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Emerging mutations in the SARS-CoV-2 variants and their role in antibody escape to small molecule-based therapeutic resistance

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Abstract

Several clinical trials started during the COVID-19 pandemic to discover effective therapeutics led to identify a few candidates from the major clinical trials. However, in the past several months, quite a few SARS-CoV-2 variants have emerged with significant mutations. Major mutations in the S-glycoprotein and other parts of the genome have led to the antibody's escape to small molecule-based therapeutic resistance. The mutations in S-glycoprotein trigger the antibody escape/resistance, and mutations in RdRp might cause remdesivir resistance. The article illustrates emerging mutations that have resulted in antibody escape to therapeutics resistance. In this direction, the article illustrates presently developed neutralizing antibodies (with their preclinical, clinical stages) and antibody escapes and associated mutations. Finally, owing to the RdRp mutations, the antiviral small molecules resistance is illustrated.

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Introduction

Recently, several SARS-CoV-2 variants have emerged in the last several months due to SARS-CoV-2 evolution [1–3]. At the same time, WHO (World Health

Organization), CDC (Centers for Disease Control and Prevention), USA (United States of America), and ECDC (European Centre for Disease Prevention and Control) have entitled the significant variants as VOC (Variant of Concern) or VOI (Variant of Interest) considering the current epidemiological status and risk. WHO has entitled the significant variants as Alpha, Gamma, Epsilon, Beta, Theta, Delta, Delta Plus, Iota, Eta, Kappa, Lambda, and so on. Some significant VOCs are Alpha variant (B.1.1.7 lineage; initially observed in the UK), Beta variant (B.1.351 lineage; first observed in South Africa), Gamma variant (P.1 lineage; initially noted in Brazil), and Delta variant (B.1.617.2 lineage; initially recorded in India). At the same time, some VOIs are Epsilon variant (B.1.427/B.1.429 lineage; initially detected in the USA), Zeta variant (P.2 lineage; initial observed in Brazil), Iota variant (B.1.526 lineage; initial observed in the USA) and Eta variant (B.1.525 lineage; initial observed in the USA) [2,4]. Researchers noticed the variants in the last quarter of the year 2020 with some changed features such as augmented transmissibility, increased disease severity, and immune escape property. Simultaneously, different mutations have been acquired from time to time during the generation of the SARS-CoV-2 variants. Scientists observed significant mutations in the S-glycoprotein and other regions of the genome. Spike mutations in SARS-CoV-2 variants have gained more attention because of the association with changes in viral characteristics [5].

Significant spike mutations (D614G, E484K, K417N/T, N501Y, L452R, T478K) are found associated with different clinical consequences throughout the globe [6]. Scientists observed successful therapeutics from the significant clinical trials, including small antiviral molecules such as remdesivir or antibody-based therapeutics against SARS-CoV-2 [7]. Several antibodies have shown significant neutralization activity against the virus. Some antibodies have received EUA (Emergency Use Authorization) for the treatment of this virus. Most of the antibodies are designed against the S-glycoprotein of this virus. Therefore, any S-glycoprotein mutations can trigger the antibody escapes/antibody resistance in SARS-CoV-2 variants and hinder the antibody-based therapeutic strategies against the virus

[6]. At the same time, the mutations in another part of the SARS-CoV-2 genome can result in antiviral small molecules resistance. One example is Nsp12 (non-structural protein 12) mutations that might cause amino acid changes in RNA-dependent RNA polymerase (RdRp), providing remdesivir resistance.

Antiviral small molecules target the 'protein class' of the SARS-CoV-2 virus (3C-like main protease (3CLpro) or main protease (Mpro), RdRp, Helicase (Nsp13), Spike (S)-glycoprotein), or host cell (Cathepsin L, Furin, Transmembrane Serine Protease 2 (TMPRSS2) and Angiotensin-Converting Enzyme 2 (ACE2) receptor) [8]. The S-glycoprotein interacts with the ACE2 receptor for the SARS-CoV-2 entry into the host cell. Therefore, S-glycoprotein is a significant drug target for the drug discovery of small antiviral molecules. These molecules act as viral entry inhibitors [9]. At the same time, due to the high antigenicity of S-glycoprotein, antibodies interact with the S-glycoprotein. Therefore, several vaccines have been developed using the S-glycoprotein or its components [10,11].

