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Pathogenic Human Coronaviruses

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Nomenclature

3CLpro	3C-like protease
ARDS	Acute respiratory distress syndrome
BAL	Bronchoalveolar lavage
C-terminus	Carboxy terminus
CDC	Centers for Disease Control and Prevention
CoV(s)	Coronavirus (es)
CTD	C-terminal domain
E	Envelope protein
EIA(s)	Enzyme immunoassay(s)
EM	Electron microscopy
ER	Endoplasmic reticulum
ERGIC	Endoplasmic reticulum Golgi intermediate compartment
GTIs	Gastrointestinal tract infections
hCoV(s)	Human coronavirus (es)
HCoV-229E	Human coronavirus 229E
HCoV-4408	Human coronavirus 4408
HCoV-HKU1	Human coronavirus HKU1
HCoV-NL63	Human coronavirus NL63
HCoV-OC43	Human coronavirus OC43
ICU(s)	Intensive care unit(s)
IFN(s)	Interferon(s)
kb	Kilobases
kDa	Kilodalton
LRTIs	Lower respiratory tract infections
M	Membrane protein
MERS	Middle East respiratory syndrome
MERS-CoV	Middle East respiratory syndrome coronavirus
N	Nucleocapsid protein

nsps	Non-structural proteins
NTD	N-terminal domain
N-terminus	Amino terminus
ORF	Open reading frame
PBM	PDZ-binding motif
pp1a	Replicase polyprotein 1a
pp1ab	Replicase polyprotein 1ab
RBD	Receptor-binding domain
RBM	Receptor-binding motif
RdRp	RNA-dependent RNA polymerase
RNA	Ribonucleic acid
RT-PCR	Reverse transcription polymerase chain reaction
RTC	Replication-transcription complex
S	Spike protein
SARS	Severe acute respiratory syndrome
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
sg	Subgenomic
TMDs	Transmembrane domains
URTIs	Upper respiratory tract infections
α	Alpha
β	Beta
γ	Gamma
δ	Delta

Properties of human coronaviruses

Coronaviruses (CoVs) are found worldwide and infect a variety of animals, causing illnesses that range from gastrointestinal tract infections (GTIs), encephalitis and demyelination; and can be fatal (Graham et al., 2013). Traditionally, the human CoVs (hCoVs) have been associated with mostly upper respiratory tract infections (URTIs) and GTIs in humans. In recent years, however, it has become increasingly evident that the hCoVs can cause more severe lower respiratory tract infections (LRTIs) such as bronchitis, pneumonia and even acute respiratory distress syndrome (ARDS) (van der Hoek, 2007), and can be lethal.

Classification

The CoVs belong to the family *Coronaviridae* in the order *Nidovirales*. The subfamily *Coronavirinae* can be further divided into four genera, viz. alpha (α)-, beta (β)-, gamma (γ)- and delta (δ)-CoVs (Table 1). Five of the hCoVs, i.e. HCoV-OC43, HCoV-HKU1, as well as the more pathogenic SARS-CoV, MERS-CoV and SARS-CoV-2, belong to the genus β-CoV. The remaining two hCoVs, HCoV-229E and HCoV-NL63, belong to the genus α-CoV (van Regenmortel et al., 2000; Pradesh et al., 2014).

Structure and genome

CoVs are spherical-shaped enveloped viruses with a diameter of roughly 100 nm (Davies and Macnaughton, 1979). The CoV particles contain a helical nucleocapsid that is formed by the viral genomic RNA and viral nucleocapsid (N) protein complex. Viewed under an electron microscope, the virus particle is surrounded by a "corona" or halo (Latin for "crown") (Fig. 1A), from which its name derives (Coronaviruses, 1968). The halo is formed by the three major structural proteins spike, membrane, and envelope (S, M, and E) projecting as spikes from the viral envelope (Fig. 1B).

CoVs have positive sense, single-stranded RNA genomes ranging in size from 26 to 32 kilobases (kb), the largest of the known viral RNA genomes. Common to all CoVs, the genome is organized in the conserved order, 5′-replicase (1a/1b), spike, envelope, membrane and nucleocapsid-3′ (Fig. 2). The genome has a 5′-cap and is 3′-polyadenylated (Pyrc et al., 2007). The 5′ two-thirds of the CoV genome contain a large 5′ frameshifted polyprotein (ORF1a/ORF1ab). The open reading frames (ORFs) produced by this polyprotein encode for proteins essential for viral RNA replication and are called non-structural proteins (nsps) (van der Hoek et al., 2006). The 3′ one-third of the genome contain the genes encoding for the major structural proteins. Interspersed among, or even overlapping, these structural ORFs is a number of accessory genes. These subgroup-specific ORFs vary in number, location and size (Liu et al., 2014).

Table 1 Classification of the selected coronaviruses.

Genus	*Species*
α-CoV	Transmissible gastroenteritis coronavirus (TGEV)
	Canine coronavirus (CCoV)
	Porcine respiratory coronavirus (PRCoV)
	Feline coronavirus (FeCoV)
	Porcine epidemic diarrhea coronavirus (PEDV)
	Human coronavirus 229E (HCoV-229E)
	Human coronavirus NL63 (HCoV-NL63)
β-CoV	Bat coronavirus (BCoV)
	Porcine hemagglutinating encephalomyelitis virus (HEV)
	Murine hepatitis virus (MHV)
	Human coronavirus OC43 (HCoV-OC43)
	Human coronavirus HKU1 (HCoV-HKU1)
	Severe acute respiratory syndrome coronavirus (SARS-CoV)
	Middle East respiratory syndrome coronavirus (MERS-CoV)
	Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)
γ-CoV	Avian infectious bronchitis virus (IBV)
	Turkey coronavirus (TCoV)
δ-CoV	Porcine Deltacoronavirus (PDV)

hCoVs in bold.

Jaiswal NK and Saxena SK (2020). Classical coronaviruses. *Coronavirus Disease 2019 (COVID-19): Epidemiology, Pathogenesis, Diagnosis, and Therapeutics*, pp. 141–150. https://doi.org/10.1007/978-981-15-4814-7_12.

