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SARS-CoV-2 Spike Glycoprotein Targets ACE2 in Humans

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Abstract: ***The interactions between SARS-CoV-2's spike transmembrane glycoprotein and human angiotensin-converting enzyme 2 (ACE2) are paramount for the Coronavirus Disease 2019 (COVID-19). Specific amino acid sequences in the receptor-binding domain of the spike protein are particularly significant for binding to the ACE2 receptor. Another central domain of the spike protein is the fusion domain. The fusion domain is accessible following host-dependent catalytic cleavage of the receptor-binding domain. The hydrophobic fusion portion is specifically responsible for facilitating the fusion events between the viral lipid envelope and the host cell's plasma membrane. ACE2 is a mammalian transmembrane protein that serves as a binding partner for the spike protein and participates in cardioprotective effects by regulating the renin-angiotensin-aldosterone system. The ACE2 receptor is expressed in various human tissues and provides a rationale for the transmissibility efficiency of the COVID-19 virus. Moreover, the concentration and structural organization of ACE2 in the human population explains the range of clinical symptoms and disease outcomes observed during the pandemic. Further investigation of the spike protein and ACE2 receptor may fuel innovative biological technologies to limit spike-ACE2 interaction to reduce SARS-CoV-2 infections and expand therapeutics to curb post-infection disease progression.***

Keywords: Spike protein; COVID-19; ACE2; SARS-CoV-2

1. Introduction

SARS-CoV-2 transmission depends on the precise molecular relationship between the trimeric spike glycoprotein on the virus's surface and the angiotensin-converting enzyme 2 (ACE2) [1]. The ligand-receptor interaction promotes viral attachment, fusion, and ultimately introduction into the host cell's cytoplasm [2]. Since the beginning of the global pandemic, researchers have conducted several studies to explore the biomolecular structure, mutational analysis, and function of the pathogenic ligand and host receptor [3-6]. Using cryo-electron microscopy, Wrapp et al. [3] resolved the confirmation of the receptor-binding domains and assessed ACE2 binding affinity. Using molecular protein modeling, Hussain et al. [6] demonstrated the significance of amino acid sequences in the critical binding region of the ACE2 receptor required to form strong associations with the SARS-CoV-2 spike protein. The purpose of this review is to explore the literature on the spike-ACE2 proteins.

2. Spike Glycoprotein

The spike glycoprotein is a trimeric protein responsible for eukaryotic cell attachment and entry. Spike protein projections on the surface of the coronavirus are visible when viewed under the electron microscope. The coronavirus spike protein is approximately 200 kDa and is made up of two central regions designated S1 and S2 (Figure 1) [7]. The S1 region consists of 685 amino acids that contain the receptor-binding domain (RBD), which binds to angiotensin-converting enzyme 2 (ACE2), the host cell receptor. Amino acid residues 331-524 located in the S1 domain are specifically responsible for binding to ACE2. The S2 part consists of 588 amino acids and contains the fusion machinery necessary for viral membrane-host cell membrane attachment. Analysis of the spike protein demonstrates that these protein molecules also contain a transmembrane domain, N-terminal domain (NTD), heptad repeat 1, heptad repeat 2, C-terminal domain (CTD), and fusion peptide.

In contrast to the fusion domain, the receptor-binding region is a highly variable region that is under extreme evolutionary stress because of its role as an antigenic determinant due to constant interactions with the human immune system. Interestingly, scientists demonstrated that the receptor-binding domain in SARS-CoV-2 has a higher binding affinity to ACE2 when compared to the binding affinity of the original SARS virus [8]. Increased binding affinity may help explain the higher number of cases and deaths associated with the current pandemic coronavirus. Many serological tests are based on antibodies that target the RBD. Andersen, Rambaut, Lipkin, Holmes, and Garry [9] identified six amino acids in the receptor-binding domain critical for ACE2 interaction (L455, F486, Q493, S494, N501, Y505).

The spike protein contains a polybasic cleavage site, which in addition to TMPRSS2, mediates cleavage from additional proteases, including furin [10] and cathepsin L [11]. From an evolutionary advantage perspective, including a polybasic cleavage site in the spike protein enhances viral tropism by increasing the numbers and types of transmembrane proteases that can cleave and activate the spike protein. Additionally, the spike protein is heavily glycosylated, which may play a role in countering the effects of the human immune system. The spike protein is characterized as a class I fusion protein. Class I fusion proteins are also found in other viruses, including influenza, Ebola, and HIV.

