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Review

Emerging SARS-CoV-2 variants: Why, how, and what's next?

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ABSTRACT

The emergence of the SARS-CoV-2 Omicron variant poses a striking threat to human society. More than 30 mutations in the Spike protein of the Omicron variant severely compromised the protective immunity elicited by either vaccination or prior infection. The persistent viral evolutionary trajectory generates Omicron-associated lineages, such as BA.1 and BA.2. Moreover, the virus recombination upon Delta and Omicron co-infections has been reported lately, although the impact remains to be assessed. This minireview summarizes the characteristics, evolution and mutation control, and immune evasion mechanisms of SARS-CoV-2 variants, which will be helpful for the in-depth understanding of the SARS-CoV-2 variants and policy-making related to COVID-19 pandemic control.

1. Introduction

Since the outbreak of COVID-19 in December 2019, 504 million cumulative cases and 6.2 million deaths have been reported globally (https://covid19.who.int/). The etiological pathogen causing the pandemic is a novel human coronavirus, named SARS-CoV-2 (also known as 2019-nCoV), which uses angiotensin converting enzyme 2 (ACE2) as a receptor to invade host cells (Chen et al., 2020a; Zhou et al., 2020). The origin of SARS-CoV-2 remains unclear, but bats are suspected to be its natural host due to the high sequence similarity between SARS-CoV-2 and some other SARS-related bat coronaviruses (Chen et al., 2020a; Zhou et al., 2020; Lu et al., 2020a; Wu et al., 2020). Several bat ACE2 orthologs can support the entry of SARS-CoV-2. Yet, there is still no direct evidence showing an initial SARS-CoV-2 spillover from bats to humans or other animals that can be served as intermediate hosts (Yan et al., 2021a; Liu et al., 2021a; Wrobel et al., 2020).

During the COVID-19 pandemic, the sequence of SARS-CoV-2 is constantly changing over time. The mutations change various viral features such as transmissibility, disease severity, drug resistance, and antigenicity. SARS-CoV-2 variants are defined by diffident lineages based on the sequences of the Spike protein, and the Pango nomenclature is the most commonly used (Rambaut et al., 2020). However, mutations also occur in regions beyond spike proteins and contribute to the variants' distinct features. The World Health Organization (WHO) is collaborating with researchers around the world to assess the increasing risk of SARS-CoV-2 variants and announces the specific variants of interest (VOIs) and variants of concern (VOCs) to fight against the pandemic. To date, there have been five VOCs, including Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.529). The Delta variant was once the dominant lineage, while the Omicron variant, which carries more than 30 mutations in the Spike protein, has taken over its place for months. Moreover, Omicron-associated lineages, such as BA.1, BA.1.1, and BA.2, BA.3 and XE (BA.1 and BA.2 recombinant), are still emerging. New variants such as the Deltacron originated from the recombination in the Delta and Omicron coinfected patients, although its risk has not been fully assessed. (Bolze et al., 2022; Colson et al., 2022). Recently, the outbreak by the Omicron variant has created great pressure on China's dynamic zero COVID-19 strategy, especially the latest wave of Omicron BA.2 infection in Shanghai. Most likely, the Omicron will not be the last variant of concern. Systematical and continuous study of the features of SARS-CoV-2 variants and the mutation mechanisms are necessary to minimize their damage to humans.

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2. Why do SARS-CoV-2 variants constantly emerge?

