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Original Article

Pattern of molecular mimicry between spike protein of SARS CoV2 and human thrombopoietin in beta, delta and omicron variants: a basic pathophysiological process of COVID-19 related thrombocytopenia

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Abstract: Thrombocytopenia is a possible problem in COVID-19. Hemorrhagic problem might be a result of thrombocytopenia in COVID-19. Due to the emergence of thrombocytopenia in COVID-19, the pathophysiology of thrombocytopenia in COVID-19 is currently a important topic in blood research. An important possible pathogenesis is the molecular mimicry. In variants of COVID-19, the change in spike might occur and the effect on molecular mimicry, which might further imply for association with thrombocytopenia. Specific study on this phenomenon can help better understand on the pathogenesis process of thrombocytopenia. In this study, the authors assessed the magnitude of molecular mimicry between the spike protein of SARS CoV2 and human thrombopoietin in wild type and important variants of COVID-19. In this work, the authors used a molecular similarity analysis to assess the impact of mutations in delta and delta plus variations. Each variant has a decreased similarity score and the omicron variant has the least similarity score. In this study, the decreased similarity score in the variant can imply decreased mimicry phenomenon. Hence, it can imply that there will be decreased COVID-19 thrombocytopenia problem in the variant.

Keywords: COVID-19, mimicry, thrombocytopenia

Introduction

Coronavirus Disease 2019 (COVID-19), the current global public health issue, has already produced a pandemic since 2020. This coronaviral infection in the lungs can lead to major respiratory problems and, in the worst-case situation, death. COVID-19 has been associated to a number of strange clinical symptoms, including hematological issues [1]. COVID-19 is linked to thrombohemostatic disease [2-5], a potentially lethal illness. COVID-19 could develop a bleeding problem, resulting in a troubling clinical appearance. The problem of coagulation can affect a variety of organs [2-5].

Since the initial appearance of classical SARS CoV2 in late 2019, scientists have been keeping a tight eye on the pathogen's genetic mutations all across the world [6]. Several pathogenic genetic mutations have been identified, and several variants have already proven to be troublesome novel variants [6, 7]. It's feasible that a genetic alteration will have an impact, leading to the emergence of a new clinical ailment. The clinical problem caused by the pathogen's genetic variation has already been recognized in COVID-19. In clinical virology, a mutation in the SARS-CoV-2 virus could emerge, and the new variant could be clinically significant. SARS CoV2 variations have been reported in a number of places.

Focusing on hemostatic disorder, the thrombocytopenia is a possible problem in COVID-19 [9]. The hemorrhagic issue in COVID-19 could be due to thrombocytopenia [10]. In a report, the incidence of thrombocytopenia in the severe COVID-19 cases was about 12.4% [11]. In blood research, the pathogenesis of thrombocytopenia in COVID-19 is still not well clarified. An important possible pathogenesis is the molecular mimicry. In a recent report, it is proven that the molecular mimicry between the

Table 1. The similarity score between spike protein of SARS CoV2 and human thrombopoietin in wild type, beta, delta and omicron variants

Type of SARS CoV2	Similarity score
Wild type	55.7%
Beta variant	55.6%
Delta variant	54.3%
Omicron variant	53.8%

spike protein of pathogen and human thrombopoietin might induce thrombocytopenia in COVID-19 [12]. A change in spike in COVID-19 variations may occur, causing an influence on molecular mimicry, which could further suggest a link to thrombocytopenia. In this study, the authors assessed the magnitude of molecular mimicry between spike protein of SARS CoV2 and human thrombopoietin in wild type and important variants of COVID-19. The authors utilized a molecular similarity analysis to evaluate the impact of mutations in SARS CoV2 variants in this study.

Materials and methods

Medical molecular bioinformatics is used for conducting the present research. It's one of a series of studies looking into the effects of molecular changes in SARS CoV2 mutants. The goal of this research is to assess the degree of similarity, which implies molecular mimicry, between the spike protein of SARS CoV2 and human thrombopoietin (GenBank: AAB33390.1).

The study spike protein sequence of SARS CoV2 included both wild type as well as variants of SARS CoV2. The primary template for sequence of the spike protein sequence of wild type SARS CoV2 is derived from PubMED database, which has NCBI Reference Sequence: YP_009724390.1. For mutant types, in silico mutation assignment by PyMol (PyMol, version 2.4) is firstly done to derive sequences. The three studied variants in this study include a) beta (with K417N, E484K, and N501Y mutations), b) delta (T478K, P681R, and L452R assigned mutations), and c) omicron (with K417N, E484K, and N501Y mutations) (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 mutations).

The conventional bioinformatics technique is used to compare the similarity of sequences. The molecular alignment between pair sequences is done. LALIGN/PLALIGN is the bioinformatics tool used in this work [13]. Basically, LALIGN/PLALIGN calculate non-intersecting local alignments of protein or DNA sequences to discover internal duplications [13]. LALIGN displays alignments and similarity [13].