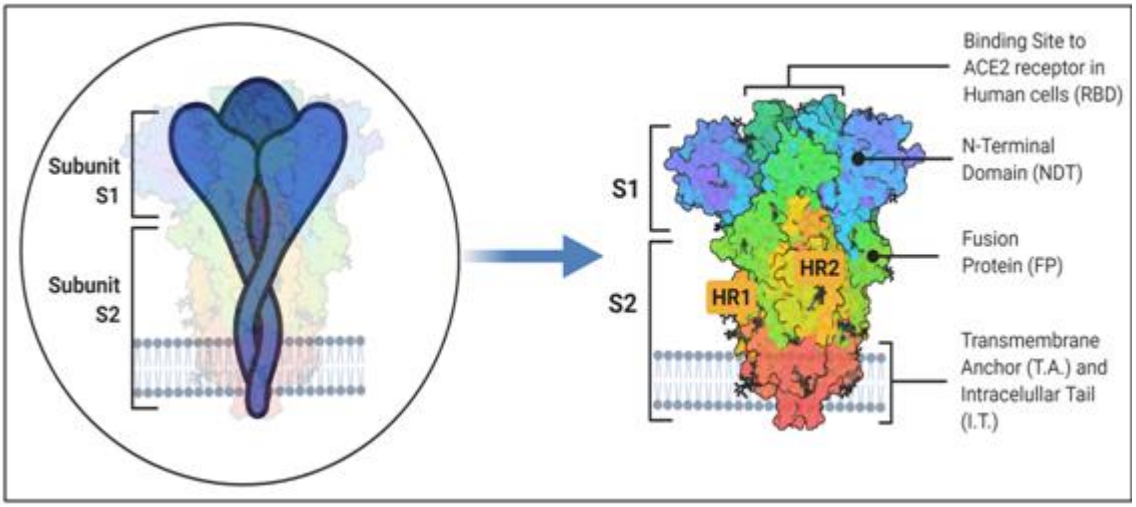

Figure 1: Schematic of the spike glycoprotein

After the spike protein binds to ACE2, TMPRSS2 separates the S1 domain from the S2 domain, exposing the fusion peptide and activating the fusion mechanism. In the first steps of the membrane fusion process, the hydrophobic S2 domain (fusion peptide) forms a hairpin structure embedded in the host cell membrane. The embedded fusion peptide then undergoes a series of conformational changes that merge the host's plasma membrane and viral envelope [12]. Membrane fusion precipitates viral entry into the host cell cytoplasm.

3. Angiotensin-Converting Enzyme 2 (ACE2)

ACE2 is a 100 kDa single-spanning type I transmembrane zinc metalloprotein in the dipeptidyl carboxydipeptidase family and found on the surface of many human cells, including cells of the lungs, kidney, heart, liver, blood vessels, gastrointestinal tract, prostate, ovary, thyroid, testis, and pancreas [12-13]. The N-terminal peptidase region of the ACE2 receptor attaches to the receptor-binding domain of the spike protein on the viral surface. Analysis of human ACE2 demonstrates that this enzyme participates in several biological functions; however, ACE2 also plays a central role in maintaining renal and cardiovascular homeostasis and regulating blood pressure through the renin-angiotensin-aldosterone system (Figure 2).

