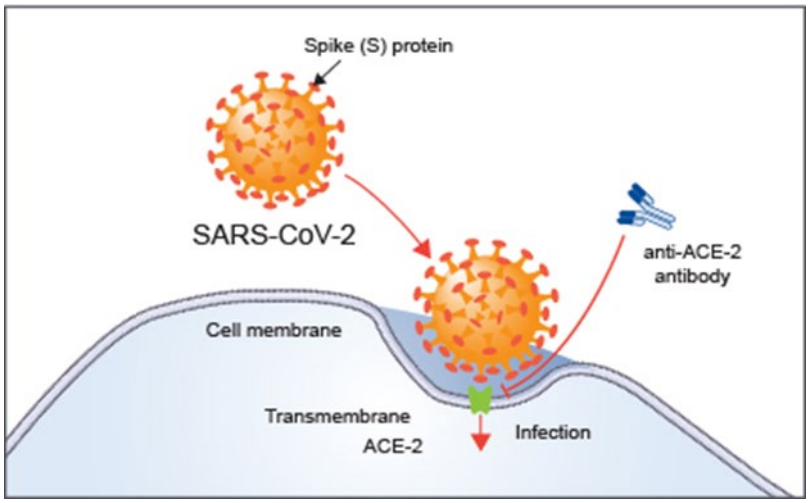
STANDARD DEVIATIONS: ACE2 is the Place?

Greetings,

Some biology today.

In order to create a vaccine or treatments for SARS-CoV2, we have to understand the mechanisms of infection. Here we look at the process of infection and the areas that hold promise for developing mitigations that offer protection.

SARS-CoV2 has to enter a cell to cause disease. To get in, it has to latch on, and then burrow into the membrane. The molecule it latches onto is Angiotensin-Converting Enzyme 2 (ACE2). The "spike" protein on the virus binds ACE2 like Velcro. But the spike-ACE2 complex has to "melt" in order for the membranes to merge. For SARS-CoV entry into a host cell, its S protein needs to be cleaved by cellular proteases at 2 sites, termed S protein priming, so the viral and cellular membranes can fuse.



ACE2 are found mainly expressed in **vascular endothelial cells**, the renal tubular epithelium, and in Leydig cells in the testes. This is why the lungs are affected and why the virus is such a respiratory agonist; the lung is the first site the virus is accumulating at, and it's rich in vascular endothelium because this is where we're sending all our blood to get oxygen.

Now, these endothelial cells are prolific; they're always dividing and growing, creating new capillaries and allowing organs to grow. The ACE2 and proteases that help these cells divide are culprits in binding the virus and allowing it entry. ACE2 complexes with the S protein and the proteases "melt" the complex causing mass tectonic changes in the membrane.

