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REVIEW

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Emerging coronaviruses: Genome structure, replication, and pathogenesis

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Abstract

The recent emergence of a novel coronavirus (2019-nCoV), which is causing an outbreak of unusual viral pneumonia in patients in Wuhan, a central city in China, is another warning of the risk of CoVs posed to public health. In this minireview, we provide a brief introduction of the general features of CoVs and describe diseases caused by different CoVs in humans and animals. This review will help understand the biology and potential risk of CoVs that exist in richness in wildlife such as bats.

KEYWORDS

coronavirus, epidemiology, pathogenesis, respiratory tract, virus classification, zoonoses

1 | INTRODUCTION

Coronaviruses (CoVs) are important pathogens for human and vertebrates. They can infect respiratory, gastrointestinal, hepatic, and central nervous system of human, livestock, birds, bat, mouse, and many other wild animals.[1–3] The outbreaks of the severe acute respiratory syndrome (SARS) in 2002/2003 and the Middle East respiratory syndrome (MERS) in 2012 have demonstrated the possibility of animal-to-human and human-to-human transmission of newly emerging CoVs.[4,5] An outbreak of mystery pneumonia in Wuhan since December 2019 has been drawing tremendous attention around the world. Chinese government and researchers have been taking swift measures to control the outbreak and conduct the etiological studies. The causative agent of the mystery pneumonia has been identified as a novel coronavirus (nCoV) by deep sequencing and etiological investigations by at least five independent laboratories of China (http://virological.org/ and https://www.gisaid.org/). On 12 January 2020, the World Health Organization temporarily named the new virus as 2019 novel coronavirus (2019-nCoV). The sporadic emergence and outbreaks of new types of CoVs remind us that CoVs are a severe global health threat. It is highly likely that new CoV outbreaks are unavoidable in the future due to changes of the climate and ecology, and the increased interactions of human with animals. Thus, there is an urgent need to develop effective therapies and vaccines against CoVs.

2 | CORONAVIRAL GENOME STRUCTURE AND REPLICATION

CoVs belong to the subfamily Coronavirinae in the family of Coronaviridae of the order Nidovirales, and this subfamily includes four genera: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus* (Figure 1A). The genome of CoVs is a single-stranded positive-sense RNA (+ssRNA) (~30 kb) with 5′-cap structure and 3′-poly-A tail. The genomic RNA is used as template to directly translate polyprotein 1a/1ab (pp1a/pp1ab), which encodes nonstructural proteins (nsps) to form the replication-transcription complex