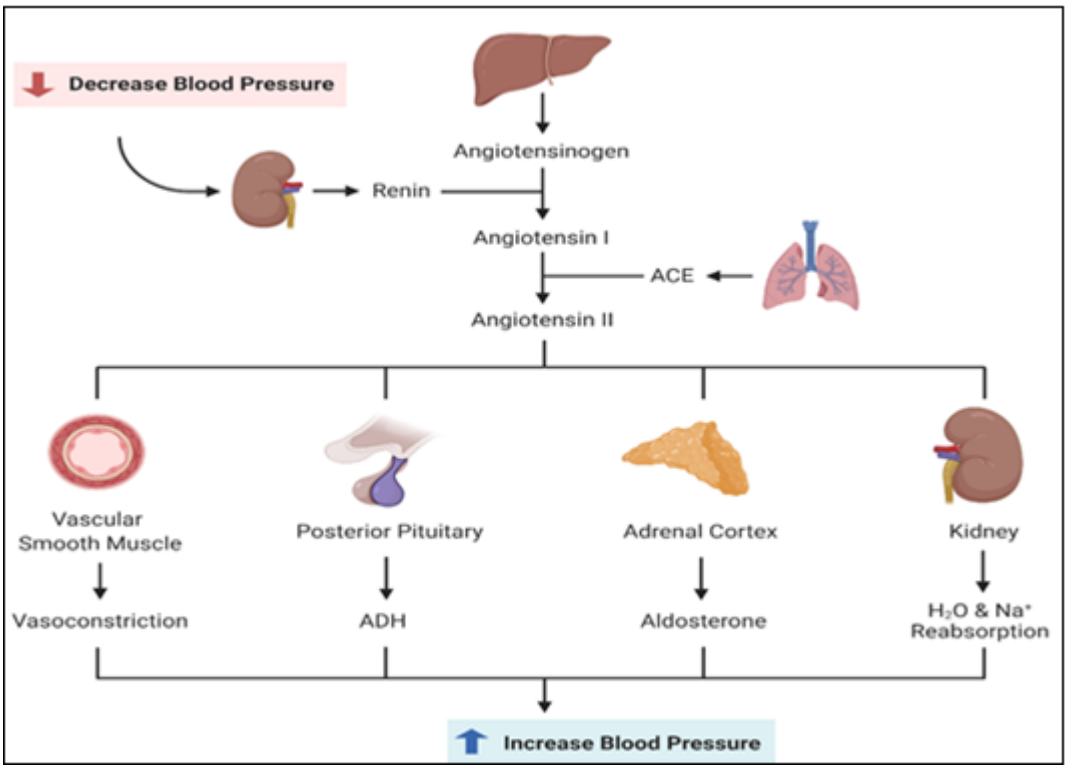

Figure 2: The renin-angiotensin-aldosterone system (RAAS) is involved with the ACE2 receptor

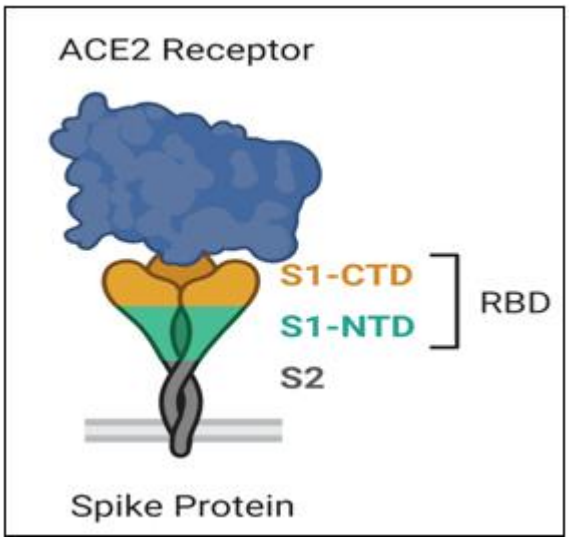

Figure 3: The viral spike-host ACE2 receptor mediates SARS-CoV-2 entry into human cells

ACE2 is the chief molecular target of the spike protein for both SARS-CoV-1 and SARS-CoV-2 (Figure 3) [14]. Additionally, ACE2 is present on epithelial cells in the human T-zone region (e. g., mouth, nose, eyes). In terms of lung tissue, ACE2 is prevalent in the membranes of type 2 pneumocytes. Pneumocytes are highly specialized cells for gas exchange (type 1) and respiratory secretions (type 2) found lining the lungs' alveoli. ACE2 is expressed in many different tissues in the body, which makes the ACE2 receptor a particularly sagacious target forSARS-CoV-2 (Figure 4). The ubiquitous expression of ACE2 also contributes to an increase in transmission routes for the virus.

Additionally, the presence of ACE2 in various human cell types and subsequent tissue distribution may help explain the spectrum of clinical presentations and symptoms associated with COVID-19. Also, the structural integrity and expression level of ACE2 may explain the range of clinical outcomes in humans (e. g., asymptomatic to severe illness). Moreover, it was shown that men have a higher ACE2 expression in the respiratory tract than women. Further, Asians have been shown to express higher levels of ACE2 compared to African Americans and Caucasians, which may further explain morbidity and mortality data [15]. Interestingly, research supports the role of ACE2 in restricting the progression of disease associated with viral infection by actively counteracting the negative clinical outcomes associated with the RAAS [16-17].

