Elucidating Interactions Between SARS-CoV-2 Trimeric Spike Protein and ACE2 Using Homology Modeling and Molecular Dynamics Simulations

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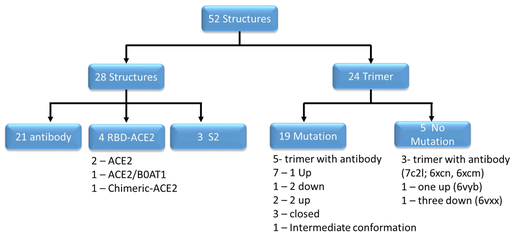
Abstract

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19), with more than 133.4 million confirmed cases and 2.8 million deaths reported, urgently needing drugs and vaccines to combat the COVID-19 pandemic. The spike protein present on the outer surface of the virion plays a major role in viral infection by binding to receptor proteins present on the outer membrane of host cells, triggering membrane fusion and internalization, which enables release of viral ssRNA into the host cell. Understanding the interactions between the SARS-CoV-2 trimeric spike protein and its host cell receptor protein, angiotensin converting enzyme 2 (ACE2), is important for developing drugs and vaccines to prevent and treat COVID-19. Several crystal structures of partial and mutant SARS-CoV-2 spike protein have been reported; however, an atomistic structure of the wild-type SARS-CoV-2 trimeric spike protein complexed with ACE2 is not yet available. Therefore, in our study, homology modeling was used to build the trimeric form of the spike protein complexed with human ACE2, followed by all-atom molecular dynamics simulations to elucidate interactions at the interface between the spike protein and ACE2. Molecular Mechanics Poisson-Boltzmann Surface Area (MMPBSA) and in silico alanine scanning were employed to characterize the interacting residues at the interface. Twenty interacting residues in the spike protein were identified that are likely to be responsible for tightly binding to ACE2, of which five residues (Val445, Thr478, Gly485, Phe490, and Ser494) were not reported in the crystal structure of the truncated spike protein receptor binding domain (RBD) complexed with ACE2. These data indicate that the interactions between ACE2 and the tertiary structure of the full-length spike protein trimer are different from those between ACE2 and the truncated monomer of the spike protein RBD. These findings could facilitate the development of drugs and vaccines to prevent SARS-CoV-2 infection and combat COVID-19.

Introduction

- COVID-19 pandemic is caused by SARS-CoV-2
- So far, more than 133.4 million confirmed cases and more than 2.8 million of deaths are reported around the world
- SARS-CoV-2 is composed of 4 structural proteins, 16 non-structural proteins and 9 accessory proteins
- Spike protein is present in the outer surface of the virion and plays a major role in the viral infection
- Spike protein binds with ACE2 of the host cells and infect its RNA into host cells
- Hence, understanding interactions between the trimeric form of the spike protein and ACE2 could help identify drugs to inhibit the binding and fusion of SARS-CoV-2 to host cells

PDB Details



Structural Details of Spike Protein

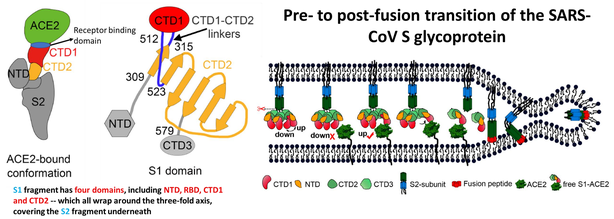
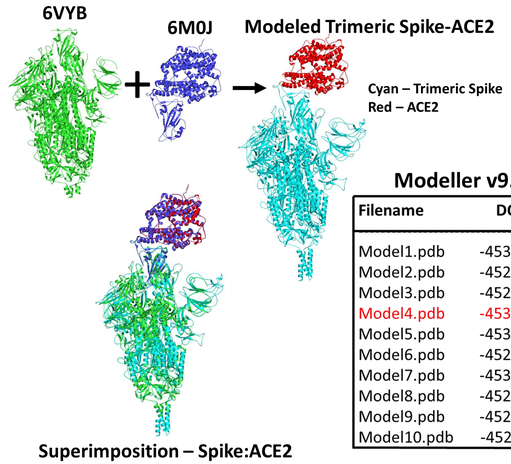


Figure 1. Cartoon representation of the Spike protein and its mechanism

Homology Modeling



Modeller v9.24

Filename	DOPE score
Model1.pdb	-453061.62500
Model2.pdb	-452078.12500
Model3.pdb	-452595.93750
Model4.pdb	-453871.81250
Model5.pdb	-453290.15625
Model6.pdb	-452068.90625
Model7.pdb	-453414.09375
Model8.pdb	-452842.59375
Model9.pdb	-452185.50000
Model10.pdb	-452439.75000

Figure 1. Homology model of the wild-type trimeric form of Severe Acute Respiratory Syndrome Coronavirus-2 spike protein complexed with ACE2. The template structures are in green and red. The chain A, chain B, and chain C of the trimeric spike protein, and ACE2 are colored in yellow, magenta, cyan and brown, respectively.

