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The role of Spike protein in infection and disease severity

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ABSTRACT:

Enveloped viruses especially Coronaviruses, Influenza viruses, and Human Immunodeficiency viruses pose a great risk to the human and animal populations. These viruses cause diseases of clinical and socio-economic importance with the help of their spike protein. Coronaviruses affect the respiratory, gastrointestinal tract, and nervous system and the influenza virus affects the respiratory system while the Human Immunodeficiency Virus affects multiple systems as it invades and destroys immune cells. We aimed to review the role of spike protein in the four viruses and their effects on disease severity. We searched through online publication databases such as PubMed, Google Scholar, and Scopus to retrieve 150 scientific published articles using keywords like 'Spike Protein', 'Viruses', 'Infection', and 'Diseases'. A total of 100 articles were used to write this article. Spike protein is an essential structure in viruses that causes infections and diseases in humans and animals. Targeting this protein in the development of antiviral drugs and vaccines should be a major concern.

Keywords: *Spike protein, Enveloped viruses, Coronaviruses, HIV, Influenza virus.*

INTRODUCTION

A virus is the most difficult disease-causing agent to treat, as well as demanding. However, research shows that viruses possess unique structures and compositions that make them different from other organisms. It is the only obligate intracellular parasite that uses the host machinery to replicate and distribute the viral particles within the body. Among these viruses, there are enveloped and non-enveloped viruses. The enveloped virus also has distinct structures that make it more complex and challenging in the development of antiviral drugs and vaccines. One of the most important structures is the spike protein which serves as the main target for drugs and vaccines against viral infections. It also mediates binding, the fusion, and entry of the virus into the host cell, as well as the evasion of the immune response[1]. However, the spike protein differs among enveloped viruses, so they are specific. Some of the important viruses with this spike protein include SARS-CoV-2, MERS-COV, Human Immunodeficiency Virus (HIV), and the Influenza Virus. Therefore, this review discusses the role of spike protein in infection and the severity of the disease.

MATERIALS AND METHODS

We searched through online publication databases such as PubMed, Google Scholar, and Scopus to retrieve 150 scientific published articles using keywords like 'Spike Protein', 'Viruses', 'Infection', and 'Diseases'. A total of 100 articles were used to write this article.

What is spike protein?

Spike proteins are structural molecules made up of protein and carbohydrates (glycoproteins) protruding on the surface of enveloped viruses. They are assembled as trimers made up of cytoplasmic tails, a hydrophobic transmembrane domain that anchors the proteins into

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the membrane[2]. The glycoproteins are bonded *via* N- and O- linked glycosylation that protrudes on the cell surface of the virus, it is usually rod-shaped and characterized by membrane proteins and external domains. Spike proteins are also Peplomers or S protein[3]. Spike protein uses important enzymes and other specific receptors to exert its effect on target cells.

Coronaviruses

Coronaviruses, severe acute respiratory syndrome (SARS-CoV), Middle East respiratory syndrome (MERS-CoV), and severe acute respiratory syndrome 2 (SARS-CoV-2) belong to the *coronaviridae* family having four genera alpha, beta, gamma, and delta coronavirus. Alphacoronavirus and betacoronavirus affects mammals while avian species are affected by gammacoronavirus and deltacoronavirus[4]. The viruses also affect humans. Indeed, it is a zoonotic disease. Coronaviruses are enveloped viruses consisting of structural proteins namely, the envelope (E), membrane (M), nucleocapsid (N), and spike (S)[5]. The most important structural protein in infection and pathogenesis is the spike protein that has attached the virus to its species-specific target cells.

SARS-CoV-2 Spike Protein

Spike protein of SARS-CoV-2 consists of the S1 region which is composed of the N terminal domain and the C terminal domain[6]. However, in some literature[6-8], the S1 region is structured into 4 domains, the N terminal domain, the C terminal domain, the Receptor binding domain, and two subdomains SD1 and SD2 which are made up of 672 amino acids.

The S1 region has a characteristic V-shaped ectotrimer that houses the Angiotensin-converting enzyme 2, an important enzyme found on different cell membranes within the body, and is an integral part of the renin-angiotensin-aldosterone system. On each S1 there is a single receptor binding domain that acts together with the Angiotensin-converting enzyme 2. However, a study[6] suggests that the treatment of SARS-CoV-2 infection can be achieved by approaching the receptor-binding domain and Angiotensin-converting enzyme 2 interaction; however, the receptor-binding domain is not a perfect site for the target in antiviral drugs development due to its mutable region.

