Structural Biology & Vaccines

By Shyamasri Biswas, PhD

Co Editor-in-Chief

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Structural Pathways to Developing Vaccines against Novel Coronavirus (SARS-CoV-2)

The Emergence of Novel Coronavirus SARS-CoV-2

Coronaviruses belong to the family of RNA viruses that are known to enter human cells when their spike glycoprotein binds cell surface receptors. The recently emerged novel severe acute respiratory syndrome coronavirus (SARS-CoV-2; officially called COVID-19) can bind the angiotensin-converting enzyme 2 (ACE2) on human cells with much higher affinity than the virus that caused SARS in 2003 [1]. The current worldwide pandemic caused by COVID-19 was first identified and confirmed on December 29, 2019 that was traced to the Huanan Seafood Wholesale Market, Wuhan city, Hubei Province in China [1]. Studies have shown that COVID-19 spreads rapidly by human-to-human transmission with a median incubation period of 3.0 days (range, 0 to 24.0), and the time from symptom onset to developing pneumonia is about 4.0 days (range, 2.0 to 7.0) [2]. The conventional routes of transmission of SARS-CoV-2 are believed to be through respiratory droplets and direct contact along with the less known route of fecal-to-oral transmission as well [1, 2].

How to Block the Spread of SARS-CoV-2

To control or block the spread of SARS-CoV-2, there are no specific antiviral treatments or vaccines available yet primarily due to the reason that it is a new emerging viral disease. To mitigate the global health risk posed by the rapid spread of COVID-19, the current research has focused on developing safe and effective vaccines for the treatment of SARS-CoV-2 [1, 2]. To this end, researchers are assuming that virus-based vaccines would prove to be valuable in combatting COVID-19. In this regard, the CoV spike (S) glycoprotein is considered to be a key target for vaccines, therapeutic antibodies, and diagnostics [3].

Besides focusing on the entire virus particle-associated inactivated or attenuated viral vaccines, researchers are also employing the subunit candidates, such as S1 protein and/or the receptor-binding domain (RBD) element of SARS-CoV-2 that are considered as valuable targets for vaccine design [3]. It is believed that a deeper

understanding of the atomic-level structure of the COVID-19 spike protein will allow for additional protein engineering efforts that could be leveraged to improve antigenicity and protein expression for vaccine development. This information could pave the way for precision vaccine design and ultimately discovery of anti-viral therapeutics that would accelerate medical countermeasure (MCM) development [3].

As for the expected timeline of vaccine development, it is anticipated that a new SARS-CoV-2-based vaccine from gene sequence to clinical testing should happen in approximately 6-8 months [1].

