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OPINION

S1 Subunit and Host Proteases as Potential Therapeutic Avenues for the Treatment of COVID-19

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The novel corona virus (SARS-CoV-2) that causes severe acute respiratory syndrome, now called COVID-19 initially originated in Wuhan city of China and later spread across borders and infected more than five million people and killed over 3.4 lakh people all over the globe. This disease has been announced as pandemic by WHO. So far, there has been not much progress in terms of drug development for fighting against this deadliest virus, also no existing drugs has been reported completely effective for COVID-19 treatment owing to lack of effective therapeutic targets and a broad understanding of the viral behavior in target cell. Some reports have found and confirmed that SARS-CoV-2 like others SARS-CoVs utilizes angiotensin converting enzyme-2 receptor for making entry into target cell by binding to the receptor with its S1 subunit and employing host cell proteases for cleaving S2 subunit at S2' in order to fuse with cell membrane. Thus, simultaneous blocking of S1 subunit and inactivation of proteases seem to be promising therapeutic targets for the development of effective novel drugs. In current write up we hypothesize that S1 subunit and host proteases as potential therapeutic avenues for the treatment of COVID-19.

Key Words: S1 subunit, SARS-CoV-2, Spike (S) transmembrane glycoprotein, COVID-19.

Background

Entry of corona viruses (CoVs) into target host cells occurs with the help of spike (S) transmembrane glycoprotein which projects out from the surface of virus in the form of homo-trimers (1). This protein (S) consists of a small intracellular tail, a trans-membrane anchor, and a large sized ectodomain composed of receptor-binding S1 subunit, and cell membrane-fusing S2 subunit (2). S1 subunit initiates the process of viral entry via attaching with cell receptor while S2 subunit facilities the viral fusion with cell membrane (3). The protein S is cleaved at S2' by proteases present in host cell (4) leading to the activation of this protein for fusion with cell membrane through a spectrum of permanent conformational modifications (5,6). Thus, viral entry is a complicated process depending on combined event of protein S- receptor binding and proteolytic protein S processing (3).

Hypothesis

Though protein S of SARS-CoV-2 shows merely 75% similarity with the S protein of SARS-CoV as depicted from sequence analysis (7,8) but S protein receptor-binding motif (RBM) analysis shows that majority of amino acid residues vital for receptor binding are conserved between SARS-CoV and, SARS-CoV-2, signifying that these two strains of CoVs make use of the same receptor for entering into host cell (9) which is Angiotensin converting enzyme 2 (ACE2) (8,10,11). Since the spike (S) protein is the viral component that with the cleaving action of host proteases facilitates the CoV-2 entry into the host cellular cytoplasm, thus a hypothesis is arises ''could the blocking of viral S1 subunit and

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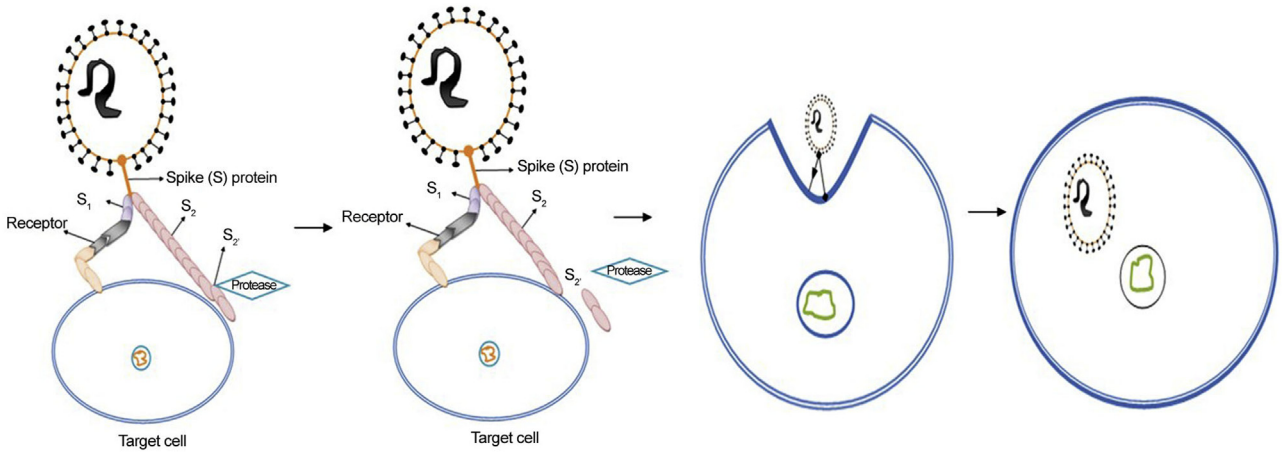