2.1. The high mutation rate of RNA viruses

All viruses change their genomic sequences over time, especially RNA viruses with lower replication fidelity. The misinsertion rate during RNA synthesis is between 10^{-3} and 10^{-5} substitutions per nucleotide and per round of duplication, much higher than that for DNA viruses (10^{-5} to 10^{-8}) (Domingo and Holland, 1997; Duffy, 2018; Domingo, 2000; Duffy et al., 2008; Gago et al., 2009). Although the low replication fidelity is associated with an increased chance of error catastrophe leading to viral extinction, it also contributes to the viral adaption under different selective pressures (Robson et al., 2020). SARS-CoV-2, as an RNA virus, has been changing its sequences from the very beginning of the COVID-19 outbreak. As shown in Fig. 1, mutations have been identified throughout the genome of VOCs, and the mutations tend to cluster on the structural proteins, especially the Spike protein. However, previous studies on coronaviruses showed that the mutations occur without sequence specificity (Smith et al., 2013; Denison et al., 2011). A reasonable explanation is that the mutations found in VOCs were retained mutations that do not impair the amplification of SARS-CoV-2. The non-structural proteins (nsps) of coronaviruses are more conserved than the structural proteins (Chen et al., 2020b), which indicates that mutations in nsps are more likely to be lethal to the viruses and thus not retained during viral evolution. For example, several mutations in key sites of the N7-methyltransferase or exonuclease of coronavirus nsp14 will affect the coronavirus' virulence and replication efficiency to varying degrees, and reverse mutations can be observed after long term passage (Zhang et al., 2021a; Ogando et al., 2020; Lu et al., 2020b; Becares et al., 2016; Pan et al., 2022). The mutations in some regions of structural proteins are more easily retained as long as they do not affect viral replication. In addition, some mutations in Spike increasing the viral fitness will rapidly outcompete their parental viruses. For example, the D614G substitution became the dominant form within a few months worldwide because of its advantage in viral transmission and entry efficiency (Yurkovetskiy et al., 2020; Plante et al., 2021).

Meanwhile, the host RNA editing machinery is considered another source of mutations on coronaviruses (Brant et al., 2021; Mourier et al., 2021; Li et al., 2022). The adenosine deaminases acting on RNA (ADAR) deaminates adenosine (A) residues to inosine (I) on dsRNA disrupting A to uracil base pairing. I is interpreted as guanosine during RNA replication and translation, and the A→I editing thus entails transition of A to guanosine (A-to-G)(Ringlander et al., 2022). And the APOBECs (the apolipoprotein-B (*ApoB*) mRNA editing enzyme, catalytic polypeptide-like proteins) can deaminate cytosine to uracil (C-to-U)(Kim et al., 2022). Notably, sequence preference was observed in the host RNA editing machinery (Ringlander et al., 2022), but the detailed mechanism is yet to be revealed. The reactive oxygen species (ROS) also can oxidate guanine to 7,8-dihydro-8-oxo-2′-deoxyguanine (oxoguanine), causing G-to-T transversions (David et al., 2007).

2.2. The features of representative mutations in the Spike

There are many studies on mutations in the SARS-CoV-2 Spike, especially several representative mutations. Here, we summarize the features of key amino acid sites and representative mutations in the

