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

Sugunadevi Sakkiah and Huixiao Hong*

Division of Bioinformatics and Biostatistics, National Center for Toxicological Research, U.S. Food and Drug Administration, Jefferson, AR 72079

Correspondence: Dr. Huixiao Hong; Tel: 870-543-7206; Email: Huixiao.Hong@fda.hhs.gov

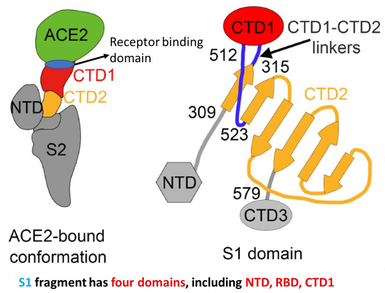
Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes a respiratory illness known as COVID-19. As of 26st August 2020, more than 24 million confirmed cases and more than 8 lakhs of deaths are reported around the world. SARS-CoV-2 spike protein presents on the outer surface of the virion and binds human ACE2 protein on the host cell, playing a key role in the virus infection. Therefore, understanding interactions between the spike protein and ACE2 protein would facilitate development of drugs for the treatment of COVID-19. Many crystal structures have been experimentally determined for various regions of the spike protein. Recent studies uncovered that ACE2 protein binds the trimeric spike protein through multiple conformational poses, for which experimentally determined structure is not available. Hence, we generated a trimeric form of spike bound with ACE using homology modeling. The best modeled spike-ACE2 complex was subjected to MD simulations to elucidate the dynamic interaction between the spike protein and ACE2 protein. Clustering analysis was used to select distinct conformation of the trimeric spike protein complex with ACE2. Our results provide valuable structural details that could facilitate development of drugs to combat covid-19.

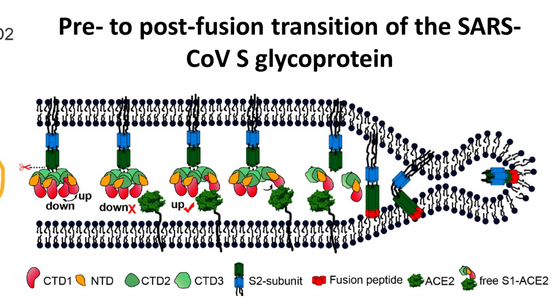
Introduction

- COVID-19 pandemic is caused by SARS-CoV-2
- As of 26th August 2020, more than 24 million confirmed cases and more than 8 lakhs of deaths are reported around the world
- Like other corona virus, SARS-CoV-2 is composed of 4 structural proteins, 16 non-structural proteins and 9 accessory proteins
- Spike protein presents in the outer surface of the virion and plays a major role in the viral infection
- Spike protein binds with ACE2 receptor of the host cells for the RNA to enter host cells
- Understanding interactions between the trimeric form of the spike protein and ACE2 could facilitate discovery of drugs that inhibit the binding of SARS-CoV-2 to ACE2

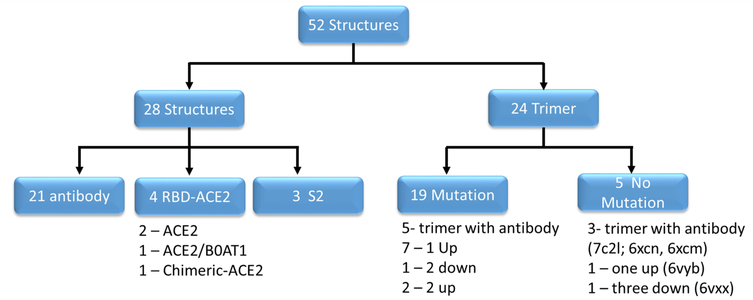
Structural Details of Spike Protein



S1 fragment has four domains, including NTD, RBD, CTD1 and CTD2 -- which all wrap around the three-fold axis, covering the S2 fragment underneath

