Chapter 1
Biology of SARS-CoV-2 Coronavirus; Origin, Structure, and Variants

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Abbreviations

+ssRNA	Positive-sense single-stranded RNA
ACE2	Angiotensin-converting enzyme 2
ADE	Antibody-dependent enhancement
AKT	Protein kinase B
APC	Antigen-presenting cells
APN	Aminopeptidase N
ARDS	Acute respiratory distress syndrome
CBP	Convalescent blood products
CEACAM1	Carcino embryonic antigen-related cell adhesion molecule 1
CFDA	China food and drug administration
CFR	Case fatality ratio
COVID-19	The Coronavirus disease-2019
CRISPR	Clustered regularly interspaced short palindromic repeats
CT	Computerized tomography
DIC	Disseminated intravascular coagulation
DMV	Double-membrane vesicles
DPP4	Dipeptidyl peptidase 4
DRF	Damage response framework
dsRNA	Double-stranded RNA
ERGIC	Endoplasmic reticulum golgi intermediate compartment
FDA	Food and drug administration
HCoV-229E	Human coronavirus 229E
HCoV-HKU1	Human coronavirus HKU1
HCoV-NL63	Human coronavirus NL63
HCoV-OC43	Human coronavirus OC43
HLA	Human leukocyte antigen
IBV	Infectious bronchitis virus
ICTV	International committee on taxonomy of viruses
IFN-γ	Interferon-gamma
IL	Interleukin
JAK	Janus kinase

kb	Kilobases
mAb	monoclonal antibodies
MERS	Middle East respiratory syndrome
MERS-CoV	Middle East respiratory syndrome coronavirus
MHC	Major histocompatibility complex
MODS	Multiple organ dysfunction syndromes
MOF	Multiple organ failure
mTOR	Mammalian target of rapamycin
NF-κB	Nuclear Factor κ-light-chain-enhancer of activated B cells
nsps	Nonstructural proteins
ORF	Open Reading Frame
PdCoV	Porcine delta coronavirus
RAS	Renin-angiotensin system
RBD	Receptor-binding domain
RBM	Receptor-binding motif
RER	Rough endoplasmic reticulum\
RTC	Replicase-transcriptase complex
RT-qPCR	Real-time quantitative polymerase chain reaction
SARS	Severe acute respiratory syndrome
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SARSCoV-2	Severe acute respiratory syndrome coronavirus-2
ssRNA	Single-stranded RNA
STAT3	Signal transducer and activator of transcription 3
TLRs	Toll-like receptors
TMPRSS2	Transmembrane protease serine 2
TNF-α	Tumor Necrosis Factor-alpha
WHO	World Health Organization

Introduction

In Wuhan, China, a positive-strand RNA virus (SARS-CoV-2) was first detected in December 2019. It rapidly spread and affected populations worldwide, and case fatality rates range from 2% to 3%. SARS-CoV-2 genome comprises ssRNA (single-stranded RNA) which is approximately ~30 kb in size [1]. Both nonstructural proteins (nsps) and structural proteins are encoded by the genome. Structural proteins include the nucleocapsid proteins (N), spike glycoproteins (S1 and S2), envelope proteins (E), and membrane proteins (M), which are all located near the 3′ end of the strand [2]. Cytokine storms are often caused by uncontrolled inflammatory responses and result in high mortality. IFN-γ, IL-1, IL-6, TNF-α, and IL-18 are crucial cytokines that are released through nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB), signal transducer and activator of transcription 3 (STAT3), Toll-like receptors (TLRs), Janus kinase (JAK), protein kinase B (AKT),