The S2 region is composed of N terminal hydrophobic domain fusion peptide, Heptad repeat domain (HR1 and HR2), and the transmembrane domains. The S2 region is an important region with a variety of domains essential for virus fusion and entry, the N-terminal hydrophobic fusion peptide and the transmembrane domain are responsible for causing commotion, interruptions of the lipid bilateral membrane, and facilitating the attachments of spike protein to the viral membrane, respectively.

Spike protein is covered by a protective covering made of polysaccharides known as the glycan shield. This protein plays a critical role in immune evasion and eliciting an immune response.

These regions or subunits S1 and S2 are divided by enzymes during the maturation process as well as during viral particle assembly[2]. These enzymes are transmembrane protease serine 2, cathepsin and furin and are found inside the host i.e., they are cellular proteases. They are also important in viral activation and pathogenicity. Other important enzymes that mediate viral activation include TMPRSS4, TMPRSS11A, TMPRSS11D, and TMPRSS11E1.

However, all the structures that make or form the spike protein structure as a whole undergo several changes ranging from shape, size and forms, and states. This change is known as pre-fusion and post-fusion conformation. A study[7] shows that angiotensin-converting enzyme 2 is one of the important factors in SARS-CoV-2 infections due to its imbalance. The expression of the cell surface angiotensin-converting enzyme, where it is removed from the cell surface by endocytosis, inhibits its activity in lung tissues leading to damage in pulmonary parenchyma and thrombosis.

Spike Receptor Binding Domain (SRBD) Mutations and Immune Escape

The present understanding of how mutations in the SARS-CoV-2 spike protein affect neutralization is based on several investigations such as traditional escape mutation work, which identifies mutations that emerge in virus populations exposed to either mAbs or convalescent plasma containing polyclonal antibodies[8], targeted characterization of specific mutations[9], and larger investigations of either large numbers of circulating variants[10] or all possible amino acid substitutions in the SRBD[11,12]. Where mutations have been demonstrated to influence polyclonal antibody recognition, an effect on either mAbs or plasma for spike residues has been observed. Escape mutations developing in viruses exposed to mAbs or polyclonal plasma ('mAb emerge' and 'plasma emerge') have been described for a lesser number of residues.

Researchers used a yeast-display system to examine all conceivable single amino acid variants and found variants that evade either nine neutralizing SARS-CoV-2 mAbs[11] or convalescent plasma from 11 persons obtained at two time periods after infection[13] in a DMS investigation. The resulting heat maps provide a wealth of information on the antigenic consequences of SRBD mutations, with plasma escape mutations of particular interest because they affect neutralization by polyclonal antibodies of the type SARS-CoV-2 encounters in infections, where significant levels of immunity have been acquired through prior exposure or vaccination. While there is significant interpersonal and intrapersonal heterogeneity in the impact of mutations on polyclonal serum neutralization, mutations that further reduce antibody binding occur in a relatively small number of RBD residues, indicating significant immunodominance within the SRBD[12].

Spike N-Terminal Domain (SNTD) Mutations and Immune Escape

The majority of evidence for immune evasion in the SNTD is concentrated in a region centred on a conformational epitope consisting of residues 140-156 (N3 loop) and 246-260 (N5 loop), which includes the antibody 4A832 epitope. SRBD and SNTD mutations were relatively evenly distributed in investigations that revealed the appearance of antibody escape mutations in virus populations exposed to convalescent plasma. In one investigation[8], escape mutations emerged in viruses exposed to the convalescent plasma of two persons, one of whom was selected only for SNTD mutations (N148S, K150R, K150E, K150T, K150Q, and S151P). Despite the plasma containing the very effective SRBD-targeting mAb C144, this was the case[8]. Individual immune responses may be variably influenced by mutations of SRBD and SNTD epitopes[8], as SNTD antibody escape mutations were not identified in the other plasma samples analyzed, and the 148-151 mutants demonstrated only modest reductions in insensitivity to the plasma tested. Deletions in the SNTD have been documented as affecting SNTD antigenicity[14] and have been detected frequently in the evolution of SARS-CoV-2.