This article illustrates emerging mutations that result in antibody escape and therapeutic resistance. In this direction, neutralizing antibodies (nAbs) against SARS-CoV-2, their preclinical and clinical developmental stages have been discussed. The article exemplifies antibody escapes due to emerging mutations in SARS-CoV-2 variants. The small antiviral molecules resistance by the mutations in RdRp of the virus has also been described. Finally, significant mutations in the variants have been discussed to properly understand the antibody escape and small molecule-based therapeutic resistance.

Neutralizing antibodies for COVID-19 and antibody escape due to emerging mutations in SARS-CoV-2 variants

nAb might hinder virus entry through their neutralization. It is known that the natural infection or vaccination helps to generate the nAbs production in our body. nAb has been used to treat different viruses from time to time, such as influenza virus, Ebola virus, respiratory syncytial virus, HIV. There are some advantages of nAb such as low toxicity, high affinity to target proteins, and high-level specificity to antigen [12]. Recently, it was noted that nAb could protect from COVID-19, which can be generated through the vaccination against SARS-CoV-2 [12,13]. Simultaneously, nAb has also been isolated from COVID-19 infected patients for therapeutic purposes.

Neutralizing antibodies against SARS-CoV-2

When SARS-CoV-2 spread, and the pandemic started, scientists isolated nAbs from SARS-CoV-2 from patients with COVID-19 [14,15]. At first, researchers

tried to understand the complexities of S-glycoprotein and the S1 and S2 subunit that activate virus fusion. In the S1 subunit, the RBD (receptor binding domain) binds with the host ACE2. Using this understanding, scientists have discovered several potent nAbs. Some of the discovered nAb against SARS-CoV-2 are B38 [16], CV30 [17], and C121 [18]. Developed nAbs were divided into different classes concerning the conformational binding to the target protein (Figure 1). Class 1 nAbs blocks the ACE2 binding against SARS-CoV-2. More specifically, these nAbs binds with the 'open up' conformation of RBDs. This class of nAb contains heavy chains encoded by gene segments such as VH3-52 and VH3-66 [19]. Class 2 nAbs can identify and interact with the RBDs both in the 'up' and 'down' conformation. While class 3 nAbs bind outside the binding site of the ACE2 [20].

Preclinical developmental stage

Some of the nAbs for COVID-19 are in the preclinical stage of development. Researchers have obtained several mAbs (monoclonal antibodies) from the B cells, which are in the preclinical stage of development. Some nAbs that are in the preclinical stage are CC6.30, CC6.29, CC12.1, P2B-2F6, P2C-1F11, 1-57, 2-7, 2-15, COV2-2130, COV2-2196, BD-368-2 [12] (Table-1).