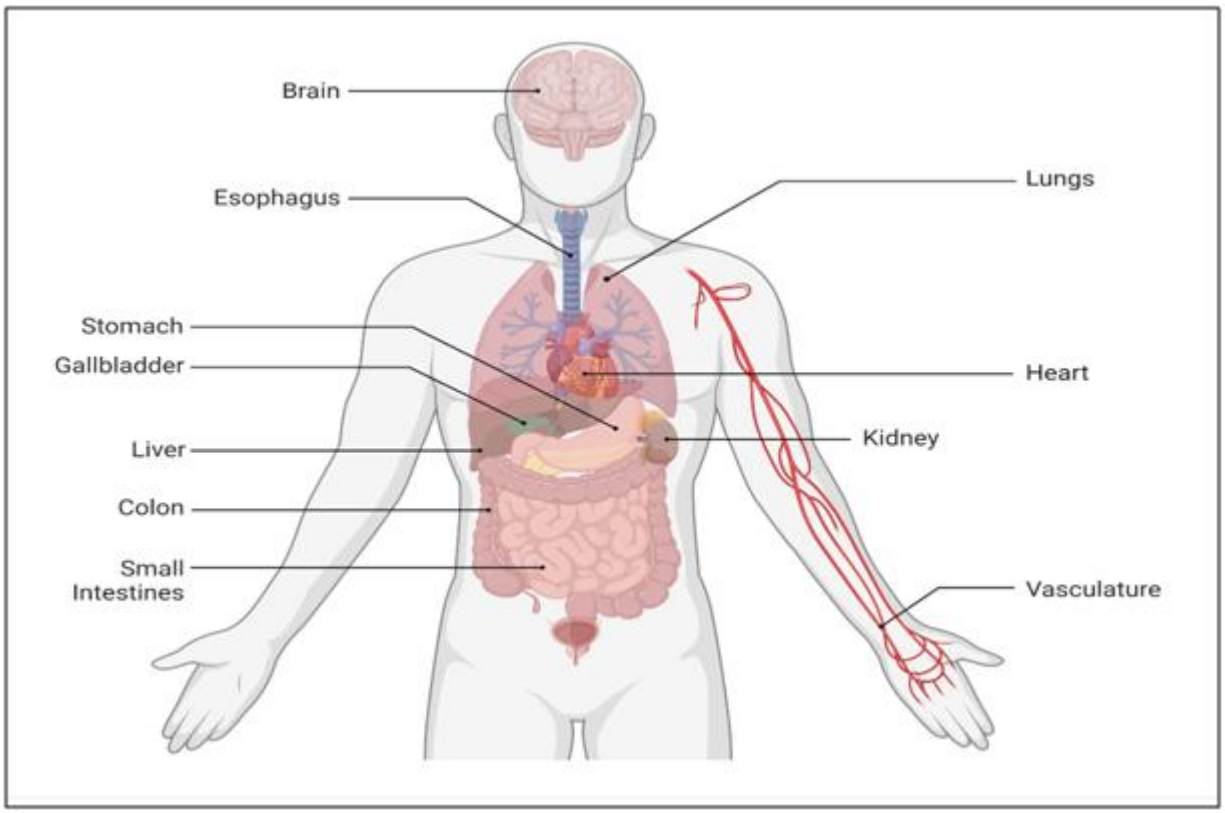

Figure 4: Host tissues known to express the ACE2 receptor

4. Conclusions

After SARS-CoV-2 overcomes anatomical innate immune defenses, the next task is for the virus to recognize and attach to the appropriate host cell receptor. The molecular interaction between the spike protein and the human surface receptor, ACE2, is followed by viral fusion and viral entry. The reproductive number of the pandemic virus is determined by the specificity between the spike protein and host receptor. Given the importance of microbial attachment mechanisms, a pivotal factor to combating COVID-19 infections centers around a complete understanding of the spike glycoprotein and ACE2 receptor binding mechanisms. Structural and biomolecular analysis will lead to developing

potent therapeutics against the deadliest pathogenic agent in over a century. Antibody-based therapeutics and inhibitor molecules will serve as protective tools to inhibit host-pathogen attachment and enhance viral clearance processes. Current experimental techniques used to study the spike protein and ACE2 protein will also be instrumental to understanding better the potential influence of SARS-CoV-2 variants on transmissibility and mortality.

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