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Protein Biochemistry
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PyMol Project: SARS-CoV-2 Spike Protein-ACE2 Binding Complexes

Introduction

The SARS-CoV-2 virus has spike proteins on its surface that bind to the ACE2 receptor on human cells. SARS-CoV-2 uses this recognition in order to enter the host cell. This report aims to illustrate the specific complex that SARS-CoV-2 and ACE2 form, including the conformation that SARS-CoV-2 is bound in, comparison of binding to mouse ACE2, and an analysis of evasion of the Omicron variant from patient antibodies.

SARS-CoV-2 spike protein binds to ACE2 in the erect conformation

The three conformations of SARS-CoV-2 spike protein are closed, open, and erect conformations. The spike protein is an oligomeric structure made of three domains (chains). Each conformation differs in the position of their chains. This change in position affects their binding ability to ACE2. The closed conformation (Figure 1A, 1D) has all three polypeptide chains in a closed conformation, the erect state (Fig. 1B, 1E) has chains in a partially open conformation and only the B domain in an upwards state, and the open state (Fig. 1C, 1F) has all three domains pointing outwards and upwards. (Walls, et al. 2020) (Wrobel, et al. 2020)

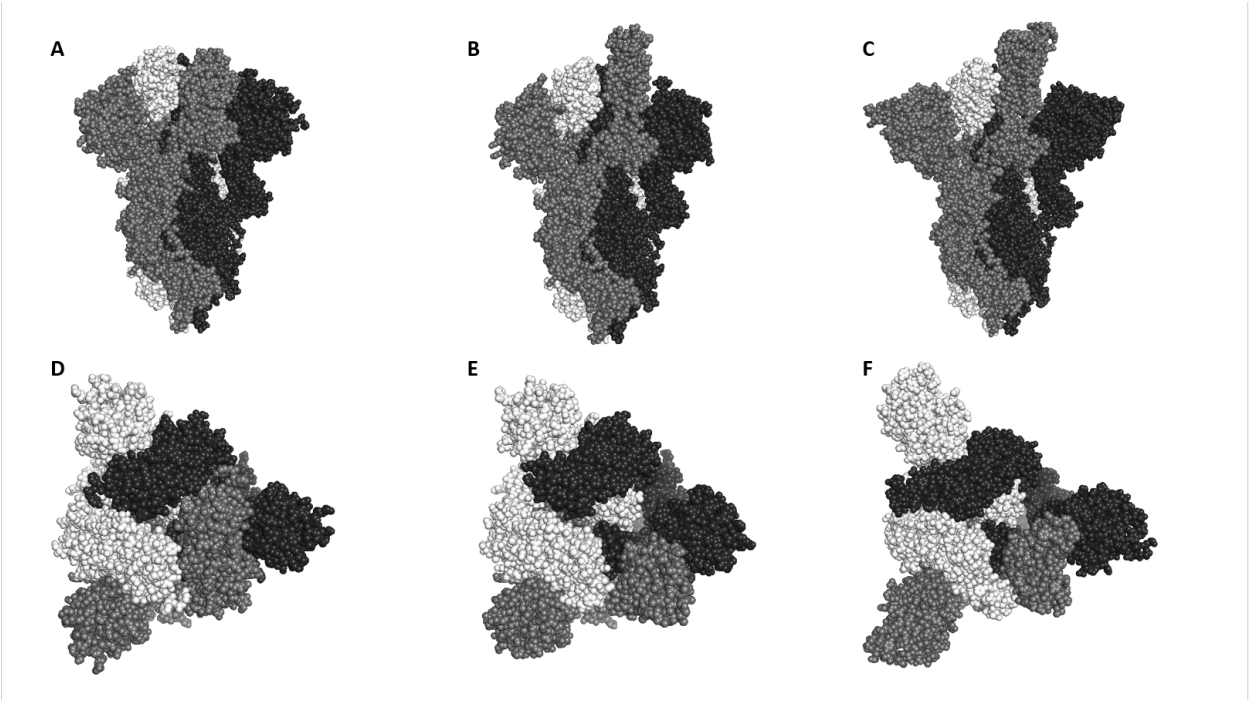

Figure 1: PyMol structures of the SARS-CoV-2 spike protein. For all three structures, the A, B, and C domains of the trimer are color-coded in white, gray, and black respectively.

(A) Side view and (D) top view of the spike protein's closed structure. (PDB ID: 6VXX)

(B) Side view and (E) top view of the spike protein's open structure. (PDB ID: 6VYB)

(C) Side view and (F) top view of the spike protein's erect structure. (PDB ID: 6ZGG)

Although the open state was noted to be able to bind to the ACE2 receptor, SARS-CoV-2's spike protein binds in the erect structure most strongly, as shown in Figure 2. (PDB code: 6ZGG) (Wrobel, et al, 2020). It is worthy of note that Wrobel's article refers to the three conformations as "closed," "intermediate," and "open," whereas we refer to the same conformations in Dr. Osmundson's Protein Biochemistry class as "closed," "open," and "erect" respectively. For maximum clarity, in this paper "open" refers to the 6VYB structure in the RCSB Protein Databank, and "erect" refers to the 6ZGG structure in the databank.