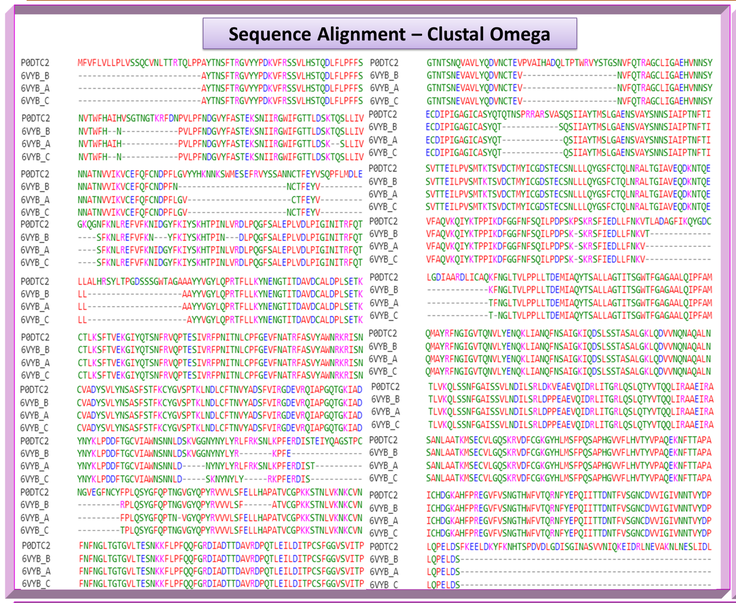


PDB Details – Spike Protein

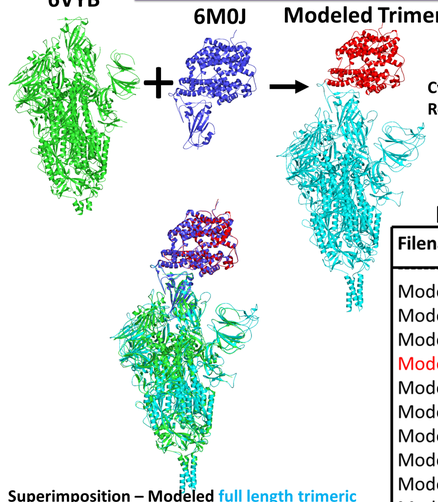


Homology Modeling

Sequence Alignment – Clustal Omega



Modelled Trimeric Spike bound with ACE2



Superimposition – Modeled full length trimeric Spike:ACE2 with X-ray trimeric spike, RBD-ACE2

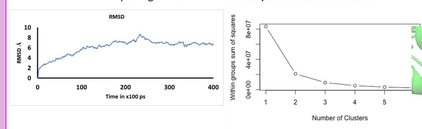
Modeller v9.24

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

Molecular Dynamics Simulations

40 ns molecular dynamics simulation was carried out for the trimeric form of spike protein with ACE2 using Amber 18

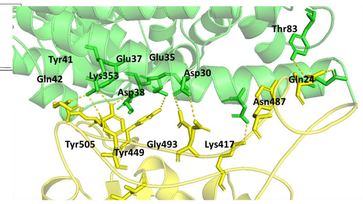
- R package used for cluster analysis: hclust and wardD



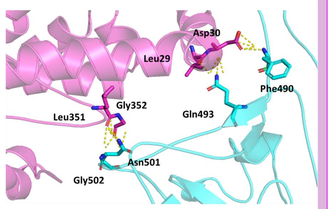
Hbond Interaction - Spike and ACE2

HBond	Crystal Structure	Structure1	Structure2	Structure3
Y505:E37	X			
Y489:Y83	X			
Y449:D38	X			
Y449:Q42	X			
T500:Y41	X			
S494:N33			X	X
Q493:L29		X	X	X
Q493:E35	X			
N501:L351		X	X	
N501:Y41	X			
N487:Q24	X			
N487:Y83	X			
K417:D30	X			
G502:G352		X	X	X
G502:K353	X			
G446:Q42	X			
F490:D30	X	X	X	X

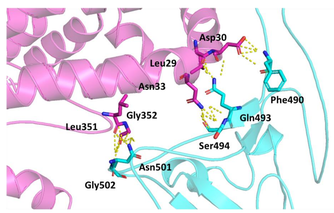
Hydrogen bond interaction between the full length and RBD spike protein with ACE2



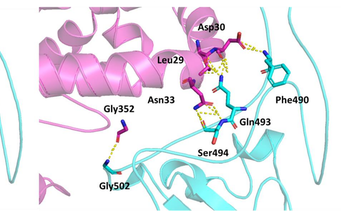
6M0J: RBD-ACE2



Full Trimeric spike-ACE2 – Structure 1



Full Trimeric spike-ACE2 – Structure 2



Full Trimeric spike-ACE2 – Structure 3

Yellow and Cyan – Spike RBD and Full length && Magenta and green ACE2

Conclusions

1) We constructed the structure of trimeric full length SARA-CoV-2 spike protein bound with ACE2 using homology modeling and molecular dynamics simulations; 2) The interactions between the spike protein and ACE2 identified in our structure are different from those reported in the crystal structure of monomeric receptor binding domain (RBD) of the spike protein bound with ACE2, indicating the RBD monomer may not represent the trimer of full length spike protein in the body; 3) Our findings shed lights on understanding the mechanism on entrance of the virus into the host and could assist development of drugs to treat COVID-19.

References

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4. Daniel et. al. PTRAJ and CPPTRAJ: Software for processing and analysis of molecular dynamics data. J. Chem. Theory Comput. 2013, 9 (7) 3084-3095