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Coronavirus Disease 2019: Taxonomy, Genomic Structure, Replication and Pathogenesis

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Abstract

The coronavirus disease-2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus-2(SARS-CoV-2). COVID-19 outbreak in Wuhan, China, has now spread too many countries across the world with an increasing death toll. At present, with the rapidly increasing number of cases around the world, which is a significant threat to public health. The World Health Organization has declared the ongoing outbreak as a global public health emergency. Presently, it is vital to control the infection, the transmission route. Due to the absence of adequate evidence, there is still no drug or vaccine that has been officially approved for the treatment. The use of existing drugs to control the progress of the disease and effective option of antiviral treatment, vaccination is currently under development and evaluation. The researchers raced to understand the define the risk factors, the pathogenesis of the disease, develop treatment options, and work on vaccine development. So, it is very vital to understand the structure of the proteins and the genome of the COVID-19. In this review, we summarize current information about the transmissibility, pathogenicity, phenotype features. Furthermore, we discuss the viral characteristics of 2019-nCoV.

Keywords: Coronavirus; SARS-CoV-2; COVID-19; Pathogenesis; Transmissions

Introduction

Coronaviruses (CoVs) are involved in humans and vertebrates. It is an important pathogen that can infect livestock, birds, bat, mouse, and many other wild animals. Besides, in humans, it primarily affects the respiratory system, but also the gastrointestinal, hepatic, and central nervous system [1,2]. In December 2019, an outbreak of pneumonia characterized by fatigue, fever, dry cough with unknown causes appeared in a seafood wholesale wet market in Wuhan City, Hubei Province of China [3]. Consequent isolation of virus from the affected patients and molecular investigations exposed that the new pathogen was a CoV, initially named as 2019 novel coronavirus (2019-nCoV), and later this disease was renamed by WHO as Coronavirus Disease 2019 (COVID-19).

On the other hand, COVID-19 is not the first outbreak of severe respiratory disease caused by CoVs. In 2002, the outbreaks of the severe acute respiratory syndrome (SARS) and the Middle East Respiratory Syndrome (MERS) in 2012 had confirmed the possibility of animal-to-human and human-to-human transmission [4-6]. At present, with the rapidly increasing number of cases around the world, which is a significant threat to public health. So, it is very vital to understand the phenotypic structure and genetic of the COVID-19, and pathogenesis is important for the invention of drugs and vaccines. Here, we review the current evidence about phenotype features of the COVID-19 and discuss viral characteristics of 2019-nCoV.

Taxonomy of CoVs

The current classification of CoVs recognizes 39 species in 27 subgenera, five genera. It has two subfamilies that belong to the family Coronaviridae, suborder Cornidovirineae, order Nidovirales, and realm Riboviria [6]. CoVs are large, enveloped, positive-strand RNA viruses divided into four genera: Alpha, Beta, Delta, and Gamma, of which Alphacoronaviruses and Betacoronaviruses are known to infect humans [7]. To date, six human CoVs (HCoVs) have been identified to cause human diseases [8]. Four CoVs (HCoV 229E, OC43, NL63, and HKU) are endemic in humans. Alphacoronavirus includes HCoV-229E and VNL63, and Betacoronavirus includes HCoV-OC43, HKU1, SARS-CoV, and MERS-CoV. The Gammacoronavirus contains viruses of whales and birds, and Deltacoronavirus includes viruses isolated from pigs and birds [9]. SARS-CoV-2 is similar to the CoV responsible for SARS with >79% sequence identity and more distant from MERS-CoV with only 50% homology [10].

Coronaviral Genomic Structure and Functional Proteins

SARS-CoV-2, 50-200 nm in diameter, belongs to the Betacoronavirus family [11]. CoVs possess the largest genomes among the RNA viruses, ranging from 27 to 32 kb [12]. Phylogenetic analysis revealed that the SARS-CoV-2 is most closely related to BatCoV RaTG13 isolated from Rhinolophus affinis bats with a 96.3% nucleotide homology [13]. SARS-CoV-2 is more related to two bat-derived SARS-like CoVs, bat-SL-CoVZC45, and bat-SL-CoVZXC21 (about 88% identity) [3,6,14] than with SARS-CoV and MERS-CoV [5,8,9].

