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Chapter 5

Pathogenesis and mutagenesis of SARS-CoV-2: cellular attachment, entry, and infection

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5.1 Introduction

Coronavirus disease 2019 (COVID-19) is a highly contagious disease characterized by higher leukocyte counts, acute respiratory distress, and increased levels of plasma proinflammatory cytokines. In order to understand the pathogenic mechanism of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, it is important to consider the general replication cycle of a virus. Although some differences could exist in the replication cycle of some species, but generally, viruses are obligate intracellular pathogens that would require the host cell machinery to replicate, thereby causing infection. There are nine basic steps in viral replication (Fig. 5.1). They are listed as follows:

1. Attachment of the virus to the host cell receptor.
2. Fusion of the virus with cellular membranes and consequent release of the viral RNA into the cytoplasm.
3. Reverse transcription to make viral DNA in the cytoplasm.
4. Integration of the viral DNA into the host DNA in the nucleus.
5. Posttranscription in the nucleus to make viral mRNA outside the nucleus.
6. Translation of the coded information of the mRNA into viral protein.
7. Assembling and packaging of viral protein and genetic materials.
8. Budding out or lysis of the viral material at the membrane level.
9. Release of the virus and subsequent reinfection of other organs with similar receptors.

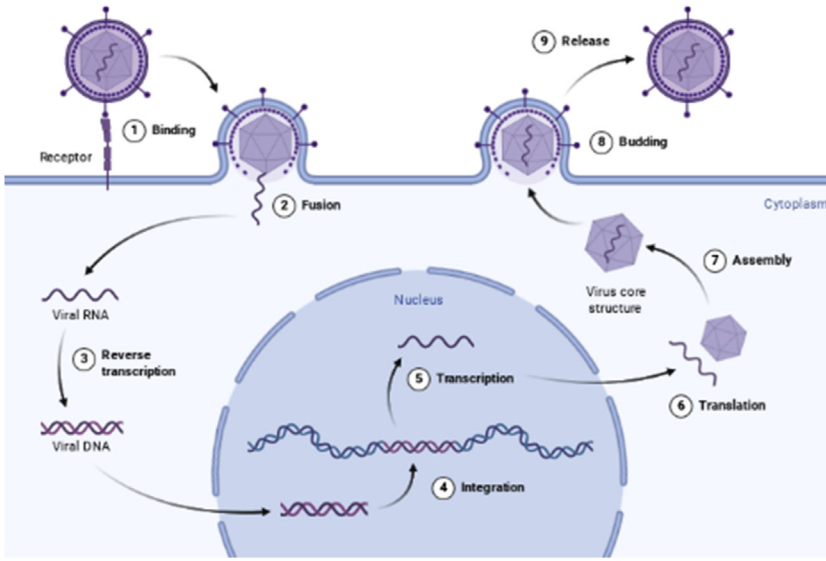

FIGURE 5.1 The general replication cycle of RNA viruses.

However, SARS-CoV-2 pathogenesis first step involves the binding of SARS-CoV-2 to the lungs epithelial angiotensin-converting enzyme 2 (ACE-2) receptor, which is inhaled from the droplets of an infected person or through other means [1]. Recently, a study showed that SARS-CoV-2 nucleic acid can be detected in the feces and urine of patients with COVID-19, an indication that SARS-CoV-2 may also be transmitted from the digestive tract through the fecal−oral route [2]. However, it is believed that the lung epithelial cells are the primary target of the virus [3,4].

The viral replication is presumed to start from the epithelium of the upper respiratory tract, and as the disease progresses, further multiplication occurs at the lower respiratory tract and in the gastrointestinal mucosa leading to mild level of viremia. At this point, the common symptoms of infections are fever and cough, though a few persons might be asymptomatic [5]. As the virus replicates, it moves to other organs that express ACE-2 such as the heart, kidneys, and gastrointestinal tract [6,7]. ACE-2 has been shown to be a co-receptor for viral entry for SARS-CoV-2 with a developing evidence that it has an extended role in the pathogenesis of COVID-19 [1]. The mechanism of the damage caused by SARS-CoV-2 infection has not been completely elucidated. However, the SARS model consists of three phases, namely, viral replication, immune hyperactivity, and pulmonary destruction [8].