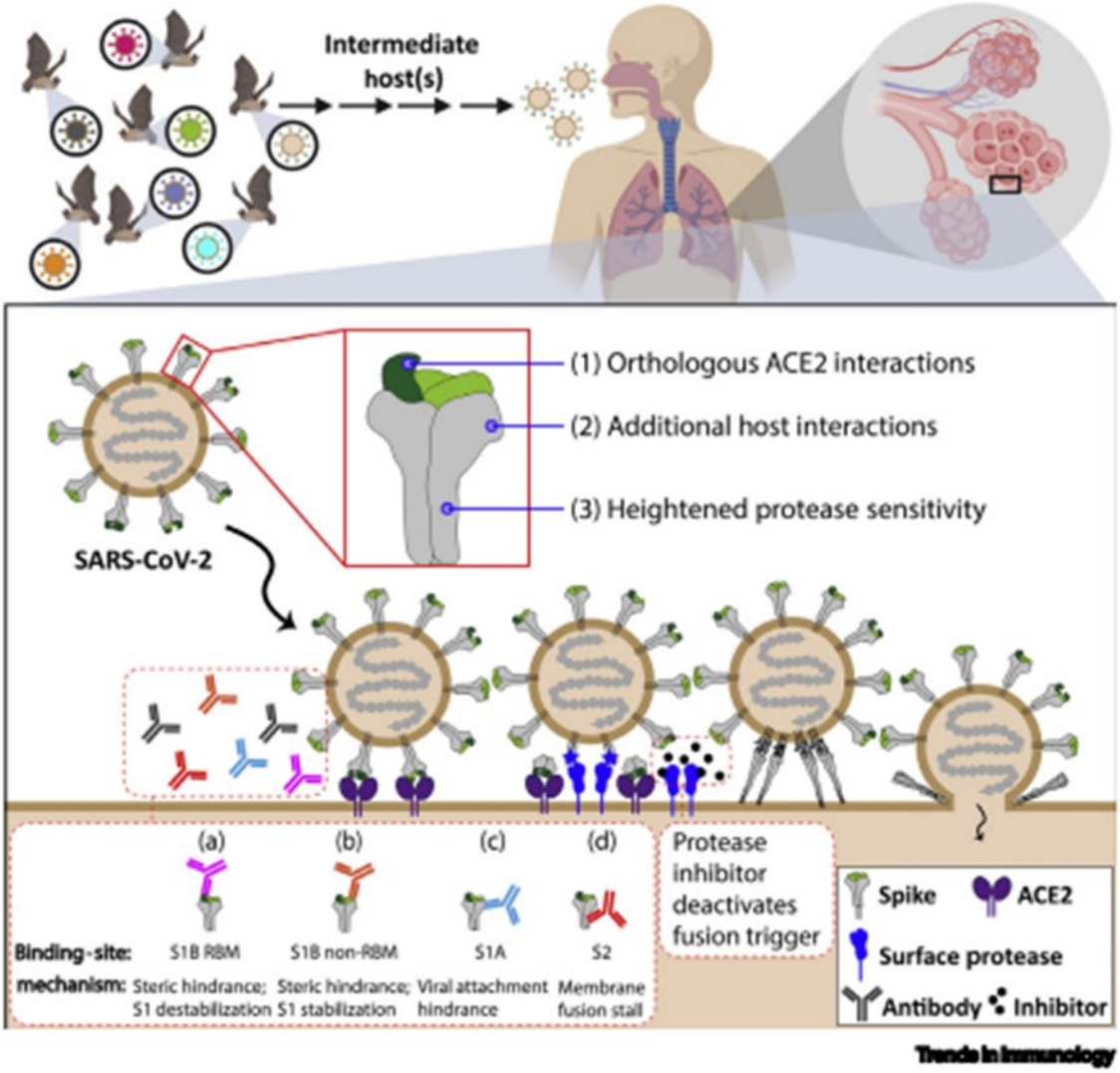
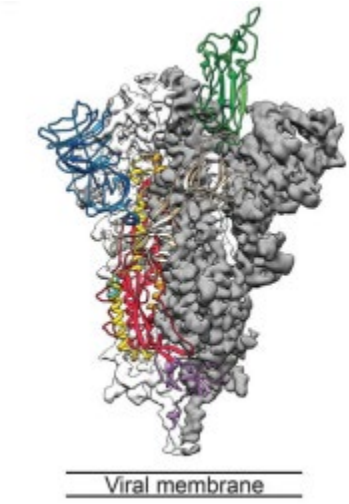
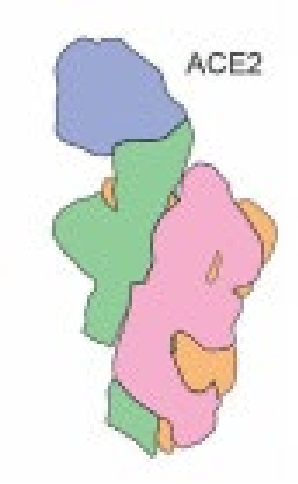