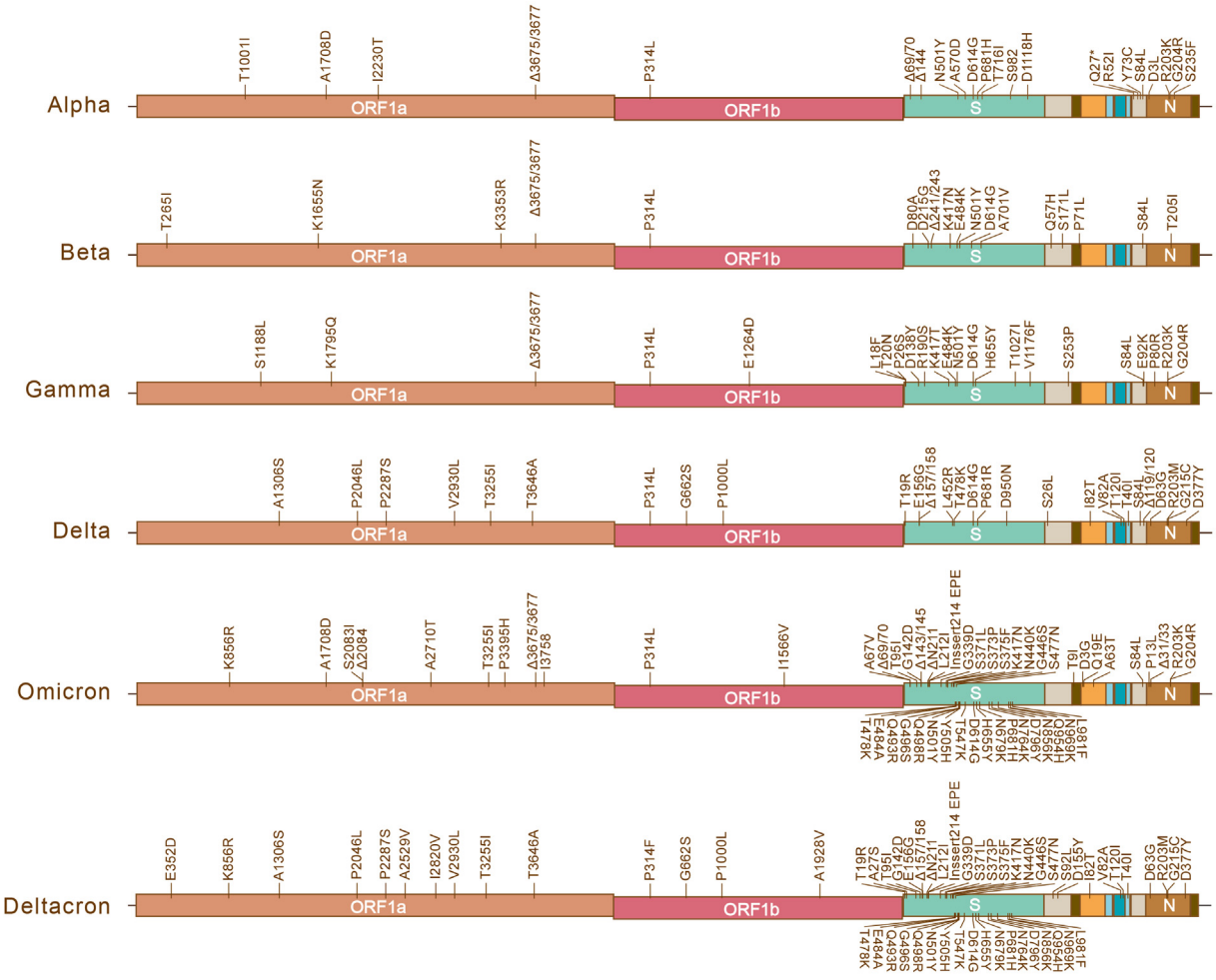

Fig. 1. The mutation site in the genome of five variants of concern (Alpha, Beta, Gamma, Delta, and Omicron) and the newly found recombined Delta-Omicron (EPI_ISL_10819657). Based on sequences from GISAID. ORF, open reading frame; S, Spike protein; N, nucleocapsid.

VOCs' Spikes (Table 1). These substitutions can achieve typical consequences, such as the alteration of viral entry efficiency, the increase of immune evasive ability, or both. For example, the mutation E484K in the SARS-CoV-2 receptor binding domain (RBD) enhances binding affinity with hACE2 and increases the viral infectivity, but reduces the binding affinity of many neutralizing antibodies (Liu et al., 2021b; Chen et al., 2021; Zhu et al., 2021; Wang et al., 2021a). Notably, the Omicron harbors over 30 amino acid substitutions in the Spike, 15 of which are in the RBD. Consequently, Omicron showed a higher hACE2-binding affinity, more remarkable immune-escape ability and weaker fusogenicity than the Delta (Du et al., 2022; Cao et al., 2021a; Liu et al., 2021c; Cui et al., 2022; Ma et al., 2022). Recent studies indicate that P681H, as well as mutations surrounding the S1/S2, S2' cleavage site, and heptad repeat 1 (HR1) in Omicron (N679K, P681H, N856K, Q954H, N969K, and L981F) contribute to the weaker fusogenicity of the Omicron, resulting in a weaker pathogenicity (Du et al., 2022).

The RBD critical for Spike-ACE2 binding is composed of a well-folded core structure, and a distant loop serves as a receptor-binding motif (RBM) that interact with ACE2 (Liu et al., 2021a). As shown in Fig. 2, although many mutations are presented in the Spike of different variants, the core structure of the RBD is not much affected. The RBMs (aa437∼aa508) loops of the WT, Delta, and Omicron variant also showed a high similarity structure in the hACE2-Spike complex (Xu et al., 2021; Wang et al., 2022a; Yin et al., 2022). In addition, the highly conserved key amino acids (G447, Y449, A453, Y475, N487, Y489, T500, and G502) maintained their relative position when interacting with hACE2.