The recent spike again in cases of COVID-19 after about a month of downturn, which led to ease in worldwide lockdown supports an earlier observation of mutation in SARS-CoV-2 [9]. One study found that infected samples of genomes collected from more than 7500 patients worldwide have identified mutations in the virus [10]. This development is scary because mutation could either make the virus more virulent (resistant to drugs) or less contagious. A comprehensive review on this and the pathogenic mechanisms of SARS-CoV-2 were discussed.

5.2 Pathogenesis of SARS-CoV-2

SARS-CoV-2 is the causative agent of COVID-19, a novel fatal disease with great global and public health concerns. The symptoms associated with COVID-19 patients include elevated levels of leukocytes, abnormal respiratory functions, and increased levels of proinflammatory cytokines in the plasma [11]. The leading pathogenesis of SARS-CoV-2 infection is known for targeting the respiratory system with pneumonia, RNAaemia, in addition to the incidence of ground-glass opacities, and acute cardiac injury [12]. High blood levels of cytokines and chemokines were recorded in COVID-19 patients which included interleukin (IL) 1 beta (IL-1β), IL-1RA, IL-7, IL-8, IL-9, IL-10, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1Aα, MIP1β, PDGFB, TNF-α, and VEGFA [12]. However, some of the severe cases that were admitted into the intensive care unit of hospitals had elevated levels of proinflammatory cytokines including IL-2, IL-7, IL-10, GCSF, IP10, MCP1, MIP1α, and TNF-α thought to promote the severity of the disease [12].

SARS-CoV-2 utilizes the ribosomes of the host cell to translate mRNA into polyproteins. These polyproteins are the structural framework of the viral molecule [13,14]. The synthesized polyproteins in turn will utilize the host RNA-dependent RNA polymerase to replicate itself, increasing the viral load within the host cell. The polyproteins use the host enzymes such as proteinases, which will degrade the polyproteins to create the individual spike proteins, E protein, nucleocapsid (Figs. 5.1 and 5.2) [15]. These structural components, together with the replicated ssRNA, give rise to a mature SARS-CoV-2 that would bud off the type II pneumocyte, back into the alveolus [16]. Type II pneumocytes are damaged in the process of SARS-CoV-2 budding off of the host cell. The destruction of type II pneumocytes will release specific inflammatory mediators which will stimulate macrophages. Stimulated macrophages trigger the release of certain cytokines such as IL-1, IL-6, and TNF-α [17]. In cases of acute inflammation, IL-1 and IL-6 are the major cytokines released leading to fever [11]. Furthermore, IL-1, IL-6, and TNF-α enter the blood circulation, causing the dilation of smooth muscles along with contraction of blood vessel endothelial cells resulting to increased capillary permeability. Increased capillary permeability causes plasma from the bloodstream to leak into the interstitial spaces, leading to alveolar edema.

Damage to type II pneumocytes within the alveoli occasioned by SARS-CoV-2 causes a decrease in the production of surfactants since the primary function of type II pneumocyte is the production of surfactant. Decreased surfactant within the alveolus will cause alveolar collapse due to increased surface tension as well as alveolar edema [15]. This collapse of the alveoli will impair gaseous exchange causing refractory hypoxemia and increased work associated with breathing in an attempt to breathe in as much air as possible to reopen the collapsed alveolar and interstitial edema. This is the mechanism

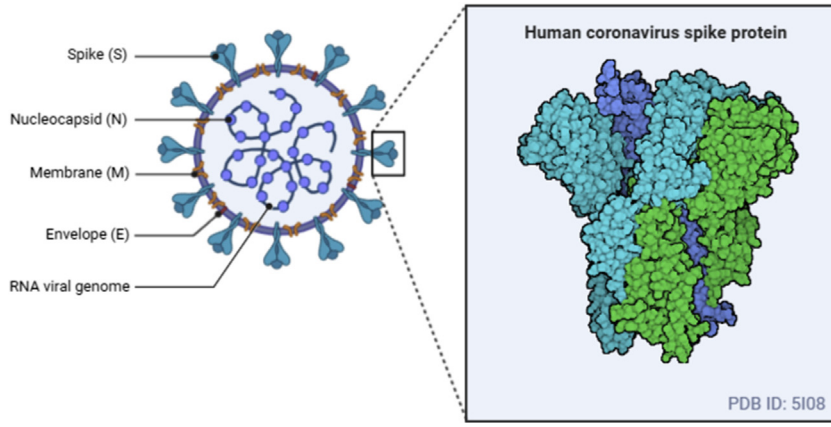

FIGURE 5.2 The SAR-CoV-2 virus.

that causes acute respiratory distress syndrome (ARDS) in SARS-CoV-2 infection. Another feared complication alongside ARDS has been disseminated intravascular coagulation which is a manifestation of coagulation failure and an intermediate link in multiorgan failure [16].

