Reagan Richardson

Scientific Literary Background Essay

The Structure, Function, and Mutations of the Sars-Cov-2 Spike Protein

In this scientific literary essay, five prominent mutations of the Sas-Cov-2 virus spike protein are discussed, along with the structure and mechanism of the spike protein. In addition, this essay will examine the impact of Sars-Cov-2 mutations on infection rates.

The first mutation of the Sars-Cov-2 spike protein that is of interest to researchers is the L452R mutation. In this name, L refers to the amino acid leucine, the number 452 indicates a mutation at the 452nd amino acid, and R refers to the amino acid arginine. Therefore, this mutation substitutes leucine for arginine (Greenwood, 2021). For reference, leucine is non-polar because its side chain only contains methyl (CH3) and ethyl (CH2) groups, while arginine is positively charged due to the presence of a positively charged nitrogen. As the spike protein contains 1273 amino acids, this mutation occurs in the S1 subunit of the polypeptide chain (Huang, 2020). For reference, the S1 subunit is a receptor binding domain that encodes for the receptor characteristics of the spike protein. Therefore, these mutations are significant because the altering of the receptor sites will negate any damaging effects from previous COVID antibodies. To continue with the L452R mutation, the positive charge created by the arginine side group results in a change to the shape and structure of the protein, which results in evasion to immunity. This mutation is of concern because it has increased in prevalence in California and some areas of Europe starting in January of 2021 (Greenwood, 2021).

The second mutation mentioned is E484K, where the amino acid glutamic acid (E) becomes replaced with lysine (K) at the 484th amino acid. Also located at the S1 unit, the E484K mutation appears in multiple lineages, including the beta and gamma strains of the Sars-Cov-2 virus (Corum and Zimmer, 2021). Since glutamic acid is negatively charged (-O) and lysine is positively charged ($NH3^+$), there is a significant enough change in structure to where this mutation allows the virus to evade antibody attacks (Corum and Zimmer, 2021).

The third mutation that is raising concerns is the E484Q mutation, where glutamic acid (E) becomes replaced with glutamine (Q) at the 484th amino acid. Similar to the L452R mutation, the E484Q mutation also occurs at the S1 subunit of the polypeptide chain. Since glutamic acid contains a negatively charged R group and glutamine contains a polar R group, most likely there are conformational changes that alter the binding patterns of the protein. Therefore, the E484Q mutation that falls under the B.1.617 variant enhances how this variant evades the effects of antibodies produced by the original mRNA vaccines (Corum and Zimmer, 2021).

The fourth mutation of significance is the N501Y mutation, where asparagine (N) becomes replaced with tyrosine (Y) at the 501st amino acid. Since both asparagine and tyrosine both contain a polar R group, it is unlikely that there are many conformational changes that would affect the receptor-binding characteristics of the spike protein. However, a study by Lu et al indicates that the variants including the N501Y mutation are of concern because of their demonstrated increase in transmissibility and disease severity (Ferreira, 2021).

The fifth mutation discussed is the P681H mutation where proline (P) becomes replaced with threonine (T) at the 681st amino acid. Since proline is non-polar and threonine is polar, it is most likely that the structure and conformation of the spike protein is significantly altered. However, according to a 2021 study on the B.1.1.7 variant that contains this mutation, Lubinski et al did not discover any major increases in the transmission of the B.1.1.7 variant compared to previous variants (Lubinski, Fernandes, and Frazier, 2021).

As observed with these mutations in the spike protein, it is evident that the genetic identity of the spike protein is of utmost importance to researchers due to its ability to mutate rapidly. The Sars-Cov-2 virus utilizes its spike protein, a transmembrane fusion protein, to interact with the angiotensin-converting enzyme 2 (ACE2) receptor to gain entry and begin to infect cells (Huang, Yang, Xu, Xu, and Liu, 2020). In healthy human cells, ACE2 generates smaller proteins by cleaving angiotensin, a protein that regulates blood pressure and inflammation in the body by inhibiting angiotensin II (ANGII) activity (Sririam, K, Insel, P, and Loomba, R, 2020). However, when someone becomes infected with the Sars-Cov-2 virus, ACE2 acts as an easy entryway into human cells. When the spike protein binds to ACE2, the functions of ACE2 are inhibited, which deregulates ANGII signaling, which in turn increases inflammation throughout the body (Sririam, K, Insel, P, and Loomba, R, 2020). Therefore, this widespread inflammatory response may be the underlying cause of serious heart and lung damage in COVID-19 patients.

When understanding the mechanism of how the spike protein binds to ACE2, it is important to understand the structure of the spike protein. The structure of the spike protein contains an extracellular N-terminus (1-13) and the S1 (14-685) and S2 (686-1273) subunits (Huang, Yang, Xu, Xu, and Liu, 2020). It is important to note that the S1 subunit contains the receptor binding domain while the S2 subunit contains a fusion peptide domain, two heptapeptide repeat sequences 1 (HR1 and HR2), a TM domain, and a cytoplasmic domain fusion (CT) (Huang, Yang, Xu, Xu, and Liu, 2020). Under normal conditions, the spike protein exists in a closed conformation (Huang, Yang, Xu, Xu, and Liu, 2020). However, once the virus enters a cell, the spike protein adopts an open conformation where the S1 and S2 subunits cleave (Huang, Yang, Xu, Xu, and Liu, 2020). This conformational change allows the open S1 subunit to bind to and neutralize the ACE2 receptor, which in turn allows the S2 subunit to utilize its several aforementioned domains to fuse the viral envelope with the host cell membrane (Huang, Yang, Xu, Xu, and Liu, 2020). After the fusion of the viral and host cell membranes, viral particles are able to freely diffuse into the cytoplasm of the host cell, which causes infection.

Despite the rollout of COVID-19 vaccines to slow the spread of infection, new mutations emerged where there were noticeable changes in the structure of the spike protein as discussed earlier. Since antibodies created by original vaccines only target the S1 and S2 subunits of previous Sars-Cov-2 viruses, they are unable to protect against new mutations that alter the structure of the S1 or S2 subunits. For example, the E484K mutation that has been linked to the beta and gamma variants is located in the receptor binding domain of the S1 subunit (aa 484) (Corum and Zimmer, 2021). This conformational change in the RBD allows the mutated spike protein to evade antibody detection and continue to infect host cells. In this way, the evasion of antibodies is a cause of high concern, especially with the new variant B. 1.640.2 (omicron) (Freund, 2022). Despite the emergence of the omicron variant and its high transmission rate, scientists are not overly concerned as recent research has indicated that previous immune responses from human T cells are effective against 70-80% of cases (Freund, 2022). In this way, people who have been previously infected or vaccinated have an acquired immune response towards the omicron variant, which can prevent serious complications. Although the omicron variant poses less risks than other variants, its high transmission rate indicates that the mutation caused a conformational change in the S1 and S2 subunits of the spike protein that allowed for the virus to infect host cells without detection. Therefore, taking preventive measures such as social distancing, wearing masks, and vaccinations can prevent the spread of COVID-19 and the development of future mutations.

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