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Research Article

SARS-CoV-2 Structural Analysis of Receptor Binding Domain New Variants from United Kingdom and South Africa

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Abstract

SARS-CoV-2 has caused more than 80 million infections and close to 2 million deaths worldwide as of January 2021. This pandemic has caused an incredible damage to humanity being it medically and/or financially halting life as we know it. If it were not enough, the current virus is changing to a more deadly form because of the mutations that are arising on its genome. Importantly, two variants have emerged in recent months, one in United Kingdom and the other in South Africa that are more infectious and escape antibody binding. These two variants have mutations in the receptor binding domain of the spike glycoprotein namely N501Y (UK, SA), K417N (SA) and E484K (SA). Here, I present a structural analysis of spike glycoprotein bound to ACE2 (angiotensin converting enzyme 2) where the mutations have been introduced in silico showing the reason why these variants bind better to ACE2 receptors.

Keywords

SARS-CoV-2, United Kingdom, South Africa, coronavirus, variants, in silico, chimera, molecular dynamics, RBD, spike, mutations, computational biology, immunology

Introduction

New variants of SARS-CoV-2 present a particular risk of infecting humans which we are starting to see these days (Fig. 1). COVID19 infections are rising exponentially and new lockdowns are starting again since May 2020 when the pandemic was hitting hard. United Kingdom is facing more than a thousand deaths in a single day and the new variant is more transmissible than the previous virus. I have been analyzing a recently published structure of SARS-CoV-2 spike bound to ACE2 receptor (PDB 7DF4, Xu et al. 2020) and found why the new variants are more transmissible. These findings have been obtained using UCSF Chimera software and molecular dynamics simulations (NAMD and VMD) in a supercomputer Frontera from TACC (Texas Advanced Computing Center). The spike glycoproteins that protrude from the surface of the virus have a region called receptor binding domain (RBD) from amino acids 333 to 526 being the location of binding with the ACE2 receptor. There are many interactions between these two protein partners. The UK new variant has a particular mutation in the receptor binding domain N501Y and according to many reports it is more transmissible but it is not certain why. Tyrosine (Y) is an aromatic amino acid therefore this property should be the cause of this higher transmissibility. On the other hand, the South African variant has two more mutations besides the UK mutation which are K417N and E484K (Chand 2020,Suppl. material 1).

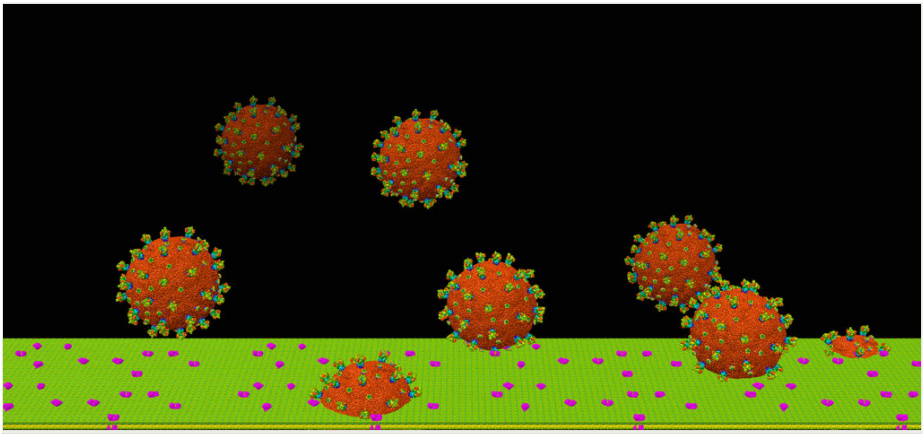

Figure 1. doi

SARS-CoV-2 viral infection at atomic resolution. Counting eight viruses, each of which has spikes (big protrusions) and E membrane proteins (small protrusions) rainbow colored and a core in sienna color, this picture shows how the viruses approach the cell membrane (green). The ACE2 receptors are colored magenta. The field of view is 1 micrometer.

The goal of this structural analysis is to give an explanation why these mutations in RBD increase transmissibility and therefore device strategies for passive immunity and vaccination that previous approaches have not accounted for.

Material and methods

Structural analysis has been performed with UCSF Chimera software, Visual Molecular Dynamics (VMD) and PyMol. Molecular Dynamics has been performed with Nanoscale Molecular Dynamics (NAMD) with default parameters and implicit solvent. Mutations have been introduced in silico in Chimera and analyzed (Humphrey et al. 1996, Pettersen et al. 2004, Phillips et al. 2020, Schrodinger LLC 2020).

Results

In the United Kingdom variant (Fig. 2), N501Y is a mutation from asparagine to tyrosine conferring one more aromatic amino acid to RBD. According to the structural analysis Y501 (RBD) interacts with Y41 (ACE2) and form aromatic-aromatic interactions. They are at a distance of 5 Angstroms while these interactions are strong within 7 Angstroms. This new interaction should be the one that confers more binding energy to the complex ACE2-RBD (spike) and causing higher transmissibility making the virus to bind stronger to cells.