Inflammatory mediators released by the destruction of type II pneumocytes will increase the influx of neutrophils into the alveolus, releasing reactive oxygen species and proteases in which neutrophils will attempt to destroy the virus. In an attempt to destroy the invading virus, neutrophils will cause mass destruction of all alveolar cells: type I and type II pneumocytes. Damaged type I pneumocytes will cause impaired gaseous exchange as they play integral role in gas exchange. Type II pneumocytes are also destroyed by the neutrophils causing increased surface tension, leading to alveolar collapse. Damaged cells will collect at the basement of the alveolar membrane and into the center of the alveolus creating a collection of fluid, along with cellular debris comprising type I pneumocytes, type II pneumocytes, neutrophils, and macrophages, leading to consolidation. The consolidation will also hinder gas exchange, causing hypoxemia [11]. On the other hand, hypoxemia will trigger the release of peripheral chemoreceptors causing the sympathetic nervous system to increase respiration rate and heart rate to compensate for a reduced partial pressure of oxygen. Consolidation will lead to cough induction and may also cause the presentation of dyspnea due to decreased gas exchange. During the infection, inflammation of the lungs can advance to systemic inflammatory response syndrome as cytokines circulate in the vascular system, causing increased capillary permeability [18]. Capillary permeability uses the same mechanism as in the lungs to deposit plasma within tissue spaces, decreasing the blood volume. The vasodilation of blood vessels will decrease the total peripheral resistance, causing hypotension. The hypotension will cause decreased perfusion, leading to multisystem organ failure [17]. Also, decreased perfusion to the kidneys causes an increase in blood urea nitrogen and creatinine levels. Kidneys are unable to filter the blood urea nitrogen and creatinine from the blood, causing acute renal injury. Consistently, this causes IL-1 and IL-6 to circulate the vascular system and enter the central nervous system, targeting the hypothalamus, known for its role in maintaining body temperature. The elevated levels of IL-1 and IL-6 within the hypothalamus will cause it to release prostaglandins that will help reset the core body temperature to be higher than normal resulting in fever. The role of IL-1 and IL-6 in increasing the core body temperature is important as the most common initial symptom of COVID-19 [14].

5.2.1 SARS-CoV-2 cellular attachment

SARS-CoV-2 attaches itself to the host through virus−host interaction occasioned by the attachment of the viral structural protein with a specific receptor on the host cell. Once the virus attaches to the host via receptors,

it enters the host cell through the process of endocytosis pathway triggered by the spike protein [19] followed by incorporation of the virus, release of the viral genome, transcription and translation, and assembly of the new viral particles as well as the final release of the virus from the host cell [20]. As previously discussed, once the virus has access to the mucosal membranes of the host, it travels through the respiratory tract and enters the lung alveoli. In the alveoli, the SARS-CoV-2 binds specifically to the ACE-2 receptor, present on the type II pneumocyte. There is a spike glycoprotein present on the outer membrane of the SARS-CoV-2 which has a high affinity for the ACE-2 receptor [21]. Once the viral particle binds to the ACE-2 receptor, the virus is endocytosed into the cytoplasm of the type II pneumocyte where the lysosomal enzymes of the host cell will break down the lipid bilayer of the virus.

