The Omicron Variant Increases the Interactions of SARS-CoV-2 Spike Glycoprotein with ACE2

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ABSTRACT

Recently detected Omicron variant of SARS-CoV-2 (B.1.1.529) is heavily mutated on the receptor-binding domain ($RBD_{Omicron}$) of its spike glycoprotein (S). RBD plays a critical role in viral infection by binding to the peptidase domain (PD) of angiotensin-converting enzyme 2 (ACE2) receptors in host cells. To investigate how Omicron mutations affect RBD-PD interactions, we performed all-atom molecular dynamics simulations of the $RBD_{Omicron}$-PD in the presence of explicit water and ions. Simulations revealed that $RBD_{Omicron}$ exhibits a more dispersed interaction network on both sides of the RBD-PD interaction surface. Mutations resulted in an increased number of salt bridges and hydrophobic interactions between $RBD_{Omicron}$ and PD compared to wild-type RBD (RBD_{WT}). Using the conformations sampled in each trajectory, the Molecular Mechanics Poisson-Boltzmann Surface Area (MMPBSA) method estimated ~44% stronger binding free energy for $RBD_{Omicron}$ compared to RBD_{WT}, which may result in higher binding efficiency of the SARS-CoV-2 virus to infect host cells.

KEYWORDS
Coronavirus, COVID-19 pandemic, molecular dynamics, molecular recognition, binding free energy

The recent appearance and the rapid rate of infection of a heavily mutated B.1.1.529 variant of SARS-CoV-2, named Omicron, have raised concerns around the world, with many countries limiting their international travel. This variant comprises 30 mutations on the spike glycoprotein (S), 15 of which are located on its receptor-binding domain ($RBD_{Omicron}$). RBD interacts with the peptidase domain (PD) of angiotensin-converting enzyme 2 (ACE2) receptors and plays a critical role in the host cell entry of the virus. RBD is a critical antibody and drug target, and all of the available vaccines produce antibodies that neutralize the RBD-PD interaction. Mutations on $RBD_{Omicron}$ are surface-exposed and being targeted by various antibodies (Figure S1) and nanobodies. In addition, 11 of these 15 mutations (K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H; Figure 1) are located on the ACE2 binding interface. Our previous all-atom Molecular Dynamics (MD) simulations[1] showed that 5 of these mutated residues form pairwise interactions between wild-type (WT) S and ACE2 (salt bridges between K417-D30 and E484-K31 salt bridges, and hydrogen bonding between Q493-E35, Q498-Q42, Q498-K353, and Y505-E37). It remains unclear how these mutations affect the binding strength of $RBD_{Omicron}$ to ACE2 and the ability of existing SARS CoV-2 antibodies to neutralize this interaction.

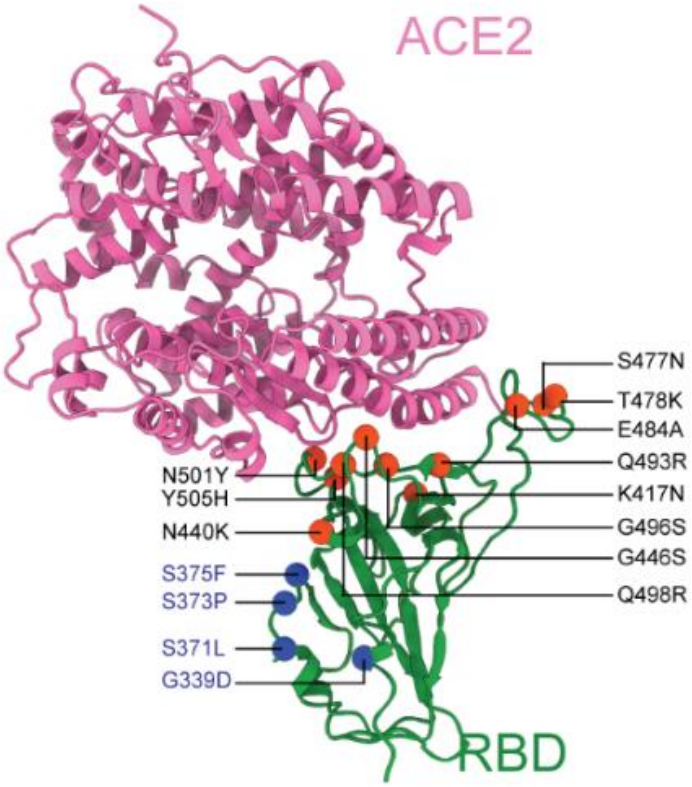

Figure 1. Location of RBD mutations for the Omicron variant. Mutations at the RBD-ACE2 interface are highlighted with red beads, while the remaining are shown with blue beads.