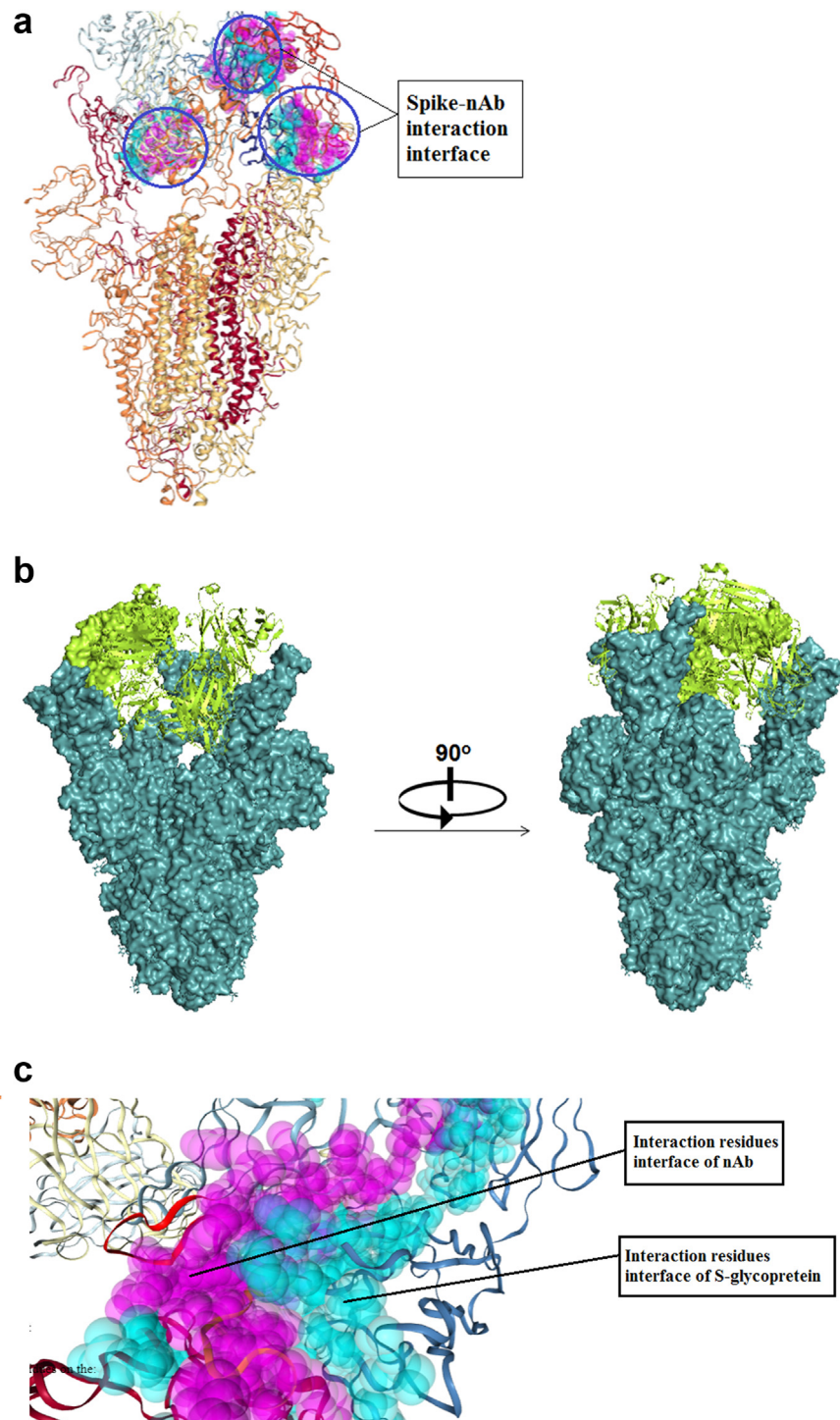
Clinical developmental stage

A few nAbs (mAbs and polyclonal IgG) against SARS-CoV-2 have entered into the different phases of clinical trials (Table-2). Some examples of nAbs that have progressed to the clinical trials are nAb LY-CoV555 and the mAb combinations of REGN10933 and REGN10987. The mAb combination (REGN10933+REGN10987) has completed the phase-III clinical trial (ClinicalTrials.gov; Clinical trial ID: NCT04426695). It has been noted that this mAb combination also shows effectiveness against the SARS-CoV-2 variants [12]. Similarly, LY-CoV555 entered the phase-II/III clinical trial (ClinicalTrials.gov; Clinical trial ID: NCT04427501). Renowned US-based pharmaceutical company (Eli Lilly) is performing the clinical trial with two collaborators (Shanghai Junshi Bioscience and AbCellera Biologics). In phase-II clinical trial, it was found that the application of LY-CoV555 declined the viral load in patients with COVID-19 [21].

Antibody escapes due to emerging substitution mutations in SARS-CoV-2 variants

Recently, it has been noted that different mutations might trigger the antibody escape phenomena, which causes antibody escapes/antibody resistance (Figure 2). Recently, Weisblum et al. pointed out the nAbs escape instance by SARS-CoV-2 variants. They observed some abundant mutations at the RBD and NTD (N-terminal domain). The RBD substitutions are V445E and K444 R/N/Q. While NTD substitutions are K150 R/E/T/Q and N148S. It was observed that some mutations

Figure 1



Current Opinion in Pharmacology

Interaction interface of a nAb (C118) with S-glycoprotein of SARS-CoV-2 (a) Figure shows the ribbon structure interaction interface of a nAb (C118) with S-glycoprotein (b) Figure shows the ribbon structure of a nAb (C118) and surface structure of S-glycoprotein (c) Interaction interface of a nAb (C118) with S-glycoprotein. The figure was generated using PDB ID: 7RKV.