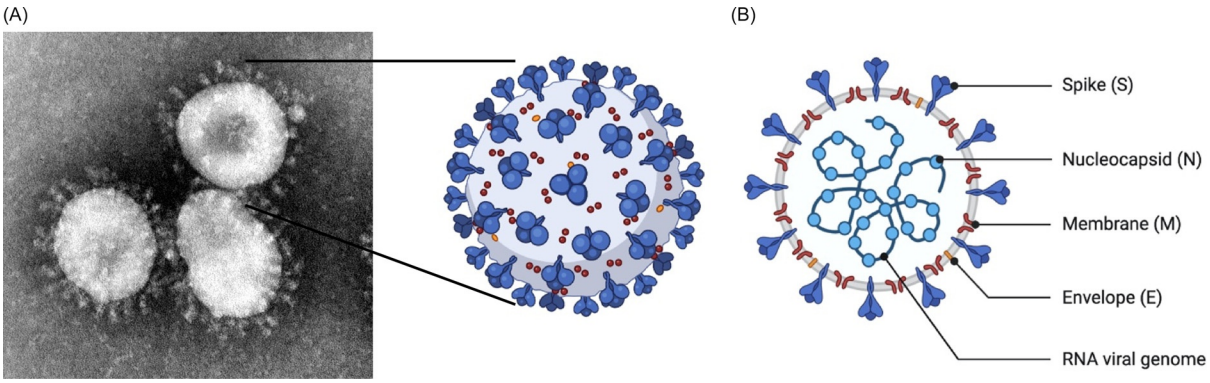

Fig. 1 Coronavirus morphology and structure. (A) Negative contrast electron microscopy of SARS-CoV particles, showing the large spikes and characteristic halo. (CDC/Dr. Fred Murphy—This media comes from the Centers for Disease Control and Prevention's Public Health Image Library (PHIL), with identification number #4814. This image is in the public domain and thus free of any copyright restrictions). (B) Representation of the CoV virion structure, showing the single-stranded, positive-sense RNA genome in complex with the nucleocapsid (N) to form ribonucleoprotein. The (N) is packaged into the core of the virus particle, with the spike (S), envelope (E), and membrane (M) proteins embedded into the envelope (created with BioRender.com). (A) Centers for Disease Control and Prevention's Public Health Image Library (PHIL), (B) Reprinted from *Human Coronavirus Structure*, by BioRender.com (2020). Retrieved from https://app.biorender.com/biorender-templates.

Genes and proteins

Spike protein (S)

S is a large protein (about 150 kDa) that trimerizes to form the distinctive spike structures on the surface of the virion. This protein facilitates viral entry into the host cell by mediating attachment of the virus to the host cell surface receptors. This is then followed by fusion between the viral and host cell membranes (Siu et al., 2008; Kirchdoerfer et al., 2016; Song et al., 2004). Attachment and fusion are facilitated by host proteases processing the S into S1- and S2-subunits (Millet and Whittaker, 2015). Next, the two subunits trimerize and fold into a metastable pre-fusion conformation. Research now shows that it's the S1-subunit that mediates receptor binding, while the S2-subunit is responsible for membrane fusion. The S1-subunit typically possesses two domains capable of binding to host cell receptors: an amino (N)-terminal domain (NTD) and a carboxy (C)-terminal domain (CTD) (Fig. 3) (Mou et al., 2013; Li et al., 2003).

For some CoVs, the expression of S at the cell membrane stimulates cell-to-cell fusion between infected and neighboring, uninfected cells. This formation of syncytia (i.e. giant, multinucleated cells) could possibly be a viral strategy that allows direct

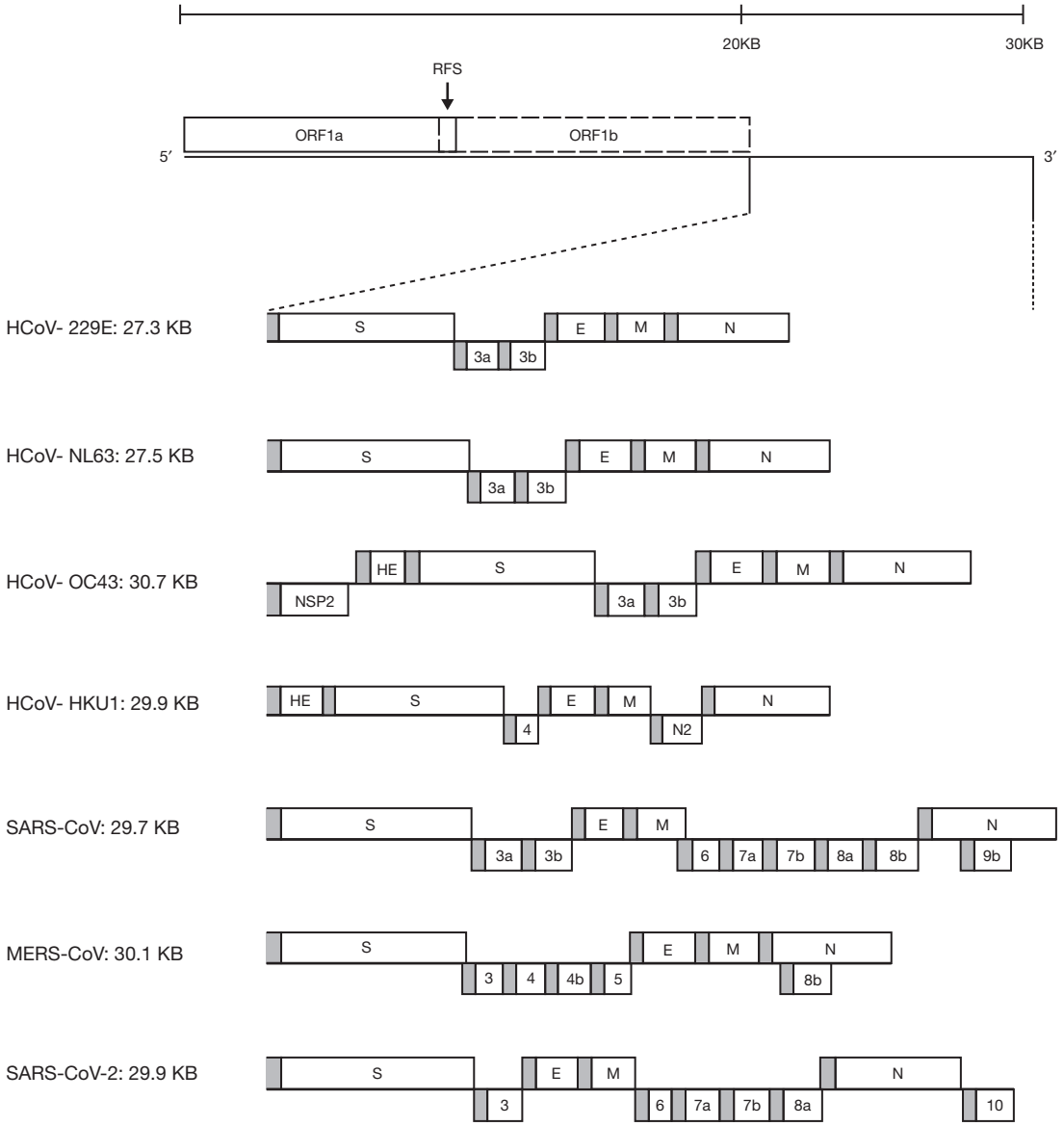

Fig. 2 Schematic organization of human coronavirus (α and β CoVs) genomes. hCoVs contain large genomes about 26–32 kb in size. The 5′-end, two-thirds of the genome contain the overlapping open reading frames 1a and 1b. The remaining 3′-end one-third of the genome (expanded region) encodes for the structural spike (S), nucleocapsid (N), membrane (M), envelope (E), and accessory proteins (vary depending on the specific CoV).

spread of the virus between cells, thereby avoiding virus-neutralizing antibodies in the host serum (Glowacka et al., 2011; Qian et al., 2013).