Here, we performed all-atom simulations of the $RBD_{Omicron}$-PD in the presence of explicit water and ions (~200k atoms in total) using NAMD3.[2] Full-length glycans on RBD and ACE2 were included in simulations.[3, 4] Four sets of MD simulations totaling 900 ns in length were performed using the parameters of our previous RBD-PD simulations for the WT,[1] alpha, and beta variants.[5] Simulations revealed a more extensive interaction network between $RBD_{Omicron}$ and PD compared to RBD_{WT}. We detected seven salt bridges $RBD_{Omicron}$ and PD and the disappearance of the two salt bridges that form between RBD_{WT} and PD (Table S1). The $RBD_{Omicron}$ forms all of the ten hydrophobic interactions that were observed for RBD_{WT}-PD and forms an additional hydrophobic interaction between Y501-Y41. Compared to eight hydrogen binding between RBD_{WT} and PD, six hydrogen bonds were observed between $RBD_{Omicron}$ and PD. Only two of these interactions was also observed for the WT, while other four are newly formed. Collectively, the total number of salt bridges, hydrophobic interactions, hydrogen bonds at the S-ACE2 interface changed by 250%, 10% and -25%, respectively.

Binding free energies of two sets of RBD_{WT}-PD and four sets of $RBD_{Omicron}$-PD simulations were calculated via the Molecular Mechanics Poisson-Boltzmann Surface Area (MMPBSA) method[6, 7] using the Visual Molecular Dynamics (VMD)[8] plugin CaFE[9] (Table S2). MMPBSA calculations estimated 44% stronger binding free energy (-39 ± 6 kcal/mol, mean ± s.d., N = 4 sets) for $RBD_{Omicron}$ compared to RBD_{WT} (-27 ± 2.6 kcal/mol, N = 2 sets). In particular, an increase in the number of salt bridges in the S-ACE2 interface resulted in this higher binding strength of RBD to PD, which may result in a higher efficiency of the SARS-CoV-2 virus to infect host cells.

Simulations also revealed a change in the distribution of RBD-PD interactions due to the mutations in the Omicron variant. Between RBD_{WT} and PD, salt bridges are concentrated at the interface of contact region 1 (CR1) and CR2, while hydrogen bonding and hydrophobic interactions are concentrated in CR3 and CR1, respectively (Figure 2A).[1] In comparison, $RBD_{Omicron}$ exhibits a more dispersed interaction network on both sides of the RBD-PD interaction surface (Figure 2). This may result in an altered binding mechanism and negatively impact the current inhibition mechanism by neutralizing antibodies and nanobodies.