Figure 1. Severe Acute Respiratory Syndrome (SARS)-CoV-2 Zoonosis and Cell Entry. Bat SARS-related CoVs (top left) are thought to transmit through intermediate host(s), with a select subset of viruses having features necessary to infect the human respiratory tract (top right). Infection (lower panel) requires SARS-CoV-2 spike (S) engagement with host angiotensin converting enzyme 2 (ACE2) receptors. Subsequently, surface proteases cleave S2, the fusion-mediating subunit of S, which triggers a series of conformational changes that result in fusion between the viral envelope and the target cell membrane. Features of SARS-CoV-2 that may facilitate human infection include: (1) S1B receptor-binding motifs (RBMs) (in green) that bind orthologous ACE2 receptors; (2) a S1A domain that may confer additional host interactions; and (3) a furin protease cleavage substrate that may confer heightened sensitivity to host protease cleavages [9]. Antiviral antibodies (lower-left inset) prevent infection by: (a) binding S1B RBMs, blocking receptor access; (b) binding distal to RBMs, sterically interfering; (c) binding S1A, possibly preventing alternative attachment to distinct receptors; and (d) binding S2, arresting membrane fusion. Attractive antiviral compounds include protease inhibitors [10], which deactivate membrane fusion triggering and suppress virus entry. This figure was created using BioRender (https://biorender.com/).

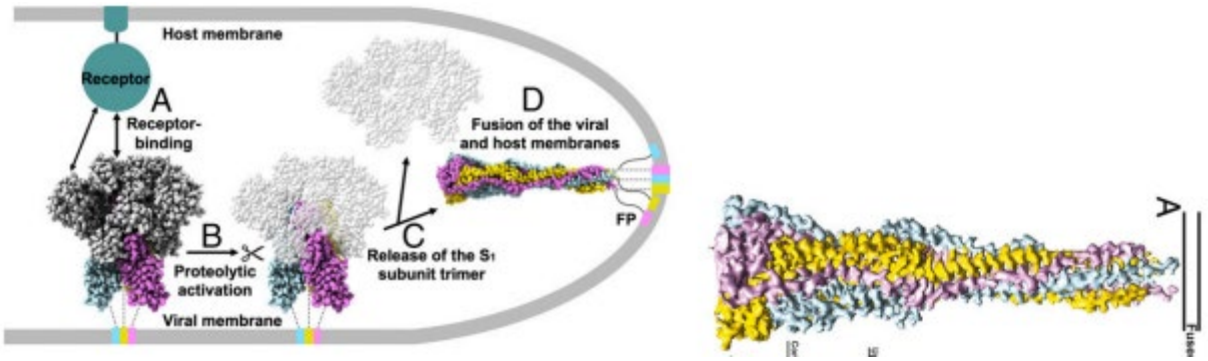
The S protein is depicted below. The Receptor Binding Domain (RBD) gloms onto ACE2, and when it does the proteases are able to access the sites that cleave the molecule. That cleavage changes not only the shape but the entire chemistry of the complex and membranes fuse. This is what allows the virus entry to the cell.



{EM crystallography graphic of S protein. RBD in green.}



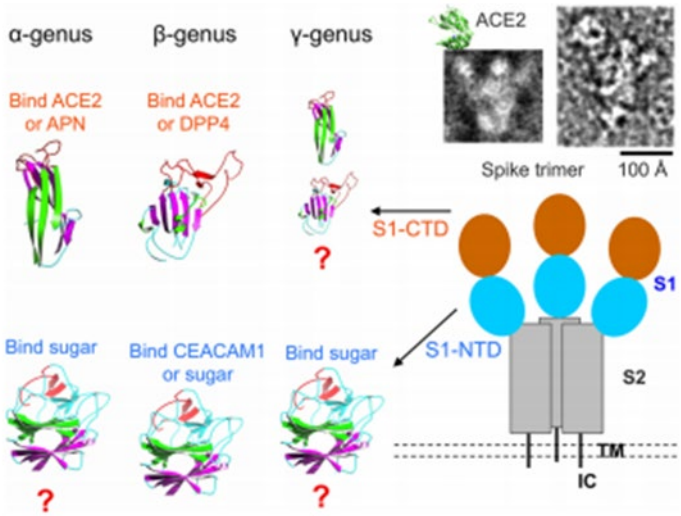
{Schematic of S-ACE2 complex – **pre-fusion**}