Nucleocapsid protein (N)

The CoV N contains three conserved and highly distinct domains; two structural and independently folded structural regions, the NTD and a CTD, separated by an intrinsically disordered central region called the RNA-binding domain (Fig. 4). All three regions are capable of binding RNA, allowing N to bind the viral genome in a beads-on-a-string type conformation (McBride et al., 2014; Fehr and Perlman, 2015). N is a multifunctional protein and is abundantly produced within infected cells. Important functions of N include, binding to viral RNA to form the ribonucleocapsid and it has been proposed to play key roles in virus replication, transcription and translation. In host cells, N has been shown to target and interact with many host proteins, potentially leading to deregulation of the cell-cycle and inhibition of interferon (IFN) production, which probably plays a role in viral pathology (McBride et al., 2014).

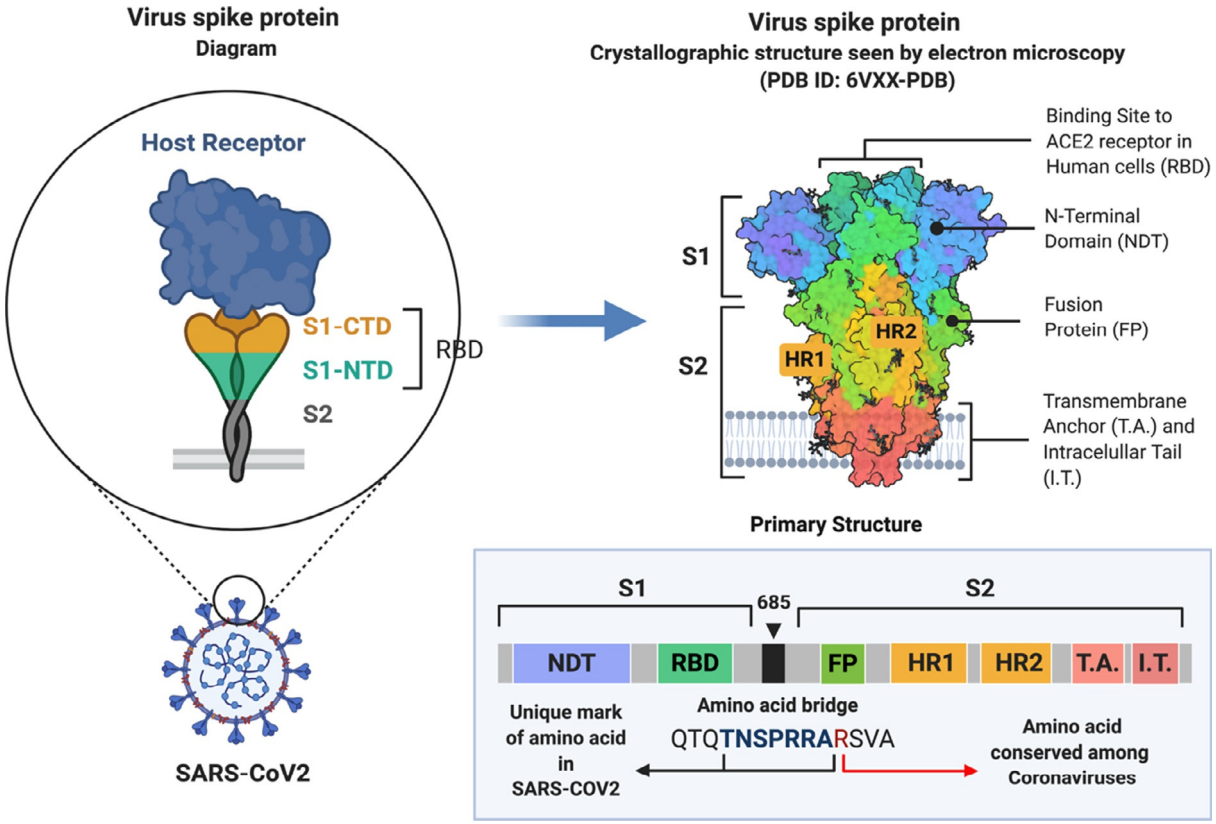

Fig. 3 The S glycoprotein of the newly discovered SARS-CoV-2. Representation of the three-dimensional structure of coronavirus S. *S1*, receptor-binding subunit; *S2*, membrane fusion subunit; *TA* (*or TM*), transmembrane anchor; *IT (or IC)*, intracellular tail. The one-dimensional structure of coronavirus S shows the NTD (N-terminal domain). FP (fusion protein or peptide), HR1 (heptad repeat 1), and HR2 (heptad repeat 2) are structural units in coronavirus S2 that function in-membrane. S1 and S2 are linked together by a polybasic amino acid bridge, which may be important in studying viral targeting (created with BioRender.com). Based on *An In-Depth Look Into the Structure of the SARS-CoV2 Spike Glycoprotein* and *Schematic of Spike-Receptor Binding Mechanism of SARS-CoV-2*, by BioRender.com (2020). Retrieved from https://app.biorender.com/biorender-templates.