mammalian target of rapamycin (mTOR) signaling pathways during cytokine storms [3]. In brief, infected epithelial cells with the SARS-CoV-2 express angiotensin-converting enzyme 2 (ACE2), which induces activation of immune cells resulting in acute respiratory distress syndrome (ARDS) [4]. Beyond vaccination, there is no fully efficient agent or method recommended for pre- and post-exposure with SARS-CoV-2; however, several medications are used. For instance, Remdesivir as an anti-viral drug is prescribed for coronavirus disease 2019 (COVID-19) patients with respiratory symptoms, which causes faster recovery [5]. Hydroxychloroquine is used to prevent viral replication in severe acute respiratory syndrome (SARS), as used in the Middle East respiratory syndrome (MERS) patients years ago. Lopinavir/Ritonavir are recommended as anti-viral agents in viral infections such as HIV; corticosteroids such as dexamethasone and methylprednisolone [6] are used to reduce the mortality rates of patients and decreases the inflammatory reactions and the macrophage activation syndrome. Tocilizumab is used in patients with ARDS and reduces the elevated levels of IL-6 [7]. Aside from chemical agents, herbal medicines such as curcumin and quercetin are used to treat COVID-19 by suppressing the inflammatory signaling pathways and cytokines [8].

Method of Search

From PubMed, Google Scholar, Scopus, and Cochrane library, we collected data on published clinical and animal studies between 2000 and April 2021 in English. Also, search terms included “SARS CoV-2” or “COVID-19” and “Biology” or “Variants” or “Structure” or “Origins” or “Inflammatory response.”

The SARS-CoV-2 Biology

Coronaviruses are classified as a subgroup of RNA viruses with the ability to cause diseases in mammalian and avian species. They compose a positive-sense single-stranded RNA (+ssRNA) genome ranging from 26.4 to 31.7 kb in size. The genome has a 5′ methylated cap and a 3′ polyadenylated tail [9]. Coronaviruses contain the largest genome among the RNA viruses, making them capable of plastic gene adaptation and modification [10]. This family causes numerous viral infections while more lethal variants give rise to SARS, MERS, and COVID-19 [11]. Molecular biology revealed that the disease caused by the coronaviruses family is a consequence of virus genome transcription and replication and delayed or disturbed immune responses [12, 13]. Subsequently, upregulation of the inflammatory pathways and the immune cells invasion in different tissues provokes a malfunctioning cycle of the host immune response [14–16]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a strain of coronaviruses responsible for the ongoing COVID-19 pandemic. It is the seventh identified coronavirus capable of causing illness in

humans after human coronavirus 229E (HCoV-229E), human coronavirus NL63 (HCoV-NL63), human coronavirus OC43 (HCoV-OC43), human coronavirus HKU1 (HCoV-HKU1), Middle East respiratory syndrome coronavirus (MERS-CoV), and severe acute respiratory syndrome coronavirus (SARS-CoV) [17]. The genome sequence of SARS-CoV-2 is 79% similar to SARS-CoV and 50% to MERS-CoV [18]. The bat coronavirus (RaTG13), spotted in *Rhinolophus affinis* from Yunnan province, China, shares 96.2% full-length genome sequence and 90% open reading frames in the genome with SARS-CoV-2 [19, 20]. However, recent reports are still speculating about the virus reservoir. It remains elusive how the virus was transmitted to humans and which animals acted as an intermediate reservoir [21, 22]. As Fig. 1.1 exerts [23], the virus morphology is simple. The coronavirus virion consists of the RNA genome, helical nucleocapsid, and viral membrane containing S1, S2, M, and E [24]. All coronaviruses have a similar structure. The first two-thirds of coronaviruses genomes are open reading frame (ORF) (contain ORF1a and 1b), which encode the 16 nsps [9]. The later reading frames encode S1 and S2, E, M, and N [25]. The differences between the coronaviruses are owed to the number and function of accessory proteins. The reading frames between the nonstructural and structural proteins encode the accessory proteins. The distinguishing point of these viruses is the spike that controls the virus activities and virulence and the diverse accessory proteins that combat against the host immune system [26, 27]. The differences between the functional domains of the spike protein genome of SARS-CoV and