Many COVID-19 vaccines have been developed based on the original SARS-CoV-2 strain, including inactivated vaccines, mRNA vaccines, protein subunit vaccines, and viral-vector vaccines (Li et al., 2021; Russell et al., 2021; Callaway, 2020). The widely used COVID-19 inactivated vaccines (Wang et al., 2020a; Xia et al., 2021), mRNA vaccines (Polack et al., 2020; Walsh et al., 2020), and protein subunit vaccines (Cao et al., 2021b; Yang et al., 2021) are generally safe and elicit effective humoral immunity against SARS-CoV-2, and mRNA vaccines have been reported able to elicit long-term cellular immunity (Strengert et al., 2021; Stumpf et al., 2021). However, the unbalanced distribution of vaccines, the failure of keeping social distance, and the infection of immunocompromised patients limited the effect of SARS-CoV-2 vaccines and led to the further evolution of the virus under selective pressures. Through Spike mutations, SARS-CoV-2 variants can escape from the immune protection elicited by the vaccines or prior infection to varying degrees (Liu et al., 2021b, 2021c; Cao et al., 2021a; Hoffmann et al., 2021; Wang et al., 2021b; Planas et al., 2021; Cele et al., 2021), resulting in breakthrough infections (SARS-CoV-2 infection or reinfection in vaccinated individuals or SARS-CoV-2 convalescents) (Abu-Raddad et al., 2021; Butt et al., 2021; Shastri et al., 2021). In addition, the possibility of reverse mutations should be considered (Bashor et al., 2021).

2.3. The mutations beyond the Spike

Unlike the Spike mutations, mutations in the nsps, noncoding sequences, and other structural proteins are not extensively studied. As mentioned above, it is more difficult for the nsps mutations to be retained, and the known mutations or deletions in pp1a and pp1a/b are relatively rare. However, it is still important to study these mutations or deletions, considering their importance in coronavirus' replication and regulation. For example, Lucy et al. found that B.1.1.7 evolved beyond the Spike coding region to more effectively antagonize host innate immune responses through upregulating specific subgenomic RNA synthesis and increasing protein expression of key innate immune antagonists, including Orf9b, Orf6, and the nucleocapsid (N) protein (Thorne et al., 2021).

3. How does SARS-CoV-2 "control" the mutation rate?

A finely tuned balance between replication fidelity and variability is critical for SARS-CoV-2 adaptation and evolution. Coronavirus stands for the known RNA virus with the largest (∼30000 nt) genome, and the unique 3′–5′ exonuclease (ExoN) proofreading function plays an important role in the stability of the genome (Chen et al., 2020b; Chen and Guo, 2016). The unique proofreading activity can be attributed to the N

Table 1
The features of key amino acid sites and representative mutations in SARS-CoV-2 Spike.

	Site	Mutation	VOCs	Features (compared to wild-type)
Key sites with representative mutations	H69–V70	Deletion	Alpha, Omicron	Increases Spike infectivity (Meng et al., 2021)
	G339	D	Omicron	Increases hACE2 binding (Cao et al., 2021a); leads to evasion of antibody neutralization (Cui et al., 2022)
	K417	N	Beta, Omicron	Decreases hACE2 binding (Liu et al., 2021b; Cui et al., 2022; Barton et al., 2021); evade antibody neutralization (Cao et al., 2021a; Yi et al., 2021)
		T	Gamma	Decreases hACE2 binding (Barton et al., 2021); leads to evasion of antibody neutralization (Deshpande et al., 2021)
	G446	S	Omicron	Leads to evasion of antibody neutralization (Cao et al., 2021a)
	L452	R	Delta	Increases hACE2 binding; leads to evasion of antibody neutralization (Motozono et al., 2021; Deng et al., 2021)
	E484	K	Beta, Gamma	Increases hACE2 binding; leads to evasion of antibody neutralization (Liu et al., 2021b; Chen et al., 2021; Wang et al., 2021a; Cui et al., 2022; Khan et al., 2021)
		A	Omicron	Decreases hACE2 binding; leads to evasion of antibody neutralization (Cui et al., 2022)
	G496	S	Omicron	Increases hACE2 binding; leads to evasion of antibody neutralization (Cui et al., 2022)
	N501	Y	Alpha, Beta, Gamma, Omicron	Increases hACE2 binding (Barton et al., 2021); leads to evasion of antibody neutralization (Cao et al., 2021a; Chakraborty, 2022)
	Y505	H	Omicron	Decreases hACE2 binding; leads to evasion of antibody neutralization (Chen et al., 2022; Dejnirattisai et al., 2022)
	D614	G	Alpha, Beta, Gamma, Delta, Omicron	Produces a more open conformation of Spike, increases viral transmission and fitness (Yurkovetskiy et al., 2020; Plante et al., 2021; Zhang et al., 2021b)
	P681	R	Delta	Facilitates cleavage of the Spike and enhances viral fusogenicity (Du et al., 2022; Saito et al., 2022)
		H	Alpha, Omicron	Slightly increases S1/S2 cleavage, which does not significantly impact viral entry or cell-cell spread (Du et al., 2022; Lubinski et al., 2022)
Highly conserved key sites	G447 Y449 A453 Y475 N487 Y489 T500 G502	No mutation	Alpha, Beta, Gamma, Delta, Omicron	Basic amino acids in RBD-hACE2 binding (Cao et al., 2021a; Cui et al., 2022; Xu et al., 2021; Wang et al., 2020c)