Table 1

Neutralizing antibodies in the preclinical developmental stage.

Sl. No.	Name of neutralizing antibodies (nAbs)	Type of nAbs	Target site	Remark	Reference
1.	Vh–Fc ab8	Human mAb	Receptor-binding domain (RBD)	Attached to S-protein trimer, and neutralized pseudotyped, live SARS-CoV-2 infections	[52]
2.	Convalescent plasma	IgG Ab	SARS-CoV-2	Retained neutralizing activity against the infection of SARS-CoV-2	[53]
3.	LY-CoV555	Human mAb	S-protein	Stopped the viral attachment and entry into human host cells, neutralizing the SARS-CoV-2 infection	[54]
4.	P2C–1F11 and P2B–2F6	Human mAb	Receptor-binding domain (RBD)	Participated with ACE2 to interact with RBD, neutralizing pseudotyped and live SARS-CoV-2 infection	[55]
5.	SAB-185	Human IgG	S-protein	Neutralized live SARS-CoV-2 infection	[56]
6.	4A8, 5–24, 2–17 and 4–8	Human mAb	N-terminal domain	Reduced the effects of pseudotyped and live SARS-CoV-2 infections	[57]
7.	n3088 and n3130	Human single domain Abs	Receptor-binding domain (RBD)	Reduced pseudotyped and live SARS-CoV-2 infections	[58]
8.	VIR-7831	Human mAb	S-protein	Bind with a conserved epitope on the S-proteins and neutralized the live SARS-CoV-2 infection	[59]
9.	CC6.29, CC6.30 and CC12.1	Human mAb	Receptor-binding domain (RBD)	Reduced pseudotyped and live SARS-CoV-2 infections, protective hamsters against SARS-CoV-2 (specific for CC12.1)	[14]
10.	Ty1	Alpaca-derived nanobody	Receptor-binding domain (RBD)	Bind to RBD in up-and-down conformation and blocked the binding of RBD–ACE2	[60]
11.	H11–D4 and H11–H4	Llama-derived nanobodies	Receptor-binding domain (RBD)	Blocked RBD–ACE2 binding, neutralizing live SARS-CoV-2 infection	[61]
12.	S304, S309 and S315	Human mAbs or Fabs	Receptor-binding domain (RBD)	Attached to SARS-CoV-2 RBD, but did not compete with RBD–ACE2 binding, neutralizing pseudotyped and live SARS-CoV-2 infections	[62]

(E484K, N440K, F490L, Q493K) occurred at high frequency in S-glycoprotein during the passage experiment with replication component of chimeric virus (rVSV/SARS-CoV-2/GFP). Because of the presence of these mutations, antibody escape activity is more common [22].

The same research group has performed an experiment using the replication-competent of a chimeric virus. The study used rVSV encoding a green fluorescent protein and S-glycoprotein of SARS-CoV-2 (rVSV/SARS-CoV-2/GFP) [23]. This experiment has adapted two high-titer variants of this recombinant construct (rVSV/SARS-CoV-2/GFP) and generated three to four passages. The genome was sequenced during the passage experiment (third or fourth passage), and the mutations were analyzed. Here, researchers found those mutations with high frequency in S-glycoprotein (E484K, N440K, F490L, Q493K) [22].

Another study reported C144 resistance mutations (Q493 R/K and E484 K/A/G) using SARS-CoV-2/rVSV. The study revealed that E484K substitution causes resistance to two antibodies (C051 and C052) [24]. Similarly, Hoffmann *et al.* observed nAbs escape by