5.2.2 SARS-CoV-2 entry

Human ACE-2 is a functional receptor for the attachment of SARS-CoV-2 for cell entry, similar to SARS-CoV (Fig. 5.4) [22–24]. ACE-2 is a type I membrane protein which is expressed in the lung, heart, kidney, and intestine but mainly associated with cardiovascular diseases [25]. The ACE-2 protein is made up of an N-terminal peptidase domain and a C terminal collectrin-like domain that ends with a single transmembrane helix and a ~40-residue intracellular segment [25]. In addition to cleavage of angiotensin I to produce angiotensin (1–9), ACE-2 also provides a direct binding site for the spike proteins of coronaviruses [25]. The spike protein of coronaviruses exists in a metastable prefusion conformation that goes through a structural rearrangement to fuse the viral membrane with the host cell membrane [26]. The above process is initiated by the S1 subunit and a host–cell receptor binding, which destabilizes the prefusion trimer, resulting in the S1 subunit shedding and the S2 subunit transition to a highly stable postfusion conformation [26]. To engage a host–cell receptor (Fig. 5.3), the receptor-binding domain of

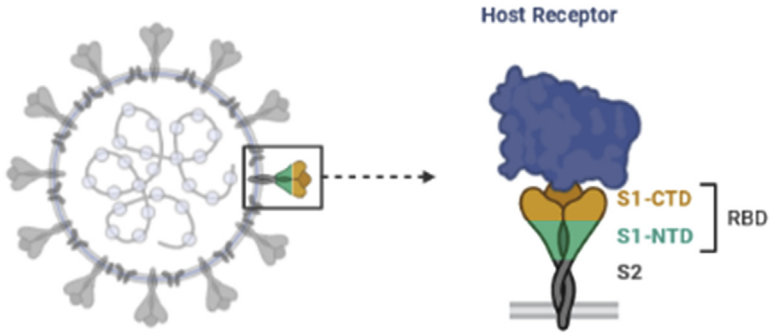

FIGURE 5.3 Spike receptor binding mechanism of SARS-CoV-2.

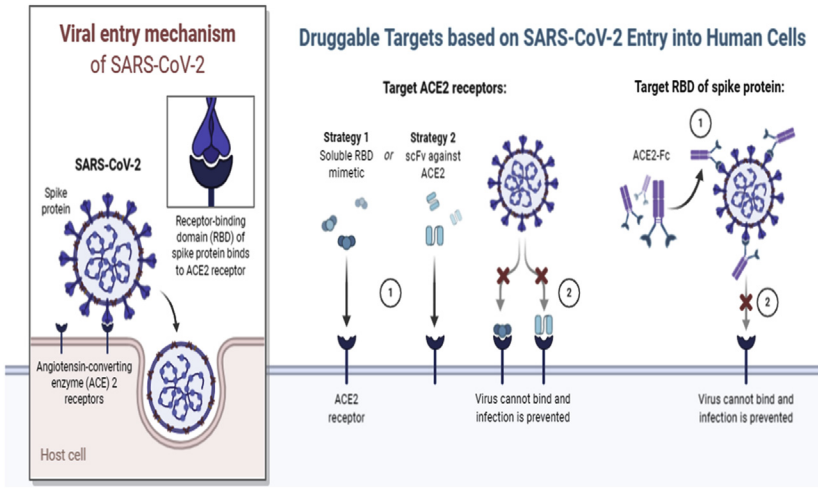

FIGURE 5.4 Proposed therapeutic sites targeting SARS-CoV-2 viral entry mechanism.

S1 undergoes hinge-like conformational movements that transiently hide or expose the determinants of receptor binding [27]. The biophysical and structural evidence of the receptor-binding domain of its spike protein in contact with ACE-2 suggests that SARS-CoV-2 the protein likely binds to human ACE-2 with 10−20 fold higher affinity than SARS-CoV [28]. According to Zhou et al. [24], another structural evidence suggests that the ACE-2−B0AT1 complex can bind two spike proteins simultaneously.

5.2.3 SARS-CoV-2 infection

Severely infected COVID-19 patients are currently the major source of transmission. Although some infected persons are asymptomatic, they could still spread the disease [29]. Additionally, it was found the samples taken from patients after recovery continuously show a positive RT-PCR test (Fig. 5.5) [30], which is something that has never been seen in the history of human infectious diseases. This trend may pose serious challenges for disease prevention and control. As reported by Epidemiology Working Group [31], COVID-19 has been considered as a type of self-limiting infectious disease, and most cases with mild symptoms can recover in 1−2 weeks. SARS-CoV-2 infection can cause five different outcomes: asymptomatically infected persons (1.2%); mild to medium cases (80.9%); severe cases (13.8%); critical case (4.7%); and death (2.3% in all reported cases). In a study conducted by Lu et al. [31], the proportion of asymptomatic infection in children under 10 years old was as high as 15.8%.