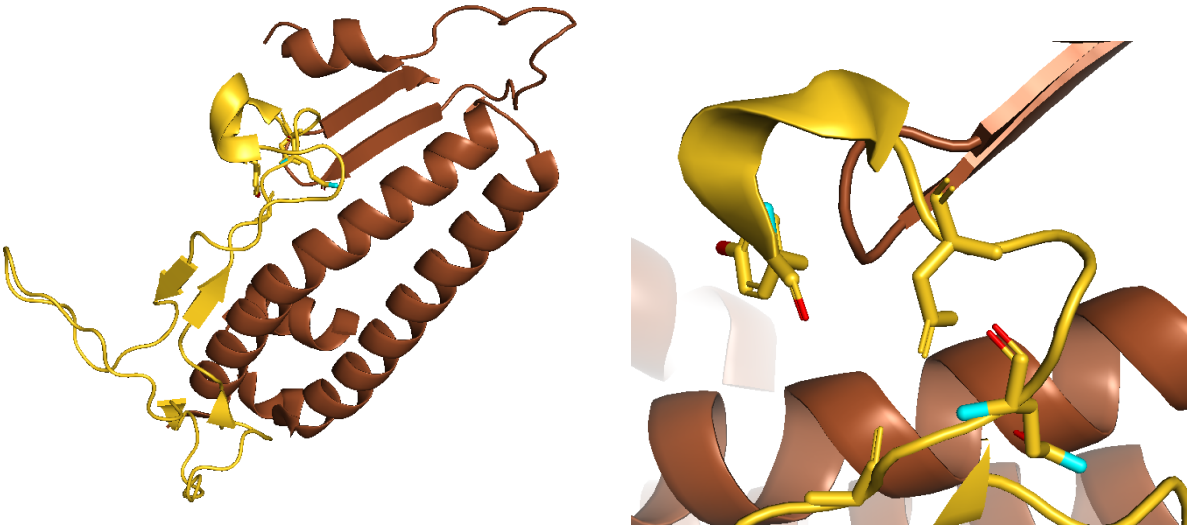

Figure 2: RBD of SARS-CoV-2 complexed with human ACE2. (PDB ID: 6VW1)

Interaction sites of the spike protein and ACE2 have been discussed in detail with studies of the spike protein's function and antigenicity. A set of residue positions have been proposed to play a major role in ACE2 binding present for both SARS-CoV and SARS-CoV-2, with several residues only being semi-conserved. (Walls, et al. 2020) Examples of conserved residues include T402, R426, and Y436, with an example of a semi-conserved position being R426 from SARS-CoV correlating to a N439 position in SARS-CoV-2. Despite the position change, these two residues play a similar role across the two coronaviruses. Sequence alignments have also been performed on the RBDs, analyzing specific motifs responsible for binding. (Shang, et al. 2020)

Omicron variant of SARS-CoV-2 Spike protein binds to mouse ACE2

A study on mouse variants of SARS-CoV-2 leading up to the omicron (BA.2) variant has shown that the omicron variant's mutations surprisingly have improved binding affinity to mouse ACE2 (mACE2) than human ACE2. This data has been interpreted as the omicron variant having mutated in mice as a reservoir before spreading to humans. (Zhang et al. 2020) In support of this claim, SPR assays and pseudovirus entry assays show the omicron variant RBD's ability to bind to mACE2. The prototypic (WA1) variant's RBD was shown to not bind to mACE2.

The interaction region between the spike protein and omicron and WA1 variants of hACE2, the omicron variant of mACE2 is located on the A chain, in positions 19 to 100 and 321 to 359. (Fig. 3) (Zhang et al. 2020) Hotspot regions were also noted at locations 33 and 353. (not shown)