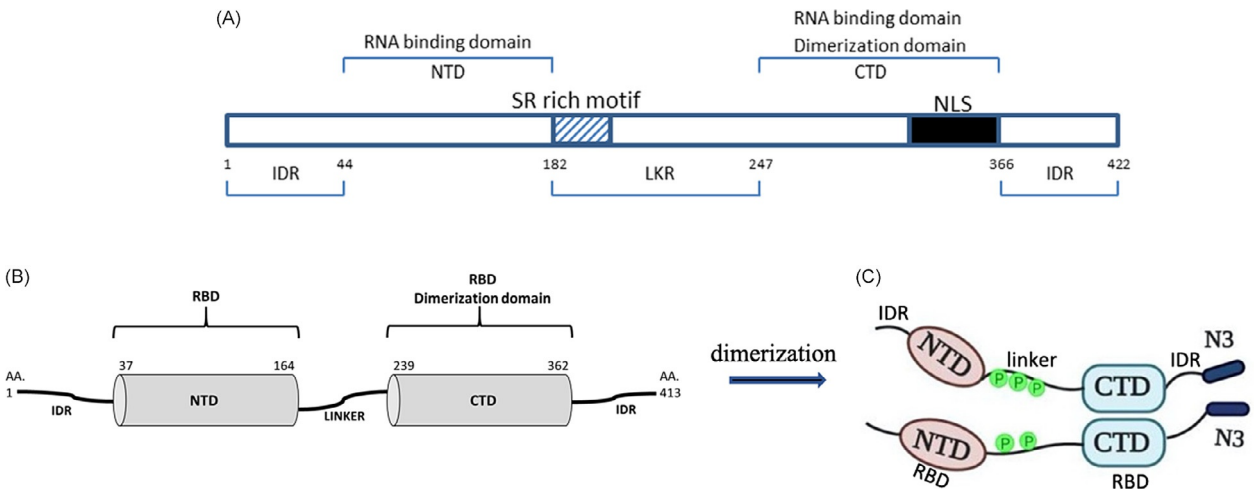

Fig. 4 The coronavirus nucleocapsid (N). (A), (B) Domain organization of the SARS-CoV N protein with the intrinsically disordered regions (IDR), N terminal domain (NTD), linker region (LKR), and C-terminal domain (CTD) shown. In (A) the charged SR rich (striated box) and the nuclear localization signal (NLS, *solid box*) motifs are shown (McBride et al., 2014). (C) Phosphorylation (P, *green*) of the SR/RS dipeptides by cellular kinases prevents aggregation of N and leads to the assembly of soluble dimers with the acidic carboxyl-tail domains (N3) exposed (McBride et al., 2014; Nikolakaki and Giannakouros, 2020). (A) and (B) Mcbride R, Van Zyl M, and Fielding BC (2014). The coronavirus nucleocapsid is a multifunctional protein. *Viruses* 6: 2991–3018, (C) Nikolakaki E and Giannakouros T (2020). SR/RS motifs as critical determinants of coronavirus life cycle. *Frontiers in Molecular Biosciences* 7: 219. https://doi.org/10.3389/fmolb.2020.00219.

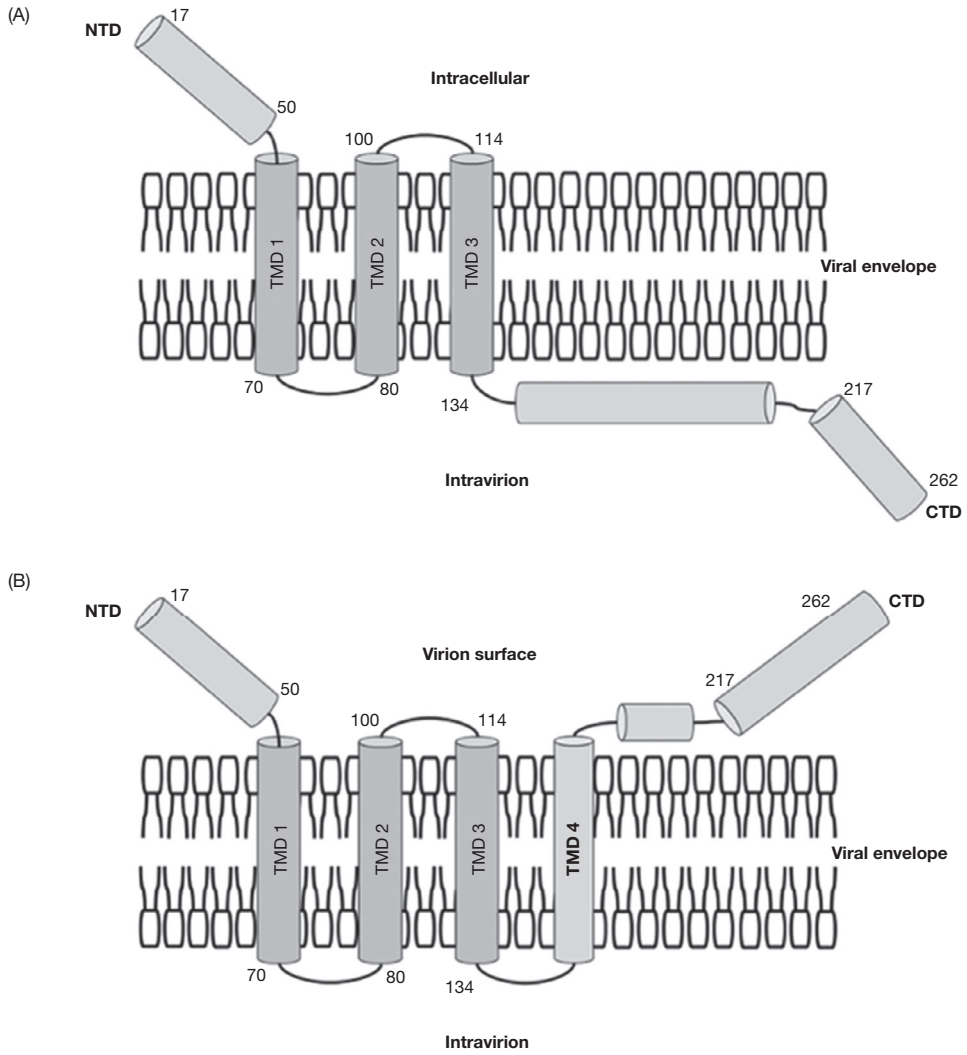

Fig. 5 The two predicted topologies of the coronavirus membrane (M). (A) In the first prediction, the M has three transmembrane domains (TMDs) located within the viral envelope. In this topology of the coronavirus M, the N-terminus domain (NTD) is found on the outside of the virion envelope and the C-terminus domain (CTD) on the inside of the virion. (B) In the second prediction, the M is presented with both the NTD and CTD at the outer surface of the virion. The TMDs are labeled 1–4.

Membrane protein (M)

M is the most abundant structural protein and defines the shape of the viral envelope (Neuman et al., 2011). This is a small (about 25–30 kDa) protein and contains three or four transmembrane domains (TMDs) (Fig. 5). Moreover, the protein has a small N-terminal glycosylated ectodomain and a larger C-terminal endodomain that extends into the virus particle (Fehr and Perlman, 2015). Homotypic interactions between the M proteins are the major driving force behind virion envelope formation but, on its own, is not sufficient for virion formation (de Haan et al., 2000). M needs to interact with all the major CoV structural proteins to drive the process of viral assembly (Masters, 2006). Critical for the incorporation of S into new virions, the interaction between S and M facilitates the retention of S in the endoplasmic reticulum (ER)-Golgi compartment (ERGIC)/Golgi complex where this incorporation can proceed (Mortola and Roy, 2004). M also interacts with N to stabilize the nucleocapsid (N-viral RNA complex), as well as the internal core of virions, thereby promoting completion of viral assembly (Narayanan et al., 2000). Together, M and E make up the viral envelope and their interaction is enough for the assembly and release of virus-like particles (Corse and Machamer, 2003).