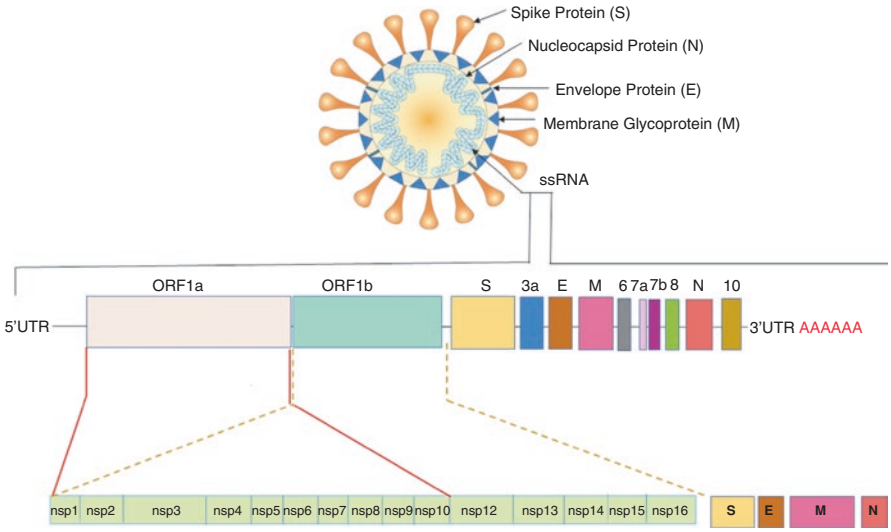

Fig. 1.1 The SARS-CoV-2 morphology and genome sequence. Schematic representation of the coronavirus virion entailing RNA genome, nucleocapsid (N), membrane (M), envelope (E), and the spike (S) proteins on the surface of the virus. The RNA genome has a 5′ cap and 3′ poly (A) tail. The replicas contain open reading frames (ORFs) 1a and 1b encoding 16 nonstructural proteins (nsp1-nsp16). The remaining ORFs encode the structural protein (S, E, M, and N) and accessory proteins [23]

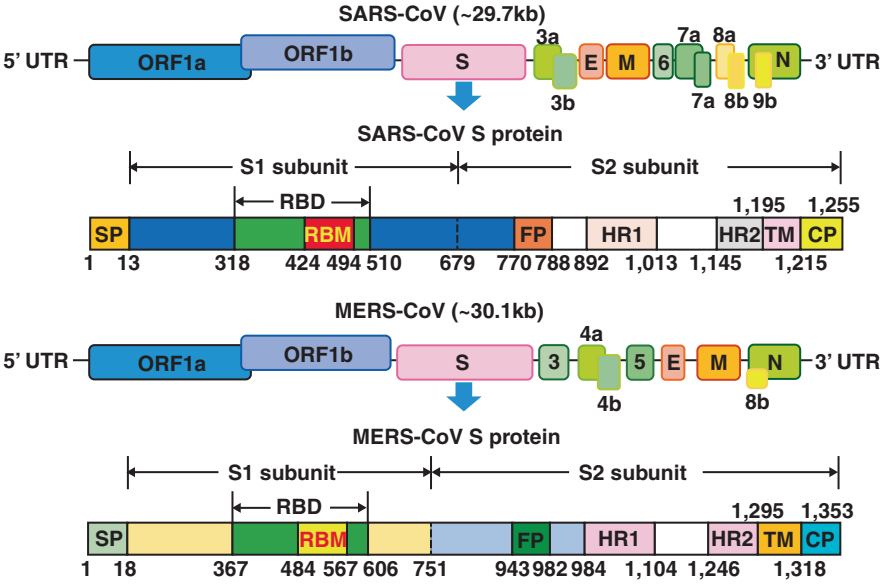

Fig. 1.2 The genome sequence of SARS-CoV and MERS-CoV, differences between the spike protein of each genome. The S protein consists of two functional subunits (S1 and S2). The S1 subunit comprises a receptor-binding domain (RBD), and the RBD comprises a receptor-binding motif (RBM). The S2 subunit includes heptad repeat regions (HR1 and HR2), fusion peptide (FP), transmembrane domain (TM), and fusion peptides (FP)

