SARS-CoV-2 Omicron Variant Binds to Human Cells More Strongly than Wild Type: Evidence from Molecular Dynamics Simulation

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Abstract

The emergence of the variant of concern Omicron of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) aggravates the COVID-19 pandemic due to its very contagious ability. The high infection rate may be due to the high binding affinity of Omicron to human cells, but both experimental and computational studies have yielded conflicting results on this issue. In this work, we calculated the binding free energy of the receptor binding domain (RBD) of the WT and Omicron spike protein to human ACE2 using all-atom molecular dynamics simulation and molecular mechanics Poisson-Boltzmann surface area (MM-PBSA) method. We showed that Omicron binds to human cells more strongly than WT due to increased RBD charge, which enhances electrostatic interaction with negatively charged hACE2. N440K, T478K, E484A, Q493R and Q498R mutations in RBD have been found to play a critical role in the stability of the RBD-hACE2 complex. In addition, glycans have little effect on the binding affinity of WT RBD to hACE2.

Methodology

The structure of RBD and peptidyl domain (PD) of human ACE2 was obtained from the Protein Data Bank (PDB) with PDB id 6LZG. The Omicron variant was generated from WT RBD using the CHARMM-GUI webserver

We used 2 sets of glycans, the AMBER19SB and GLYCAM06j force fields were used.

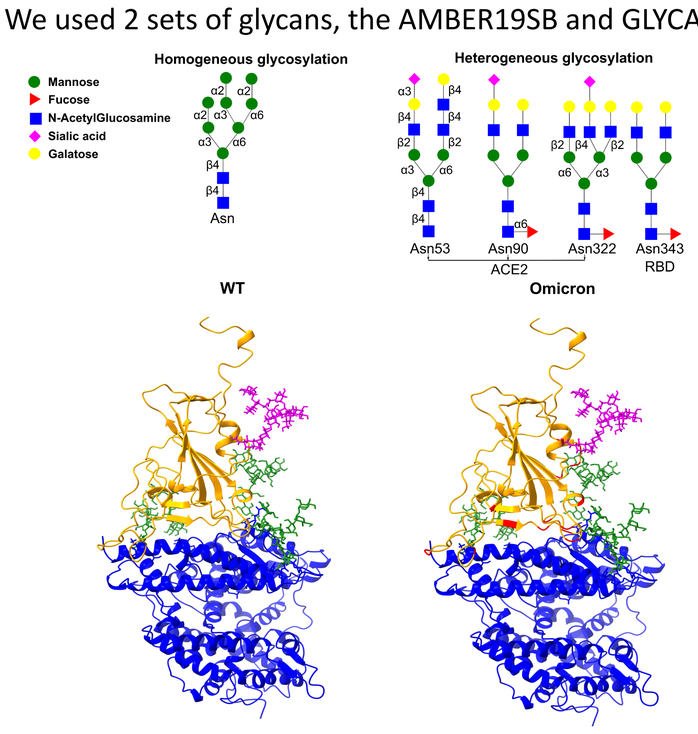
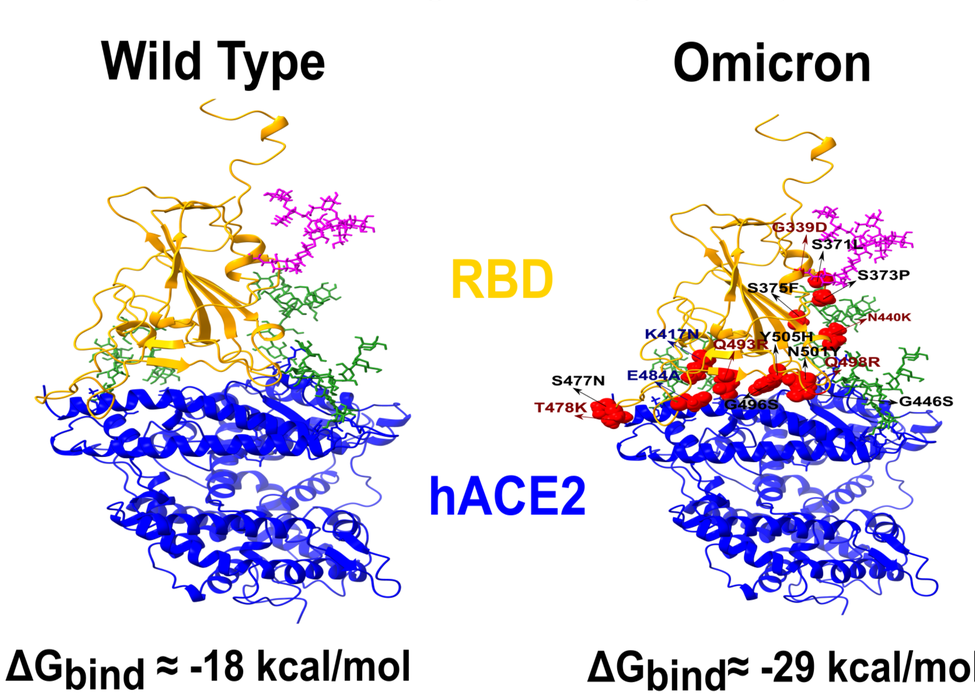