Envelope protein (E)

E is a small protein (~8–12 kDa) present in low quantity within the viral structure. Interestingly, the sequence of CoV E proteins is not well conserved, but all have a common architecture (Fehr and Perlman, 2015). The E protein is a transmembrane protein, containing an N-terminal ectodomain and a C-terminal endodomain (Fig. 6). More recent studies have shown that the CoV E likely

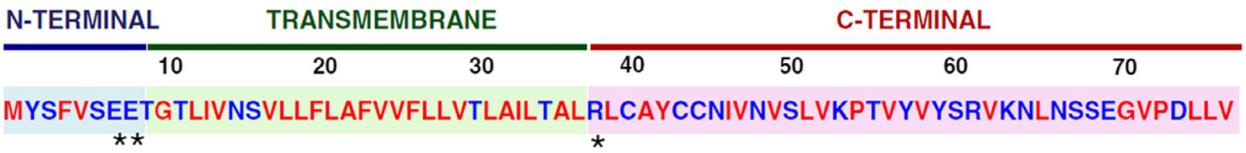

Fig. 6 The primary structure of the coronavirus envelope (E). The primary amino acid sequence and predicted structural domains of the SARS-CoV E, which consists of the N-terminal domain (NTD), the transmembrane domain (TMD), and the C-terminal domain (CTD). The NTD is predicted to be on the external surface of the virion, with the CTD on the inside. The amino acid properties shown: hydrophobic *(red)*, hydrophilic *(blue)*, polar, charged *(asterisks)* (Schoeman and Fielding, 2019). Schoeman D and Fielding BC (2019). Coronavirus envelope protein: Current knowledge. *Virology Journal* 16: 69.

plays crucial roles in the viral replication cycle and immunopathology, including virion assembly, budding and release, apoptosis, inflammation and even autophagy (Schoeman and Fielding, 2019, 2020).

Accessory proteins

The accessory proteins are subgroup-specific ORFs that vary in number, location and size in the CoV genome (Liu et al., 2014). These ORFs share no similarity with accessory genes of CoVs belonging to other subgroups (Lai and Cavanagh, 1997), nor to any other known viral or cellular proteins. Even though CoV accessory proteins are believed to be mostly dispensable for growth in vitro (Oostra et al., 2007), these genes are maintained in the virus genomes under selective pressures. This is evidence that they likely confer some biological advantage to the virus in the natural environment, i.e. these proteins have a function in vivo in the natural host. These accessory proteins normally act by interfering with cellular processes, or by modulating virus-host interactions at the organism level. In fact, recent research proposes a wide range of possible functions for CoV accessory proteins, including modulation of viral pathogenicity and replication, acting as cell death inducers, and IFN antagonists, to name a few. Some of these accessory proteins have also been identified as minor viral structural components (McBride and Fielding, 2012; Oostra et al., 2007).

Viral replication

After binding to the cellular receptor, the CoV S undergoes conformational changes that lead to fusion between the viral envelope and the cell membrane (Fig. 7). The CoV then deposits its RNA genome into the host cytoplasm through endocytosis or direct membrane fusion. To synthesize viral subgenomic (sg) mRNAs, CoVs employ a discontinuous replication strategy (Pyrc et al., 2004). During the first stage of virus replication, the positive strand viral RNA serves as the mRNA for translation of two large proteins—ORF 1a and 1b—each encoding units of the RNA-dependent RNA polymerase (RdRp). The synthesis of the 1ab polyprotein involves a −1 ribosomal frameshift during translation of the 1a gene (Sawicki et al., 2007; Pyrc et al., 2004). The 1a and 1ab polyproteins (pp1a and pp1ab) are then cleaved by viral-encoded proteases to produce, on average 15–16, nsps. Typically, the 1a polyprotein is cleaved to form nsp 1–11, and the 1ab polyprotein gives rise to nsp 12–16. These nsps form the replicase-transcriptase proteins of CoVs and assemble, along with host and other viral proteins, into a membrane-bound replication-transcription complex (RTC). The active RNA polymerase transcribes full-length complementary (negative-sense) RNA, which is then copied into a positive sense sg mRNA. The subsequent transcription of the positive sense sg mRNA produces six distinct mRNAs, which includes the full length RNA genome, as well as a nested set of 3′-coterminal overlapping sg mRNAs. Each of the sgRNAs serves as a code for one of the ORFs downstream of the replicase gene. With the exception of ORF-E, the 5′-end of each ORF contains a transcription regulatory sequence of AACUAAA, which is essential for sg mRNA synthesis. Also, all the positive sense mRNAs share a leader sequence of approximately 70 nucleotides which is identical to the leader sequence of the genomic RNA. The viral membrane proteins insert into the ERGIC. As this happens, the full length viral RNA genome associates with the N. Next, the newly formed ribonucleoprotein complex interacts with the M in the ERGIC membrane and viral particles form as the nucleocapsid complex buds into the lumen of the ERGIC. The virus then moves through the ERGIC and exits the cell, most likely via exocytosis (Marra et al., 2003).

Pathogenic coronaviruses

Before 2003, only two CoVs, HCoV-OC43 and HCoV-229E (Tyrrell and Bynoe, 1965; Hamre and Procknow, 1966), were known to infect humans. In the years following the severe acute respiratory syndrome (SARS) outbreak, two additional HCoV were identified, viz. HCoV-NL63 (van der Hoek et al., 2004) and HKU1 (Woo et al., 2005). As far as we know, only HCoV-OC43, HCoV-229E, HCoV-NL63 and HKU1 continuously circulate in the global human population, resulting in infections throughout the year (Fielding, 2011). The first pathogenic CoV to cause severe acute respiratory tract disease in humans was identified in early 2003 (Drosten et al., 2003; Peiris et al., 2003b; Ksiazek et al., 2003). This novel CoV was eventually named severe acute respiratory syndrome CoV (SARS-CoV). In September 2012, the second pathogenic novel CoV was identified in two patients, of which one died

