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SARS-CoV-2 variants, immune escape, COVID-19 vaccine, and therapeutic strategies

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The global pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has brought considerable challenges to worldwide public health and the economy. Over 535 million confirmed cases and 6.3 million deaths of COVID-19 were reported as of June 17, 2022 (https://covid19.who.int/). Unfortunately, these numbers rapidly increase with the continuous mutations of SARS-CoV-2 variants, especially those viruses of concern (VOCs) (Alpha or B.1.1.7, Beta or B.1.351, Gamma or P.1, Delta or B.1.617.2, and Omicron or B.1.1.529). Understanding the mutational patterns of VOCs contributes to explaining their increased transmissibility and potential immune evasion. Effective responses to SARS-CoV-2 variant evolution and VOC infection have received intensive attention worldwide.

Spike protein mutations of SARS-CoV-2 variants. The structural gene in SARS-CoV-2 genome encodes four structural proteins consisting of the spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins. N protein protects the genome of SARS-CoV-2 by encapsulating viral genomic RNAs. Antiviral RNA interference immunity of N protein also contributes to the pathogenicity of SARS-CoV-2 (Mu et al., 2020). S glycoprotein is a homo-trimeric complex composed of two functional subunits (S1 and S2), which enable virion binding and viral fusion to target cells. SARS-CoV-2 infects host cells *via* specific recognition of the receptor-binding domain (RBD) in the S protein to human angiotensin-converting enzyme 2 (ACE2) receptor on host cells (Lazarevic et al., 2021). Like other RNA viruses, SARS-CoV-2 possesses a high mutation rate, constantly mutating as transmission continues. The accuracy of ancestral inferences and derived mutations of SARS-CoV-2 strains could be evaluated by molecular evolution simulation (Li et al., 2020). The mutation frequencies of S and N genes are significantly higher than the other two structural protein genes. Currently, most attention is focused on S gene mutations, an essential component for mediating invasion and the ideal target for immune response.

A variant becomes more common as long as its selective advantage persists. Five VOCs have been identified by the World Health Organization (WHO) that feature higher transmissibility, less efficacy in treatment, and immune escape. Among them, four variants (B.1.1.7, B.1.351, P.1 , and B.1.617.2 variants) have been listed as previously circulating VOCs, whereas B.1.1.529 variant is currently circulating globally. B.1.1.7 variant harbors two deletions and seven amino acid substitutions in the S protein (Figure 1). The only receptor-binding motif (RBM) mutation, N501Y, may increase the affinity of S protein to human ACE2 receptor *via* π-π stacking or hydrogen bonding (Xia et al., 2021; Zhu et al., 2021). P681H makes the amino acid string more basic and favors furin (a host enzyme that can cut S protein at a site of five amino acids) cleavage (Scudellari, 2021). D614G makes RBD shift prone to the up position, which benefits

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RBD binding to ACE2. These mutations make B.1.1.7 variant more infectious and transmissible than ancestral SARS-CoV-2 strains. B.1.351 variant, has seven mutations and three deletions in the S protein (Figure 1). Three mutations (K417N, E484K, and N501Y) located in RBD region also increase the binding to human cells, favoring transmission. P.1 variant owns twelve S protein mutations (Figure 1). Some mutations are shared with the B.1.1.7 and B.1.351 variants (N501Y), while others are shared only by the B.1.351 lineage (K417T, E484K), which are responsible for viral transmission and immune escape as well as reinfection rates. B.1.617.2 variant, has resulted in a secondary wave of COVID-19 infections in India. Ten mutations exist on the S protein (Figure 1). RBD mutations L452R and T478K increase ACE2 binding and stabilize RBD-ACE2 complex. Like the P681H mutation in the B.1.1.7 variant, the initial proline amino acid replaced by an arginine (P681R) makes the sequence less acidic, facilitating the recognition and cleavage of furin to S spike and viral transmission (Scudellari, 2021). Guangdong Provincial Center for Disease Control and Prevention in China showed that viral loads in B.1.617.2 variant infections are ~1,000 times higher than 19A/B lineage infections, emphasizing faster viral replication and greater virulence of B.1.617.2 variant during early infection (Li et al., 2022). B.1.1.529 variant, harbors up to 36 mutations in the S protein, including 15 within the RBD region. Some mutations (K417N, N501Y, D614G, and P681H) have been found in other VOCs and are associated with increased infectivity and the ability to evade immunological surveillance (Figure 1). An artificial intelligence model showed that the B.1.1.529 variant might be ten times more contagious than the wild-type SARS-CoV-2 and nearly 2.8 times more contagious than B.1.617.2 variant, mainly ascribed to its mutations N440K, T478K, and N501Y (Chen et al., 2022).