MERS-CoV Spike Protein

MERS-CoV belongs to the same family as SARS-CoV-2, and also has some similarities in characteristics. The MERS-CoV also has a spike protein which is also divided into S1 and S2 subunits, which is a receptor-binding domain, and the membrane fusion subunit[15]. Almost all the structures of SARS-CoV-2 spike protein are similar to that of MERS-CoV but the major difference is the S1 receptor binding domain which does not use angiotensin-converting enzyme-2 rather than Dipeptidyl Peptidase-4 as a receptor when binding to the host cell. The S2 subunit is also responsible for fusion of viral particles into the cell membrane[16].

Human Immunodeficiency Virus

The human immunodeficiency virus (HIV) is a member of the *retroviridae* family of the genus lentivirus. It is a single-stranded positive-sense RNA virus with envelope humans. The HIV envelope is responsible for binding to the target cell.

Human immunodeficiency Virus Spike Protein

The HIV spike protein is also made of glycoproteins, known as gp160. The glycoproteins 160 are subdivided into two units: gp120 and gp41, which are the upper region and lower region, respectively. gp120 is made up of conserved and variable protein domains, five of which are assigned respectively (C1-C5) and (V1-V5)[17]. The conserved domain is part of the gp120 core. Then, the variable domain is located around the spike protein surface. gp120 is divided into two regions inner and outer domain. The inner domain is responsible for the formation of trimeric envelope spikes, and it also interacts with gp41. The outer domain forms part of the outer spikes. However, a third domain is formed as a result of CD4 binding to gp120 which causes changes in conformation and it is known as the bridging sheet[18]. The mechanism by which the gp120 acts on the host cell is through binding to CD4, which is an immunoglobulin. CD4 is the major receptor for HIV. This binding occurs in a hollow area that closes to an inner domain, outer domain, and the bridging sheet. The gp41 unit is made up of three domains: ectodomain, transmembrane, and endodomain, where the ectodomain consists of three important regions namely fusion peptide, and two 4-3 heptad repeats. The fusion peptide is located at the amino terminus of gp41 while the two heptad repeats regions are located near the N and C- terminal region of the ectodomain, respectively. Following the interaction of gp120 and the co-receptors, the fusion peptide is introduced into the cellular membrane which anchors the virus on the host cell[19]. There are about three distinguishable conformational changes that occur in gp41 glycoproteins. These changes are pre-fusogenic, pre-hairpin intermediate, and fusogenic state. HIV gets into the host cell *via* three mechanisms, binding of gp120 to CD4 (CD4 cells, also known as T cells, are white blood cells that fight infection and play an important role in the immune system), binding of gp120 to a co-receptor and finally gp41 mediate fusion of the virus to host cell membrane[17].

Influenza Virus

Influenza viruses belong to the *orthomyxoviridae* family, consisting of four genera, Alphainfluenzavirus, Betainfluenzavirus, Gammainfluenzavirus, and Deltainfluenzavirus. They are segmented negative-sense RNA with enveloped. There are two types of spike protein found in influenza viruses, rod-shaped hemagglutinin glycoprotein, and mushroom-shaped neuraminidase glycoprotein[20]. 16 and 9 types of hemagglutinin and neuraminidase have been identified. Host, origin, year of identification of hemagglutinin and neuraminidase, and the number of strains is included.

Influenza Virus Spike Protein

There is a surface spike protein of the influenza virus, hemagglutinin (HA), and neuraminidase (NA). However, there are 18 and 11 hemagglutinin and neuraminidase subtypes that are known to exist. Hemagglutinin has a spherical domain, a homotrimer, the trimer is formed by two disulfide bond polypeptides, distal and proximal membranes[21], with receptors binding site for sialic acid. Hemagglutinin attaches the virus to the sialic acid and other receptors on the host cell to initiate infection[22]. Hemagglutinin consists of three molecules that are indistinguishably fused from a cylindrical shape. It has a globular head with three chains and a stem with three

chains also. These chains play a critical role in binding the viral particles to pulmonary cells.

Neuraminidase is an enzyme that destroys the host cell wall for virus particles to enter. It breaks the bond that exists between the cellular glycoproteins and sialic acid on the cell wall. Neuraminidase consists of four identical polypeptides; the four monomers are divided into structural domains[23]. Cytoplasmic tail, a transmembrane region, stalk, and catalytic head.

The cytoplasmic tail has an essential role in viral function. Some neuraminidases lack a cytoplasmic tail, it may be the result of the absence of interaction with membrane-associated matrix viral protein.