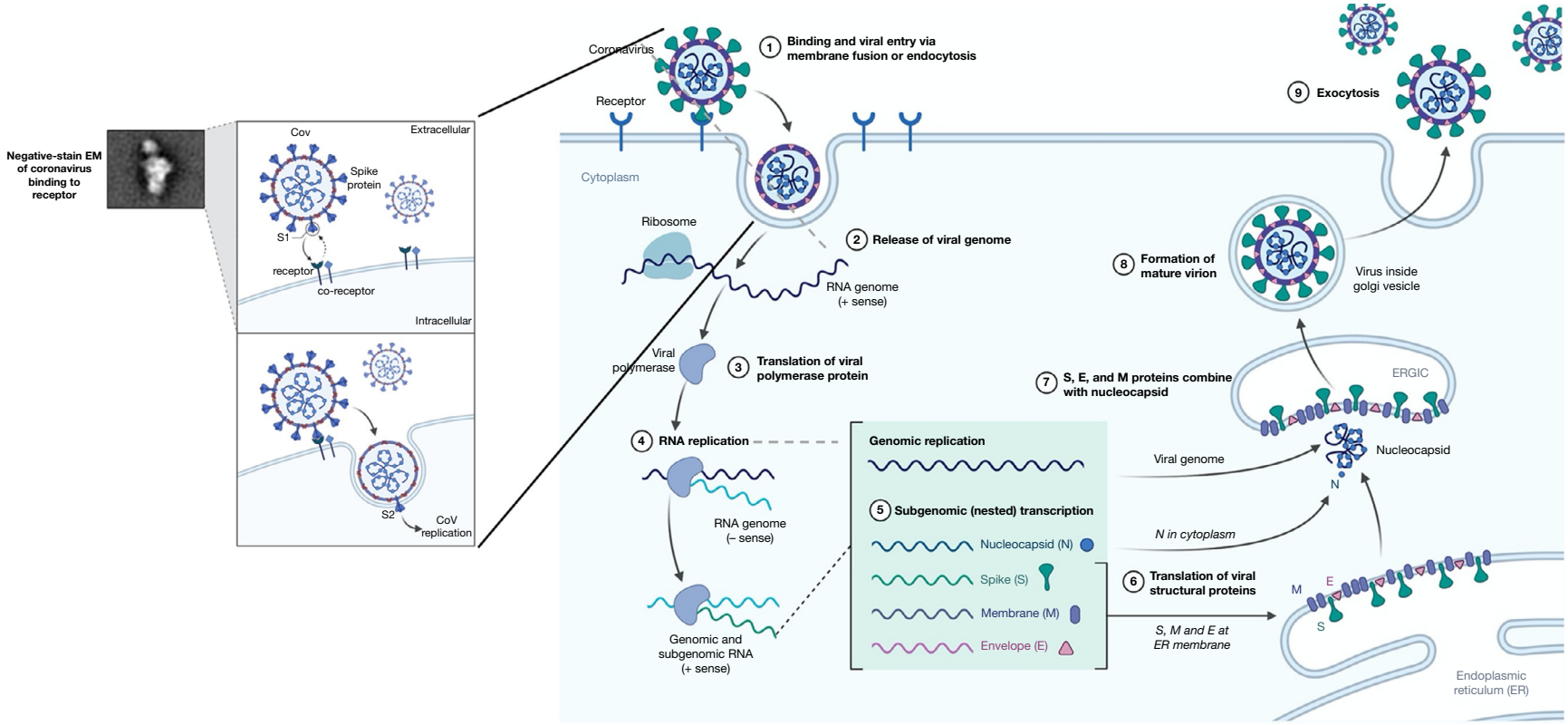

Fig. 7 Overview of the coronavirus (CoV) replicative cycle. After the CoV binds to its specific host cell receptor, the virus enters the cell by receptor-mediated endocytosis (1), and the genomic RNA is released into the cytosol (2); the latter is a result of the fusion of the endosomal and viral membranes. Next, translation of the viral genome yields the pp1a and pp1ab replicase polyproteins 1a and 1ab (pp1a and pp1ab) (3). Numerous internal proteases then cleave the polyproteins, and the resultant viral non-structural proteins (nsps) assemble into an replication-transcription complexes (RTCs) that engages in minus-strand RNA synthesis (4). During this step, both full-length and subgenomic (sg)-minus strand RNA are produced; the sg-minus strand RNA is then used as templates in the synthesis of the sg mRNAs which are needed to express the CoV structural and accessory protein genes (5,6). Ultimately, the (full-length) genomic RNA is encapsidated by multiple copies of the N protein and meets the structural proteins at the endoplasmic reticulum (ER)-Golgi intermediate compartment (ERGIC) and become enveloped by budding from smooth intracellular membranes (7,8). Finally, the new virions leave the cell by following the exocytic pathway (9) (de Wilde et al., 2018) (created with BioRender.com). Based on *SARS-CoV-2 Targeting of ACE2 Receptor and Entry in Infected Cell* and *Coronavirus Replication Cycle*, by BioRender.com (2020). Retrieved from https://app.biorender.com/biorender-templates.

(Zaki et al., 2012); this virus was eventually named Middle East respiratory syndrome CoV (MERS-CoV). Not until early 2020, was the third pathogenic hCoV—and only seventh CoV known to infect humans—identified and eventually named SARS-CoV-2 (Huang et al., 2020b).

Severe acute respiratory coronavirus (SARS-CoV)

SARS-CoV eventually spread to more than 30 countries, infecting ~8000 people with a mortality rate of ~10% (Fielding and Tan, 2007). The spread of the virus was eventually controlled by an unprecedented global health response and the virus has not been detected in the human population since April 2004.

Clinical features and pathogenesis

Even though SARS affects people of all ages, the majority of infections occur among adults with the median age 42–57 years. The elderly and individuals with a history of chronic comorbidities, including diabetes mellitus or chronic kidney failure, may have atypical presentations, such as lack of fever. Infections among children and adolescents, especially those younger than 12 years of age, are not common, and even if they do become infected, the disease is considerably less severe; the outcome is also much more favorable (Stockman et al., 2007).

The severity of SARS varies from asymptomatic infection to fatal acute ARDS, with asymptomatic or mild illness very uncommon. The initial, prodrome of symptoms of the disease are nonspecific and similar to a flu-like illness. One to two days after exposure to the virus, the patient develops early symptoms that could include fever, headache, chills, rigors, malaise, and myalgias (Pormohammad et al., 2020). Fever develops in all patients and is typically the first symptom, but it can also develop after the other initial symptoms. The lower respiratory tract phase of the illness follows after a further 3 or more days—but typically appears in week two—comprising of non-productive cough, shortness of breath and increasing respiratory distress sometimes requiring mechanical ventilation (Coleman and Frieman, 2014). Gastrointestinal symptoms, including diarrhea, vomiting and nausea have been recorded, but are not very common, with vomiting the least common; the diarrhea is often self-limiting. SARS-CoV has also been detected in other organs, including the kidneys, liver and spleen (Peiris et al., 2003a).