The variations in S gene pose high risks of increased transmissibility and greater virulence, even the escape of current antibody-mediated immunity. Consequently, optimal testing frequency and speed of reporting for full population screening should be offered.

Immune escape in VOCs. SARS-CoV-2-induced humoral immune response is mainly mediated by antibodies specific to S protein. These specific antibodies neutralize the binding of virus to ACE2 receptors and reduce the infection rate. The variants with novel spike epitopes can impact antibody binding and neutralization. Five VOCs can reduce or ablate the neutralizing activity of convalescent plasma and the sera of vaccinees to a varying degree. The global rapid spread of SARS-CoV-2 variants is associated with escaping from N-terminal domain (NTD)-specific and RBD-specific antibodies targeting the S protein.

The exact location of mutated amino acids in the S protein explains the effect of each substitution. RBM mutation N501Y results from viral adaptive evolution and is shared by four SARS-CoV-2 VOCs (B.1.1.7, B.1.351, P.1, and B.1.1.529). The modified light-chain contacts with residue 501 make the B.1.1.7 variant less sensitive to public antibodies, whereas N501Y alone, rather than coupling other RBD mutations, does not impair the neutralization of the B.1.351 variant.

In RBD, three mutation sites (K417N/T, E484K, and N501Y) are mainly the same in B.1.351 and P.1 variants. B.1.351 variant has aroused much concern for immune escape. K417N is a vital mutation for viral escape, effectively obstructing the neutralization of many antibodies. K417N combined with N501Y can increase the affinity of S protein to ACE2 (Planas et al., 2021). E484K is located in RBD binding cleft and acts as a dominant neutralizing epitope and may increase the binding affinity of N501Y to ACE2 and elicit immune escape by significantly augmenting other RBD mutations. The loss in neutralization levels of B.1.351 variant was 11- to 33-fold for convalescent sera and 3.5- to 8.5-fold for vaccinees' plasma (Lazarevic et al., 2021). Unsurprisingly, a significant loss of monoclonal antibodies (mAbs) neutralization of P.1 is similar to B.1.351 due to the semblable RBD mutations.

The immune escape from B.1.617.2 is impacted mainly by RBD mutants L452R and T478K and the synergy of NTD amino acid substitutions and deletions. The RBM mutant L452R reinforces spike stability and viral replication and exhibits modestly reduced sensitivity toward BNT162b2 mRNA vaccine-elicited antibodies (Motozono et al., 2021). Notably, L452R was reported to escape HLA-A24-restricted cellular immunity, indicating a threat of escape from cellular immunity during the COVID-19 pandemic (Motozono et al., 2021). As for B.1.1.529 variant, considerable humoral immune evasions are suggested from the significantly decreased neutralizing capacity of broadly human anti-SARS-CoV-2 antibodies to B.1.1.529 variant (Cao et al., 2022). K417N, G446S, E484A, and Q493R mainly impair neutralizing antibodies with epitope groups overlapping ACE2-binding motif (Cao et al., 2022). Also, pre-existing immunization may not occur of the B.1.1.529 variant for the steric interference created from G446S, Q493R, and G496S, and the loss of interactions resulting from E484A and Y505H.

Heavily glycosylated S trimers also affect the virus sensitivity to neutralizing antibodies through many glycosylation site modifications. For example, N165Q and N709Q mutations can increase sensitivity to neutralizing mAbs, but N234Q, L452R, A475V, and V483A mutations significantly decrease the sensitivity (Li et al., 2020). Other mutations such as N149H, N1173Q, and N331Q show enhanced reactivity to human convalescent sera (Gstöttner et al., 2021; Li et al., 2020).