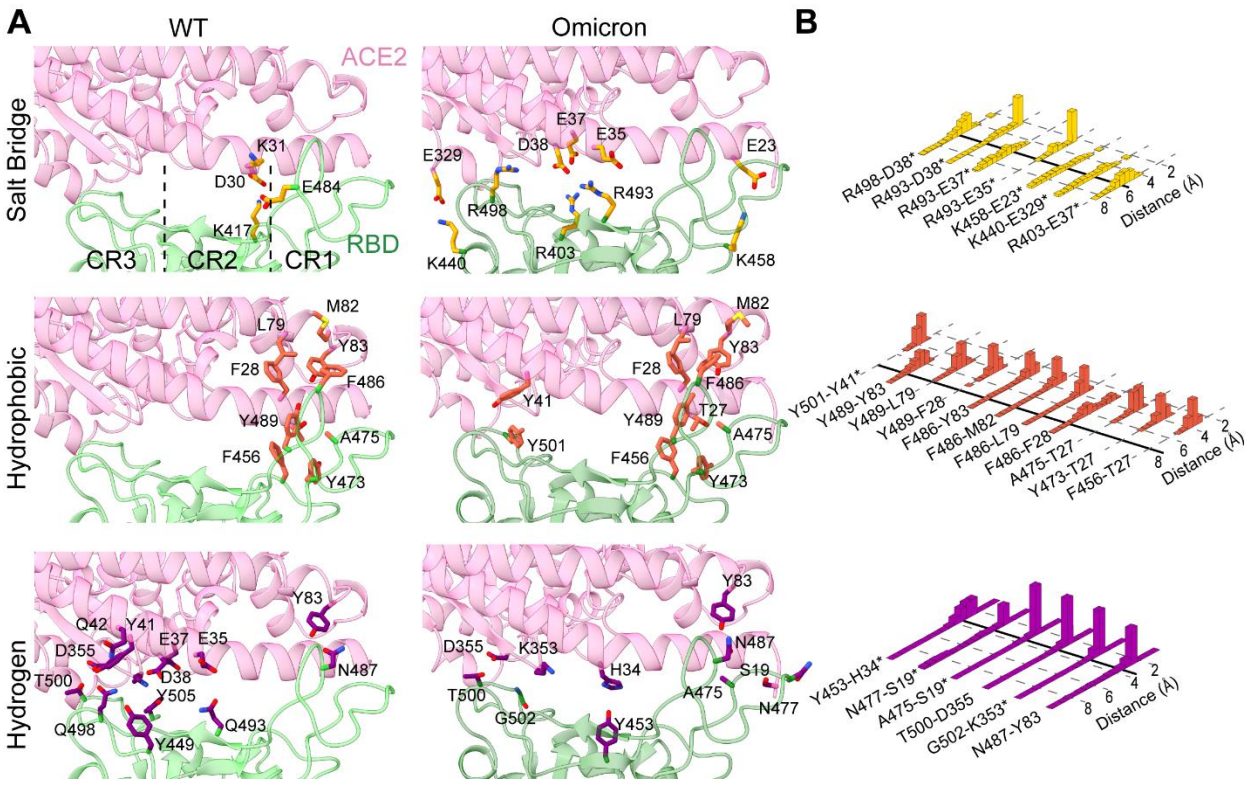

Figure 2. Interactions between RBDOmicron of the SARS-CoV-2 S protein and the PD of human ACE2. (A) Representative snapshots of the all-atom MD simulations highlight salt bridges, hydrophobic interactions, and hydrogen bonding between RBDWT-PD and RBDOmicron-PD. The interaction surface is divided into three distinct regions (CR1-3)1, 10 (B) Normalized distributions of the distances between the amino-acid pairs that form salt bridges (orange), hydrophobic interactions (red), and hydrogen bonds (purple) between RBDOmicron-PD. Newly formed interactions due to mutations are marked with an asterisk.

$RBD_{Omicron}$ mutations may also affect the binding affinity and neutralizing capability of SARS-CoV-2 S antibodies and nanobodies, such as H11-H4, H11-D4, and Ty1.[5, 11, 12] For example, we expect E484A mutation to eliminate E484-R52 salt bridge and E484-S57 hydrogen bonds in H11-H4 and H11-D4, and E484-N56, and E484-Y335 hydrogen bonds in Ty1. Additionally, Q493R mutation would eliminate the hydrogen bonds Q493-Y104 and Q493-S104 in H11-H4, and H11-D4, respectively. Neutralizing antibodies were categorized into 4 classes according to their binding regions and mechanisms.[13] Mutations introduced by the Omicron variant overlap with critical interactions for all of these antibody classes. For example, mutations are expected to eliminate salt bridge E484-R96 and hydrogen bonds E484-H35, Q493-R97, and Q493-S99 between RBD and a class 2 antibody C002 (Figure S2). Consistent with this view, point mutation Q493R mutations was reported to decrease the RBD dissociation constant of C002 from 11 nM to 596 nM.[13] Future

studies are required to determine whether mutations in $RBD_{Omicron}$ increase the resistance of the Omicron variant to these antibodies and nanobodies.

ASSOCIATED CONTENT

Supporting Information.

Supporting Information Available: MD simulations system preparation, MD simulations procedure, and binding free energy predictions via MMPBSA methodologies; Pairwise interactions of RBD_{WT} and $RBD_{Omicron}$ with ACE2; Predicted binding free energies using MMPBSA method; Antibody binding poses on RBD; Class 1-4 Antibody binding poses on RBD (PDF)

Notes

The authors declare no competing financial interests.

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