MERS-CoV have been demonstrated in Fig. 1.2 [28]. There are two subunits of spike protein, S1 and S2. The S1 subunit has a receptor-binding domain (RBD) that binds the receptor-binding motif (RBM) to the host surface. Moreover, the S2 subunit mediates the receptor attachment and the host membrane fusion [23, 29]. The primary host receptor for SARS-CoV and SARS-CoV-2 is the ACE2, while for MERS-CoV is dipeptidyl peptidase 4 (DPP4) [30–33]. Afterwards, in an outbreak of SARS-CoV in 2000, scientists started to search for other human viruses that can cause severe illnesses. In 2010, the MERS-CoV appeared, and the existing research platform from SARS-CoV empowered the scientists to develop a DNA-based vaccine against MERS-CoV infection in March 2020 [34]. When SARS-CoV-2 appeared in 2020 and caused the pandemic, the previous vaccine design methods were reproducible, and the RNA-based COVID-19 vaccine was presented in 2021 [35, 36].

The SARS-CoV-2 Origins

Coronaviruses can typically be categorized into four different genera: alphacoronavirus, betacoronavirus, gammacoronavirus, and deltacuronavirus. Alpha coronaviruses include HCoV-229E and HCoV-NL63 [37]. Beta viruses contain HCoV-OC43, MERS-CoV, SARS-CoV-2, HCoV-HKU1, and SARS-CoV. Likewise, gamma

coronaviruses are comprised of the avian infectious bronchitis virus (IBV) [38]. Delta coronaviruses categories are concluded swine delta coronavirus (PdCoV). Coronavirus is one of the newly emerging viruses that led to many deaths. Its evolution is high-speed, and the virus mutates in different ways and creates various strains [39]. Understanding the virus's evolutionary patterns will help discover more effective treatments and vaccines. The members of the coronaviridae family have been studied in different species of fish, birds, camels, and bats [40]. The most common viruses that infect mammals are alpha and beta coronaviruses, while gamma and delta coronaviruses infect birds. Understanding the evolution or mutation pattern that the virus may have in the future may be helped by evolutionary history [41].

HCoV-229E

Initially, this coronavirus strain was called B814. Another infection with an unidentified respiratory virus led to the formation of a strain cell culture that initiated the infection. This strain eventually became a prototype for HCoV-229E [42]. Under the electron microscope, the B814 and the HCoV-229E strain are very analogous to the avian coronavirus, IBV. HCoV-229E contains ether and is composed of 89 nm particles and has single-stranded RNA, coated as genetic material, and after 6 days causes cytopathic effects. The main methods of the HCoV-229E transmission were droplet respiration and foaming [43, 44].

HCoV-OC43

HCoV-229E was discovered after virus samples from common cold patients were taken, and no antibodies were detected toward this virus, proving there was no B814 mutation equivalent to the HCoV-229E [45]. The OC43 strain was spread and eventually formed the HCoV-OC43 species. The HCoV-OC43 species is an enveloped ssRNA virus in the same way as the HCoV-229E species. HCoV-OC43 is the reason for one-third of the common colds. It is an RNA virus with a 31.5 kb size. The HCoV-229E is also involved in one-third of those cases [46].

SARS-CoV

Despite discovering the role of HCoV-229E and HCoV-OC43, these species were initially thought to be the only two types of human coronaviruses. However, a new strain of coronavirus was distinguished in 2002, the SARS-CoV [21] reported in China that is transferred from palm civets to humans. SARS-CoV was found in 2003 in horseshoe bats. It was found to be an enveloping ssRNA virus. The virus has about 14 ORFs with about 30 kb RNA [47].

HCoV-NL63

An immunocompromised infant with respiratory symptoms in The Netherlands was found to have HCoV-NL63 in 2004 [48]. Studies have elucidated that HCoV-NL63 is isolated from the ancestors of HCoV-229E. Also, HCoV-NL63 possesses an ssRNA genome encased and polyadenylated with 27,553 nucleotides. The virus is more prevalent in winter and milder weather [49].

HCoV-HKU1

HCoV-HKU1 was primarily detected in Hong Kong in January 2005 that is related to the Group II prototype of HCoV-OC43. The positive samples of HCoV-HKU1 were often established in temperate countries like Italy and the USA during winter and spring [50]. The virus is a + ssRNA virus with 29,926 nucleotides. RT-PCR performs rapid diagnosis of HKU1 infections with the assistance of specific monoclonal antibodies (mAb) related to HKU1 [51].