Therefore, a comprehension of the immunogenicity of

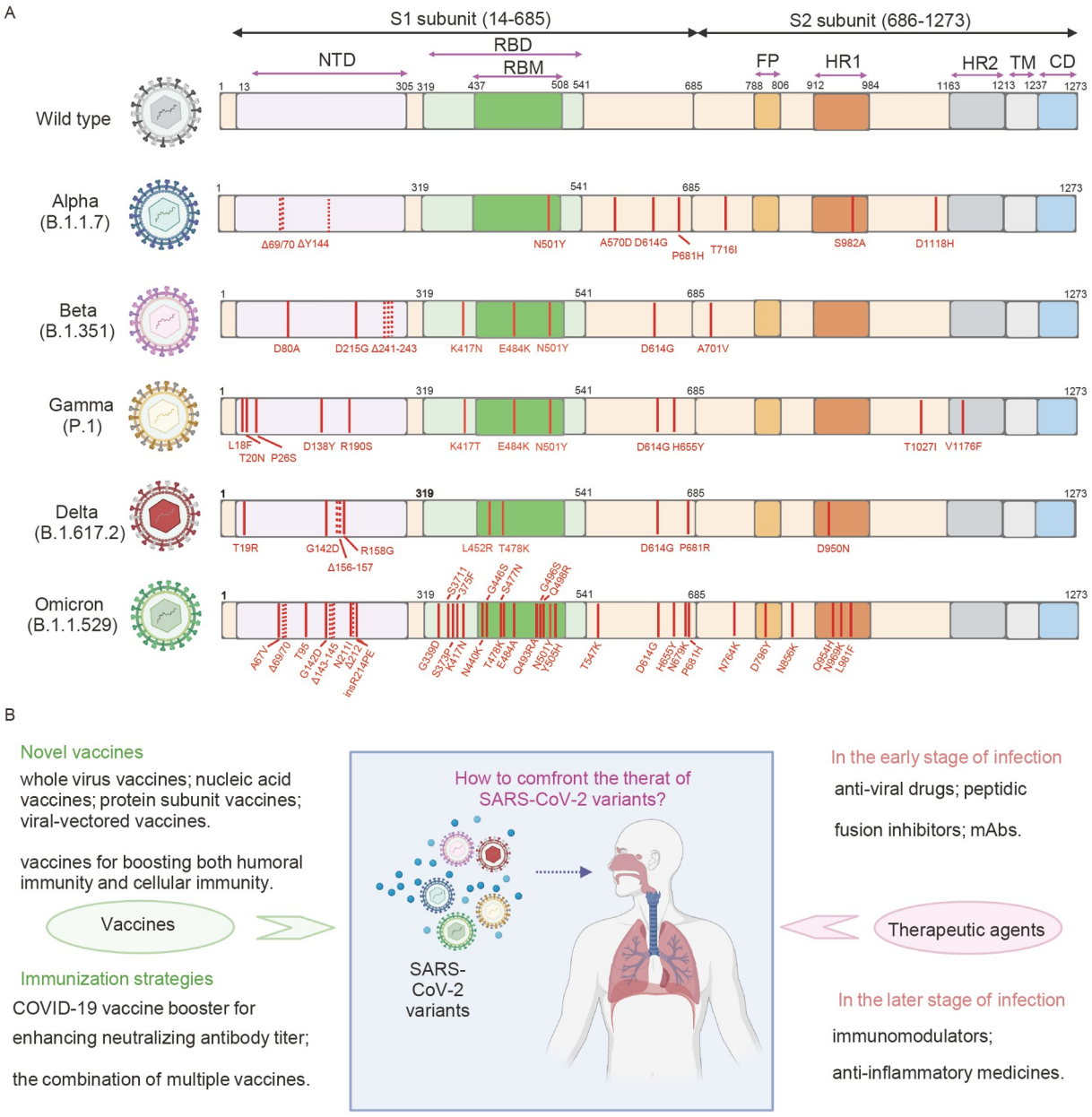

Figure 1 Mutation patterns of five VOCs and the responses to SARS-CoV-2 variants. A, The composition of S protein and the key mutations in S protein. B, Strategies to confront SARS-CoV-2 variants. Δ represents the deletions in the S protein. FP, fusion peptide; HR1, heptapeptide; HR2, heptapeptide domain 2; TM, transmembrane domain; CD, cytoplasmic domain. The mutation sites and structure information of S trimers are based on the data from CoVariants at https://covariants.org/variants.

modified S domain contributes to our understanding of immunity against SARS-CoV-2 variants. For delivering reliable protection against emerging variants, adjusted vaccination approaches, and modified vaccines, are suggested to maintain high neutralization titers.

Confronting the threat of SARS-CoV-2 variants-*Vaccines*. The groundbreaking COVID-19 vaccines are based on scientific advancements of classic vaccines and multiple immunization strategies to meet the challenges associated with various SARS-CoV-2 variants (Figure 1). Currently, 36 vaccines have been approved by at least one country or under an emergency use authorization (EUA) (Table S1 in Supporting Information).

Great efforts are dedicated to developing multiple vaccine candidates, including whole virus vaccines, nucleic acid vaccines, protein subunit vaccines, and viral-vectored vaccines based on innovative technologies to stay ahead of emerging variants. Promising immune strategies to combat the variants can be achieved by tweaking the sequence of mRNA vaccines to include new mutations and developing multivalent vaccines based on different types of vaccines. Moderna developed mRNA-1273.351, delivering instruc-

tions for producing SARS-CoV-2 spike with critical mutations in B.1.351 virus variant. GSK collaborated with CureVac to research and develop mRNA multivalent vaccine candidates, aiming to provide broader protection against SARS-CoV-2 variants and enable a rapid response to diverse variants potentially emerging in the future. Although neutralizing antibodies are undoubtedly considered a pivotal indicator of an intensively protective vaccine, the elicitation of specific cellular immunity could synergize antibody-based protection (Nathan et al., 2021). The immunoinformatics pipeline targeting the spike protein of SARS-CoV-2 is leveraged to design immunogenic epitopes (cytotoxic T cell, helper T cell, and B cell) vaccines against emerging variants. Further investigations of SARS-CoV-2 in cell-mediated immunity and its role in selecting viral variants are ongoing.

