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Original Article

Change in binding affinity with ACE2 receptor in beta, delta and omicron SARS CoV2 variants

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Abstract: Background: COVID-19 is still an important public health problem. After a pandemic, there is already new emerging mutant type of COVID-19. Starting from mutant with few mutations, the new mutant types with several mutations occur. Omicron variant is the new variant of concern that starts outbreak from Africa and might be the new problem worldwide. Method: Pathogenesis may change as a result of molecular changes. An important possible effect of mutation is a change in binding affinity with receptor. Here, the authors performed a study to assess the effect of mutations of ACE2 receptor binding affinity in important COVID-19 variants, beta, delta and omicron variants. Results: According to the analysis, change of binding affinity to receptor in each studied mutated variant comparing to classical wild type SARS CoV2 is observed. Conclusion: This exploratory research on changes in ACE2 receptor binding affinity revealed that changes do occur and may contribute to the pathophysiology. The omicron variation has a greater degree of alteration than the well-known significant variants, beta and delta. Rapid spread due to simpler transmission is envisaged as a result of affinity modification. Nevertheless, the authors only examined the affinity with bioinformatics analysis. It is different from experimental analysis, therefore, it may not real and further studies are required for confirmation.

Keywords: Omicron, variant, COVID-19, ACE2, receptor, binding

Introduction

COVID-19 is still a global public health problem at present. Since its first appearance in 2019, disease outbreak has been continued. The outbreak has yet to be successfully contained [1]. Even though new treatments and vaccines are being deployed, the outbreak is still out of control as of December 2021 [2]. Following the pandemic, new mutant types of COVID-19 have emerged. Starting with a few mutations, new mutant types with several mutations emerge. Beta, delta, and omicron variants of COVID-19 are examples of well-known mutant COVID-19. If a new clinically significant mutation occurs, a new troublesome variation may emerge, resulting in a new emerging disease.

A variant is a virus with one or more mutations in its genome (genetic code). Due to shared qualities and characteristics that may necessitate public health action, public health organizations may designate a set of variations with similar genetic alterations, such as a lineage or group of lineages, as a Variant of Concern (VOC) or a Variant of Interest (VOI) [3-5]. There are many important variants of SARS CoV2 that should be mentioned. The beta variant (501.V2 variant) was discovered in South Africa [6-8]. Because of the main three changes in the receptor-binding domain of the viral spike glycoprotein, the variant contains multiple mutations that allow it to connect more easily to human cells. Delta variant is another well-known problematic variant, which was firstly reported from the Indian subcontinent [9-12]. Delta variant caused outbreak worldwide in 2021 [10]. The delta variant is a well-known mutation that has been discovered in over 185 countries. It was discovered in October 2020 and has since propagated internationally as a descendant of lineage B.1.617. It spreads faster than the original version of the SARS CoV2.

In November 2021, the newest problematic variant of concern, omicron variant, is observed in Africa [12-16]. Structurally, there are several mutations within the molecule of this new variant. On November 26, 2021, the World Health Organization declared the Omicron variety, also

known as lineage B.1.1.529, a variant of concern. The variant contains a huge number of alterations, some of which are potentially harmful. In all parts of South Africa, the number of cases with the B.1.1.529 lineage is increasing. According to some research, this variation has a higher chance of reinfection [17].

The clinical effect of the mutation in omicron is still unknown. With molecular change, there might be an alteration in pathogenesis. For beta and delta variants, there are many reports on clinical effects of its internal molecular mutations. A raid spreading of omicron occurs and many countries already report increasing number of cases [14]. Regarding the effects of the variants of SARS CoV2, there might be a change in binding affinity receptor. On this subject, there is a scarcity of information. The electrostatic potential change is noted in the Indian variation as being responsible for a greater transmission rate [18]. The study on the effects of SARS CoV2 variant on the binding affinity receptor property can give an innovative insight on the pathological mechanism of the SARS CoV2 variant. In this study, the authors looked at the impact of mutations on ACE2 receptor binding affinity in three significant COVItD-19 variants: beta, delta, and omicron.

Materials and methods

Aim of the study

The present study is a medical molecular bioinformatics study. It is a study in the set of studies to clarify the impacts of molecular change in mutant SARS CoV2. The specific aim of this study is assessment of change of binding affinity for ACE2 receptor.

Bioinformatics analysis

Principle: We used a standard informatics technique, as described in a previous publication [6], for analysis of ACE2 receptor binding affinity change. According to standard protocol [6], the three-dimensional structure of SARS-CoV-2 spike glycoprotein complex with neutralizing antibody (PDB code: 6XC4 chain A), was used as the primary template [6]. A computational tool, DUET was used for predicting the impact of mutations of variant on ACE2 receptor binding affinity [19]. Basically, the binding affinity can be represented by free energy, which is associated with entropy. For measurement of changing, vibrational entropy difference (ΔΔS) is an indicator. The computational tool for measurement of ΔΔS is the standard tool, namely DynaMut [20]. Comparison between wild-type and mutant structure was done in order to derive ΔΔS. Regarding ΔΔS, a positive value indicates increased flexibility, which means increased transmissibility [18].

Type of SARS CoV2: The studied types of SARS CoV2 included wild type SARS CoV2 with no new mutation. An silico mutation assignment is performed by PyMol (PyMol, version 2.4) [21]. The studied variants were a) beta variant (K417N, E484K and N501Y assigned mutations), b) delta variant (T478K, P681R and L452R assigned mutations) and c) omicron variant (A67V, T95I, G142D, L212I, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K and L981F assigned mutations).

