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Spike (S) Protein: A Potential Target for the SARS-Cov-2 is Being Explored

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Abstract:

Corona virus disease 2019 is a newly emerging infectious disease which is caused by a novel coronavirus, severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). The spike (S) protein, which plays a key role in the receptor recognition and cell membrane fusion process. Out of two subunit S1 contains a receptor-binding domain that recognizes and binds to the host receptor angiotensin-converting enzyme 2, while the S2 sub-unit mediates viral cell membrane fusion by forming a six-helical bundle via the two-heptad repeat domain. Exploration of potential target using PDB, ExPasy: ProtParam and Swiss Model are performed. In this present work, we have analyzed Spike S protein as potential therapeutic and vaccine candidate in control of infection. It may improve covid infection management in managing patients in reoccurrences of infections in future.

Keywords: SARS-CoV-2, S protein, Modeling, Ramachandran plot, Drug Target.

Introduction

COVID-19, caused by the novel coronavirus SARS-CoV-2, has been the defining global health crisis of our time since its emergence in late 2019. The COVID-19 pandemic has had far-reaching consequences beyond the spread of the disease itself and efforts to quarantine it (Stawicki, Stanislaw P., et al. 2020). As the virus has spread globally, concerns have shifted from a singular focus on health care to the broader spectrum of socio-economic issues, The virus, originating in Wuhan, China, has spread rapidly across the globe, leading to significant morbidity and mortality. Mental health, education, and the continuity of basic services.(Chu, Isaac Yen-Hao, et al., 2020). It has also highlighted the need for concerted international cooperation in health response. The unprecedented nature of this pandemic, despite the lessons learned from previous outbreaks of similar diseases, has exposed the vulnerabilities of our global health systems (Haldane, Victoria, et al., 2021).

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has underscored the critical importance of understanding viral mechanisms, particularly those related to drug resistance. Central to this is the Spike (S) protein of SARS-CoV-2, which plays a crucial role in viral entry into host cells and is the primary target of most therapeutic interventions and vaccines.However, the emergence of drug resistance in the S protein poses a significant challenge to these therapeutic strategies (Murgolo, Nicholas, et al., 2021). Mutations in the S protein can lead to changes in the virus's susceptibility to drugs and the effectiveness of vaccines, potentially leading to reduced treatment efficacy and vaccine breakthrough infections (Zhang, Mengxin, et al. 2022). This paper aims to explore the phenomenon of drug resistance in the S protein of SARS-CoV-2. It will delve into the mechanisms behind the development of resistance, the implications for treatment and prevention strategies, and the ongoing research efforts to combat this issue.

The spike (S) protein of SARS-CoV-2 has been a focal point of extensive research due to its crucial role in viral entry and pathogenesis. The S protein is a key target for vaccine development, therapeutic interventions, and understanding the host range of the virus (Du et al., 2009; Wang et al., 2020; Zhu et al., 2020; Jahangir & Marnik, 2021; Chi et al., 2020). Cryo-electron microscopy studies have revealed the dynamic conformational changes of the receptor-binding domain (RBD) of the S protein, which is essential for its interaction with the host cell receptor ACE2 (Yuan et al., 2020). Monoclonal antibodies targeting the S protein have shown potent neutralizing activity, making them promising candidates for therapeutic interventions (Chi et al., 2020). Furthermore, the S protein has been implicated in the ability of SARS-CoV-2 to overcome the species barrier, indicating its significance in the transmission of the virus from animals to humans (Du et al., 2009).The S protein of SARS-CoV-2 exhibits distinct features from SARS-CoV-1, such as the presence of a furin-cleavage site, which influences the virus's reliance on host cell proteases for entry (Ou et al., 2021). Additionally, computational studies have explored the binding mechanisms between the S protein and ACE2 from various mammals, shedding light on the host range of SARS-CoV-2 (Xie et al., 2020). The S protein has also been identified as a dominant target for neutralizing antibody responses, emphasizing its importance in vaccine design and immune response dynamics (Zhu et al., 2020).Moreover, the S protein's post-translational modifications, such as palmitoylation and glycosylation, have been investigated for their roles in viral entry and pathogenesis, providing insights for vaccine design and understanding viral pathogenesis (Li et al., 2021; Dong et al., 2020). Additionally, the S protein has been implicated in modulating the activity of epithelial sodium channels, potentially contributing to pulmonary edema observed in COVID-19 patients (Grant & Lester, 2021).

