery is hijacked to cleave the S protein in immature virions into the S1 and S2 subunits. This is achieved by a proprotein convertase called **furin** in the Golgi apparatus.

- The S1 subunit is responsible for binding to a receptor on the host cell surface during entry, for which it has a **receptor binding domain (RBD)**.
- The S2 subunit acts as an anchor in the viral membrane. It also has a short amino acid sequence, called the **fusion peptide**, that allows for the fusion of the viral and host membranes.
- The S1 subunit is wrapped around the S2 subunit, which exists as a helical bundle. This central helix has a sequence called the **heptad repeat 1 (HR1)**, near which the fusion peptide is present.
- HR1 is connected to **heptad repeat 2 (HR2)** and the transmembrane (TM) domain of S2.

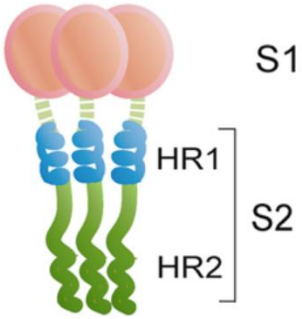

Figure 1: Schematic of the S protein

ACE2 receptor

- The **angiotensin-converting enzyme 2 (ACE2)** is the host cell receptor for the spike protein.
- ACE2 is a carboxypeptidase that plays a crucial role in the renin-angiotensin-aldosterone system (RAAS), a key regulator of normal physiology.
- It has been found that the catalytic site of ACE2 plays no role in the binding of the spike protein. Hence, targeting this site using inhibitory drugs would not prevent viral infection.

Receptor-binding

- The receptor-binding domain of S1 engages ACE2, causing a conformational change in S2.
- A region of the S2 subunit called the **S2' site** is exposed.
- Cleavage at this site by a serine protease called **transmembrane protease, serine 2 (TMPRSS2)** leads to the release of the fusion peptide.
- The S1 subunit then dissociates from S2.
- However, if a target host cell expresses TMPRSS2 at very low levels, the virus gets 'internalized' by endocytosis. This leads to the formation of an endosome.
- Inside this structure, a protease called **cathepsin L** cleaves the spike protein at the S2' site, releasing the fusion peptide.