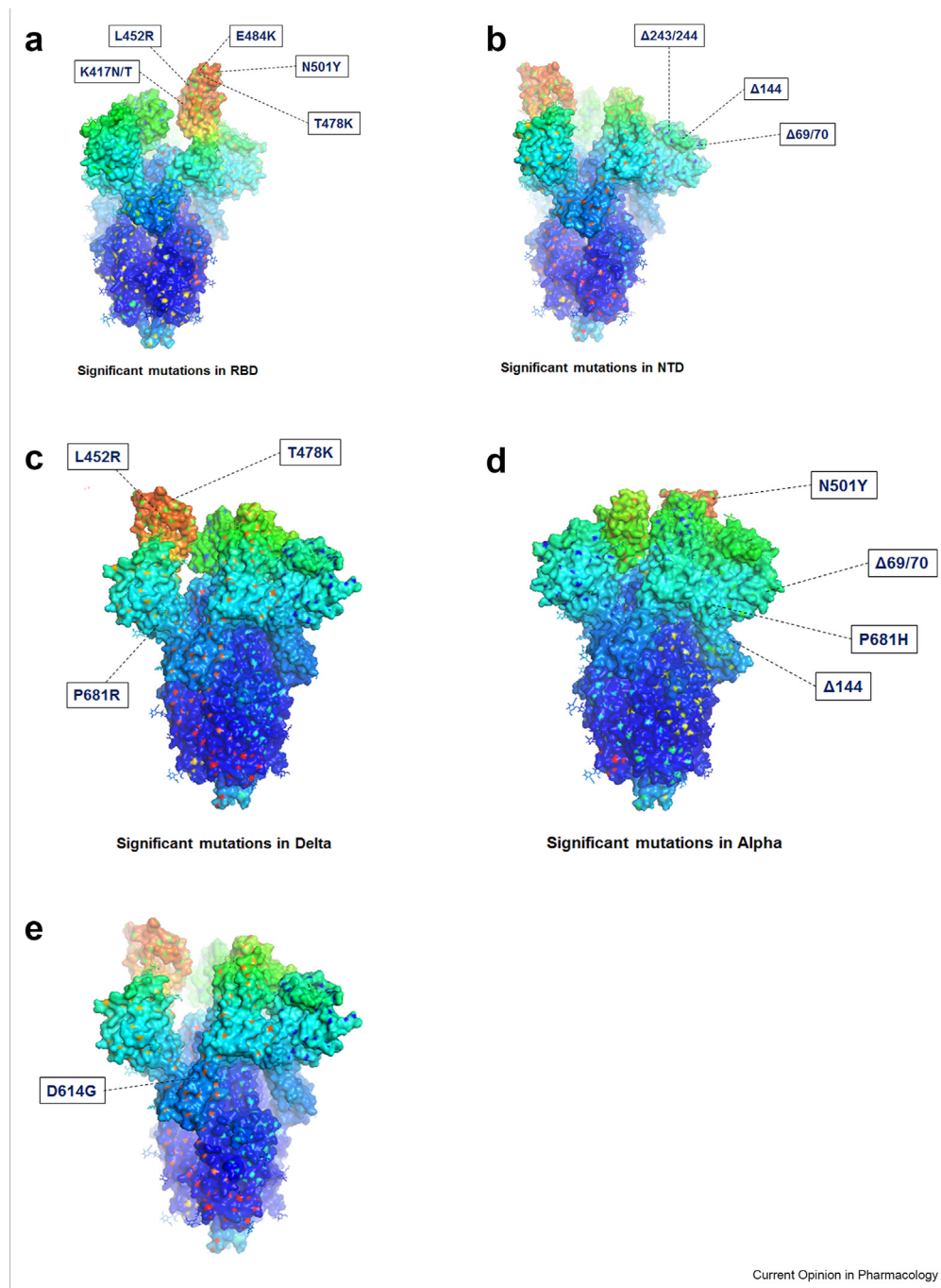
two SARS-CoV-2 variants (P.1 and B.1.351). The research group observed three RBD mutations (E484K, K417N/T, and N501Y). The study reported the occurrence of total antibody escape against Bamlanivimab and partial antibody escape phenomena for Casirivimab [25]. A study by Liu *et al.* also reported antibody-resistant or antibody escape phenomena. They found that S477N mutation causes antibody-resistant instances to several mAbs. Similarly, E484K mutation is also responsible for antibody escape occurrence [26]. Another research group reported different mutations in the RBD that might cause antibody escape of the different classes of antibodies. The study observed E484K, K417N/T, and L452R substitution responsible for other classes of antibody escape. They concluded that the K417N/T substitution causes class 1 antibody escape, and these mutations are frequently observed in two SARS-CoV-2 lineages (P.1 lineage and B.1.351 lineage). Similarly, class 2 antibody escape is attributed to the E484K substitution which is observed in several lineages of this virus (B.1.526 lineage, B.1.351 lineage, P.1 lineage, P.2 lineage, and so on). Likewise, the L452R substitution, found in B.1.617 lineage and B.1.427/429 lineage, is accountable for class 3 antibody escape. In

Table 2

Status of the neutralizing antibodies in different phases in clinical trials.