The present study is not a mathematical modeling study but a sequence homology analysis. A pairwise sequence comparison is done based on comparative bioinformatic analysis using the previously mentioned bioinformatic tool. Regarding statistical analysis, the present bioinformatics comparison is based on Blocks Substitution Matrix (BLOSUM) [14]. In brief, the BLOSUM matrix is a substitution matrix used in bioinformatics for protein sequence alignment. To score alignments between evolutionarily diverse protein sequences, BLOSUM matrices are used. They are built on the basis of local alignments. The similarity score, which represents the percentage of homology between the investigated pairs sequences, is the result of BLOSUM matrices statistical analysis. The degree of homology is calculated using a simple mathematical computation based on percentages. The formula for calculation of homology score is as the following "homology score = [number of matched homologous positions in s both studied sequences of SARS CoV2 type and human thrombopoietin/overall number of positions in the template sequence of human thrombopoietin] × 100".

Since this study is a clinical bioinformatics study and does not involve any human, animal or clinical samples, it does not require informed consent or ethical approval.

Results

According to this study, the similarity score between the spike protein of SARS CoV2 and human thrombopoietin in wild type, beta, delta and omicron variants are determined and presented in **Table 1**. Each variant has a decreased similarity score and the omicron variant has the least similarity score.

Discussion

The pathophysiology of COVID-19-related thrombocytopenia has been linked to molecular mimicry [12]. In COVID-19 patients, thrombocytopenia, which is defined by a low platelet count, increases mortality. Antibodies can mistakenly attack human proteins due to molecular mimicry between pathogen and human proteins, resulting in acute or chronic autoimmune diseases [15]. In COVID-19 patients, thrombocytopenia is prevalent, and it has been linked to a roughly 5-fold increase in mortality [15]. The cytokine thrombopoietin plays role in regulating platelet production. Thrombocytopenia in COVID-19 resembles immunological thrombocytopenia, in which autoantibodies mistakenly target human thrombopoietin and/or its receptor, resulting in a decreased platelet count [12]. According to the report by Castilla et al., there is a considerable possibility for cross-reactivity between spike and thrombopoietin involving the epitope, which could disrupt platelet formation and result in thrombocytopenia [12]. The molecular mimicry is also proposed as a possible clinical problem linking to adverse effect of COVID-19 vaccine [16]. After COVID-19 vaccination, molecular mimicry may cause cross antibody reactions, and it may be a plausible underlying etiology of post-vaccination/thrombocytopenia [16].

Regarding emerging variants of SARS CoV2, the effect of molecular change on molecular mimicry pattern is an interesting research question in clinical hematology. Here, the authors can demonstrate that there is a change of the molecular mimicry pattern. For analysis, the standard bioinformatics tool is utilized, as it has been in previous papers [15]. In this study, the decreased similarity score in variant can imply decreased mimicry phenomenon. As a result, it's possible that the COVID-19 thrombocytopenia problem will be reduced in the variant of SARS CoV2. In fact, there are few reports on thrombocytopenia in new COVID-19 variants, delta and omicron. However, due to the brief history, it's probable that new variants haven't been adequately recorded for its clinical problem. As a result, more research may be required to confirm the preliminary findings of the present study.

Currently, the need for a third dose of COVID-19 vaccine has been discussed [17]. While the third dose offers the prospect of improved immunoprotection efficacy, there is growing concern about the possibility of higher antibody reaction if there is cross reactivity to human thrombopoietin. The third dosage of vaccination, as previously stated, is proposed to protect against the novel SARS CoV2 strains. Nonetheless, when compared to wild type, there is no growing homology to human thrombopoietin in the beta, delta, and omicron variants of SARS CoV2. This could mean that the problem of cross-reactivity of antibodies to viruses that cause thrombocytopenia should be less of a concern.

In fact, the effect of molecular mimicry between spike protein of SARS CoV2 and human thrombopoietina is an example of genetic variation effect. The variation in either pathogen or host can affect the final clinical phenotypic expression in COVID-19. This phenomenon is marked in some specific situations. Generally, the factors that influence COVID-19 susceptibility are interesting. Lansiaux et al. performed a study in Italy, where thalassemia is a common genetic disorder, and hypothesized that COVID-19 immunity might be reated to the incidence of beta thalassemia [18]. The aberrant globin in hemoglobin might be a major COVID-19 resistance factor [18, 19]. Similarly, in Southeast Asia, where the hemoglobin E, another genetic disorder with defect of beta chain of hemoglobin is common, resistance to COVID-19 might also be observed. As previously stated, the exact link requires more precise data on the COVID-19 incidence rate. A multitude of factors, including regional, socioeconomic, and demographic features, can influence COVID-19 occurrence. Of interest, the abnormality of thrombopoietin in hemoglobin E and hemoglobinopathy is also observed [20]. In this such complex situation, the effect of molecular mimicry versus the genetic resistance nature is an issue for further evaluation. A promising issue for future investigation is the pathophysiological link between genetic background and COVID-19.

Finally, the shortcomings of the present study should be mentioned. This research is based on a sequence homology study conducted via bioinformatics. The result is based on a computer simulation that may mirror the genuine phenomena. For the results to be approved, more research is required. In vitro research on

the biological interaction between antibodies to distinct SARS CoV2 types and human thrombopoietin can add to the evidence of the biological interaction's existence and degree, which could lead to thrombocytopenia.

Conclusion

The authors utilized a molecular similarity analysis to evaluate the impact of mutations in SARS CoV2 variants in this study. The omicron type gets the lowest similarity score of all the variants. Lesser similarity scores in the variation could imply a lower level of imitation in this study. As a result, it's probable that the COVID-19 thrombocytopenia issue in the variant of SARS CoV2 will be alleviated.

Disclosure of conflict of interest

None.

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