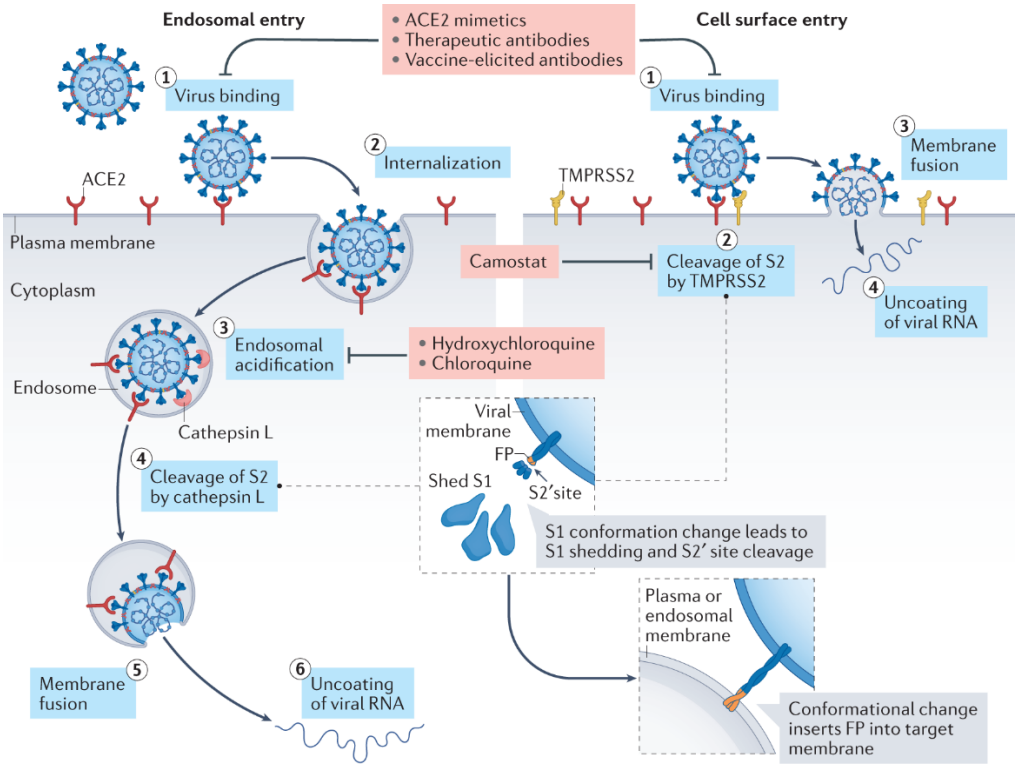

Figure 2: Two possible entry pathways for SARS-CoV-2, and potential inhibitors at various steps

Membrane fusion

- Following the dissociation of S1, the HR1 component of the S2 subunit is driven towards the host membrane and the fusion peptide is inserted.
- HR2 then folds back onto H1, bringing the two membranes in proximity, ultimately leading to fusion.
- Viral RNA can then be released into the cell.

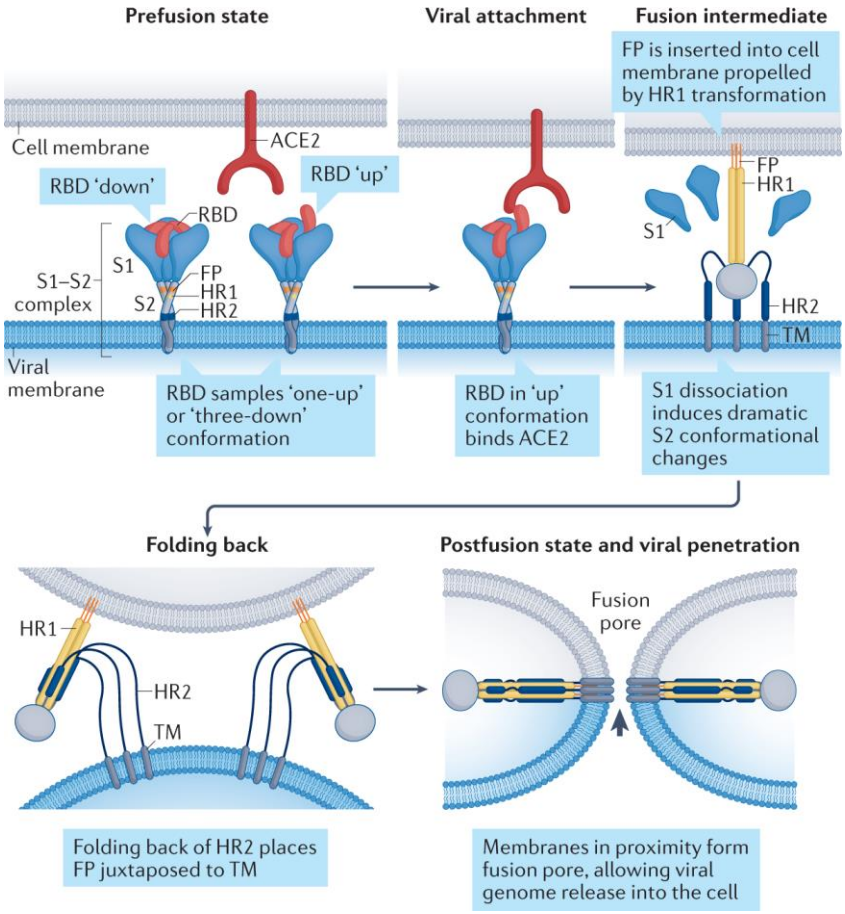

Figure 3: Mechanism of membrane fusion

Viral Genome in Infected Cells

- The question of whether or not SARS-CoV-2 integrates its genome with the host genome has been controversial since the start of the pandemic.
- A paper in May 2021 showed that the reverse transcribed RNA of the coronavirus can integrate into the genome of human cells. This leads to the production of chimeric transcription products that contain both viral and host sequences.
- Following up on this claim, an August 2021 paper showed that there was no evidence of such genome integration by sequencing the DNA of SARS-CoV-2-infected human cells.
- The current consensus on this topic holds that the viral genome **does not integrate** into the host genome.

References

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