Sl. No.	Name of nAb	Type of nAbs	Clinical trial No.	Status	Target site	Remarks
1.	JS016	Human mAb	NCT04441918	Phase I	Spike protein	Anti-SARS-CoV-2 monoclonal antibody targets spike protein and blocks binding of the virus to host cells
2.	TY027	Engineered human IgG	NCT04429529	Phase I completed/Phase III	SARS-CoV-2	Used for treatment of patients with COVID-19 to slow the progression of the disease and accelerate recovery, and providing temporary protection from infection
3.	BR11-196	Convalesced-derived human mAb	NCT04479631	Phase I	SARS-CoV-2	Non-overlapping epitope binding regions provide a high degree of neutralization activity against SARS-CoV-2.
4.	BR11-198	Convalesced-derived human mAb	NCT04479644	Phase I	SARS-CoV-2	
5.	ABBV-47D11	Human mAb	NCT04644120	Phase I	Full-length spike protein (conserved region)	The cross-neutralizing antibody targets a shared epitope on viruses and could potential for prevention and treatment of COVID-19
6.	STI-1499	Cocktail mAb	NCT04454398	Phase I	Spike protein	Potent neutralizing activity against SARS-CoV-2 virus isolates, including the emerging spike D614G variant
7.	MW33	Humanized IgG1κ Ab	NCT04533048	Phase I	Receptor-binding domain	Recombinant fully human antibody applied for patients with mild or moderate COVID-19
8.	HFB30132A	Recombinant mAb	NCT04590430	Phase I	Spike protein	Fc modified IgG4 with minimized binding to the human FcγRs, which leads to decrease of risk for antibody-dependent enhancement of SARS-CoV-2 infection,
9.	ADM03820	Cocktail mAb	NCT04592549	Phase I	Spike protein	Mixture of two human IgG1 non-competitive binding anti-SARS-CoV-2 antibodies.
10.	HLX70	Human mAb	NCT04561076	Phase I	Receptor-binding domain	Genetically engineered, fully humanized mAb that targets RBD of SARS-CoV-2 for the treatment of COVID-19 and acute respiratory disorder
11.	DZIF-10c	Human mAb	NCT04631705	Phase I & Phase II	Receptor-binding domain	Intravenous infusion and by inhalation protection from virus infection in the respiratory tract.
12.	COVI-AMG	Hamster mAb	NCT04584697	Phase I & Phase II	Spike protein	The reduced activity and protected against the SARS-CoV-2 and the highly infectious spike (D614G) isolate.
13.	BGB DXP593	mAb cocktails	NCT04532294	Phase I	Spike ectodomain trimer	Overlaps with the RBD-ACE2 complex structure, and inhibiting the entrance of SARS-CoV-2
14.	SCTA01	Human mAb	NCT04483375	Phase I	Spike protein	Efficiently neutralized SARS-CoV pseudoviruses and SARS-CoV-2 by blocking the (RBD) S-protein
15.	CT-P59	Human mAb	NCT04525079	Phase I	Receptor-binding domain	Reduced the viral load in the upper and lower respiratory tracts and has therapeutic potential for patients with COVID-19.