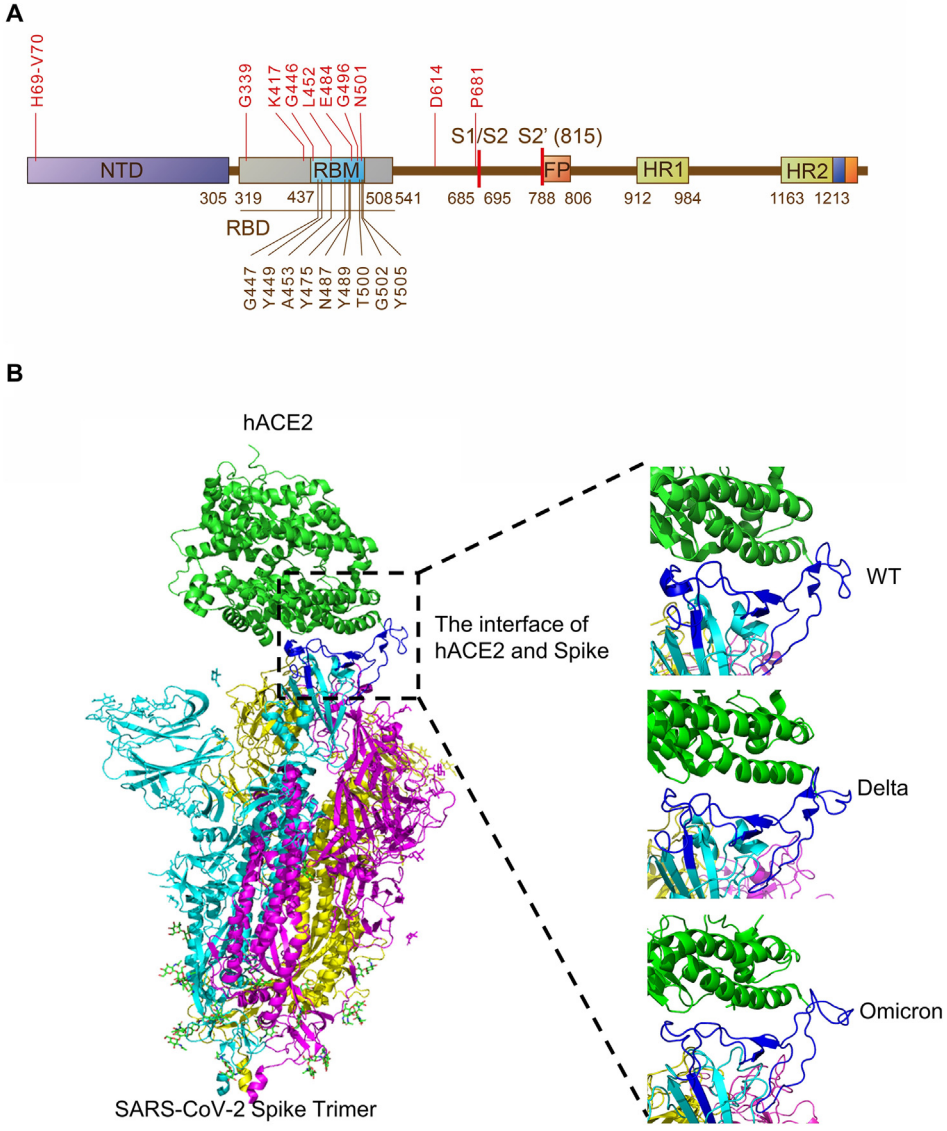

Fig. 2. Partial key sites in the Spike of SARS-CoV-2 and the SARS-CoV-2 Spike trimer (WT) complexed with hACE2. The key sites with mutation are in red, and the highly conserved key sites are in black. The interface of the hACE2 and Spike from indicated variants was at the right panel of **(B)**. Green, hACE2; blue, RBM; cyans, magenta, and yellow represent the indicated monomer of Spike. This figure is based on the structure data from the Protein Data Bank (accession code: 7DF4 (Xu et al., 2021), 7W98 (Wang et al., 2022a), and 7WPA (Yin et al., 2022)) NTD, N-terminal domain; RBD, receptor-binding domain; RBM, receptor-binding motif; FP, fusion peptide; HR, heptad repeat.