MERS-CoV

MERS-CoV was derived from the sputum of a 60-year-old man hospitalized due to renal failure and severe acute pneumonia in 2012. Subsequent serological evidence confirmed the presence of MERS-CoV in camels in the Middle East, North Africa, and East Africa, indicating camels as a reservoir of MERS-CoV [52]. MERS-CoV has a +ssRNA genome of 30.1 kb. The MERS-CoV replicates in virus-induced bilayer vesicles lacking host pattern recognition receptors, preventing its dsRNA host from being detected [53].

SARS-CoV-2

There have been several cases of pneumonia with an unknown cause reported in Wuhan in December 2019. The virus has been renamed Wuhan coronavirus, but the ICTV (International Committee for the Classification of Viruses) named it SARS-CoV-2 and COVID-19 [35]. SARS-CoV-2 shows more minor mutations because of its corrective function. About 13 mutation sites were detected in the SARS-CoV-2 regions of ORF-1ab, −3a, −8, N, and S, including 8782 in ORF1a and 28,144 in ORF8 with mutation rates of 29.47% and 30.53%, respectively [54]. Genetic analysis of a population of 103 genomes associated with SARS-CoV-2 showed that SARS-CoV-2 advanced into two major forms, L and S, which are well characterized via two members of single nucleotide polymorphisms (SNPs) [55]. Cuttings of the spike protein are located at the S1 and S2 junction, as two significant subunits,

which determine the extent of viral infection and the range of host species. The difference in mortality rates is related to viral mutations and evolutionary ability [21].

The SARS-CoV-2 Structure

Coronaviruses are large—average diameter of 80–120 nm and average molecular mass of 40,000 kDa—roughly spherical and relatively pleiomorphic with distinctive surface spikes projections [56]. Their RNA is in the center of the virus and is protected by the nucleocapsid, membrane protein, and lipid bilayer envelope [57, 58]. The viral capsid possesses a lipid bilayer and four types of structural proteins, namely, S, M, E, and N proteins—an approximate molar ratio of S:E:M is 20:1:300 (Fig. 1.1). The S protein is essential to form an interaction with the host cell. In addition to the S protein, the viral surface also encompasses hemagglutinin-esterase dimer (HE), which is not necessary for replication but is vital for the virus entry [59, 60]. The E protein is the minor structural protein and differs diversely among the coronaviruses [61]. Among the primary structural proteins, M is responsible for shaping the envelope [62]. The N protein is tied to the RNA and empowers the virus to take over the host cells [63, 64]. The genome of coronaviruses includes various ORFs. The gene order in all members is 5′-leader-UTR-replicase (ORF1ab)-S-E-M-N-3′UTR-poly (A) tail [65]. Their genome seems to have a bias against cytosine (C) and guanine (G) nucleotides with the highest composition of uracil (U) and adenosine (A) [66]. In addition to these components, 16 nsps (nsp1 to nsp16) differ between the genera of coronaviruses [9]. These nsps perform vital roles in assembling the replication/transcription complex (RTC), RNA polymerization, RNA proofreading, mRNA capping, allosteric activation, and repression of the host immune system [67, 68].

The coronaviruses spike (S) protein anchors to the ACE2 receptors for viral entrance, expressed on numerous cell surfaces. The transmembrane protease serine 2 (TMPRSS2) and lysosomal proteases also play significant roles in the SARS-CoV-2 entry [69]. Following the cytoplasm entry, the virus induces spatial alteration in the endosome, uncoating the viral nucleocapsid (N). Finally, the viral genome is ultimately released within the cytoplasm, and the RTC initiates [70]. Moreover, the SARS-CoV-2 sustains the largest genome with 30,000 bases in the RNA sequence length. A unique feature of SARSCoV2 is its capacity to cleave the spike protein at its polybasic site through furin-mediated cleavage, which increases its virulence. Moreover, it was proposed that the furin-cleavage region at the SARS-CoV-2 spike protein was needed to enable the virus to infect humans as well as animals [21].