The transmembrane domain N-terminal hydrophobic site is responsible for attaching neuraminidase to the viral envelope[24]. The spike protein of each enveloped viruses shows distinct features that are receptor-specific. When there are mutations of these viral spike proteins they lead to several strains of the virus which result to the severity of infection.

Spike protein is the major virulence factor of diseases associated with enveloped viruses, it has a pivotal role in the pathogenesis of the disease, being it the only structure capable of detecting, binding to receptors, and fusion of the viral particles into the target cell. This is the primary reason why the spike protein is targeted in developing antiviral drugs and vaccines. The spike protein is also receptor-specific, it is a lock and key mechanism. The spike protein usually enters a target cell and initiates an infection following replication and spread of the viral particles, it enters the cell using viral-cell fusion. This is accomplished by fusion proteins on the spike protein which differs in sequence, and structure and is stimulated by a variety of mechanisms. The initial stage of infection of enveloped viruses begins with the interaction of cellular receptors followed by fusion with cell membranes that are mediated by the spike protein.

Role of Spike Protein in HIV, SARS-CoV-2 and Influenza virus severity

There are two major strategies used by these viruses to enter a host, direct fusion into the host cell or endocytosis[25]. These are also known as fusogenic or endocytic. Immediately after the virus and the cell membrane come in contact, the virus enters directly into the cell, it is dependent on the binding of the receptor to spike protein of the host cell and virus membrane, respectively. This activates the embedded fusion peptide. On the other hand, the virus particle is internalized first by the host cell which wraps it in a vesicle before it is fused with the endosomal membrane which is activated by a PH less than 7 or before it is degraded as the endosome is acidified[25].

HIV

HIV uses both mechanisms to gain access to a host cell (direct fusion and endocytosis). Based on a previous study[26], Human Immunodeficiency Virus (HIV) binds to the host receptor CD4 to get into the host cell by endocytosis, and *via* direct fusion, it binds to receptor CD4 in couple with co-receptors CXCR4 or CCR5[26]. However, studies[17,18,19,26] show that coronaviruses and influenza viruses exploit direct fusion and endocytosis mechanisms and are also PH dependent.

The Spike protein of these viruses fuses to the membrane after being attached to the cell surface, conformational changes of membrane fusion occur which are mediated by receptors in the case of Human immunodeficiency virus[27].

SARS-CoV-2

The effect of spike protein on transmission, virulence, and severity of SARS-CoV-2 is not well understood[28]. This is because the spike protein undergoes a genetic alteration which may be the reason why it possesses a rapid spread worldwide. As discussed above, SARS-CoV-2 spike protein is cleaved by an enzyme; however, it is cleaved into S1 and S2 after that virion is attached by a protease enzyme called TMPRSS2 on the cell surface or in the lysosomes after the virus is vein internalized. After the cleavage of spike protein S1, the S2 begins the process of viral fusion and lysosomal membrane. The severity of infection is attributed to spike proteins of these viruses as a result of the genetic alteration of the viruses; however, this is why the spike protein becomes the main target in developing antiviral drugs, monoclonal antibodies, and vaccines[29]. Approaches such as the inhibition of spikes protein from binding to its specific receptor on the target cell or using receptor antagonists will be useful in preventing attachment by the spike protein.

Influenza Virus

To enter and exit host cells, influenza viruses rely on the collaboration of two viral surface proteins: haemagglutinin (HA) and neuraminidase (NA). The influenza virus's host cell receptor is sialic acid, a sugar chain that is found on the surface lipids and proteins of most host cells, as well as soluble proteins. HA binds to sialic acid on the surface of respiratory epithelial cells preferentially, allowing the virus to enter host cells. The influenza virus releases its RNA once inside, which is copied and produced into new viral particles. Newly produced virus particles, on the other hand, are unable to exit infected cells as long as HA is attached to sialic acid on cell surfaces. NA breaks down sialic acid on the cell surface, releasing HA and allowing offspring viruses to leave infected cells and disseminate further.

CONCLUSIONS

Spike protein is the most important virulence factor in enveloped virus-associated diseases, considering how it plays role in infection ranging from attachment, fusion, and spread of viral particles within the infected cells.

Therefore, targeting this protein in the development of antiviral drugs and vaccines should be a major concern, thereby inhibiting the protein from binding to the receptors and many other approaches.

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