The most disturbing clinical feature of SARS is how fast many patients develop symptoms of acute ARDS. This is also the most common reason for admission to an intensive care unit (ICU). As soon as the second week after the onset of symptoms, pneumonia and hypoxemia linked to a rapid deterioration in the clinical condition of the patients may occur. Between 20% to 30% of patients admitted to hospital with SARS-CoV infection were admitted to an ICU, and about 75% of these patients required mechanical ventilation. Mechanical ventilation was required in approximately 16% of all SARS patients, and was associated with a mortality rate of about 50% (Fowler et al., 2003; Poutanen et al., 2003).

Epidemiology

SARS-CoV was originally believed to originate in civet cats, but these mammals were later shown to serve as intermediary hosts providing a source of infection to humans (Guan et al., 2003). Subsequent field epidemiological and molecular screening studies revealed that the most likely natural reservoir of SARS-CoV is horseshoe bats. Not only do many wild populations of horseshoe bats harbor several distinct SARS-like CoVs, many others have developed antibodies, indicating previous infection by the these CoVs (Lau et al., 2005; Wang and Eaton, 2007). Serological studies have now shown that SARS-CoV is a new human pathogen and had not previously circulated to any significant extent in humans prior to the outbreak in 2003 (Guan et al., 2003). The transmissibility of SARS-CoV between individuals is high and the virus appears to be transmitted primarily by large droplet spread and close contact. Transmission through fomites likely occurs as the virus remains viable for long periods on contaminated surfaces. Airborne spread, via droplets, is also likely to play a role in transmission between individuals (Low, 2004).

Middle East respiratory syndrome coronavirus (MERS-CoV)

MERS-CoV was the first pathogenic hCoV to be identified following the 2003 SARS-CoV outbreak. This CoV was originally isolated in June 2012 from a patient presenting with severe respiratory illness. Eleven days after admission to a hospital in Jeddah, Saudi Arabia, the patient—a 60-year-old man—died from renal and respiratory failure (Zaki et al., 2012). Since then, MERS-CoV infections were reported in more than 27 countries across the Middle East, Europe, North Africa and Asia, with the virus currently posing a potential threat in the Middle East where it is still sporadically detected in the human population (Chafekar and Fielding, 2018).

Clinical features and pathogenesis

MERS-CoV infections disproportionally affect adults, especially males, with children rarely affected (Arabi et al., 2014; Al-Tawfiq et al., 2016). Moreover, the virus typically causes more severe clinical manifestations in older people and, based on some evidence,

people with weakened immune systems. Those with chronic co-morbidities such as hypertension, obesity, diabetes, chronic lung disease, cardiovascular diseases or end-stage renal disease are also much more likely to be hospitalized when infected with MERS-CoV (Kim et al., 2017). In actuality, about 75% of MERS patients have at least one co-morbidity and MERS-associated fatalities are more likely to have other underlying medical conditions (Zumla et al., 2015).

Similar to SARS-CoV, MERS-CoV infection causes a clinical spectrum that ranges from asymptomatic (Drosten et al., 2014) to rapidly progressive, ARDS, septic shock and multi-organ failure, which can result in death (Al-Dorzi et al., 2016). In symptomatic individuals, the early symptoms are typically nonspecific, with patients reporting anything from general malaise, to a sore throat, low-grade fever, non-productive cough, chills, headache, shortness of breath and/or muscle pain. Less frequently, MERS-CoV patients present with gastrointestinal symptoms such as nausea, vomiting, anorexia, abdominal pain and diarrhea (Kapoor et al., 2014). Radiographs and computed tomography (CT) findings of the patient's chest are generally consistent with viral pneumonitis and ARDS (Zumla et al., 2015). Laboratory findings also include elevated lactate dehydrogenase levels, lymphopenia and thrombocytopenia (Arabi et al., 2014; Senga et al., 2017), with some cases resulting in elevated levels of creatinine, lactate dehydrogenase and liver enzymes (Zumla et al., 2015; Senga et al., 2017).

Patients who require hospitalization are typically admitted approximately 4 days after the onset of symptoms and the mean time spent in hospital is 41 days (Arabi et al., 2014). Worryingly, as much as 50% of adult symptomatic patients are admitted to ICUs, followed by between 40% and 70% then requiring mechanical ventilation within 7 days (Oboho et al., 2015). Reports indicate that between 22% and 70% of critically ill patients require renal replacement therapy (Arabi et al., 2014; Senga et al., 2017), but this needs to be confirmed since the higher end of this range could also be a result of hospital-acquired infections in patients with pre-existing kidney disease. In the end, MERS has a case mortality rate of about 36%, with the median time from the onset of symptoms to death about 11.5 days (Senga et al., 2017).

Epidemiology

Even though there is no conclusive evidence supporting bats as a source for transmission of MERS-CoV to humans, bats are hosts to MERS-CoV-like viruses (Corman et al., 2014). So, even though these viruses are genetically distinct from MERS-CoV, the possibility that bats serve as a primary animal host for MERS-CoV cannot be excluded (Memish et al., 2013). Importantly, the jump of MERS-CoV from bats directly to humans is currently purely speculative. There is some, although weak, evidence that the virus could have been transmitted to humans from dromedary camels (Reusken et al., 2013; Chan et al., 2015). This is primarily based on the presence of MERS-CoV-specific neutralizing antibodies specific in dromedary camels (Reusken et al., 2013), and one incidence of MERS-CoV infection in humans that could be linked to camels (Haagmans and Osterhaus, 2014). The transmissibility of MERS-CoV between individuals is low, and human-to-human transmission has only been observed in situations with prolonged close contact, such as health care settings, or in immunocompromised individuals with co-morbidities (Sharif-Yakan and Kanj, 2014).

Severe acute respiratory coronavirus-2 (SARS-CoV-2)

Clinical features and pathogenesis

The incubation period of COVID-19 is typically between 1 and 14 days, with most people showing signs of disease around a median time of 5–8 days. However, recent reports suggest that symptoms might even manifest up to 24 days after infection (Lauer et al., 2020; Bai et al., 2020; Guan et al., 2020). Following the incubation period, infected persons develop fever, dry cough, dyspnea, myalgia, and fatigue, features resembling pneumonia. Studies in China revealed that less common symptoms could include headache, diarrhea, hemoptysis, nausea, vomiting, sore throat, chest pain, chills, and a productive cough. ARDS is a feature seen in more severe cases (Chen et al., 2020a; Guan et al., 2020; Huang et al., 2020a; Wang et al., 2020b). Olfactory and taste disorders were also self-reported by patients from Italy (Giacomelli et al., 2020).

