Introduction

COVID-19 has swept the globe, with over 236 million cases and 4.5 million deaths. While much research focuses on the receptor-binding domain (RBD) of the S1 subunit of the SARS-CoV-2 spike protein, it is possible that potent neutralizing antibodies targeting the S2 subunit exist and can be harnessed for therapies and vaccines. Supportive evidence can be found in the precedent HIV-1 virus, the structural conservation of S2, the neutralization and cross-reactivity potential of S2 antibodies, and the T-cell response to S2.

Methods

PubMed and GoogleScholar were used to complete a full search of peer-reviewed articles. The aim was to explore the evidence for the potential advantages and disadvantages of using S2 as a target of therapy and vaccine design.

Results

1. Promising research of HIV-1’s gp41 (analogous to S2) warrants exploration of S2 for vaccine development. HIV-1’s gp120 (analogous to S1) is more likely to retain mutations than gp41. Also, broadly neutralizing antibodies (nAbs) have been found against HIV-1’s MPER, so those against SARS-CoV-2’s MPER, located in S2, may exist.

2. Since S2 is more conserved among coronaviruses than S1 and is thus less likely to harbor mutations, cross-reactive nAbs against S2 are likely to already be in populations due to prior exposure to common cold coronaviruses (HCoVs). Immunogens that include FP and HR2, which are both in S2, may induce production of more broadly active nAbs, fight other betacoronaviruses, cause a stronger memory response, and decrease the chance of mutations rendering the vaccine ineffective.

As S2 is more structurally conserved, it is less likely to harbor mutations. Earlier in the pandemic, a mutation in S1 (D614G) occurred; this strain grew more pseudotyped virions and was shown to have greater viral loads. A vaccine ideally should be just as effective if more infectious mutants arise.

Figure 1: SARS-CoV-2 spike glycoprotein showing (A) domains and (B) comparison of sequence with SARS-CoV and other isolates.

3. Because nAbs against S2 exist, harnessing SARS-CoV-2 nAbs present pre-COVID via a vaccine that elicits a memory immune response could be more effective. A study found that 51.5% of 33 convalescent samples reacted to 1+ non-SARS-CoV-2 coronaviruses. Thus, antibodies against conserved sites are likely very prevalent.

4. T-cell reactivity to conserved epitopes that circulated pre-COVID could be crucial to vaccine development. 20% - 50% of 5 different multi-continental cohorts with individuals who never had SARS-CoV-2 had reactive T-cells against sequences of SARS-CoV-2, likely due to prior exposure to common cold coronaviruses.

Conclusions

S2 is an important vaccine immunogen, particularly from an epidemiological standpoint; its conservation could lead to fewer COVID boosters. Furthermore, due to population exposure to common cold coronaviruses, nAbs, B-, and T-cell responses against SARS-CoV-2 may already exist in individuals who have never had COVID-19.

Literature cited

Acknowledgments

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More information