terminal of non-structural protein 14 (nsp14) (Robson et al., 2020; Denison et al., 2011; Eckerle et al., 2007), and promoted by nsp10, which also contributes to CoV replication fidelity (Pan et al., 2008; Smith et al., 2015). Recently, Yan et al. reported the cryo-EM structure of the SARS-CoV-2 replication-transcription complex (RTC) in a form identified as Cap(0)-RTC coupled with nsp10/14 demonstrated the backtracking mechanism for nsp14 ExoN facilitating the proofreading of the RNA in concert with polymerase nsp12. In this speculative backtracking model, the mis-incorporated nucleotides in one Cap(0)-RTC are excised by nsp14 in another Cap(0)-RTC as the catalytic center of nsp14 ExoN is distal from the polymerase reaction center of nsp12 in one Cap(0)-RTC (Fig. 3) (Yan et al., 2021b). Since the proofreading of nsp14 occurs along with the RNA

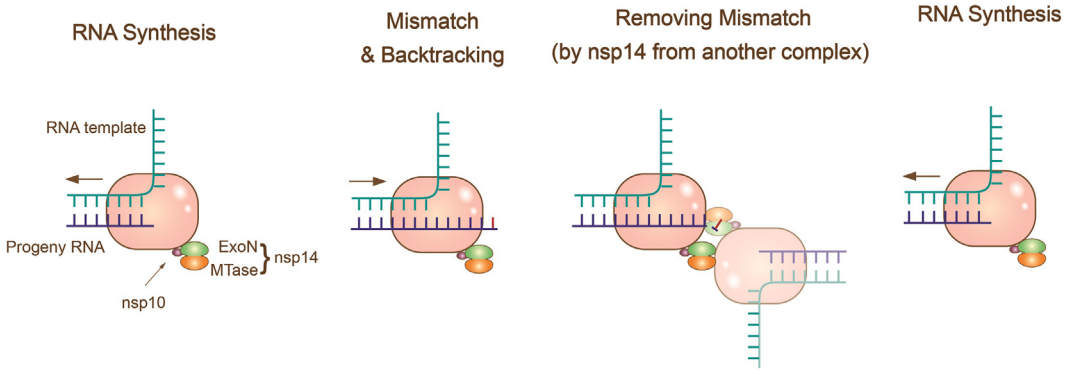

Fig. 3. An in trans backtracking model for proofreading (Yan et al., 2021b).

replication, the rate of ExoN's mismatch excision should be precisely tuned to "control" the mutation rate for better adaption.

The ExoN activity of the nsp10/14 complex contributes to the control of the mutation rate and plays a role in the resistance against some types of antiviral nucleoside analogs. As Remdesivir impairs the elongation of RNA products, it was initially expected to be a highly competent drug candidate against SARS-CoV-2 (Yin et al., 2020; Peng et al., 2021; Gordon et al., 2020). Studies in mouse hepatitis virus (MHV) also supported that the GS-5734 can be a potential effective pan-CoV antiviral, and an MHV mutant lacking ExoN proofreading was even more sensitive to remdesivir (GS-5734) (Smith et al., 2015; Agostini et al., 2018). However, the clinical improvement rate for patients receiving remdesivir within 7 days was only 3% against SARS-CoV-2, while ~66% of subjects developed adverse effects (Beigel et al., 2020; Wang et al., 2020b). Meanwhile, favipiravir, another nucleoside analog that can mimic both A and G nucleotides during RNA synthesis, also showed limited effect against SARS-CoV-2 in clinical trials (Peng et al., 2021; Udwadia et al., 2021; Cai et al., 2020; Doi et al., 2020; Solaymani-Dodaran et al., 2021). The detailed mechanism of SARS-CoV-2's resistance to these nucleoside analogs and the role of the nsp10/14 complex in mismatch excision remains unclear.