The RNA genomic structure of CoVs is arranged in the order of 5' UTR-replicase-Spike (S)-Envelope (E)-Membrane (M)-Nucleocapsid (N)-3 'UTR, in which S, E, M, and N encode the structural proteins (Figure 1) [5]. The 5′-UTR most proximal gene of the CoV genome, gene 1, occupies about two-thirds of the genome, and that consists of two large overlapping open reading frames (ORF1a and ORF1b) with a ribosomal frameshifting signal at the junction of the two [15,16]. Upon entry into the host cells, the incoming viral genome is translated to produce two large precursor polypeptides, 1a (pp1a) and 1ab (pp1ab). These polypeptides are processed by the virally-encoded 3-chymotrypsin-like protease (3CLpro) or the main protease (Mpro) and one or two papain-like proteases into 16 nonstructural proteins (nsp1–nsp16) [11]. The nsp1–nsp11 is encoded in ORF1a, whereas the nsp12–16 is encoded in ORF1b. However, many of the nsps are involved in either RNA synthesis or proteolytic processing required for viral

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replication [17]. The nsps play an important role in many processes in viruses and host cells. The 16 nsps of CoVs and their functions are summarized in (Table 1) [18-21].

Nonstructural protein (nsps)	Functions
nsp1	Inhibition of IFN signaling and blocking of host innate immune response by promotion of cellular mRNA degradation. Also suppresses the antiviral host response.
nsp2	Binding to prohibition protein.
nsp3	Papain-like protease involved in protein cleaving, blocking of host innate immune response, and promotion of cytokine expression.
nsp4	DMV formation (contributes to the structure of DMVs as a transmembrane scaffold protein)
nsp5	Cleaves 3CLpro (Mpro) polypeptides and inhibits IFN signalling.
nsp6	Participates in DMV formation, restricting autophagosome expansion.
nsp7	Makes a complex with nsp8 to form a primase, where nsp8 is a second RdRp domain that is proposed to function as a primase and produce primers utilized by the primer-dependent nsp12 RdRp.
nsp8	Processivity clamp for RNA polymerase by formation of a hexadecameric complex with nsp7. Also a cofactor of nsp12 primase.
nsp9	Dimerization, responsible for RNA binding and protein phosphatase activity.
nsp10	Scaffold protein for nsp14 and nsp16
nsp11	Unknown
nsp12	Primer dependent RdRp (replication enzyme)
nsp13	RNA helicase, 5′ triphosphatase
nsp14	A 30–50 exoribonuclease, N7-MTase; involved in proofreading of the viral genome
nsp15	A poly(U)-specific endoribonuclease, involved in evasion of dsRNA sensors, and chymotrypsin-like protease
nsp16	An S-adenosylmethionine-dependent 2′-O-MTase; contributes to avoidance of MDA5 recognition, negatively regulating innate immunity.
Abbreviations: 3CLpro: 3C-like protease domain; DMV: Double-Membrane Vesicle; dsRNA: double-stranded RNA; IFN: Interferon; mRNA: messenger RNA; Mpro: main protease; RdRp: RNA-dependent RNA polymerase; MTase: methyltransferase; MDA5: Melanoma Differentiation-Associated Gene 5.	

Table 1: Nonstructural proteins of coronaviruses and their functions.