Figure 2



Different locations of significant mutations in S-glycoprotein that might be responsible for the antibody escape phenomena, which causes antibody escapes/antibody resistance. (a) Location of the multiple mutations in the RBD (b) Location of the significant mutations in the NTD (c) Location of the major mutations in the S-glycoprotein of the Alpha variant (d) Location of the important mutations in the S-glycoprotein of the Delta variant (e) The first mutation was observed D614G in the S-glycoprotein. The mutation is located S1 subunit near the S1/S2 boundary, and the furin cleavage site is also found in this particular point (S1/S2 boundary). All the figures were generated using any of the two PDB ID (6ZP0 and 7DK3).

this study, researchers mapped all mutations using the yeast-display system and high-resolution structures of the different classes of antibodies [27]. Conversely, a reduction in the effectiveness of the bamlanivimab

against the delta variant was observed [28]. The USFDA (United States Food and Drug Administration) approved the EUA of the mAb, bamlanivimab, for the COVID-19 therapy recently.

However, scientists are trying to solve the antibody escapes occurrence for flawless antibody therapy. In this direction, Miersch et al. [29] have developed tetravalent nAbs, which have shown improved effectiveness of the nAbs toward the antibody resistance or antibody escapes.

Significant mutations and small molecule-based therapeutic resistance

Recently, various scientists have observed several small molecule-based therapeutics resistance phenomena. Favipiravir or Remdesivir (GS-5734) are small molecule-based antiviral therapeutic, and these two molecules received EUA by the regulatory authorities from several countries to treat patients with COVID-19 [30,31]. It was noted that the RdRp (RNA-dependent RNA polymerase) is the drug target for favipiravir and remdesivir. Recently, remdesivir resistance was observed by several scientists due to the several mutations in RdRp (Figure 3). Nsp12 gene encodes the RdRp enzyme, and the polymerase structure (nsp12 polymerase) is bound with the two co-factors (nsp7 and nsp8) [32]. These two co-factors significantly trigger polymerase activity [33]. Simultaneously, the scientists reported several mutations in RdRp variants [34]. However, Mari et al. observed significant mutations in the RdRp (V557L, V473F, N491S, and F480 L/S/C) that are significantly responsible for remdesivir resistance [35]. It was noted that the V557L mutation in Nsp12 changes binding affinity to the RNA template and ultimately to remdesivir [36]. Similarly, V473F is a potential escape mutation described by Mari et al. It is one of the essential residues in the structural context of RdRp, which is associated with the fingers region. At the same time, researchers found an association between V473F mutation and an SNP, which is positioned at 24,378 genomic positions

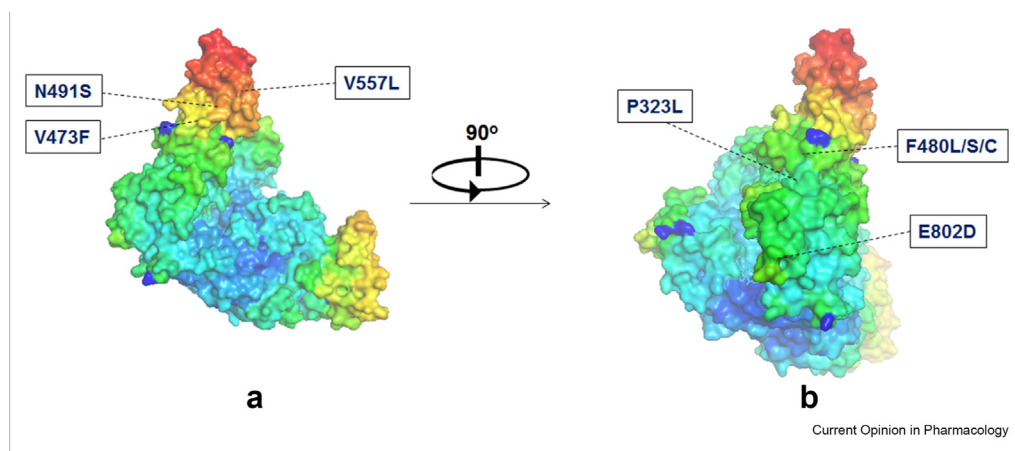
[35]. Simultaneously, scientists found that N491S in Nsp12 is associated with high-frequency nsSNPs (non-synonymous SNPs) related to escape mutations. It is also associated with the fingers region. Similarly, F480 L/S/C, another key mutation in Nsp12, is found to destabilize the interface between diverse sub-domains ('palm' and 'fingers') of the RdRp protein.