Furthermore, the passage of WT MHV in the presence of GS-441524 (remdesivir parent nucleoside) leads to the two mutations in the nsp12 (F476L and V553L in RdRp) at residues conserved across all CoVs, conferring up to 5.6-fold resistance to Remdesivir (Agostini et al., 2018). These acquired resistance mutations remind us that drug resistance should be taken into serious consideration in antiviral drug development.

4. What's next?

The emergence of new SARS-CoV-2 variants is probably inevitable based on the following facts: 1). There is a large number of SARS-CoV-2 infected populations; 2). The mutation rate of SARS-CoV-2 is relatively high; 3). SARS-CoV-2 has jumped to wild animals that can serve as a reservoir for virus evolution. Therefore, this COVID-19 pandemic will most likely not end with Omicron. SARS-CoV-2 may finally coexist with humans as other seasonal human coronaviruses (such as 229E, OC43, NL63, and HKU1, which cause common cold-like respiratory symptoms). However, this coexistence should be maintained based on full completion of massive highly-effective vaccinations and convenient access to anti-CoV drugs rather than out of control.

Generally speaking, the continuous viral transmission in humans may lead to higher infectivity and lower severity of the disease, as Omicron shows (Chen et al., 2022; Abdullah et al., 2022; Meo et al., 2021; Wolter et al., 2022). However, we should stay alert because the potential animal-to-human transmission might result in higher virulence, although only a few animal-to-human transmission cases have been reported so far (Sawatzki et al., 2021; Oude Munnink et al., 2021). Considering the frequent spillovers from humans to animals (for example, white-tailed deer, ferrets, cats, and dogs)(Kuchipudi et al., 2022; Kim et al., 2020; Gaudreault et al., 2020; Sit et al., 2020), we may find more animal-to-human transmission cases in the future. Meanwhile, the newly reported Delta-Omicron variant (also known as "Deltacron" or "Deltamicron") indicates the possibility of SARS-CoV-2 recombination in humans. However, the infectivity and disease severity of this "Deltacron" remains undetermined (Bolze et al., 2022; Colson et al., 2022). The recombination of SARS-CoV-2 and other coronaviruses in the wild should also be monitored, which might give birth to the virus with higher virulence or transmissibility, leading to a new wave of the coronavirus outbreak.

5. Perspective

COVID-19 has raged across the world for two more years. The emergence of the Omicron variant with a striking immune-escape ability rendered this pandemic long-lasting. Nevertheless, we can see several positive changes in the pandemic over time: 1) the development and massive vaccination of effective COVID19 vaccines; 2) the dominant Omicron variant is less pathogenic given lower hospitalization rates and shorter hospital stays (Danza et al., 2022; Halfmann et al., 2022; Shuai et al., 2022). Even though the Omicron can still infect the vaccinated and convalescents, the symptoms are usually mild or asymptomatic; 3) oral antiviral drugs such as Paxlovid and Molnupiravir, which targets 3C-Like protease (nsp5) and RdRp (nsp12), respectively, have shown promising antiviral effects for the treatment of COVID-19 (Mahase, 2021; Jayk Bernal et al., 2022); 4) there are still some broadly neutralizing antibodies effective in preventing the infection of SARS-CoV-2 variants, including the Omicron (Cameroni et al., 2021; Wang et al., 2022b; Ju et al., 2022); 5) the effectiveness of quarantine has been proved in defeating SARS-CoV-2, even in large cities with more than ten million populations (Cao et al., 2020).

The effectiveness of Paxlovid and Molnupiravir indicates that the nsps are ideal targets for developing antiviral drugs, the activity of which are almost unaffected by spike mutations. Besides, the third dose of vaccines, based on the original SARS-CoV-2 Spike, can still significantly improve the immunity against Omicron (Ma et al., 2022; Zhang et al., 2022; McMenamin et al., 2022). Meanwhile, the spike-sequence-updated vaccines and pan-coronavirus vaccines are around the corner (Ying et al., 2022; Gagne et al., 2022; Liu et al., 2022). Finally, the global vaccinated populations gradually increased in both developed and undeveloped countries. Overall, with the constant growing arsenal of antivirals against COVID-19, the human beings will probably gain the upper hand in the battle against SARS-CoV-2.

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