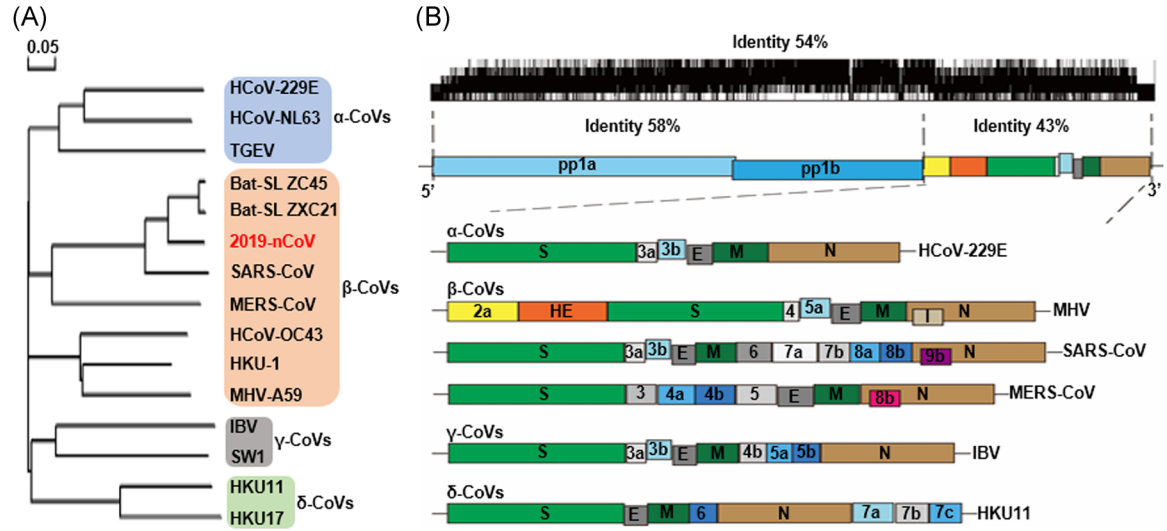

FIGURE 1 The genomic structure and phylogenetic tree of coronaviruses. A, The phylogenetic tree of representative CoVs, with the new coronavirus 2019-nCoV highlighted in red. B, The genome structure of four genera of coronaviruses. Pp1a and pp1b represent the two long polypeptides that are processed into 16 nonstructural proteins. S, E, M, and N indicate the four structural proteins spike, envelope, membrane, and nucleocapsid. 2019-nCoV, 2019 novel coronavirus; CoVs, coronavirus; HE, hemagglutinin-esterase. Viral names: HKU, coronaviruses identified by Hong Kong University; HCoV, human coronavirus; IBV, infectious bronchitis virus; MHV, murine hepatitis virus; TGEV, transmissible gastroenteritis virus

(RTC) in a double-membrane vesicles (DMVs).[6] Subsequently, a nested set of subgenomic RNAs (sgRNAs) are synthesized by RTC in a manner of discontinuous transcription.[7] These subgenomic messenger RNAs (mRNAs) possess common 5′-leader and 3′-terminal sequences. Transcription termination and subsequent acquisition of a leader RNA occurs at transcription regulatory sequences, located between open reading frames (ORFs). These minus-strand sgRNAs serve as the templates for the production of subgenomic mRNAs.[8,9]

The genome and subgenomes of a typical CoV contain at least six ORFs. The first ORFs (ORF1a/b), about two-thirds of the whole genome length, encode 16 nsps (nsp1-16), except *Gammacoronavirus* that lacks nsp1. There is a −1 frameshift between ORF1a and ORF1b, leading to production of two polypeptides: pp1a and pp1ab. These polypeptides are processed by virally encoded chymotrypsin-like protease ($3CL^{pro}$) or main protease (M^{pro}) and one or two papain-like protease into 16 nsps.[10,11] Other ORFs on the one-third of the genome near the 3′-terminus encodes at least four main structural proteins: spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. Besides these four main structural proteins, different CoVs encode special structural and accessory proteins, such as HE protein, 3a/b protein, and 4a/b protein (Figure 1B, lower panel). All the structural and accessory proteins are translated from the sgRNAs of CoVs.[7]

The genome sequence alignment of CoVs shows 58% identity on the nsp-coding region and 43% identity on the structural protein-coding region among different CoVs, with 54% at the whole genome level (Figure 1B, upper panel), suggesting the nsps are more conserved and the structural proteins are more diverse in need of adaptation to new hosts. Since the mutation rates in the replication of RNA viruses are much higher than that of DNA viruses, the genomes of RNA viruses are usually less than 10 kb in length. However, the CoV genome is much larger, with roughly 30 kb in length, the largest known RNA viruses. The maintenance of such a large genome of CoVs may be related to the special features of the CoV RTC, which contains several RNA processing enzymes such as the 3′-5′ exoribonuclease of nsp14. The 3′-5′ exoribonuclease is unique to CoVs among all RNA viruses, probably providing a proofreading function of the RTC.[12–14] Sequence analysis shows that the 2019-nCoV possesses a typical genome structure of CoV and belongs to the cluster of *betacoronaviruses* that includes Bat-SARS-like (SL)-ZC45, Bat-SL ZXC21, SARS-CoV, and MERS-CoV. Based on the phylogenetic tree of CoVs, 2019-nCoV is more closely related to bat-SL-CoV ZC45 and bat-SL-CoV ZXC21 and more distantly related to SARS-CoV (Figure 1A).

3 | FUNCTIONS OF NONSTRUCTURAL AND STRUCTURAL PROTEINS IN CORONAVIRAL REPLICATION

Most of the nsps of nsp1-16 have been reported for their specific roles in the replication of CoVs. However, the functions of some of the nsps are unknown or not well understood. The known functions of the 16 nsps are summarized in Table 1.