Figure 1. Mechanism of SARS-CoV-2 entry into target cell.

inhibiting of proteases simultaneously with host-friendly inhibitors make the CoV-2 handicapped and prevent its complete entry into target cells''. Figure 1 shows the mechanism of CoV-2 entry into target cell. The theoretical model for inhibiting receptor-binding S1and S′-proteases interplay is depicted in Figure 2. We suggest that S1 subunit and host proteases as potential therapeutic avenues for the treatment of COVID-19.

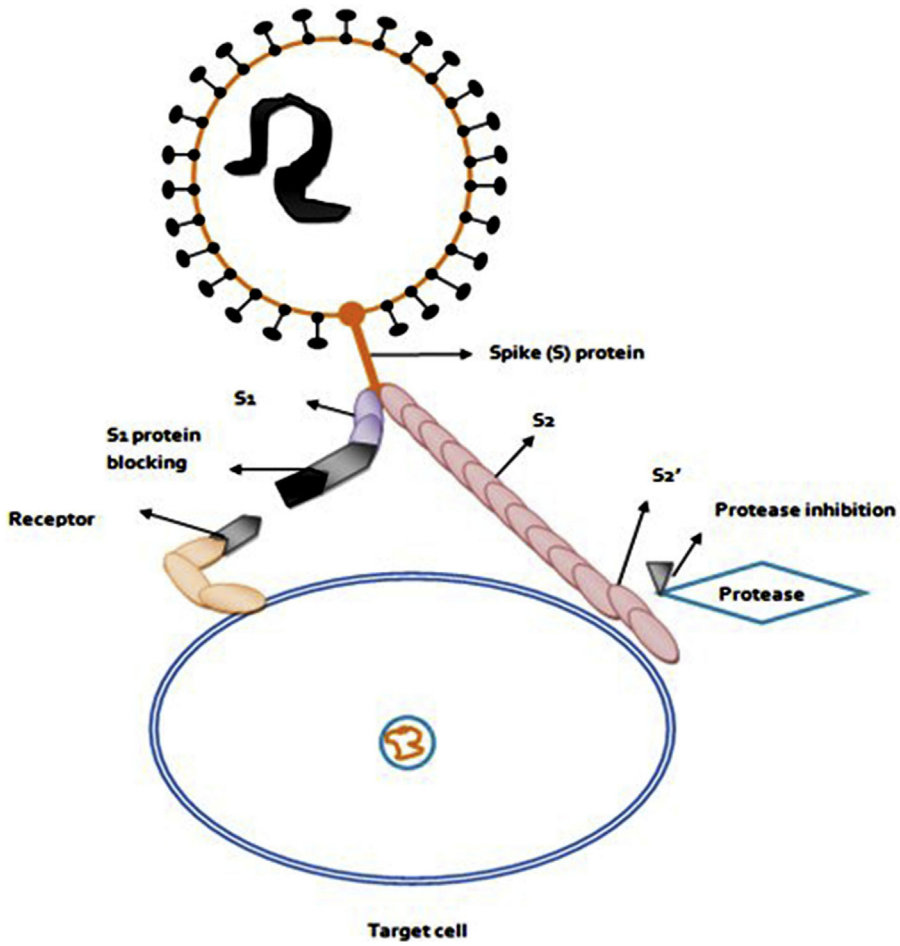

Figure 2. Blocking of S1 Subunit and protease inhibition prevents the SARS-CoV-2 entry into target cell.

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