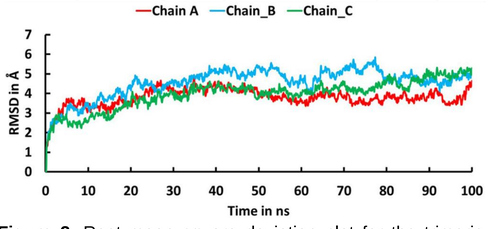


Figure 2. Root mean square deviation plot for the trimeric form of spike protein (Chain A in red, Chain B in cyan, Chain C in green) and ACE2 (brown) during the 100 ns molecular dynamics simulations.

Molecular Dynamics Simulations

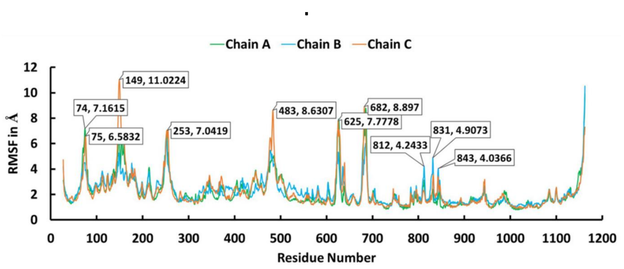


Figure 3. The root mean square fluctuation (RMSF) plot for Cα atoms in chain A (green), B (cyan), and C (brown) of the trimeric form of Severe Acute Respiratory Syndrome Coronavirus-2 spike protein and ACE2 (red) during the 100 ns molecular dynamics simulations. The X axis indicates residue number and Y axis represents RMSF value in Å.

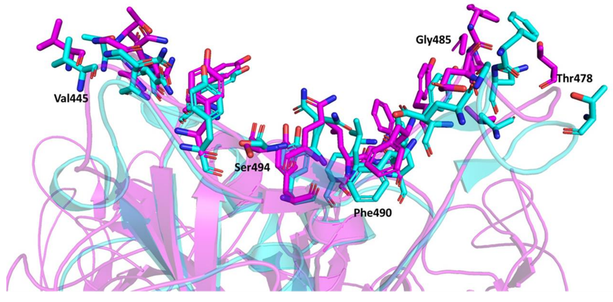


Figure 5. Superimposition of the spike protein-ACE2 complexes using the full-length trimeric spike protein (Magenta) and the truncated spike protein RBD monomer (Cyan). The interacting residues are represented by stick model illustrations, while the rest of the ACE2 proteins are depicted in ribbon model form. The five new interacting residues identified using the full-length trimeric spike protein complexed with ACE2 are labeled.

Table 1. The residues involved in the hydrogen bond interactions between the trimeric form of the Severe Acute Respiratory Syndrome Coronavirus-2 spike protein and ACE2 complex.

Energy Component	Spike-Ace2	Spike	ACE2	ΔG kCal/mol
vdW	-31291.75	-26670.04	-4534.55	-87.16
EEL	280175.11	-238713.69	-40760.46	-700.95
EGB	-43799.29	-33677.43	-10860.35	738.49
ESURF	1395.71	1141.73	264.89	-10.90
G gas	-36997.86	-35045.80	-1163.95	-788.12
G solv	-42403.58	-32535.70	-10595.46	727.58
Total	-19401.44	-67581.51	-11759.40	-60.54

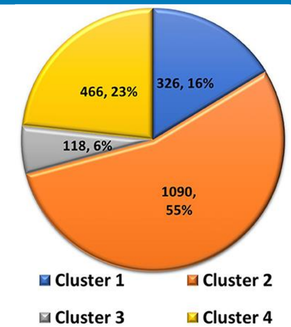


Figure 4. Pie chart of statistics of the 4 clusters of Severe Acute Respiratory Syndrome Coronavirus-2 spike protein complexed with ACE2. Number of structures and percentages are indicated in each pie segment.

Table 2. The residues involved in the hydrogen bond interactions between the trimeric form of the Severe Acute Respiratory Syndrome Coronavirus-2 spike protein and ACE2 complex.

Residue in Spike	Residue in ACE2	Distance Å
Tyr489*	Glu23	2.715
Gln493*	Leu29	3.033
Phe490	Asp30*	3.184
Thr500*	Leu351	2.938
Asn501*	Leu351	2.909
Gly502*	Gly352	2.834

Conclusion

- Twenty interacting residues in the spike protein were identified to tightly bind to ACE2, of which five residues (Val445, Thr478, Gly485, Phe490, and Ser494) were not reported in the crystal structure of the truncated spike protein RBD
- The interactions between ACE2 and the full-length spike protein trimer are different from those between ACE2 and the truncated monomer of the spike protein RBD
- The interacting residues identified in this study provide
  - ✓ New insights to understand the mechanisms of SARS-CoV-2 infection of host cells
  - ✓ Facilitate the development of drugs and vaccines to prevent SARS-CoV-2 infection and to combat COVID-19.

References

❖Sakkiah et. al. Front Chem. 2020; 8: 622632
❖Song et. al. PLoS Pathog. 2018 Aug 13; 14 (8):e1007236