Molecular Therapy
Nucleic Acids
Editorial

Can the RBD mutation R346X provide an additional fitness to the "variant soup," including offspring of BQ and XBB of SARS-CoV-2 Omicron for the antibody resistance?

The COVID-19 pandemic has resulted in nearly billions of infected cases and millions of deaths. Monoclonal antibodies (mAbs), antiviral drugs, vaccines, and several non-pharmaceutical interventions have been employed to control the virus's spread and diminish the disease's harms.[1–4] However, antibody escape or resistance is a significant concern for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants, which has been reported from time to time.[5–7] Spike mutations in the variants and subvariants of SARS-CoV-2 are reported as a significant cause of antibody resistance.[8–10]

The SARS-CoV-2 Omicron variant continues to spread with higher infectivity in triple-vaccinated persons, even though vaccines and SARS-CoV-2 infections have led to many antibody-positive individuals.[11] A newly discovered point mutation in the SARS-CoV-2 virus is the spike mutation of R346X, primarily R346T, located in the spike receptor-binding domain (RBD) region (Figure 1A). The surge in SARS-CoV-2 infections is directly connected to the quick appearance of the R346T mutation, which is predominantly expressed in many Omicron subvariants. The mutation in the R346 position results in improved immunological evasion by the neutralizing antibodies.[12] A comparative study using the sera from people who already received three doses of the COVID-19 mRNA vaccine and patients infected by the BA.1 or BA.2 subvariants highlighted the property of neutralization resistance of the Omicron subvariants. Wang et al. conducted VSV-based pseudovirus neutralization assays to assess the antigenic properties of the newly emerged Omicron subvariants, namely BA.5.9, BA.4.7, and BA.4.6. They also used a panel of twenty-three mAbs to confirm the results of this neutralization assay. Compared with BA.5, BA.4.6 subvariants were marginally but considerably more resistant than BA.5 to the BA.2 breakthrough sera. Still, the BA.4.7 and BA.5.9 sublineages displayed similar binding with the ACE2 receptor and related antibody resistance compared with the BA.1 subvariant offspring. Moreover, because of the presence of R346X (T/S/I) mutation, BA.5.9, BA.4.7, and BA.4.6 displayed increased resistance to the certain class of mAbs (Figures 1B–1D).[13]

At the end of 2022, novel subvariants with improved transmissibility rates that descended from BA.2 or BA.4/BA.5 rapidly increased and created a massive surge across the globe. They have a diverse geographic distribution and possess very few extra mutations, particularly in the spike glycoprotein. For instance, BA.2.75.2, a descendant from the BA.2 subvariant, contains R346T, F486S, and D1199N mutations initially discovered in India and Singapore.[14–16] BA.4.6, which has the R346T and N658S mutations, has been found in several nations, including the USA and the UK.[17,18] BQ.1.1 started to dominate the circulating lineages in numerous countries in December 2022. It also carries the R346T mutation along with K444T and N460K substitutions, which was discovered in the BA.2.75.2.[19] The R346T mutation has been linked to antibody escape from vaccine-induced mAbs.[15,16,20] The multiple SARS-CoV-2 sublineages in circulation may have been subject to a comparable selective pressure due to imprinted or preexisting immunity, according to the convergent evolution observed in the spike protein.[20,21] Moreover, Groenheit et al. analysis demonstrated the rapid appearance of numerous R346T-expressing sublineages with a very similar or identical RBD, suggesting that the next wave of infections by the SARS-CoV-2 virus is anticipated to involve a plethora of sublineages that share a phenotype rather than by in a particular single sublineage.[22]

Numerous reports from different global sources suggest that the Omicron variant and its sublineages dominate all previously emerging variants and are responsible for most infections. Omicron's viral genome and sublineages have undergone multiple changes, which have altered the pathophysiology and transmission landscape of the virus and given it a higher level of viral fitness.[23] The diversity of the current immunity-eluding SARS-CoV-2 Omicron mutant offspring is generated as a byproduct of the different combinations of mutations, especially in the spike protein region. This intricacy makes it more challenging to anticipate the upcoming waves of infection. In some instances, it might even result in a "double wave," where one variety initially engulfs a population before being replaced by another. Scientists refer to it as a "variant soup" or "a swarm of variants."[24] According to the reports of Cao et al., it is evident that the emerging Omicron offspring possesses this R346T mutation in the RBD region of spike protein.[12] Generally, the three notable amino acid substitutions at the R346 position of the spike RBD are R346K, R346T, and R346I. Most of the offspring descended from the Omicron sublineages, including BJ.1, BR.3, and BA.2.75.5, show a strong predominance of R346T. Arora et al. sought to determine the impact of the R346T mutation and concluded that this mutation offers BA.4 and BA.5 subvariants of Omicron a significant neutralizing evasion potential.[25]

Due to the new mutations in spike protein, the XBB and BQ subvariants of SARS-CoV-2 Omicron are rapidly increasing, which may be related to altered antibody evasion capabilities.[8] In the middle of August 2022, XBB and XBB.1 were discovered for the first time in