Figure 1:(Upper) Glycan models used in this work. Magenta refers to the glycan flanking RBD, while green refers to the three glycans surrounding hACE2. (Bottom) PDB structure of the WT RBD-hACE2 PD and Omicron RBD-hACE2 PD complexes. RBD is highlighted in orange, hACE2 in blue, and mutations in red

Results

Omicron variant has higher binding affinity than wild type



ΔG_{bind} ≈ -18 kcal/mol ΔG_{bind}≈ -29 kcal/mol

Figure 2: Binding energies obtained from MM-PBSA method. Glycans are in sticks
The mutations that do not change charge have a black label.
Mutations that are charged in Omicron, but neutral in WT have a maroon label.
Mutations that are charged in WT, but neutral in Omicron have a navy label.

Electrostatic interaction plays a crucial role in the stability of the RBD-PD complex

Table 1: Binding free energy (kcal/mol) of WT and Omicron variant. Results were obtained using the MM-PBSA method and snapshots of the last 100 ns from 5 MD runs. Errors are standard deviations. The last row refers to WT without glycans.

Glycan model	Variant	ΔE_{elec}	ΔE_{vdW}	ΔG_{polar}	$\Delta G_{nonpolar}$	$-T\Delta S$	ΔG_{bind}
Homo glycan model	WT	**-856.33**	-152.18	990.29	-24.27	24.18	-18.32
	Omicron	**-1645.73**	-144.86	1752.76	-23.58	31.20	**-30.21**
Hetero glycan model	WT	**-952.72**	-159.62	1086.07	-26.17	34.87	-17.57
	Omicron	**-1909.30**	-153.72	2029.94	-25.84	30.94	**-27.97**
No glycans	WT	**-778.71**	-93.71	842.50	-14.74	24.78	-19.88

Important residues in binding of viral RBD and hACE2 PD

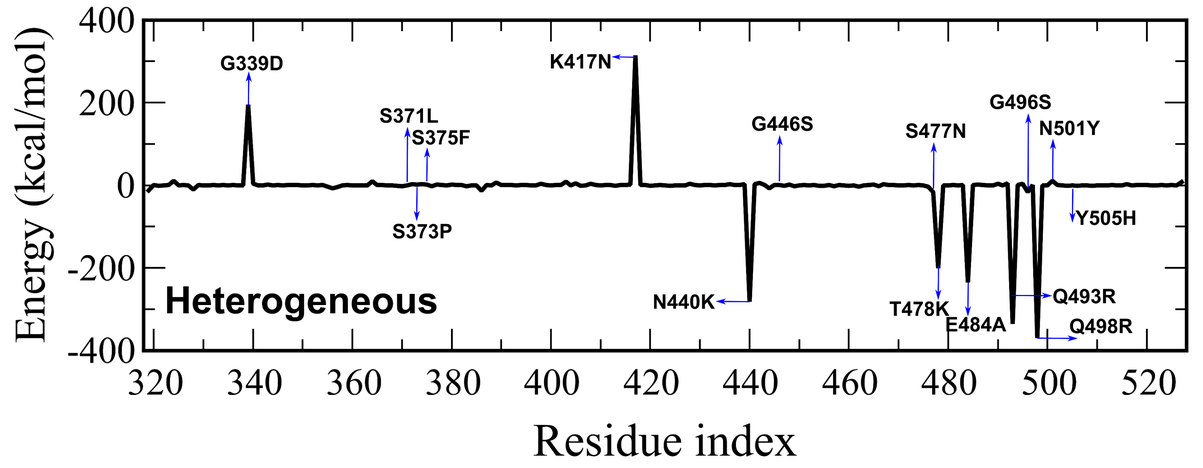


Figure 3: The difference between the interaction energies of Omicron and WT residues ($E_{Omicron} - E_{WT}$) for heterogeneous glycan models.

