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Brief Report

COVID-19, SARS-Cov-2 and Mutations: The Future of the Pandemic Still Demands Proteomics and Bioinformatics Evaluations -

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ABSTRACT

Since the emergence of the SARS-CoV-2 in China, the world wishes for a vaccine considered as the unique solution for this pandemic horrific situation. Currently, we have more than 70 vaccines on human clinical trials and more than five options already on the marketing including those from Oxford, Pfizer, China, and even Russia. Despite this so hopeful scenario, now a new fear lies ahead in the form of the virus accelerated mutations. In the several countries suffering from a second and even a third wave, such as Brazil, generally worse than the first one, this new challenge imposed by these mutations not only increased in even 10 times higher the virus load and the transmissibility but also threaten the immune effects of these newly launched vaccines. In this brief 2-page opinion we discuss specifically these mutations that are observed in these new strains and how bioinformatics may contribute to finding new treatments for COVID-19 besides the vaccine, as apparently we will need these new solutions in a near future.

INTRODUCTION

Since the report of SARS-CoV-2 in China, innumerous reviews and reports had documented the COVID-19 pandemic and SARS-CoV-2 features with lots of details and propositions/strategies for controlling this virus [1]. Different kind of information about this horrific human situation which is historic for the whole humanity has been reported including data involving genomic and structural results [2].

These genomic and structural data may help in obtaining a new antiviral that involves several steps, from the identification of a group of molecules that have a potential for interaction with a target, to the clinical tests in humans under controlled conditions to determine the efficacy, toxicity and side effects in the human body [3]. Through the analysis of the biological activity of these molecules in in vitro tests, preclinical tests in laboratory animals for verification from the efficacy, toxicity, and side effects of the molecules under physiological conditions, the process begins with a large number of molecules, wherein each phase, many of them are discarded for not meeting the necessary specifications. In the end, only a few molecules will present an adequate profile, and one will be elected as a potential candidate for a new antiviral [4].

In this scenario, the molecular modeling area is promising because it allows the early detection of molecules with problems and for orienting research towards molecules with greater potential especially when it comes to COVID-19 that presents new variants and currently relies only on the new vaccines and prevention habits such as the use of mask and social distance among other [5]. Molecular modeling has emerged as a set of bioinformatics tools that presents benefits to improve human health by its lower costs of time and money in the process of discovering new drugs, improving this process.

The molecular modeling techniques used in drug discovery vary, depending on the amount of structural information available about the therapeutic target (receptor/enzyme) and its ligands (agonists/substrates, antagonists/inhibitors) [4]. Thus, several analysis strategies can be used in the process of designing new drugs, including the known direct design, also called "Structure-Based Drug Design" (SBDD). This method is used when the 3D structure of the target is known, such as in HIV [6] and coronavirus (Table 1), in which the ligand-receptor complex can be analyzed.

The 3D structures of the target macromolecules can be obtained experimentally by X-ray crystallography - one of the most used techniques-or Nuclear Magnetic Resonance (NMR) - in which the limitation is related to the size of the protein - or theoretically, by homology modeling or comparative modeling. Regarding the mode of ligand-receptor interaction, complex structures determined experimentally by co-crystallization or obtained theoretically using docking techniques have been the most used methods.

Currently, three protein targets are known in SARS-CoV-2 as described in table 1, including spike protein, RNA-dependent RNA polymerase, and the Coronavírus Protease [7]. These structures that may be fully explored are available on Protein Data Bank not only for expertise's professionals but also for everyone interested in knowing more about this virus and its protein structures (Table 1).

When it comes to the new mutated strains, the spike protein is the most described as the one who suffers the highest level of mutations, involving the receptor-binding domain (Table 2 & Figure 1). These mutations increased transmissibility, susceptibility to re-infection and sometimes even the risk of death [8-11].

The brief analysis of the structure of the spike protein revealed that the regions of the mutations are conserved and involve directly the interaction with the human host cell (eg. receptor ACE2) (Figure

Table 1: Current Protein Targets/subjects of SARS-CoV-2 Variants for planning new treatments using antivirals.

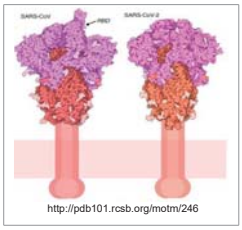
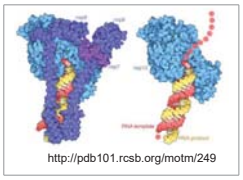
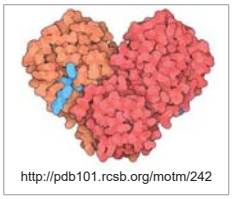
SUBJECTS/TARGETS	SOME SOURCES ABOUT THE SUBJECT
SARS-CoV-2 Variants	https://www.who.int/csr/don/31-december-2020-sars-cov2-variants/en/ https://www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/scientific-brief-emerging-variants.html
SARS-CoV-2 Spike	 http://pdb101.rcsb.org/motm/246
vSARS-CoV-2 RNA-dependent RNA Polymerase	 http://pdb101.rcsb.org/motm/249
Coronavirus Proteases	 http://pdb101.rcsb.org/motm/242

Table 2: Comparison of some emerging variants involving Spike protein*.