SARS-CoV-2 Variants

Coronaviruses belong to the sub-family of *Orthocoronavirinae* in the family *Coronaviridae*, order *Nidovirales*, and realm *Riboviria* [71, 72]. As mentioned, the coronaviruses are sorted into four genera: deltacoronavirus, gammacoronavirus,

Table 1.1 The SARS-CoV-2 variants of concern

Variants of SARS-CoV-2	Linage	First outbreak	First sample detection	Notable mutations
Alpha	B.1.1.7	United Kingdom	September 2020	N501Y, P681H
Beta	B.1.351	South Africa	May 2020	K417N, E484K, N501Y
Gamma	P.1 (B.1.1.28.1)	Brazil	November 2020	K417T, E484K, N501Y
Delta	B.1.617.2	India	October 2020	L452R, T478K, P681R
Omicron	B.1.1.529	South Africa (Botswana)	November 2021	P681H, N440K, N501Y, S477N

betacoronavirus, and alphacoronavirus. However, the number of species increases and many coronaviruses are unspecified [71, 73]. The betacoronavirus and alphacoronavirus uniquely infect mammalian species, while deltacoronavirus and gammacoronavirus infect both mammalian and avian species. The coronavirus infection mostly leads to respiratory, gastrointestinal, and neurologic disorders [74, 75]. Several variants of SARS-CoV-2 are of interest and concern. Generally, a variant is called a variant of interest when it displays evidence of mutation, which is expected to circulate broadly. The Mu and Lambda variants are currently the World Health Organization (WHO) variants of interest. When a variant of interest is more transmissible and detrimental, it becomes a variant of concern. The recently acknowledged variants of concern are presented in Table 1.1 [76, 77].

Conclusion

In December 2019, the outbreak of SARS-CoV-2 spread in Wuhan, China. This virus causes various diseases, from the common cold to ARDS [78, 79]. The prevalence of ARDS also increases with the rise of inflammatory cytokines. The activation of the ACE2 and TMPRSS2 receptors are the main mechanisms of the cytokine storm [80, 81]. High levels of inflammatory cytokines and chemokines in COVID-19 patients are accounted for more elevated levels of IL-6, IL-1β, IL-10, TNF-α, and IFN-γ through the activation of the various signaling pathways such as NF-κB, STAT3, JAK, AKT, and mTOR pathways [82, 83]. Different variants of coronavirus are determined and classified into Alpha coronaviruses (HCoV-229E and HCoV-NL63), Beta viruses (HCoV-OC43), SARS-CoV, HCoV-HKU1, MERS-CoV, and SARS-CoV-2, Gamma coronaviruses (avian IBV), and Delta coronaviruses (PdCoV) [84, 85]. Nevertheless, several types of coronavirus would be distinguished after mutation in humans because of adapting coronaviruses to their human hosts. Genetic evolution in coronaviruses results in mutant versions of coronaviruses that may differ from their ancestral strains in various ways. During this

pandemic, several variants of SARS-CoV-2 have been described. Recently, different therapeutic approaches have been examined to elucidate precise treatment protocols. Therefore, various medications such as Lopinavir/Ritonavir, Hydroxychloroquine, Tocilizumab, Remdesivir, corticosteroids, as well as methylprednisolone, and dexamethasone resulted in a reduction of symptoms and improved outcomes. Furthermore, some herbal medicines such as quercetin, resveratrol, curcumin, have been tried in the treatment of COVID-19 because of their anti-inflammatory characteristics [86]. Currently, multiple vaccines are developed and distributed worldwide, such as Oxford-AstraZeneca, Pfizer- BioNTech, CoronaVac, and COVID Shield, which support people worldwide and decrease the rate and prevention of getting infected with COVID-19; however, even after injection coronavirus vaccines, with different mechanisms of action, it is possible to be infected with new variant of coronavirus due to mutation in different regions of the virus, particularly structural protein areas.

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