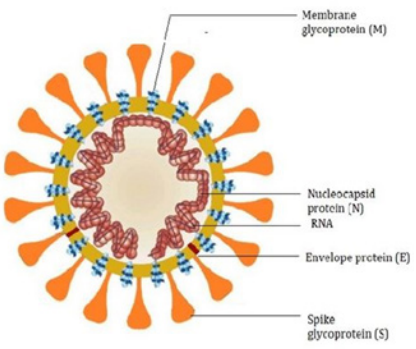

Figure 1: Scheme of the genome and structural proteins of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Coronaviral Replication

The enzymatic activities and the functional domains of many of these essential nsps are foreseen to be preserved between the different genera of CoVs. It is representing their importance in viral replication [22,23]. Then genes for the major structural proteins in all the CoVs, encoded by ORF10 and ORF11 located in the one-third of the genome near the 3'-terminus, occur in the 5'–3' order and play a vital role in viral pathogenesis [11,24,25]. The S protein is a type-I membrane glycoproteins responsible for the formation of "spikes" present on the surface of CoVs. The S protein is accountable for receptor-binding and subsequent viral entry into host cells. N protein is the utmost abundant viral phosphoprotein, and it interacts with the viral genomic RNA and helps in the packaging of the RNA genome into virus particles by recognizing a specific sequence. Intracellular co-localization of N with replicase components is required for RNA synthesis. The N protein-dependent assembly of the viral RNA packaging signal was already established in SARS-CoV [26]. The N protein also exhibits high immunogenicity, and it can be detected in either serum or urine patient samples during the first two weeks of infection, with peak viral shedding around ten days after infection. The M protein supports the shape of the virion particles and binds to the nucleocapsid, whereas the E protein is the smallest major structural protein of SARS-CoV-2 that is involved in viral assembly, virion release, and pathogenesis [27-29].

Transmission of SARS-CoV-2

Early studies reported that the first human SARS-CoV-2 infection seemingly took place in a wet seafood market where several wildlife species were also sold. The first COVID-19 cases were confirmed in individuals who had earlier visited the market, indicating possible animal-to-human transmission. Subsequently, the possibility of human-to-human transmission was considered when a large number of infected patients reported not having exposure to the market [19,30]. Epidemiological studies have increasingly demonstrated human-to-human transmission of SARS-CoV-2 through droplets or direct contact [19,23,25]. In addition to the high transmission efficiency of SARS-CoV-2, global travel's advancement and convenience had led to its worldwide spread [14].

In several studies, SARS-CoV-2 RNA was detected in stool and rectal swabs, as well as in saliva and urine, and even in esophageal erosions and bleeding sites of patients with severe peptic ulcer disease [1,30]. Recent work found that SARS-CoV-2 can be detected in the tears and conjunctival secretions of COVID-19 patients with conjunctivitis, which suggests that ocular infection may be a potential source of SARS-CoV-2 transmission [31]. Maternal-fetal transmission of SARS-CoV-2 was not detected in the majority of the reported patients, although one neonate had a positive real-time quantitative PCR result (qRT-PCR) 36 hours after birth despite being isolated from the mother [32]. SARS-CoV-2 can continue viable on different surfaces such as stainless steel, plastic, glass and cardboard for at least several hours [33]. Contact transmission occurs when a person touches a surface or object contaminated with the virus. Individuals can be infected when they subsequently touch their mouth, nose, or, possibly, eyes, so the contact transmission is plausible but has not been reported.

The basic reproductive number (R0) indicates the transmissibility of a virus that represents the average of new infections generated by an infectious person in a naive population. For R0>1, the number of infected individuals is likely to increase; for R0<1, the transmission is anticipated to decline and eventually disappear [34]. Initial evaluation of COVID-19 transmission dynamics showed that the R0 of SARS-CoV-2 was estimated between 1.4–3.9 [25]. Other studies have estimated the

R0 range to be from 1.4 to 6.49, with a mean of 3.28 with a median of 2.7 [31]. On the other hand, it is worth noting that R0 estimates may vary based upon numerous environmental factors, socio-behavioral, and biologic and must be interpreted with caution [35].