{When bound, proteases snip S protein cleavage sites and the conformational change allows the membranes to merge – **post-fusion**.}

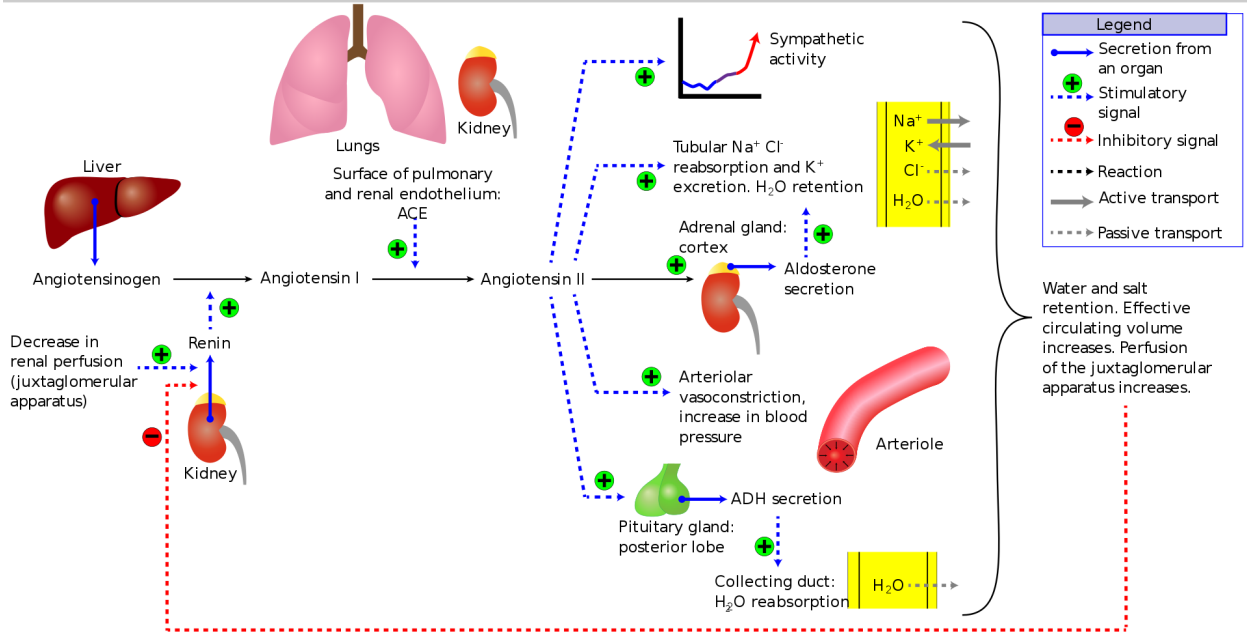
Of course, it ain't just that easy.

There are other binding domains and receptors that are in play. These ancillary reactions are contributing to the membrane changes that allow fusion; they are just not as well understood, yet.



{Binding and conformational changes are occurring at other domains.}

Angiotensin Converting Enzyme plays a major role in the Renin-angiotensin-aldosterone system, which regulates blood pressure. Hypertension is notable in the diseases we see in this pathway. ACE inhibitors that are used for treating hypertension increase ACE2 levels. This relation is problematic for people infected with SARS-CoV2 and a reason these individuals are at higher risk when infected.



Research is intensely focused on this attraction CoVs have for ACE2 and those proteases. If we can create antibodies to the complexed forms of the virus and our cellular proteins then the hope is that the entry will be blocked.

Okay, that's a bunch to absorb. Basically, a mechanism to block the binding of S protein or the fusion step is the goal for vaccines that are being developed to fight COVID-19.

Have a great week and be safe,

Bryan

p.s. I think this is cool. Want more? Let me know and I'll try to follow up. Here's something to chew on: Those membrane changes also inhibit S protein binding on an infected cell. It's like an "OCCUPIED" sign is put up to keep other virus from attaching.