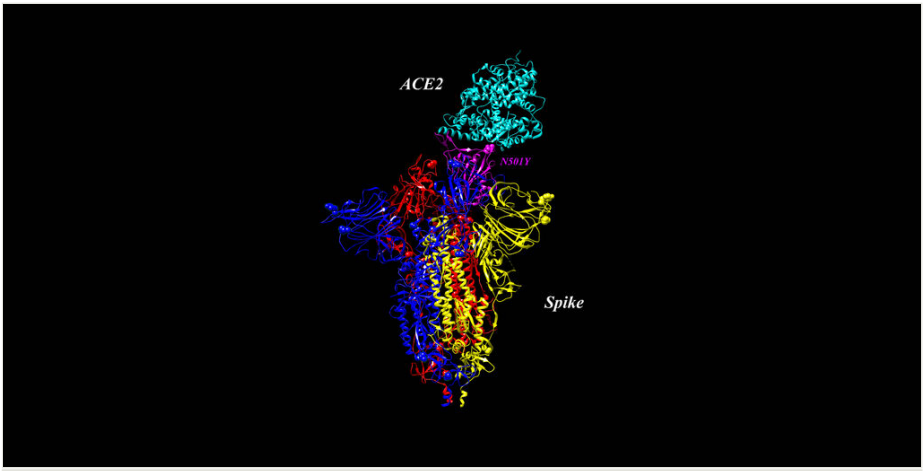

Figure 2. doi

Spike glycoprotein bound to ACE2 receptor. PDB 7DF4 (Xu et al. 2020) where ACE2 is cyan and the spike has been colored red, yellow and blue for each subunit of the trimer. This structure has been recently determined at atomic resolution. In spheres, we can see the mutations in the spike glycoprotein from the United Kingdom variant but the only mutation in the receptor binding domain (magenta) is N501Y which is labeled.

In the South African variant, besides N501Y we have K417N which provides less repulsive forces between ACE2-RBD since the wild type lysine is positive which is close to histidine (positive too) in ACE2 (H34). Changing to asparagine deletes this interaction therefore ACE2 can bind closer to the spike of the virus. Finally, E484K provides a lysine that serves as escape mutant against the immune system since interferes with the ability of antibodies to bind to this RBD region (Fig. 3).

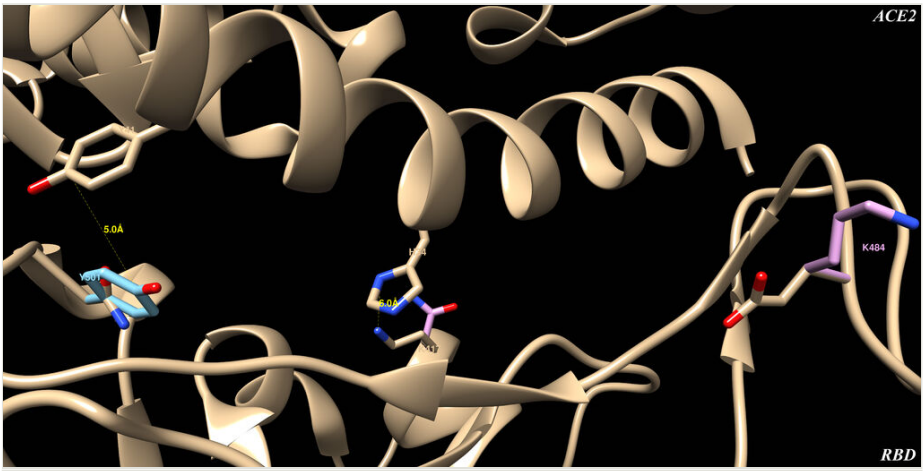

Figure 3. doi

Detail of interface between ACE2 and SARS-CoV-2 RBD. Amino acids are labeled as well as distances. For more details please see the movies in supplementary files. Wild type is beige, UK variant is light blue and SA variant is pink (Suppl. material 2, Suppl. material 3).

Discussion

The mutations in the spike glycoprotein that affect ACE2 receptor binding are N501Y for United Kingdom variant and two more, K417N and E484K for South Africa variant. The UK mutation interacts closely with Y41 in the receptor therefore producing aromatic-aromatic interactions that provide for stronger binding between receptor and spike.

On the other hand, the South Africa variant has two more mutations. K417N disrupts the repulsive forces between K417 and H34 (positive-positive) providing less repulsion between the binding partners which adds to the effect of Y501 aromatic attraction.

Finally, K484 has been recently demonstrated to be an escape mutant against the immune system since prevents binding from polyclonal human serum antibodies (Greaney et al. 2021).

These mutations are spreading rapidly and more efficiently than the previous version of the virus therefore the public health concern is very critical. Further studies are needed to quantify the binding strength of these variants compared to wild type in wet lab experiments but the distance between Y501 and Y41 is very close, even when they move (molecular dynamics). Likewise, N417 does not interact anymore with H34 since this amino acid has a shorter side chain and not positive therefore the repulsive forces are disrupted between these two amino acids (K417-H34).

Due to the public health emergency that these variants are originating I found it URGENT to publish these results as soon as possible without further testing which the future will provide.

Acknowledgements

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Supplementary materials

Suppl. material 1: RBD-ACE2 complexes doi

Authors: Dr. Victor Padilla-Sanchez, PhD
Data type: video
Brief description: RBD-ACE2 complexes. In that order from left to right: wild type, United Kingdom mutant and South Africa mutant. Shown in sticks are the residues involved in interactions namely 501, 417, 484 in RBD (bottom) and Y41 and H34 in ACE2 (top).
Download file (15.66 MB)

Suppl. material 2: RBD-ACE2 interface detail doi

Authors: Dr. Victor Padilla-Sanchez, PhD
Data type: video
Brief description: RBD-ACE2 interface detail where amino acids are labeled and distances are measured. On top is ACE2 and on bottom RBD, showing the wild type structure in beige, the UK variant in light blue and the SA variant in pink.
Download file (17.54 MB)

Suppl. material 3: United Kingdom variant interactions doi

Authors: Dr. Victor Padilla-Sanchez, PhD
Data type: video
Brief description: PyMol video of the molecular dynamics simulation ran for 6 nanoseconds with NAMD. On top is ACE2 with Y41 interacting with bottom RBD with Y501. Aromatic-aromatic interactions are strong interactions therefore this UK variant of SARS-CoV-2 binds better to ACE2 receptors infecting more efficiently the human cells.
Download file (23.94 MB)