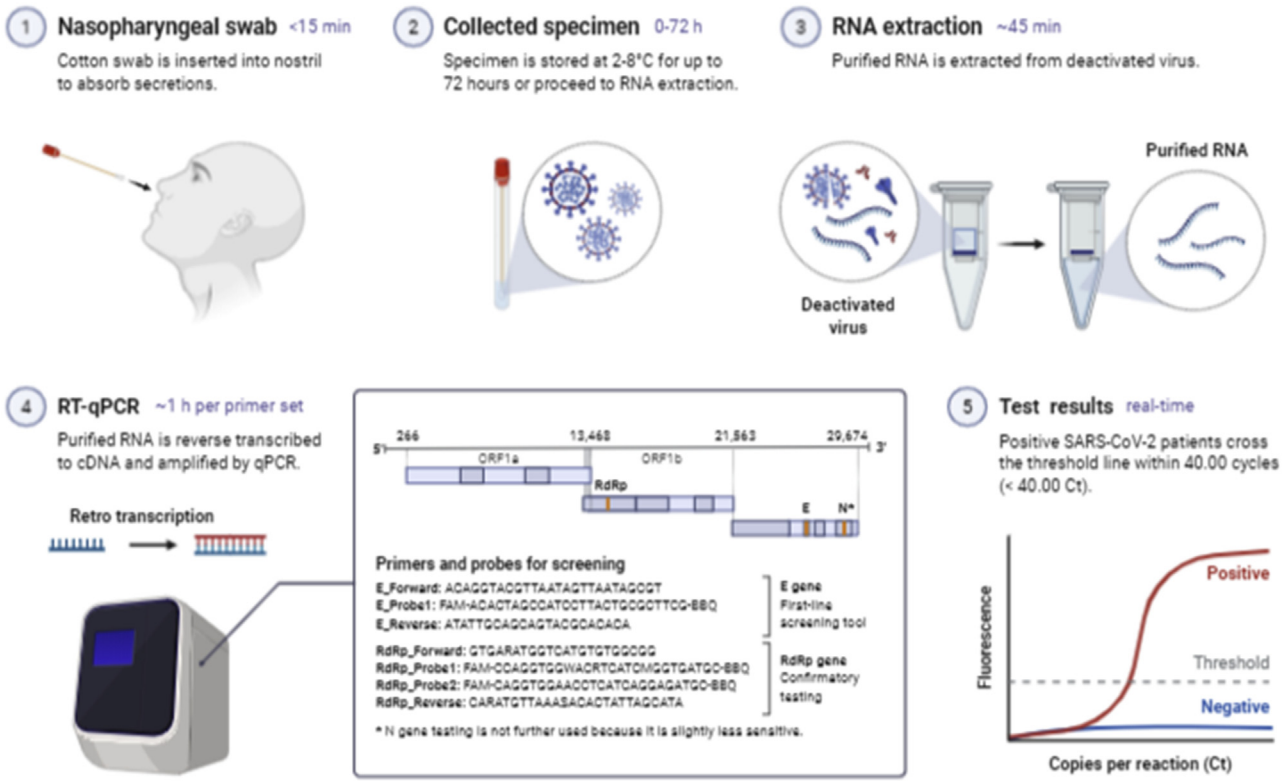

FIGURE 5.5 Coronavirus disease 2019 test through RT-PCR.