Padhi et al. [37] tried to understand the potential residues with a higher probability of mutations in remdesivir-binding sites. The study will help to understand the remdesivir-resistance phenomena. In another work, Mari et al. [38] one primary mutation (P323L) in RdRp, which might provide remdesivir resistance RdRp to the virus. A study by Szemiel et al. [39] introduced another mutation, E802D, in vitro, which reduces the remdesivir sensitivity but did not influence the replication of this virus.

Significant mutations

The first D614G mutation was observed during April 2020 [33]. D614G mutation is located at the S1 subunit near the S1/S2 boundary. The furin cleavage site is also found in this position (S1/S2 boundary). Later on, it was observed that the mutation has a high dN/dS ratio explaining the positive selection of the mutation [40,41]. After D614G, several other mutations were found associated with the epidemiological characteristics. The researchers reported the E484K mutation from different countries like Brazil, South Africa, and the New York, USA [42–46]. This mutation was first reported by Li et al. in September 2020. Understanding the mutation will help unfold the resistance properties to some nAb neutralizing antibodies by the virus [47]. Early 2021, another mutation, K417N, was noted from the different variants. It was found responsible for the

Figure 3



Different locations of significant mutations in RdRp that might be responsible for the remdesivir resistance (a) Different locations of the N491S, V473F, V557L mutations (b) Different locations of the P323L, F480 L/S/C, E802D. The figures were generated using PDB ID: 7BV2.

reduced antibody effectiveness elicited by the COVID-19 vaccines Pfizer-BioNTech (BNT162b2) or Moderna (mRNA-1273) [48]. At the same time, an additional mutation was found in the exact location (K417), which is K417T. The mutation K417T was found in the Gamma variant (P.1 lineage) [49]. K417T/N mutation occurs due to the lack of other infrequent RBD mutations. It was reported that the K417 might decrease ACE2 binding [50]. It has been observed that the RBD mutations and NTD mutations provide antibody escape. Significant RBD mutations are K417N/T, L452R, T478K, E484K, and N501Y. Similarly, important NTD mutations include three deletions (Δ 144, Δ 69/70, Δ 243/244) and L18F. Significant mutations that have been observed in Delta variants are L452R, T478K, and P681R (in spike protein). Similarly, scientists noted important mutations in the S-glycoprotein of Alpha variants which are Δ 144, Δ 69/70, N501Y, and P681H. At the same time, some significant mutations (V557L, V473F, N491S, F480 L/S/C, P323L, E802D) were found in RdRp. Those mutations might cause remdesivir resistance. However, more studies are needed in this direction.

Conclusions

Presently, scientists are trying to understand the most significant escape mutations or resistance mutations that might contribute to increased antibody escape especially neutralizing antibody escape or monoclonal antibody escape, and the small molecule-based therapeutic resistance. Understanding the antibody escape mutations or resistance mutations might help develop proper antibody therapeutic to avoid antibody resistance. Simultaneously, several researchers are preparing a complete mutations map in this direction. Recently, Starr *et al.* created a mutations map using different antibodies that might help to understand escape mutations. These mutations are present in the several variants of circulating SARS-CoV-2 [51]. At the same time, Greaney *et al.* developed a compressive antibody escape mutations map of RBD of S-glycoprotein. The researchers developed a deep mutational scanning technique to explain how all amino-acid mutations in the RBD influence antibody binding. Finally, they have applied the method in ten human mAb [50]. Understanding the complete escape-mutation maps in S-glycoprotein or major mutations in RdRp will help design perfect antibody therapeutics or small molecule-based therapeutic. These rationally designed therapeutics can compare the viral evolution and the antigenic consequences. The overall knowledge will help to discover more highly potent, next-generation antibody therapeutics or small molecule-based therapeutics. Finally, a robust scientific approach toward understanding the consequences of evolutionary mutations in the emerging variants will help end the present pandemic and help prepare for the next pandemic.

Informed consent and patient details

Not required.

Conflict of interest statement

Nothing declared.

Abbreviations

EUA	Emergency use authorization
rVSV	Recombinant vesicular stomatitis virus
RBD	Receptor binding domain
mAb	Monoclonal Antibody
nAb	Neutralizing Antibody
ACE2	Angiotensin-Converting Enzyme 2
RdRp	RNA-dependent RNA polymerase

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- ** of outstanding interest

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