Aside from focusing on developing and improving vaccines, adjusting immunization strategies is critical to combat the variants. The vaccines produced by Pfizer-BioNTech and Moderna were given as a third booster to previously vaccinated individuals to continuously induce potent immune responses. The combination of different types of vaccines (viral vector vaccine combined with mRNA vaccine as a booster) exhibits a robust immune response; thus, a mix-and-match COVID-19 vaccine is one of the most effective strategies against the ongoing pandemic. Although most vaccine candidates require intramuscular injection, mucosal and subcutaneous vaccines have also drawn attention to strengthening the immune response. Intranasal administration of adenovirus vector-based booster vaccine following prime immunization with a nucleic acid-based vaccine elicits potent mucosal antibodies, systemic antibodies, and T cell responses, leading to favorable neutralization of B.1.1.7, B.1.351, and P1 variants. In addition, the subcutaneous vaccine offers expanded possibilities for efficient, feasible delivery across the globe (Rice et al., 2021).

Confronting the threat of SARS-CoV-2 variants-*Therapeutic agents*. Antiviral drugs, peptidic fusion inhibitors, and mAbs mainly act on viral replication in the early stage of infection, whereas immunomodulators and anti-inflammatory medicines primarily work in the inflammatory phase in the later stage of infection (Figure 1). Currently, various therapeutic agents are available under EUA to treat COVID-19 (Table S2 in Supporting Information).

Data from *in vivo* and *in vitro* studies indicate that classic antiviral drugs such as remdesivir, hydroxychloroquine, chloroquine, lopinavir-ritonavir, and ivermectin show less significant benefit against SARS-CoV-2 and its variants, and there are currently no specific antiviral drugs for the virus. Intriguingly, orally bioavailable antiviral drugs, including molnupiravir, fluvoxamine, and Paxlovid, effectively reduce the mortality and hospitalization rates of COVID-19 patients, demonstrating great clinical prospects (Wen et al., 2022). Besides, the conserved HR1 region is considered a key target for developing broad-spectrum viral fusion inhibitors for inhibiting 6-HB formation and blocking fusion (Jiang et al., 2021). Currently, three anti-SARS-CoV-2 mAbs products, including bamlanivimab plus etesevimab, casirivimab plus imdevimab, and sotrovimab, are in use with EUAs. However, cell-culture-based analysis of neutralizing mAb activity against the Omicron variant demonstrates that several available therapeutic antibodies would be less beneficial (VanBlargan et al., 2022). Genome monitoring based on the types and proportions of circulating SARS-CoV-2 variants and studies on the sensitivity of various mutations to existing anti-SARS-CoV-2 mAbs will be of great significance for determining the use of specific mAbs in the future.

Immunomodulatory agents such as corticosteroids, IFN-β-1a, IL-1 antagonists, IL-6 receptor inhibitors, JAK inhibitors, and Bruton's tyrosine kinase inhibitors have been evolved to treat COVID-19. Notably, dexamethasone is currently considered the standard of care either alone or in combination with remdesivir in critically ill patients. Besides, non-steroidal anti-inflammatory drugs are remedies extensively used to alleviate fever, pain, and inflammation in COVID-19 patients by effectively blocking prostaglandins production by suppressing cyclooxygenase enzymes. Unfortunately, SARS-CoV-2 will persistently evolve as ever-greater immunity spreads through the human population, even though ever-greater immunity is reached in humans. Therefore, a thorough evaluation of these potent or potential therapies against new variants must be conducted before clinical use to ensure effective therapeutic effects and safety.

In summary, it seems impossible to restrict the continuous mutation of SARS-CoV-2 in the context of error-prone replication and selective pressure. Efficient spread rather than damage to the host is more relevant to most mutations. Well-coordinated real-time monitoring of emerging novel SARS-CoV-2 variants is required. Specific broadly neutralizing antibodies to restrict SARS-CoV-2 variants is recommended, but developing a universal coronavirus vaccine remains a huge challenge. Accordingly, worldwide efforts to evaluate the effectiveness of vaccines against SARS-CoV-2 variants and prevent COVID-19 super spreader events are of great importance in confronting the threat from evolving viral variants.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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SUPPORTING INFORMATION

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