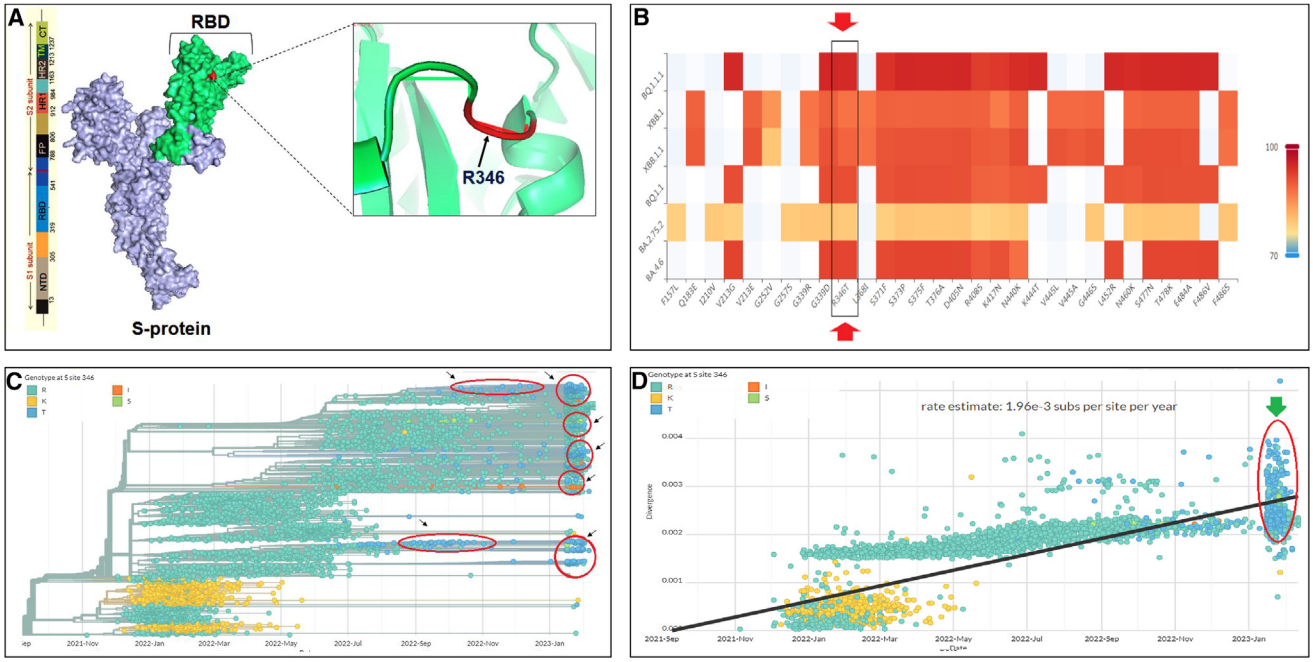

Figure 1. Location and occurrence of R346X RBD mutation

(A) The position of R346X in the spike protein. (B) The heatmap-like representation shows the occurrence of R346T mutation in the different subvariants of Omicron (BQ.1.1.1, XBB.1, XBB.1.1, BQ.1.1, BA.2.75.2, and BA.4.6). (C) The phylogenetic tree of the genotype of the spike of R346 shows that R346 is changing in recent genome sequences, especially in the last part of 2022 onward, and it is converting into T346. The genotype change of the T346 has been marked in the figure. (D) The figure depicts the divergence of the current genotype of 346 positions of spike (S) protein with a linear regression line. The divergence also illustrates the mutation in the position of R346 in present genome sequences and the conversion into T346. A cluster of RBD mutation R346T is found in the upper portion of the regression line. The cluster of R346T has been marked in the figure.

India, and they swiftly spread to Singapore and other parts of Asia. BA.5 rose to BQ.1 and BQ.1.1, whereas BJ.1 and BA.2.75, two lineages of BA.2, recombined to produce XBB and XBB.1. These two sublineages are still evolving and diversifying, and the complexity of the spike mutations is getting more and more intricate. The N460K and K444T mutations are present in the spike protein of the dominant BQ.1 subvariant in addition to those identified in BA.5, and the BQ.1.1 possesses a different mutation, namely R346T (Figure 1B).[8] According to Miller et al., BQ.1.1 and XBB.1 subvariants containing the R346T mutation potently escaped the neutralization efficacy elicited by the monovalent mRNA boosting and bivalent mRNA boosting more significantly than the BA.5 variant. In the monovalent booster cohort and the bivalent booster cohort, the neutralizing antibody titers to BQ.1.1 and XBB.1 were noticeably lower than the titers of the earlier Wuhan strain.[19] These findings imply that the protection from vaccines against severe diseases caused by the BQ.1.1 and XBB.1 subvariants may depend on CD8 T cell responses and that the BQ.1.1 and XBB.1 polymorphisms may impair the efficiency of current mRNA vaccines.[26] The elevation in the antibody titers against the Omicron variants in the 2022 cohort compared with the 2021 cohort following the monovalent mRNA boosting likely reflects the administration of larger doses of the vaccine and more prevalence of infection in the 2022 cohort. Thus, evolution is suggested by including the R346T mutation in numerous subsequent SARS-CoV-2 variants (Figure 1).[19]

The incidence of the Omicron subvariants' new descendants is very alarming for the scientific community due to its enhanced resistance against neutralizing antibodies. One of the recent RBD mutations that notably provide the additional fitness to these emerging variants is R346X. The predesigned antibodies or therapeutics may loosen their efficacy if this mutation prevails in the upcoming variants. Thus, the need to design and develop new antibodies or therapeutics considering the RBD R346X mutation, which will provide the capability to combat the infection wave in the coming days, is essential. It, in turn, will be a potent weapon to eradicate the COVID-19 pandemic.

DATA AVAILABILITY

The authors confirm that the data supporting the findings of this study are available within the article.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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