The S protein of SARS-CoV-2 is a pivotal focus of research, with studies elucidating its structural dynamics, antigenicity, post-translational modifications, and implications for vaccine design, therapeutic interventions, and understanding viral pathogenesis (Haas, Paige, et al. 2021). This paper aims to provide a comprehensive research and advancements in S protein based therapeutic and vaccine development (Dhama, Kuldeep, et al. 2020). It is hoped that this work will contribute to the understanding and management of global crisis. By shedding light on this critical aspect of SARS-CoV-2 biology, this research hopes to contribute to the global efforts to control the COVID-19 pandemic and prepare for future viral threats (Donia, Ahmed, et al. 2021).

Methods

1. RCSB Protein Data Bank (https://www.rcsb.org)

By providing access and tools for exploration, visualization, and analysis of experimentally determined 3D structures in the Protein Data Bank (PDB) archive, the RCSB Protein Data Bank (RCSB PDB) enabled breakthroughs in science and education. The structure and FASTA format sequence of spike protein with PDB ID: 7YBM were retrieved from PDB(https://www.rcsb.org/structure/7ybm).

2. ProtParam (https://web.expasy.org/protparam/)

A protein sequence of spike S protein (7YBM) used to infer a variety of physico-chemical properties, which ProtParam computes. Regarding the protein in query, no further details are needed. The protein can be supplied as a raw sequence or as an ID or Swiss-Prot/TrEMBL accession number. Numbers and white space are disregarded. An complete sequence segment was provided for analysis (https://web.expasy.org/cgi-bin/protparam/protparam).

3. SWISS-MODEL(https://www.expasy.org/resources/swiss-model)

Included in SWISS-MODEL are the SWISS-MODEL Workspace and the SWISS-MODEL Repository. It is a platform for automatically modeling protein structures homology that uses a comparative method to create 3D models of proteins. It also includes a database of annotated models for important reference proteomes that is based on UniProtKB. Research on COVID-19 and SARS-CoV-2 is supported by this resource. (https://swissmodel.expasy.org/interactive/YkVxXz/models/)

Result

The results obtained from different used methodology are listed below:

1. Sequence and Structure

   Sequence retrieved from pdb in fasta format is used for structure prediction is given below: >7YBM_1|Chains A, B, C|Spike glycoprotein|Severe acute respiratory syndrome coronavirus2 (2697049) (https://swissmodel.expasy.org/assess/n4Yb85/03).

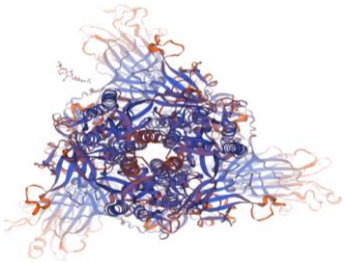

Figure 1: structure prediction and assessment using Swiss model using PDB ID.

