Molecular informatics indicates better binding-energetic of Delta variant (B.1.617.2) with ACE2 than wild, D614G or N501Y CoV-2 is fully blocked by 84 amino-acid cut of wild CoV-2 spike.

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Abstract

The B.1.617.2 known as Delta-variant harbored diverse Spike-mutations. It is more transmissible than other (wild/D614G/N501Y) with developed immune-evasion mechanism. Currently, the binding-affinity of these variant spikes with human lung-ACE2 was evaluated aiming at some preventive/therapeutic strategies. Structure of spike-variants were retrieved from PDB/GISAID and used for homology-modeling (SWISS-MODEL). Different combination of spike-ACE2 binding 1:1 or competitive blind-docking was performed using Haddock2.4 web-server. After screening, two cut-segments (84 amino-acid of wild-spike, 432-516 Cut1 and Cut2, an in-silico desired-mutation T500S in Cut1) were tested (Swiss-model Expasy-server) as blocker/inhibitor of spike-variants (PyMOL-V2.2.2). Results explored the molecular-basis and energetic of Delta binding-affinity to ACE2 is far more than others. The numbers of H-bonding with their average-length, bonding-energy, Van-Der-Walls energy, Haddock-score were highly favorable for more stable-binding of Delta-RBD. The Ramachandran-plot (Zlab/UMassMed Bioinfo) data supports a post-binding stable structural-complex. The best Haddock scores of -120.8 +/- 2.6 were observed for Delta with Van-Der-Walls and electrostatic-energy of -62.9 and -208.7, respectively with highest binding-affinity (ΔG) of -10.7 kcal/mol. Its THR500 and GLN506 strongly bind with ACE2 LYS353. The Delta-ACE2 complex showed 5 H-bond (1.7Å-2.8Å) interactions. The Cut1 and its mutant T500S; Cut2 completely blocked Delta-spike binding to ACE2 with ΔG -8.4 and -10.6 kcal/mol, respectively. But during competition between 2 Cuts, Cut1 showed better results. Bioinformatics/molecular-modeling is an emerging field for screening of some drug/therapeutic targets from numerous options minimizing time and expenses. Present data unraveled the molecular-basis of higher affinity of Delta-spike to ACE2 and its therapeutic-strategies. Laboratory experimental outcome will help for further validation.

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