Four structural proteins are essential for virion assembly and infection of CoVs. Homotrimers of S proteins make up the spikes on the viral surface and they are responsible for attachment to host receptors.[50,51] The M protein has three transmembrane domains and it shapes the virions, promotes membrane curvature, and binds to the nucleocapsid.[52,53] The E protein plays a role in virus assembly and release, and it involved in viral pathogenesis.[54,55] The N protein contains two domains, both of which can bind virus RNA genome via

TABLE 1 The 16 nonstructural proteins of coronaviruses and their functions

nsps	Functions	References
nsp1	Cellular mRNA degradation, inhibiting IFN signaling	15,16
nsp2	Unknown	17,18
nsp3	PLP, polypeptides cleaving, blocking host innate immune response, promoting cytokine expression	19,20
nsp4	DMV formation	21,22
nsp5	$3CL^{pro}$, M^{pro}, polypeptides cleaving, inhibiting IFN signaling	23–25
nsp6	Restricting autophagosome expansion, DMV formation	26,27
nsp7	Cofactor with nsp8 and nsp12	28,29
nsp8	Cofactor with nsp7 and nsp12, primase	28–30
nsp9	Dimerization and RNA binding	31,32
nsp10	Scaffold protein for nsp14 and nsp16	33–36
nsp11	Unknown	37
nsp12	Primer dependent RdRp	28,38,39
nsp13	RNA helicase, 5′ triphosphatase	40–42
nsp14	Exoribonuclease, N7-MTase	12,43–45
nsp15	Endoribonuclease, evasion of dsRNA sensors	46–48
nsp16	2′-O-MTase; avoiding MDA5 recognition, negatively regulating innate immunity	34,35,49

Abbreviations: $3CL^{pro}$, chymotrypsin-like protease; DMV, double-membrane vesicle; dsRNA, double-stranded RNA viruses; IFN, interferon; mRNA, messenger RNA; M^{pro}, main protease.

different mechanisms. It is reported that N protein can bind to nsp3 protein to help tether the genome to RTC, and package the encapsidated genome into virions.[56–58] N is also an antagonist of interferon (IFN) and viral encoded repressor of RNA interference, which appears to be beneficial for the viral replication.[59]

3.1 | Diversity of CoV pathogenesis

Different CoVs display diverse host range and tissue tropism. Usually, *alphacoronaviruses* and *betacoronaviruses* infect mammals. In contrast, *gammacoronaviruses* and *deltacoronaviruses* infect birds and fish, but some of them can also infect mammals.[4,60] Before 2019, there were only six CoVs that were known to infect human and cause respiratory diseases. HCoV-229E, HCoV-OC43, HCoV-NL63, and HKU1 cause only mild upper respiratory disease, and in rare cases some of them can cause severe infection in infants, young children and elders. SARS-CoV and MERS-CoV can infect lower respiratory tract and cause severe respiratory syndrome in human.[56,61] Some CoVs can infect livestock, birds, bats, mice, whales, and many other wild animals, and they can cause great economic loss. For example, in 2016, an HKU2-related bat CoV, swine acute diarrhea syndrome CoV, caused a large-scale outbreak of fatal disease in pigs in Southern China, and more than 24 000 piglets were dead.[62] This is the first documented spillover of a bat CoV that caused severe disease in livestock.[4,63]

The new CoV, 2019-nCoV, which belongs to *betacoronaviruses* based on sequence analysis (Figure 1A), can also infect the lower respiratory tract and cause pneumonia in human, but it seems that the symptoms are milder than SARS and MERS. Up to 20 January 2020, 291 cases in total have been confirmed in China by sequence analysis, clinical diagnosis and epidemiological examination, including 270 cases in Wuhan and 21 cases in Beijing, Shanghai, and Guangdong (http://www.nhc.gov.cn/yjb/new_index.shtml). In addition, four cases were confirmed in three other countries, including two cases in Thailand, one case in Japan, and one case in South Korea; all these patients had stayed in or visited Wuhan 2 weeks before the onset of the symptoms. Six deaths and 63 patients with severe symptoms were reported in Wuhan (http://wjw.wuhan.gov.cn/). Among the six death cases, four patients with published information are elder people of over 60 years old and have other illnesses before the infection, such as abdominal tumor and chronic liver disease, myocarditis and renal dysfunction, and cardiovascular disease.