2. Physico-chemical characteristics of the spike (S) protein of SARS-CoV-2:

The different characteristics properties are computed and described below:

1. **Number of Amino Acids: This** represents the total count of amino acid residues in the given protein sequence. In given sequence total count of amino acid residues are **1271**.
2. **Molecular Weight (141052.47):** It is the total mass of the protein in atomic mass units (amu) or daltons.
3. **Theoretical pI (6.64):** The isoelectric point (pI) is the pH at which a protein carries no net electrical charge. A theoretical pI of 6.64 indicates the pH at which the protein is expected to be electrically neutral.
4. **Amino Acid Composition List (106/8.5):** This likely refers to the ratio or percentage of a specific amino acid in the protein. For example, 106 residues out of 1271 are of a particular type with a pKa value of 8.5.
5. **Total Number of Negatively Charged Residues (107):** This indicates the sum of amino acid residues that contribute to a negative charge in the protein.
6. **Total Number of Positively Charged Residues (104):** This represents the sum of amino acid residues that contribute to a positive charge in the protein.
7. **Total Number of Atoms (19703):** The count of all atoms in the protein structure.
8. **Abs 0.1% (=1 g/l) (1.066):** This may refer to the absorbance at 0.1% concentration, which is a measure of how much light is absorbed by the protein solution.
9. **Estimated Half-life (30 hours):** The half-life is the time required for half of a substance to undergo decay or be metabolized. In this context, it indicates an estimate of how stable the protein is over time.
10. **Instability Index (II) (33.74):** The instability index predicts the stability of a protein. A value of 33.74 suggests moderate stability, with higher values indicating potential instability.
11. **Aliphatic Index (84.19):** The aliphatic index reflects the relative volume occupied by aliphatic side chains (e.g., alanine, valine, isoleucine, and leucine). A higher aliphatic index often correlates with higher thermostability.
12. **GRAVY (-0.082):** The GRAVY (Grand Average of Hydropathy) is a measure of the hydrophobicity of a protein. Negative values, like -0.082, suggest a tendency for the protein to be more hydrophilic.

Sr No.	Parameter	Value
1	No. of amino acids	**1271**
2	Molecular Weight	**141052.5**
3	Therotical PI	**6.64**
4	Amino acid composition list	**106/8.5**
5	Total number of negatively charged residues	**107**
6	Total number of positively charged residues	**104**
7	Total number of atoms	**19703**
8	Abs 0.1% (=1 g/l)	**1.066**
9	The estimated half-life	**30 hours**
10	Instability index (II)	**33.74**
11	Aliphatic index	**84.19**

12	GRAVY Index	**-0.082**

Table 1: Computation of Physico-chemical characteristics of the spike (S) protein of SARS-CoV-2 using ProtParam.

3. Protein modeling

The Structure Assessment of Spike protein integrates various tools and annotations with sequence and structure viewers to simplify exploration of quality and structural features of macromolecular models. The assessment may be standalone or with comparison to a reference structure. The various parameters calculated for structural assessment are as below:

Parameters	**Value**
Biounit Oligo State	Homo-trimer
QSQE	0.89
Method	EM, 3.44 Å
Seq Similarity	0.61
Coverage	1.00
Range	14-1160

Table: 2 Spike glycoprotein Structural bases for enhanced infectivity and immune evasion of SARS-CoV-2 variants.

3.1 Ramachandran Plot Analyses:

Mol Probity Score (1.29): MolProbity is a tool for validating the three-dimensional structures of biomolecules. A score of 1.29 suggests a relatively good structural quality, where lower scores generally indicate better structures.

Clash Score (0.73): The clash score assesses the steric clashes between atoms in the structure. A lower clash score, such as 0.73, indicates minimal atomic overlap and better spatial arrangement in the molecule.

Ramachandran Favored (92.95%): This parameter measures the percentage of amino acid residues in favorable regions of the Ramachandran plot, reflecting the backbone torsion angles. In this case, 92.95% of the residues are in favorable regions, suggesting a well-structured protein.

C-Beta Derivations (47): C-Beta deviations refer to discrepancies in the placement of C-beta atoms in amino acids. The value of 47 indicates the number of such deviations in the structure.

Bad Bonds (35/27893): Bad bonds represent improper covalent bonds in the structure. In this case, there are 35 bad bonds out of a total of 27,893 bonds, indicating a low percentage of problematic bond interactions.

Bad Angles (202/38002): Bad angles refer to distorted bond angles in the structure. The value of 202 indicates the number of such problematic angles out of a total of 38,002 angles.