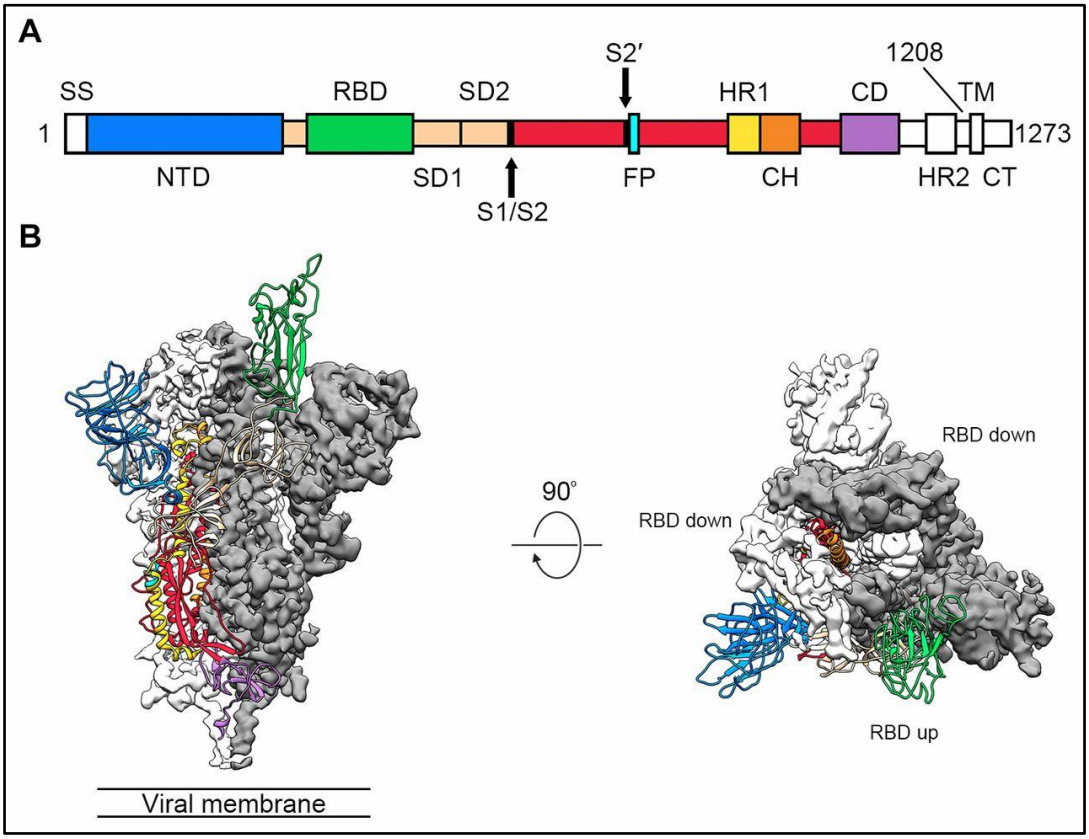

Figure 1: Structure of SARS-CoV-2 S in the prefusion conformation obtained by Cryo-EM. (A) Schematic representation of SARS-CoV-2 S primary structure that is colored by domain (the ectodomain expression construct are colored white). SS represents signal sequence and NTD represents N-terminal domain. RBD is receptor-binding domain and SD1 represents subdomain 1, whereas SD2 corresponds to subdomain 2, S1/S2= S1/S2 belong to protease cleavage site and S2' is the S2' protease cleavage site. FP corresponds to fusion peptide and HR1 is heptad repeat 1. Further, CH is the central helix and CD: connector domain. HR2 is heptad repeat 2 and TM is transmembrane domain, whereas CT corresponds to cytoplasmic tail. (B) Side and top views of the prefusion structure of the SARS-CoV-2 S protein with a single RBD in the up conformation. The two RBD-down protomers are shown as cryo-EM density in either white or gray. The RBD-up protomer is shown in ribbons which is colored corresponding to the schematic shown in (A) [Source: Science (2020)].

Solving Structure of Key Coronavirus Protein: A Significant Step Forward to Developing Vaccines

As we described in the preceding section, COVID-19 virus makes use of a densely glycosylated S protein to gain entry into host cells. The S protein is known to be a trimeric class I fusion protein, which exists in a metastable prefusion conformation state [3, 4]. This conformation subsequently undergoes a dramatic structural rearrangement that helps fuse the viral membrane with the host-cell membrane, which is triggered by the binding of S1 subunit to a host-cell receptor (Figure 1) [3]. This process is then followed by destabilizing of the prefusion trimer by the receptor binding that results in shedding of the S1 subunit and transition of the S2 subunit to a stable post fusion conformation (Figure 1) [3].

Further, studies have shown that the RBD of S1 undergoes hinge-like conformational movements, which transiently hide or expose the determinants of receptor binding in order to engage a host-cell receptor [3]. Since the S protein offers indispensable function, it represents a target for antibody-mediated neutralization. Simultaneously, the characterization of the prefusion S structure can provide atomic-level information to guide vaccine design and development [3]. To this end, to rapidly facilitate MCM development, researchers in a recent research of major significance, determined a 3.5 Angstrom resolution structure of the SARS-CoV-2 S trimer by employing a cryo-EM in the prefusion conformation (Figure 1) [3].

Researchers expressed ectodomain residues 1−1208 of SARS-CoV-2 S and added two stabilizing proline mutations in the C-terminal S2 fusion machinery based on a previous stabilization strategy that produced the domain organization of the expression construct and figure S1 shows the cryo-EM structure of the S-domain(Figure 1) [3]. This strategy proved effective for other betacoronavirus S proteins [3].

This study on solving the key protein structure of SARS-CoV-2 virus is considered a major breakthrough that results in a significant step toward developing a vaccine against the virus as well as treatments for COVID-19 [3].

Concluding Remarks

Solving the key protein structure of SARS-CoV-2 virus is a major step forward to rapidly develop vaccines and also therapeutics. We anticipate a rapid progress in vaccine development happening in the near future.

References for further reading

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