5.3 Mutagenesis of SARS-CoV-2

The complete knowledge of the pathogenicity of SARS-CoV-2 might take years to be fully elucidated. This includes the evolutionary mechanism, its emergence, and mutation rate. Characterizing the mutation rate will open doors to understanding the mechanism of action, immune invasion, and possible resistance of this deadly virus to drugs or vaccines. It has been reported that there is slow mutation rate in genome of SARS-CoV-2 which can modulate the viral transmission in different parts of the globe [9]. This mutation rate in turn depends upon the replicating enzymes, host enzymes, abrupt nucleic acid damage due to different physiochemical processes, and recombination [32,33]. Usually, the mutation rate in RNA viruses is on a higher side than that of the host which could increase the virulence and adaptability of the pathogen [34]. Recently, 13 variation sites in SARS-CoV-2 have been characterized, ORF1ab, S, ORF3a, ORF8, and N regions, among which positions 28144 in ORF8 and 8782 in ORF1a had showed a mutation rate of 30.53% and 29.47%, respectively [21]. This mutation rate might affect the disease severity and transmission rate. There have been eight novel recurrent mutations characterized of SARS-CoV-2, located at positions 1397, 2891, 14408, 17746, 17857, 18060, 23403, and 28881. Mutations in 2891, 3036, 14408, 23403, and 28881 positions are predominantly observed in Europe, whereas others located at positions 17746, 17857, and 18060 were found in North America; other silent mutation was detected in RNA-dependent RNA polymerase (RdRp) gene in England (UK) on February 9, 2020 while a different mutation in RdRp changing its amino acid composition emerged on February 20, 2020 in Italy [9]. Another study reported that SARS-CoV-2 is rapidly evolving across different regions across the globe and new mutations are evolving [35]. Lately, it has been found that among 103 sequenced strains of SARS-CoV-2, there have been 149 sites of mutations in genome of the virus [36]. These mutations showed differences in geographical distribution, transmission ability, and severity of the disease, causing more difficulty in drug and vaccine development. Therefore, tracking such mutations is very pivotal in order to find a strong cure against SARS-CoV-2 [37].

Koyama et al. [35] conducted a study to examine the rate of variation in the genome of SARS-CoV-2. Their study was conducted between February 1 and May 1, 2020. They downloaded 10,022 SARS-CoV-2 infected genomes from 68 countries of four databases and compared the genomes using the reference genome, NC_045512 with EMBOSS needle. Clad studies were conducted using Bayesian evolutionary analysis by sampling trees, version 2.5. In their findings, authors identified six major clads (basal, D614G, L84S, L3606F, D448del, and G392D) (Table 5.1), out of which D614G (a G-to-A base change at position 23403 in the Wuhan reference strain) was found to be the most

TABLE 5.1 Major clades of SARS-CoV-2 genomes, 2019–2020.

Clade/sublevel 1/sublevel 2	First observation of strain			No. of samples
	Date	Accession no.	Country	
Basal[a]	December 2019	MN90894	China	670
D614G//	January 24, 2020	EPI_ISL_422425	China	1889
D614G/Q57H/	February 26, 2020	EPI_ISL_418219	France	469
D614G/Q57H/T265I	February 21, 2020	EPI_ISL_418218	France	2391
D614G/203_204delinsKR/	February 25, 2020	EPI_ISL_412912	Germany	1330
D614G/203_204delinsKR/T175M	March 1, 2020	EPI_ISL_413647 and EPI_ISL_417688	Portugal and Iceland	215
			Total	6294
L84S//	December 30, 2019	MT291826	China	525
L84S/P5828L	February 20, 2020	EPI_ISL_413456	The United States	1137
			Total	1662
L3606F//	January 18, 2020	EPI_ISL_408481	China	182
L3606F/V378I/	January 18, 2020	EPI_ISL_412981	China	127
L3606F/G251V/	January 29, 2020	EPI_ISL_412974	Italy	419
L3606F/G251V/P765S	February 20, 2020	EPI_ISL_415128	Brazil	260
			Total	988
D448del//	February 8, 2020	EPI_ISL_410486	France	248
G392D//	February 25, 2020	EPI_ISL_414497	Germany	160

del, deletion; *delins*, deletion–insertion.
[a]*The reference genome (NC_045512) used belongs to the basal clade.*
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re-occurring clad. Authors also identified 14 subclads (Table 5.1). Variants was also found in the open reading frame 1ab of SARS-CoV-2 genomes (Table 5.2). In order to examine variants in nucleotides, the nucleotides within the coding areas were converted to amino acid residues. The findings suggest that the C>T mutation was the most common with 1670 distinct variants. In summary, the most common variants are the synonymous 3037C>T in 6334 samples (Table 5.3), P4715L in the open reading frame 1ab of 6319 samples (Table 5.3), and D614G in the spike protein in 6294 samples (Table 5.1).