QMEANDisco Globad (0.72±0.05): QMEANDisco is a composite score that evaluates the global quality of a protein structure. The value of 0.72, with a standard deviation of ±0.05, provides an overall assessment of the structure's quality, where higher values are generally indicative of better quality.

Table 3: Ramachandran Plot Analysis by MolProbity is a tool for validating the three-dimensional structures of Biomolecules.

Mol Probity Result (Ramachandran Plot Analysis)						
Mol probity score	**Clash score**	**Ramachandron favoured**	**C- Beta Derivations**	**Bad Bonds**	**Bad Angles**	**QMEAN Disco Globad**
1.29	0.73	92.95%	47	35/27893	202/38002	0.72±0.05

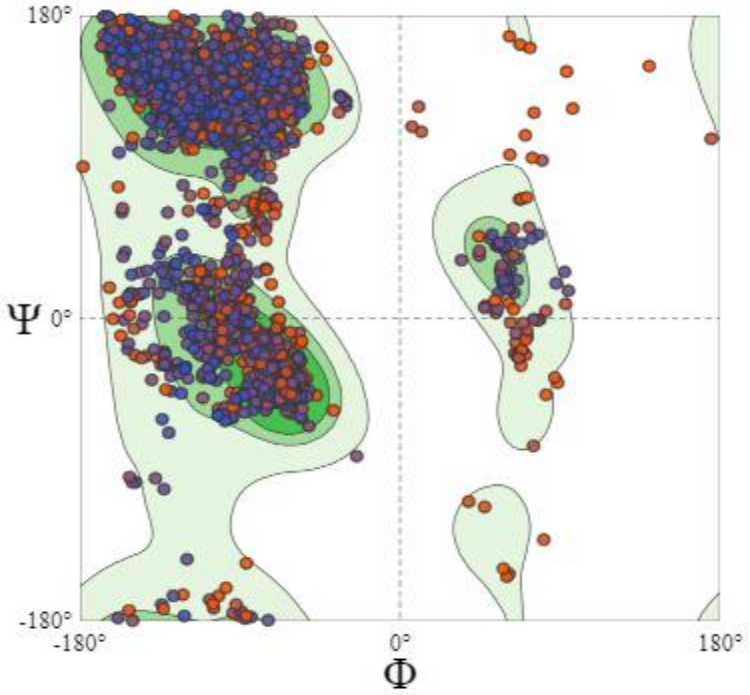

Figure 2: Ramachandran Plot for Spike S protein of SARS-CoV-2.

Discussion

In the course of the COVID-19 (coronavirus disease 2019) pandemic, caused by the SARSCoV-2 virus, millions of people have lost their lives, as well as a devastating socioeconomic impact across the globe (Zhang, Mengxin, et al. 2022; Akdeniz, Munevver, et al..2024). A wide range of interventions are urgently needed due to the development of this disease, in order to control the crisis. However, in order to achieve these objectives, a deeper knowledge of viral structure and function relationships, as well as host-related factors, is necessary(Zhang, Mengxin, et al. 2022; Akdeniz, Munevver, et al..2024). In the development of diagnostics, therapeutics, and vaccines, the trimeric spike (S) protein is important target.Rapid advancement in the underlying research of SARS-CoV-2 S protein has been made since the beginning phase of the pandemic, propelling our insight on the viral passage process impressively (Xia, Xuhua., 2021; Stawicki, Stanislaw P., et al. 2020; Akdeniz, Munevver, et al., 2024). In this present research, we have analyzed

structure of the SARS-CoV-2 S protein and discussed the implications for vaccines and therapeutics development in future.

Conclusion

Since the initial outbreak of SARSCoV-2, significant progress has been made in understanding its structure. Besides filling a significant gap in our understanding of viral entry, structural knowledge requires the development and optimization of vaccines and therapeutics in order to combat current and future corona virus pandemics.

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