OPINION

SARS-CoV-2 S glycoprotein: Synthesis, processing, and trafficking

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ABSTRACT

The Rough Endoplasmic Reticulum (RER), the SARS-CoV-2 S glycoprotein is produced as a 1273-amino-acid polyprotein precursor. At the N terminus of the unprocessed precursor is an Endoplasmic Reticulum (ER) signal sequence, which directs the S glycoprotein to the RER membrane and is degraded by cellular signal peptidases in the ER lumen. The S protein's C terminus has a single stop-transfer, membrane-spanning motif that inhibits it from being fully released into the ER lumen and subsequent secretion from the infected cell. During synthesis, N-linked, high-mannose oligosaccharide side chains are added co-translationally. The S glycoprotein monomers trimerize shortly after synthesis, which may help in transport from the ER to the Golgi complex. Most high-mannose oligosaccharide side chains are changed to more complex forms in the Golgi complex, and O-linked oligosaccharide side chains are also added. The SARS-CoV-2 S glycoprotein, which contains numerous arginine residues not present in the closely related SARS-CoV, is proteolytically digested at the S1/S2 cleavage site in the trans-Golgi network by cellular furin or furin-like proteases. Surface component S1, which connects the virus to the host cell surface receptor, and transmembrane subunit S2, which facilitates the fusion of viral and host cell membranes, are produced via cleavage at the S1/S2 site. In a metastable prefusion state, noncovalent interactions keep the S1 and S2 subunits together.

INTRODUCTION

The Furin-like cleavage is necessary for effective SARS-CoV-2 infection of human lung cells and airway epithelial cells, as well as for S-protein-mediated cell-cell fusion and viral infectivity. Following cleavage, an ER Retrieval Signal (ERRS) containing a conserved motif near the extreme C terminus ensures that the mature SARS-CoV-2 S protein accumulates near the ER-Golgi Intermediate Compartment (ERGIC), where it participates in virus particle assembly and is incorporated into the virus envelope, driven by interactions with another structural protein, the membrane (M) protein. A portion of mature SARS-CoV-2 S proteins also travels to the plasma membrane via the secretory route, where they can promote the fusion of infected and uninfected cells to create multinucleated giant cells (syncytia). This might allow the virus to travel directly across cells, thereby altering the aggressiveness of SARS-CoV-2. A deletion of 20 amino acids from the cytoplasmic tail of the SARS-CoV-2 S protein has been shown to increase the infectivity of single-cycle Vesicular Stomatitis Virus (VSV)-S pseudo types and replication-competent recombinant. Single-cycle human immunodeficiency virus (HIV)-S or other retrovirus-S pseudo types. This deletion is thought to increase cell surface expression of the SARS-CoV-2 S glycoprotein, allowing the S protein to be more easily incorporated into pseudo virions and replication-competent virions. The SARS-CoV-2 S glycoprotein, like other class I fusion proteins such as HIV envelope (Env) glycoprotein and influenza virus haemagglutinin (HA), has structural, topological, and mechanistic properties with other class I fusion proteins. The SARS-CoV-2 S glycoprotein, like other class I viral fusion proteins, is a conformational machine that promotes viral entrance by rearranging from a metastable unliganded state to a stable postfusion state through a pre-hairpin intermediate state. A variety of structures for the SARS-CoV-2 S glycoprotein trimer segments in both the prefusion and postfusion phases have been discovered since the initial genome sequence of SARS-CoV-2 became publically accessible. The overall architecture of the prefusion SARS-CoV-2 S ectodomain, which was stabilised by two consecutive proline mutations in two conformations determined by single particle cryo-electron microscopy (cryo-EM), is a 160-long trimer with a triangular cross-section, with the S1 subunit adopting a "V" shape that contributes to the overall triangular appearance and the S2 subunit forming the stalk. The sole structural change between these two conformations is where one of the three S1 RBDs is located. When all three RBDs are in the "down" position, the ensuing S ectodomain trimer adopts a closed conformation, in which the S1 RBD's receptor-binding surface is buried at the protomer interface and is inaccessible to its receptor. SARS-CoV-2 vaccine candidates based on various vaccine platforms, such as inactivated or live attenuated vaccines, DNA and mRNA vaccines, viral vector-based vaccines, and recombinant protein-based vaccines, have been developed since SARS-CoV-2 was identified as the causative agent of COVID-19 and its first genome sequence was released immediately and freely by a Chinese research group. The majority of these vaccines are based on the full-length S glycoprotein, which is the most important viral surface antigen. When a vaccination plan calls for the SARS-CoV-2 S protein to be recombinantly generated in the human body, the ERRS should be left out to boost the protein's cell surface expression. The native HIV-1 Env trimer found on the surface of intact virions is thought to be an ideal immunogen because most of the neutralising antibodies described so far could recognise and bind to the prefusion form of trimeric HIV-1 Env, though neutralising antibodies against this glycan-covered, sequence-variable native form are difficult to induce. Despite significant cross-reactivity in binding to the S glycoproteins of both viruses, different lines of research have shown that convalescent sera from SARS-CoV and SARS-CoV-2 patients showed no or limited cross-neutralization activity against these two viruses in pseudo typed and authentic viral infection assays. Similar findings were found in infected and immunised animals. Given that the RBM is less conserved than any other functional region or domain of the SARS-CoV-2 S protein, and that the RBM shares a high degree of amino acid sequence identity with that of SARS-CoV (76 percent overall), it can be assumed that the RBM has the most immune dominant neutralising epitope(s) of the entire S protein, capable of eliciting strong neutralising antibody responses. By assuming the closed conformation, the natural trimeric SARS-CoV-2 S protein may hide each of its immune dominant RBMs. As a result, SARS-CoV-2 evades immune surveillance through conformational masking, which has been well-documented for HIV-1, while the S protein could transiently sample the functional state to engage ACE2, which is consistent with the idea that the fusion glycoprotein of highly pathogenic viruses can engage ACE2.

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