According to BBC News of July 19, 2020, her health reporter, Rachel Schraer, was quoted as saying that the most notable mutation—named D614G (situated within the protein making up the virus's "spike" it uses to break into the cells)—is now seen in as many as 97% of samples around the world. She further stated that the D614G variant is so dominant that it is now the pandemic [38]. This correlates with the findings of Koyama et al. [35] and Korber et al. [39].

5.4 Future perspectives

There are serious concerns about rising cases and more people getting infected by the virus that can lead to an increase in the fatality rate. On the other hand, the process of treatment gets disrupted as there is a spike in number of cases. It becomes more interesting for those who are immunocompromised. At present, only a little is known about this virus, there are large number of questions which remain unanswered. The most important among which is response of host toward the virus involving cellular and humoral response. All these queries must be addressed which would help in successful vaccine development. As virus has been evolved only some months before, less data and information is available on the mechanism of pathogenesis and mutagenesis.

As the cases of COVID-19 keep soaring, authors support social distancing, wearing of face mask, and the observation of all sanitary measures such as frequent hand washing. Authors also recommend the consumption of food rich in micronutrients such as vitamins and minerals for immune system boosting. Chapters 16, 18–21 of this book presents the various food sources of these nutrients. Also, the Editor of this book and his collaborating team has worked on many related projects especially as it regards drug discovery from natural products [40–51].

As SARS-CoV-2 mutates, it is wise to sustain continuous, evidence-based analysis of evolutionary changes so that public health measures can be adjusted in response to substantive changes in the infectivity or severity of COVID-19 [52].

TABLE 5.2 Number of variants in the open reading frame 1ab of SARS-CoV-2 genomes, by final cleaved protein, 2019–2020.

Final protein	Missense mutation	Synonymous mutation	Noncoding region			In-frame		Frameshift deletion	Stop gained	Total
			Mutation	Deletion	Insertion	Deletion	Insertion			
NSP1	64	45	0	0	0	13	0	1	0	123
NSP2	237	130	0	0	0	5	0	0	0	372
NSP3	547	349	0	0	0	16	0	2	3	917
NSP4	116	113	0	0	0	1	0	0	1	232
3CLPro	67	54	0	0	0	0	0	0	0	121
NSP6	82	67	0	0	0	4	1	2	0	156
NSP7	27	21	0	0	0	0	0	0	0	48
NSP8	60	25	0	0	0	1	0	0	1	87
NSP9	29	22	0	0	0	0	0	0	1	52
NSP10	25	25	0	0	0	0	0	0	2	52
RdRp	194	157	0	0	0	2	0	1	3	357
Helicase	148	101	0	0	0	0	0	0	0	249
ExoN	141	118	0	0	0	11	0	1	2	273
EndoRNase	92	67	0	0	0	3	0	0	0	162
OMT	76	50	0	0	0	1	1	0	0	128
Total	1905	1344	0	0	0	57	2	7	13	3329

Note: Koyama et al. [36] compared 10,022 genomes to the NC_045512 genome sequence.

TABLE 5.3 Variants of SARS-CoV-2 genomes observed in more than 100 samples, 2019–2020.

Genomic change	Type of mutation	Gene/protein	Amino acid change	No. of samples
3037C > T	Synonymous	*ORF1ab*/NSP3	F924F/F106F	6334
14408C > T	Missense	*ORF1ab*/RdRp	P4715L/P323L	6319
23403A > G	Missense	*S*	D614G	6294
241C > T	Noncoding	*5′-UTR*	NA	5928
25563G > T	Missense	*ORF3a*	Q57H	2893
1059C > T	Missense	*ORF1ab*/NSP2	T265I/T85I	2442
28144T > C	Missense	*ORF8*	L84S	1669
8782C > T	Synonymous	*ORF1ab*/NSP4	S2839S/S76S	1598
28881_28883delinsAAC	Missense	*N*	203_204delinsKR	1573
18060C > T	Synonymous	*ORF1ab*/ExoN	L5932L/L7L	1178
17858A > G	Missense	*ORF1ab*/helicase	Y5865C/Y541C	1166
17747C > T	Missense	*ORF1ab*/helicase	P5828L/P504L	1147
11083G > T	Missense	*ORF1ab*/NSP6	L3606F/L37F	1070
14805C > T	Synonymous	*ORF1ab*/RdRp	Y4847Y/Y455Y	844
26144G > T	Missense	*ORF3a*	G251V	769
20268A > G	Synonymous	*ORF1ab*/endoRNase	L6668L/L216L	452

