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Molecular Dynamics of SARS-CoV-2 Delta Variant Receptor Binding Domain in Complex with ACE2 Receptor

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Abstract

COVID19 pandemic has disrupted our lives since December 2019 causing millions of infections and deaths worldwide. After more than a year we have vaccines that are effective in preventing the disease even though we are far from finished to vaccinate most of the population. Certain countries are doing better vaccinating people while others are far behind and if that is not enough new variants have appeared that put at risk our progress on defeating COVID19. The virus SARS-CoV-2 is mutating and many mutations change the spike glycoprotein which binds to the human receptor ACE2 sometimes making the virus more infectious and able to evade immunity. One virus variant of concern (VoC) is the one called delta which is becoming prevalent very quickly among new infections. The delta variant is a real threat for many people that are not vaccinated. Here I present molecular dynamics of the receptor binding domain in complex with its receptor ACE2 to shed light on the structural interactions that make this variant more dangerous.

Keywords

SARS-CoV-2, COVID19, NAMD, VMD, molecular dynamics, UCSF Chimera, ChimeraX, structural biology, computational biology, supercomputer, Frontera, virology, delta variant, spike glycoprotein, coronavirus

Overview and background

SARS-CoV-2 delta variant was first detected in India where is suspected to have contributed significantly to the second wave that devastated the country in February 2021. The spike glycoprotein of this variant presents two mutations in the receptor binding domain (RBD) that are located in the region of interaction with ACE2 (angiotensin

converting enzyme 2) human receptor, namely L452R and T478K Di Giacomo et al. 2021 Centers for Disease Control and Prevention 2021. In this analysis, these two mutations were introduced in silico into the structure of RBD-ACE2 complex, extracted from pdb 7DF4, and molecular dynamics simulation was ran for 10 ns with NAMD (nanoscale molecular dynamics) software in Frontera supercomputer from TACC (Texas Advanced Computing Center).

The goal of the experiment was to get insights on why these two mutations may drive more infectivity and immune evasion to the delta spike glycoprotein as was reported by previous research Public Health England 2021. This delta variant is causing many disruptions in many countries like United Kingdom where lockdown measures have been extended for more weeks after an increase in infections due to this variant. It is predicted that this variant will become the main COVID19 virus in the following weeks according to the trends being seen in new patients. So far, vaccines are being reported to be effective against the delta variant but the real problem will be the infection of unvaccinated people in many areas where vaccination rates are low including many countries that are just starting to vaccinate their populations or in areas where for many reasons people are reluctant to vaccinate.

A video (Padilla-Sanchez 2021b; also available at https://youtu.be/8N_MjWwxbMQ) has been produced showing the 10 ns simulation (cf. Fig. 1). This video (total 6:39 minutes) is split in two parts where the first part (3:19 minutes) shows the complete complex and the second part shows a close up view of the delta RBD-ACE2 complex interface to appreciate the details of the protein-protein interactions (Padilla-Sanchez 2021a, Pettersen et al. 2020 , Phillips et al. 2005).

Methods

NAMD simulation in Frontera supercomputer at Texas Advanced Computing Center. The structure of RBD-ACE2 complex was extracted from pdb id 7DF4 in UCSF Chimera software (Pettersen et al. 2004). The two mutations for the delta variant were introduced in silico and the resulting structure was input in VMD (Visual Molecular Dynamics) software. NAMD was run from inside VMD where the parameters were implicit solvent, 310 K of temperature (37 Celsius) to match human body temperature for the duration of 10 nanoseconds (ns) (Humphrey et al. 1996, Phillips et al. 2005).

The resulting simulation was input into ChimeraX software for visualization and analysis.

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Funding program

Frontera supercomputer at TACC (Texas Advanced Computing Center). Project # MCB20021

Conflicts of interest

The author declares no conflicts of interest.

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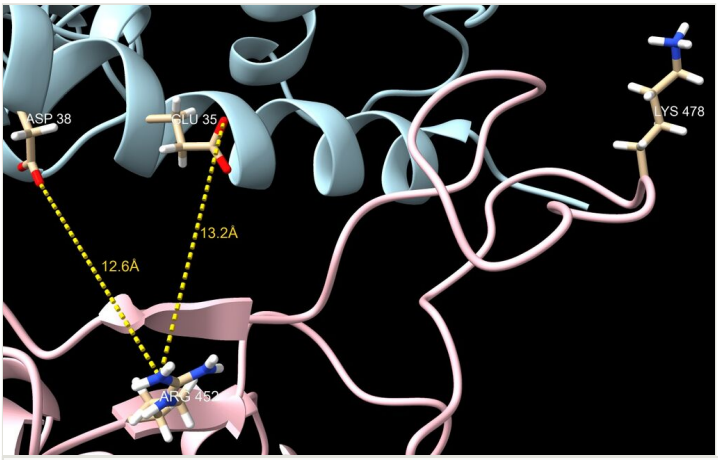

Figure 1.

Delta RBD-ACE2 complex. This is an image at 1.2 ns of MD simulation. In light blue is ACE2 structure and in pink delta RBD. Residues are labeled in white and distances are described in yellow. The distances between ARG 452 and its ACE2 negative counterparts are around 10 Angstroms which provide for attractive electrostatic interactions even though they are not very close it is enough for them to provide more attraction between the partners. Electrostatic interactions are significant within 15 Angstroms. On the other hand, LYS 478 does not interact with a negative partner within close range; therefore, it is more probable that it functions preventing antibody binding. ARG 452 can function preventing antibody binding too (Deshpande et al. 2021 Liu et al. 2021).