Residues at the RBD-hACE2 interface

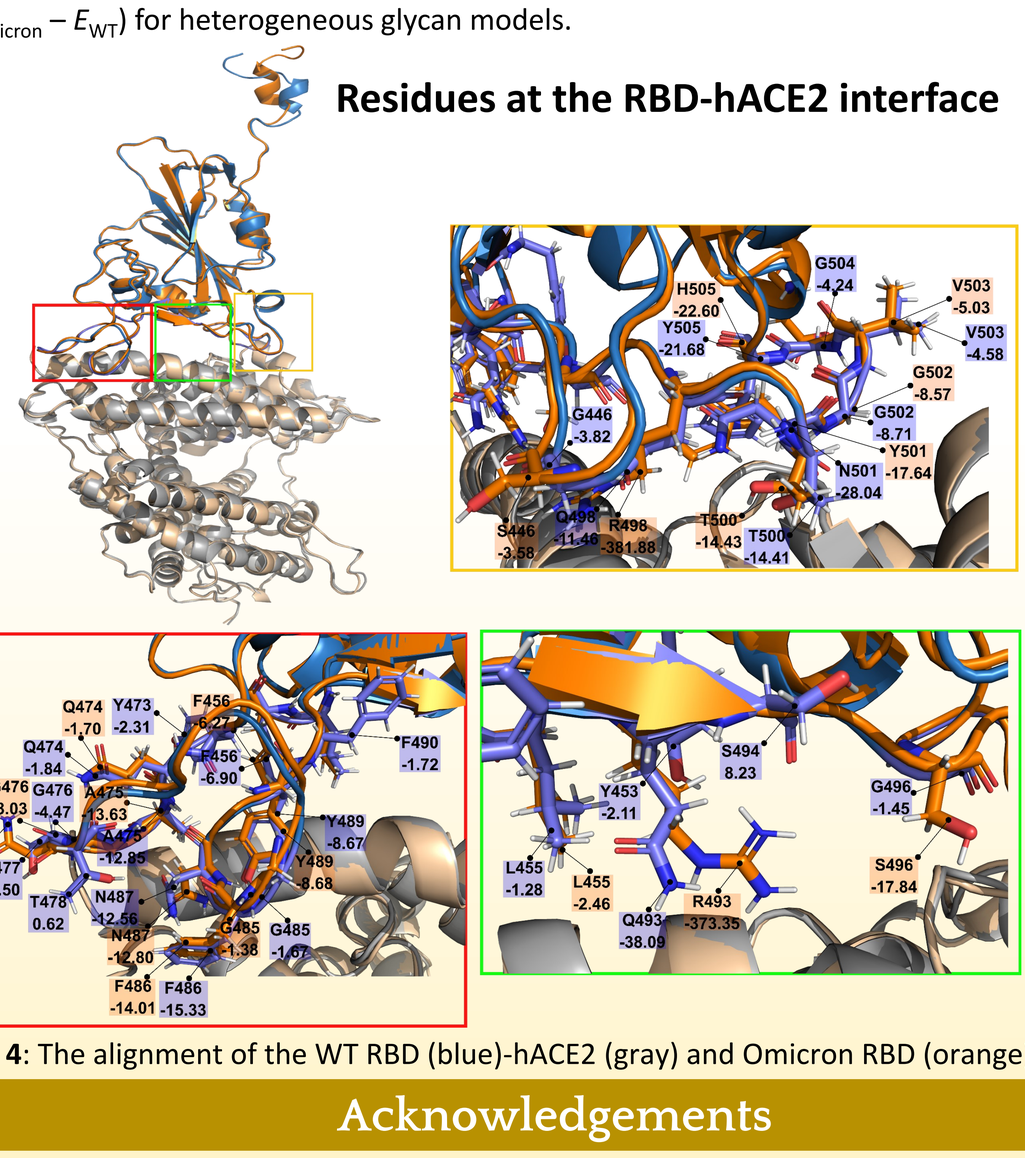


Figure 4: The alignment of the WT RBD (blue)-hACE2 (gray) and Omicron RBD (orange)-hACE2 (wheat)

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