Clinical mathematical model: As earlier mentioned, the clinical mathematical was used for assessment of ΔΔS. After in silico assignment of mutation process had been completed, DynaMut was used for determining vibrational entropy for naïve and all mutants. The comparison between the derived value for naïve and all variants was done. The formula for calculation was "ΔΔS = vibrational entropy of variant type-vibrational entropy of naïve type". This basic equation was used as basic parameter for running DynaMut. The computational calculated results were finally provided by the tool. This modelling technique is the standard bioinformatics technique and used in a standard reference [18].

Statistical analysis

The basic statistical analysis was used in this study. A direct comparison of derived ΔΔS between variant and wild type was done. The degree of change was calculated. Simple comparison of the degree of change was further performed.

The main observation outcome in this study was the binding affinity to ACE2 receptor change due to variants of SARS CoV2 and presented in kcal/Mol. This main outcome was derived from a direct comparison as earlier mentioned.

Table 1. Binding affinity to ACE2 receptor change due to variants of SARS CoV2

SARS CoV2 type	ΔΔS (kcal/Mol)*
Wild	0**
Beta variant	0.371
Delta variant	1.473
Omicron variant	5.707

* "ΔΔS = vibrational entropy of variant type-vibrational entropy of naïve type". ** In this study, the wild type is used as a referencing type for modeling. Therefore, the ΔΔS is equal to 0 kcal/Mol.

Ethical consideration

This study is a pure bioinformatics study and does not require informed consent or ethical approval.

Results

Based on data on the present binding affinity analysis, change in each studied mutated variant occurs comparing to classical wild type. Changes of binding affinity to the ACE2 receptor due to beta, delta variant and omicron variants are presented in **Table 1**. All variants have an increasing vibrational entropy compared to the wild type. Omicron variant has the most degree of binding affinity change (with ΔΔS change equal to 5.707 kcal/Mol) following by delta variant and beta variant (1.473 and 0.371 kcal/Mol, respectively). Based on the derived ΔΔS, the predicted binding affinity between viral particle and ACE2 receptor is highest in omicron variant following by delta variant beta variant and wild type of SARS CoV2. The degree of increasing affinity compared to wild type for omicron variant is 3.87 and 15.38 times higher than those of delta variant and beta variant, respectively.

Discussion

As a newly emerging disease, understanding the pathophysiology of COVID-19 remains a critical clinical concern. When a new COVID-19 variant is discovered, there is usually some concern about its clinical implications, particularly transmissibility. Because omicron is the newest variety, it is projected to have a high transmission rate [2]. The easy transmission is thought to be due to changes inside the variant's molecule. Basically, many mutations are identified in the molecular structure of omicron variant. The mutations might result in change of molecular pathogenesis. The emergence and propagation of new SARS-CoV-2 variants have piqued researchers' interest due to their potential implications in the virus's increased transmissibility, the ramifications in the individual evolution of infection, and possibly escape from present vaccine-induced immunity [22, 23]. In this study, an important property, binding affinity to receptor is assessed. Binding affinity to receptor is an important factor for transmission of SARS CoV2. It is no doubt that the transmission of the new variant is fast [21] and it is explainable by the change of the binding affinity reaction.

Hence, assessment of change of binding affinity to ACE2 receptor is useful for better understanding of disease pathogenesis. According to this study, the significant binding affinity change is observed. The direct comparison to the wild type can provide the data on the degree of change. The degree of change of binding affinity is different in different variants. The degree of affinity change is mostly in omicron variant and is more that of delta variant. The change of binding affinity to the ACE2 receptor can imply the change in pathogenesis. As already mentioned, a positive value ΔΔS shows an increased flexibility. Based on this study, significantly increased flexibility can explain the increased transmissibility due to variant.

Basically, ACE2 receptor plays important role in COVID-19. The soluble form of ACE2 can have a significant impact on illness progression and hence could be exploited in a treatment strategy [24]. Indeed, ACE2 can regulate coagulation and inflammation by acting on [des-Arg 937]-bradykinin, which is part of the kinin-kallikrein system. Understanding the role of ACE2 in diverse pathways will be crucial in understanding the impact of SARS-CoV-2/ACE2 binding on organismal physiology and in developing new therapies and diagnostic tools. ACE2 receptor binding affinity is an important determinant for pathogenesis of SARS CoV2 variant infection. Mutations on the SARS-CoV2 spike protein might affect human ACE2 binding affinity, according to evolutionary and structural research [25]. The present study used bioinformatics to assess the change of binding affinity. The technique can help fast evaluation and it can give a primary clue for further researching.

Based on the present study, it can support the importance of SARS CoV2 variant on disease transmission. Change of affinity can further imply a change of flexibility. The most degree of change in omicron variant can call for urgent concern for management of this new emerging variant. Although there many new proposed ideas that the new omicron variant of SARS CoV2 might impact binding affinity to the ACE2 receptor, but there was no previous systematical assessment of change of binding affinity. The current study may provide new information on this topic. Degree of change is studied and a comparison among important variants of SARS CoV2 is also reported.

Indeed, high transmissibility is reported in delta variant and it is expected for similar situations in omicron variant outbreak [9-15]. For responsiveness to the new easily transmissible SARS CoV2 strain, a preventive action plan is required. Although this is a bioinformatics study, it can provide preliminary information on the pathophysiology of novel variations. In addition to this in silico study, further in vitro and in vivo studies are recommended for supporting final conclusion.

Conclusion

This preliminary study of ACE2 receptor binding affinity change showed that, change occurs and might further induce in pathogenesis. Degree of change in omicron variant is more than the well-known important variants, beta and delta variants. Here, the authors performed a study to assess the effect of mutations of ACE-2 receptor binding affinity in important COVID-19 variants including the new variant of concern, omicron variant. Based on affinity change, the rapid spreading due to easier transmission is expected.

Disclosure of conflict of interest

None.

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