Many of the patients have direct or indirect contact with the Wuhan Huanan Seafood Wholesale Market that is believed to be the original place of the outbreak of the 2019-nCoV. However, transmission of 2019-nCoV from fish to human is unlikely. The 2019-nCoV and fish CoVs such as Beluga Whale CoV/SW1 belong to different genera and apparently have different host ranges. As the Wuhan seafood market also sells other animals, the natural host of 2019-nCoV awaits to be identified. Due to the possibility of transmission from animal to human, CoVs in livestock and other animals including bats and wild animals sold in the market should be constantly monitored. In addition, more and more evidence indicate the new virus 2019-nCoV is spread via the route of human-to-human transmission because there are infections of people who did not visit Wuhan but had close contact with family members who had visited Wuhan and got infected (http://www.cctv.com/).

The major pathogenic CoVs are listed in Table 2 for better understanding the pathogenesis of CoVs.

4 | TREATMENT AND PREVENTION

At present, there is no single specific antiviral therapy for CoV and the main treatments are supportive. Recombinant IFN with ribavirin only has limited effects against CoVs infection.[64] After SARS and MERS epidemics, great efforts have been devoted to development of new antivirals targeting CoVs proteases, polymerases, MTases, and entry proteins, however, none of them has been shown to be efficacious in clinical trials.[65–67] Plasma and antibodies obtained from the convalescent patients have been proposed for use in treatment.[68]

In addition, various vaccine strategies, such as using inactivated viruses, live-attenuated viruses, viral vector-based

TABLE 2 List of important pathogenic coronaviruses

Virus	Genus	Host	Symptoms
Human CoV-229E	Alpha	Human	Mild respiratory tract infections
Human CoV-NL63	Alpha	Human	Mild respiratory tract infections
PRCV/ISU-1	Alpha	Pig	Mild respiratory tract infections
TGEV/PUR46-MAD	Alpha	Pig	Diarrhea, with 100% mortality in piglets less than 2-wk-old
PEDV/ZJU-G1-2013	Alpha	Pig	Severe watery diarrhea
SeACoV-CH/GD-01	Alpha	Pig	Severe and acute diarrhea and acute vomiting
Canine CoV/TU336/F/2008	Alpha	Dog	Mild clinical signs, diarrhea
Camel alphacoronavirus isolate camel/Riyadh	Alpha	Camel	Asymptomatic
Feline infectious peritonitis virus	Alpha	Cat	Fever, vasculitis, and serositis, with or without effusions
Human CoV-HKU1	Beta	Human	Pneumonia
Human CoV-OC43	Beta	Human	Mild respiratory tract infections
SARS-CoV	Beta	Human	Severe acute respiratory syndrome, 10% mortality rate
MERS-CoV	Beta	Human	Severe acute respiratory syndrome, 37% mortality rate
Bovine CoV/ENT	Beta	Cow	Diarrhea
Equine CoV/Obihiro12-1	Beta	Horse	Fever, anorexia, leucopenia
MHV-A59	Beta	Mouse	Acute pneumonia and severe lung injuries
Beluga Whale CoV/SW1	Gamma	Whale	Pulmonary disease, terminal acute liver failure
IBV	Gamma	Chicken	Severe respiratory disease
Bulbul coronavirus HKU11	Delta	Bulbul	Respiratory disease (collected from respiratory tract of dead wild birds)
Sparrow coronavirus HKU17	Delta	Sparrow	Respiratory disease (collected from respiratory tract of dead wild birds)

vaccines, subunit vaccines, recombinant proteins, and DNA vaccines, have been developed but have only been evaluated in animals so far.[69,70]

Since there is no effective therapy or vaccine, the best measures now are to control the source of infection, early diagnosis, reporting, isolation, supportive treatments, and timely publishing epidemic information to avoid unnecessary panic. For individuals, good personal hygiene, fitted mask, ventilation, and avoiding crowded places will help to prevent CoVs infection.

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