Pathogenesis

The pathogenesis (Figure 2) of the SARS-CoV and SARS-CoV-2 are likely similar. The angiotensin-converting enzyme 2 (ACE-2) receptors found in the type-II pneumocytes in the lungs. The ACE-2 is known as the cell receptor for SARS-CoV, and SARS-CoV-2 uses the same cellular entry receptor (ACE2) as SARS-CoV [36]. Among the structural components of CoVs, the surface spike(S) glycoproteins are composed of two subunits as S1 and S2, and guiding the bond to host receptors. After binding to its receptor, S proteins catalyze the viral and cellular membrane's fusion to let right of entry of the viral genome to the cytosol. The S2 subunit in the SARS-CoV-2 contains a fusion peptide, a transmembrane domain, and a cytoplasmic domain, which is highly conserved. It has been established that when the ACE-2 receptor binds to the S protein, the compound is processed by the Transmembrane protease, serine 2(TMPRSS2), leading to cleavage of the ACE2 receptor and further to active the S protein [37]. Besides, it was shown that TMPRSS 2 primes S, the cathepsins B and L are only required in the absence of this protease [38]. Upon viral enters the cells and trigger the host's immune response and the inflammatory cascade are initiated by antigen-presenting cells (APC).

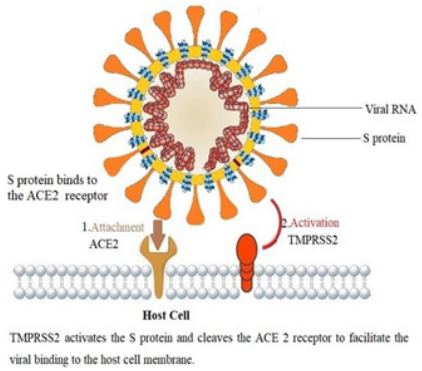

Figure 1: Pathogenesis: 1. The initial attachment of the SARS-CoV-2 virion to the host cell is initiated by interactions between the viral structural S glycoprotein and ACE2 receptor 2. The host cell, TMPRSS2 activates the S protein and promotes viral uptake by cleaving ACE2 receptor.

Treatment and Prevention

At present, there is no approved specific antiviral therapy for COVID-19. Baricitinb, interferon-α, RNA polymerase inhibitors (remdesivir and galidesivir), protease inhibitors (lopinavir and ritonavir), and nucleoside analog (favipiravir and ribavirin) have been suggested as potential therapies for patients with acute respiratory symptoms.39 However, the routine use of lopinavir and ritonavir is not recommended for COVID-19. Besides, there are currently more than 80 clinical trials to identify potential SARS-CoV-2 treatments. The current best approach to treat patients with COVID-19 includes controlling infection sources, isolating the susceptible people, and cutting off the transmission. The infected patients should be identified early and provided with timely isolation with supportive treatments. Then close contact people should be quarantined with follow-up. The definitive approach for controlling the SARS-CoV-2 is developing an effective vaccine to yield neutralizing antibodies. In this present situation, Clinical trials are in progress to facilitate the development of vaccines against COVID-19. However, in the absence of approved antiviral drugs, non-pharmaceutical interventions, includes good personal hygiene, respiratory etiquette, social distancing, and avoiding crowded places, are the most potent weapon against COVID-19.

Conclusion

IThe current COVID-19 pandemic has an unprecedented number of people to date. Moreover, it poses a major health threat on an international scale. The most likely source of SARS-CoV-2 is bats, and virus can be transmitted through droplets and close contact and is highly infectious.SARS-CoV-2 could remain viable in aerosols for hours, and more studies are needed to demonstrate its replication-competence. At present, it is vital to control the infection, the transmission route. However, considerably, the virus's definite mechanism remains indefinite, and no specific drugs for the virus have been developed and the use of existing drugs to control the progress of the disease. The effective option of antiviral treatment and vaccination is currently under development and evaluation. So, understanding the structure of the viral proteins and the genome is essential to define prevention and control measures to minimize the outbreak's impact. Finally, if we want to eliminate the threat of this novel coronavirus, we need to learn more about the pathogenesis of the virus, and this knowledge will pave the technique for the development of therapeutic drugs and vaccines.

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