Continued

TABLE 5.3 Variants of SARS-CoV-2 genomes observed in more than 100 samples, 2019–2020.—cont'd

Genomic change	Type of mutation	Gene/protein	Amino acid change	No. of samples
17247T > C	Synonymous	*ORF1ab*/helicase	R5661R/R337R	325
2558C > T	Missense	*ORF1ab*/NSP2	P765S/P585S	274
15324C > T	Synonymous	*ORF1ab*/RdRp	N5020N/N628N	267
1605_1607del	In-frame deletion	*ORF1ab*/NSP2	D448del/D268del	250
18877C > T	Synonymous	*ORF1ab*/ExoN	L6205L/L280L	234
2480A > G	Missense	*ORF1ab*/NSP2	I739V/I559V	232
27046C > T	Missense	*M*	T175M	221
11916C > T	Missense	*ORF1ab*/NSP7	S3884L/S25L	185
2416C > T	Synonymous	*ORF1ab*/NSP2	Y717Y/Y537Y	170
1440G > A	Missense	*ORF1ab*/NSP2	G392D/G212D	164
27964C > T	Missense	*ORF8*	S24L	164
36C > T	Noncoding	*5′-UTR*	NA	163
2891G > A	Missense	*ORF1ab*/NSP3	A876T/A58T	159
28854C > T	Missense	*N*	S194L	155
1397G > A	Missense	*ORF1ab*/NSP2	V378I/V198I	139
28657C > T	Synonymous	*N*	D128D	139

28688T > C	Synonymous	*N*	L139L	138
18998C > T	Missense	*ORF1ab*/ExoN	A6245V/A320V	137
28311C > T	Missense	*N*	P13L	136
28863C > T	Missense	*N*	S197L	136
9477T > A	Missense	*ORF1ab*/NSP4	F3071Y/F308Y	136
25979G > T	Missense	*ORF3a*	G196V	132
29742G > T	Noncoding	*3′-UTR*	NA	131
25429G > T	Missense	*ORF3a*	V13L	128
24034C > T	Synonymous	*S*	N824N	118
29870C > A	Noncoding	*3′-UTR*	NA	115
28077G > C	Missense	*ORF8*	V62L	113
26729T > C	Synonymous	*M*	A69A	106
27_37del	Noncoding deletion	*5′-UTR*	NA	106
19_24del	Noncoding deletion	*5′-UTR*	NA	105
514T > C	Synonymous	*ORF1ab*/NSP1	H83H/H83H	105
23731C > T	Synonymous	*S*	T723T	102
3177C > T	Missense	*ORF1ab*/NSP3	P971L/T1198K	101

del, deletion; *delins*, deletion–insertion; *NA*, not applicable. 10,022 genomes were compared to the NC_045512 genome sequence.
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5.5 Conclusion

At present, COVID-19 is the biggest challenge faced by people across the globe and remains a top concern. The experience from previous disease outbreaks due to SARS-CoV and MERS-CoV helps in understanding the pathogenesis and spread of this viral infection. Interaction between host and viral particles plays an important role in viral pathogenesis, thus by using receptor analog and inhibitors can prevent this binding. Therefore, controlling this binding can disable the viral entry into host cells and this could play an essential role in combating the spread of COVID-19. Continuous research and sequencing might play a vital role in understanding the mutagenic rate of reported strains throughout the globe, which in turn will help in successful drug and vaccine development.

List of abbreviations

3CLPro 3C-like protease
ACE-2 Angiotensin-converting enzyme 2
ARDS Acute respiratory distress syndrome
CLD Collectrin-like domain
COVID-19 Coronavirus disease 2019
ExoN 3′-5′ exonuclease
IL Interleukin
M Membrane glycoprotein
mRNA Messenger RNA
N Nucleocapsid phosphoprotein
NSP Nonstructural protein
OMT O-methyltransferase
ORF Open reading frame
RdRp RNA-dependent RNA polymerase
S Protein Spike glycoprotein
SARS-CoV-2 Severe acute respiratory syndrome coronavirus-2
SNS Sympathetic nervous system
ssRNA Single-stranded RNA
TNF-α Tumor necrosis factor-alpha
UTR Untranslated region

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