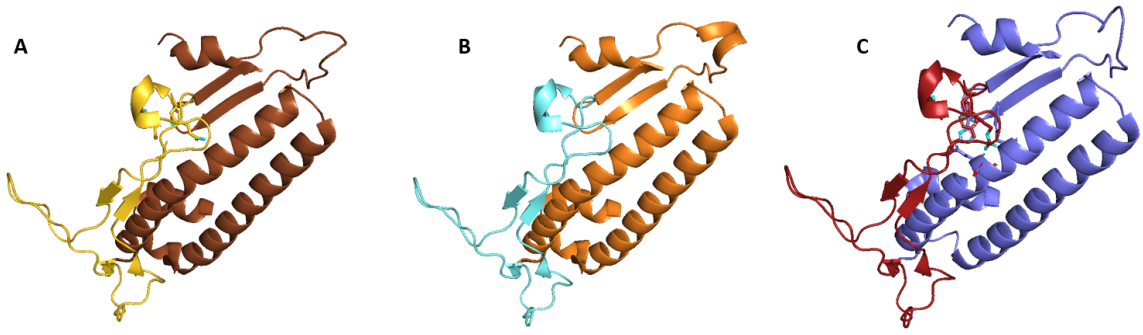

Figure 3: Binding regions of hACE2-WA1 complex, hACE2-BA.2, and mACE2-BA.2. ACE2 receptors of human (hACE2) and mouse (mACE2) in bound complex with the WA1 (prototypic) and BA.2 (omicron) variants of the SARS-CoV-2 spike protein. Chains A and E of the spike protein are shown. WA1 spike protein does not bind to mACE2, so it is not shown here. (A) hACE2 (gold) and WA1 (brown) complex. (PDB ID: 6VW1) (B) hACE2 (aquamarine) and BA.2 (orange) complex. (PDB ID: 7UFK) (C) mACE2 (dark red) and BA.2 (dark blue) complex. (PDB ID: 7UFL)

Significant differences between mouse and human ACE2 have been noted at the hotspot-353 location. Compared to human ACE2, mouse ACE2 is suggested to possess a histidine in place of lysine in position 353 of the A chain. Histidine bears a bulkier side chain than lysine does, so it is speculated that histidine fits into the spike protein binding region less strongly, and therefore prevents said spike from binding with mouse ACE2.

Omicron evasion of patient antibodies

The evasion of omicron variants, and therefore the effectiveness of antibodies acquired from previous variants, is a controversial topic. Some sources have argued that a cocktail of pre-existing treatments will raise proper antibody responses against omicron variants, (Parzych et al. 2022) while others express a lack of ability in antibody therapies to provide an immune response to all omicron variants, due to differing mutations in each. (Iketani et al. 2022)

In this report, the omicron variant BA.2 will be the focus. There are multiple antibodies identified that can interact with BA.2's spike proteins, including DMAb 2196, ZCB11 Fab, and 553-49. (Fig. 4) Although these PDB structures are not able to demonstrate the supposedly worse binding of omicron to pre-existing antibodies, it is concluded in both Parzych et al and Iketani et al's papers that omicron evades the current immune response due to various mutations in its genome.