Features	D614G mutation	B.1.1.7 lineage (20I/501Y.V1 Variant of Concern – VOC -202012/01)	B.1.351 lineage (20H/501Y.V2)	P.1 lineage (20J/501Y.V3)
Spike protein Mutation location	Position 614	Position 501 of the receptor binding domain (RBD) Position 69/70 Position 68 close to the S1/S2 furin cleavage site.	Position 501 of the receptor binding domain (RBD) Position 484 Position 417	Position 501 of the receptor binding domain (RBD) Position 484 Position 417
Aminoacids involved	D614G -> Aspartic Acid replaced by Glycine	N501Y -> Asparagine (N) replaced by tyrosine (Y). P681H -> Proline (P) replaced by Histidine (H) 69/70 deletion leading to conformational change effect	N501Y-> Asparagine (N) replaced by tyrosine (Y). E484K – Glutamic acid (E) replaced by Lysine (K) K417N -> Lysine (K) replaced by glutamine (N)	N501Y-> Asparagine (N) replaced by tyrosine (Y). E484K – Glutamic acid (E) replaced by Lysine (K) K417T -> Lysine (K) replaced by Threonine (T)
Virus infection	increased infectivity and transmission	increased transmissibility and risk of death	It may affect neutralization by monoclonal and polyclonal antibodies.	raises the transmissibility and/or susceptibility for re-infection
Emergence location	Kingdom of Denmark (February 2020).	United Kingdom (September, 2020)	Nelson Mandela Bay, South Africa (October 2020)	Brazil (first reported by Japan in four Brazilian travelers in January 2021)

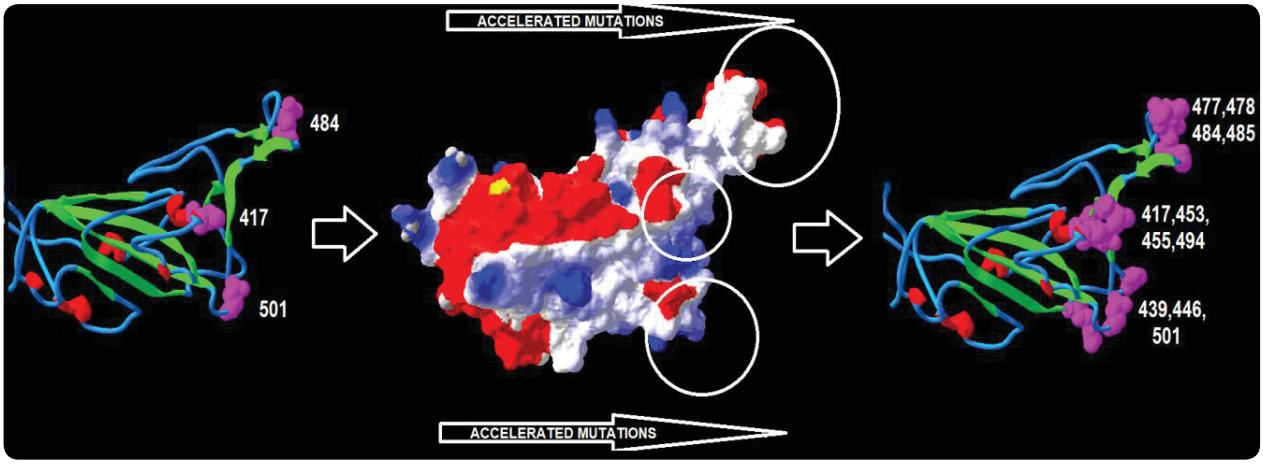


Figure 1: Comparison of the location of the most common mutations (417, 484, 501 in pink) on the spike protein (left) and the conservation of these binding locations as the number of mutation increases in these new strains (right). In the middle, the electrostatic potential map of the structure where red represents negative areas and blue, the positive ones. Figure constructed using DeepView/Swiss-PDBViewer based on the report of GISAID site and the PDB file of the receptor binding domain (6VW1.pdb).

1). The flexibility of these mutation regions is useful to the virus to target with higher affinity the receptor of the host. It is possible to observe remarkable substitutions such as an acid residue replaced by a basic aminoacid (E484K), polar ones replaced by less polar or more hydrophobic ones (D614G, N501Y, K417T/N) and even a Proline replaced by a Histidine (P681H). These replacements features indicate that this virus has a mutation profile that can worry those who understand about protein structure, immunogenicity and binding interaction mode, due to its flexibility (high changing acceptance) in these regions.

This brief analysis of the spike protein mutations inferred that other mutated strains can emerge and may seriously compromise some vaccines effects; especially those designed using the spike protein as the antigen for human immunization. This increase the importance of proteomics and bioinformatic evaluations for deeper studies that may elucidate and help on planning new vaccines and antivirals that are able to act against these new strains in a faster way and lower costs for the whole humanity [12-17].

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