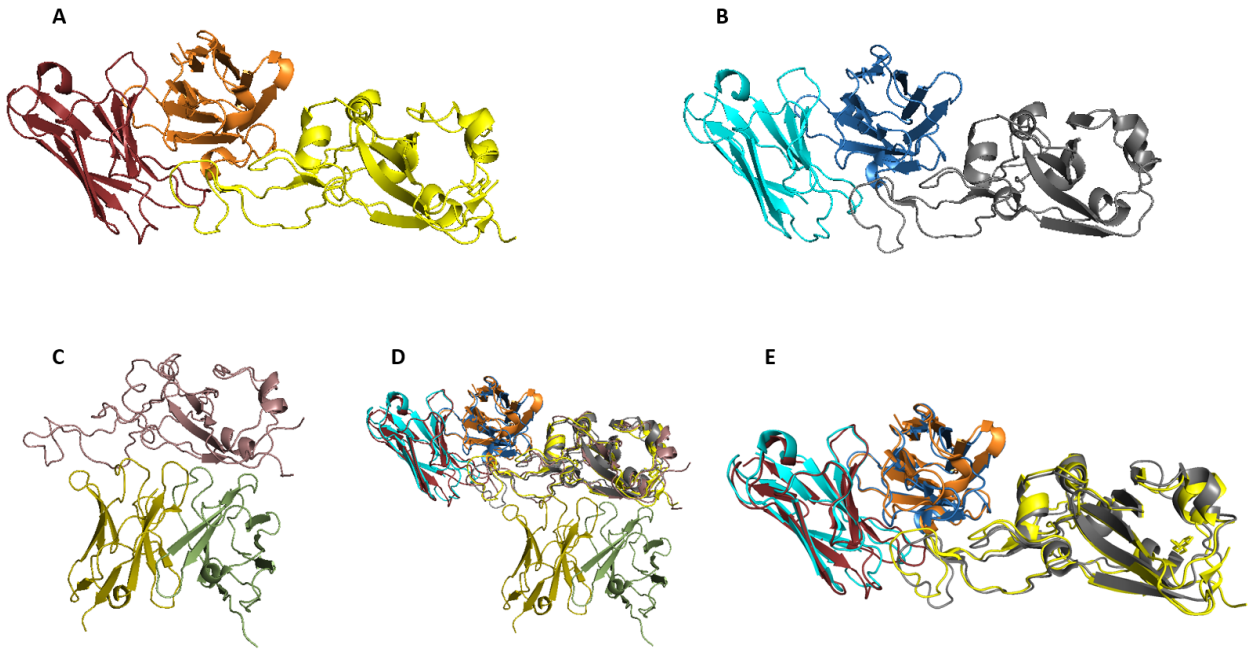

Figure 4: Compilation of SARS-CoV-2 omicron spike protein binding to DMAb2196, ZCB11 Fab, and 553-49 antibodies. (A) SARS-CoV-2 BA.2 spike protein bound to DMAb2196. (PDB ID: 8D8R) (B) BA.2 spike protein bound to ZCB11 Fab. (PDB ID: 7XH8) (C) BA.2 spike bound to 553-49. (PDB ID: 7WOG) (D) Overlap of DMAb2196 complex and ZCB11 complex. Notice the general shape of these complexes are similar to one another. (E) Overlap of A, B, and C complexes. Notice the lack of overlap in 553-49 complex's domain A and B compared to the other complexes. These structures imply BA.2's spike can be bound by various antibodies of differing shapes, but the maintained strength of these interactions cannot be verified without more data.

A high amount of mutations from the WA1 variant has given BA.1 much in the way of evading antibody responses (Patzych et al, 2022) Since BA.1 and BA.2 have been established to harbor different mutations from each other, it can be expected for vaccines against one variant to

not trigger an equally strong response against the other. At least eight spike interactions specific to BA.2 were identified, and affect the binding of BA.2 to antibodies. (Iketani et al, 2022) One notable example was S371F, which changes out the relatively unhindered serine for a bulky phenylalanine. This change is speculated to be particularly responsible for the worsened binding of BA.2 to antibodies.

Unfortunately, the Protein Databank does not currently have spike protein structures available for the BA.2 variant, but I have highlighted the approximate locations of the mutations from the prototypic WA1 to BA.2.

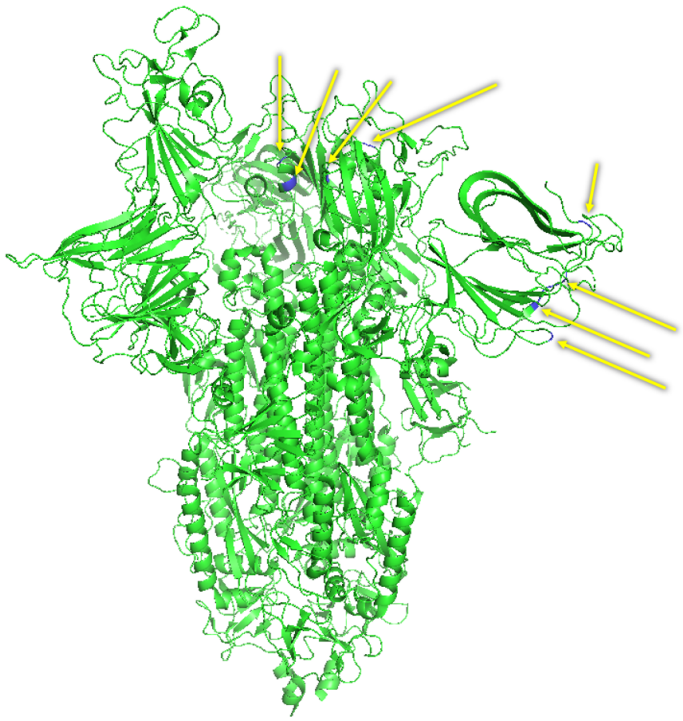

Figure 5: Approximate locations of mutations leading from erect state of WA1 prototypic spike protein to BA.2. Mutations are in deep blue, with yellow arrows pointing at their approximate positions in the protein. The positions appear to be in the RBD.

Discussion

Among the three different conformations, SARS-CoV-2 spike protein binds to ACE2 in the erect form, with all three domains pointing upwards and outwards. (6VYB) Such a conformation should allow binding to the ACE2 receptor with minimum steric hindrance. The omicron (BA.2) variant of the spike protein binds to mouse ACE2, but the prototypic/WA1

variant does not. This is due to differences between the mouse and human ACE2 that affect binding. The higher binding affinity of the BA.2 spike implies that the mouse population acted as a reservoir for the omicron variant before spreading to humans. The omicron variants' evasion of patient antibodies appears to be the result of significant mutations near or in the receptor binding domain. These mutations weaken their binding to antibodies, thus lowering the efficiency of immune responses acquired from previous SARS-CoV-2 variants. Omicron's BA.1 and BA.2 sub-variants have also been noted to have accumulated different mutations, further contributing to antibody evasion.

References

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