From a report in China, involving 72,314 cases, the majority of patients (~81%) only develop a mild form of pneumonia, or not at all; more severe pneumonia, characterized by shortness of breath, low oxygen saturation, and involvement of at least 50% of lung parenchyma in chest imaging, was seen in 14% of patients; and only 5% of patients became critically ill, developing shock or respiratory failure that required medical ventilation, or multi-organ dysfunction (Wu and McGoogan, 2020). Similar to SARS and MERS, the leucocyte count in majority of infected persons revealed lymphopenia, while the total white blood cell count may either be elevated or lower than normal. Additional biochemical factors such as procalcitonin, hepatic transamines, D-dimer, and prothrombin time were elevated in critical patients. The levels of plasma cytokines were reportedly higher in ICU patients than in non-ICU patients, suggesting that the cytokine storm is the basis for immunopathology (Huang et al., 2020a; Chen et al., 2020b; Yang et al., 2020). Almost all patients also exhibited abnormal chest radiographic features (Huang et al., 2020a). Chest X-rays frequently showed bilateral patchy shadows and ground-glass opacifications were seen in ARDS patients. Multiple ground-glass opacifications with or without reticular pattern, and parenchymal consolidations that involve both lungs were among the typical CT findings (Chung et al., 2020; Zhou et al., 2020b). It is worth noting that a report noted changes in CT scans from patients before the onset of clinical symptoms, even before viral RNA was detected in specimens from the upper respiratory tract (Shi et al., 2020). Recovery time varied depending on the extent of the infection; most patients recovering from mild infections were discharged after 2 weeks, whereas more severe cases recovered between 3 and 6 weeks, and approximately 2.3% of patients died from the infection

with a median time of 16 days after illness onset (Wu and McGoogan, 2020; Chen et al., 2020b; Wang et al., 2020b; Guan et al., 2020).

The pathogenesis of SARS-CoV-2 can range from merely manifesting as mild symptoms to more severe manifestations, such as respiratory failure. Pathogenesis begins after SARS-CoV-2 binds to epithelial cells in the respiratory tract and initiates replication, permitting migration of the virus deeper into the lungs to reach the alveolar epithelial cells. In the lungs SARS-CoV-2 replicates rapidly and can induce a strong immune response. This response is brought on by a cytokine storm syndrome, which culminates in ARDS and can be accompanied by respiratory failure. This is considered to be the main cause of death in patients with severe COVID-19 (Huang et al., 2020a; Mehta et al., 2020). Multiple organ failure, or dysfunction, is another serious sequelae reported in some cases of COVID-19 (Wu and McGoogan, 2020; Chen et al., 2020a; Yao et al., 2020). Although the exact nature of the SARS-CoV-2 pathophysiology is not yet clear, the immune system clearly plays an integral role as a combination of the cytokine storm and viral evasion of the cell-mediated immune response play very important roles in the progression and severity of the disease (Channappanavar and Perlman, 2017). Elevated levels of inflammatory cytokines and chemokines have been reported to result in lung injury and required patients to be urgently administered to the ICU (Huang et al., 2020a).

Given the target tissue of SARS-CoV-2, it stands to reason that the histopathological changes seen in patients with COVID-19 occur mainly in the lungs. Common histopathological features include bilateral diffused alveolar damage, formation of hyaline membranes, desquamation of pneumocytes, and in severe COVID-19 patients, fibrin deposits in the lungs. In some cases, exudative inflammation was also seen. Antigens of SARS-CoV-2 were detected in several tissue sites: the upper airway, submucosal gland epithelium, bronchiolar epithelium, as well as pneumocytes (type I and II), alveolar macrophages, and hyaline membranes in the lungs (Huang et al., 2020a; Chen et al., 2020a; Martines et al., 2020; Zeng et al., 2020).

Epidemiology

The SARS-CoV-2 outbreak occurred in China and was traced to Huanan Wholesale Seafood Market, citing the market as the source of the outbreak (Ji et al., 2020). Based on the genetic evidence, SARS-CoV-2 was likely to have originated in animals, although when and where humans were first exposed to the virus is not known for certain. With some of the first reported cases having no epidemiological link to the Huanan seafood market, it is possible that the market may not have been the initial source of human exposure to SARS-CoV-2 (Li et al., 2020a). Horseshoe bats, however, are a particularly important source of both α- and β-CoVs (Zhou et al., 2020a; Fan et al., 2019; Li et al., 2005). The *Rhinolophus affinis* bat carries a CoV designated "RaTG13," which is 96.2% identical to the full-length genome of SARS-CoV-2. All SARS-CoV-2 ORFs, including the hypervariable S protein and ORF8, are more than 90% similar to those of RaTG13 (Zhou et al., 2020a). More recently, *R. malayanus* was also reported to carry a CoV designated "RmYN02" which shares 93.3% of its genome with SARS-CoV-2. Both the clustering and the high genetic similarity between these bat CoVs and SARS-CoV-2 suggests that SARS-CoV-2 originated in bats (Paraskevis et al., 2020). The diverse number of bat CoVs found to be closely related to SARS-CoV-2 suggests that bats are the likely reservoir of SARS-CoV-2 (Lau et al., 2020).

Pangolins were initially the suspected source of the SARS-CoV-2 outbreak. Comparison of pangolin CoV genomes from the Guangxi and Guangdong provinces to the SARS-CoV-2 genome revealed that their sequences were 85.5% and 92.4% similar, respectively, to SARS-CoV-2 (Lam et al., 2020). The RBD of the Guangdong pangolin CoV is also highly similar to that of SARS-CoV-2, with only one variation in the RBM while still containing the five residues critical for ACE2 receptor binding (Xiao et al., 2020b). However, despite these similarities and having found SARS-CoV-2-related CoVs in pangolins, pangolins cannot be regarded as reservoirs for these CoVs (Xiao et al., 2020b; Lam et al., 2020). Bats, for one, can maintain a healthy physiological state while carrying CoVs. Pangolins infected with CoVs, however, exhibit clinical signs and histopathological changes indicative of CoV infection, suggesting that they are not natural hosts or reservoirs of SARS-CoV-2 (Xiao et al., 2020b).

Transmission

Although animals are the original source of the pathogenic hCoVs—transfer between the animal host or reservoir and humans after a spill-over event—global spread is driven by human-to-human transmission. The primary route of transmission for the pathogenic hCoVs is via the respiratory tract—i.e. pathogenic hCoVs are present in respiratory tract secretions, with tracheal secretions and bronchoalveolar lavage(BAL) specimens containing higher viral loads than nasopharyngeal swabs. Transmission typically occurs through close contact with an infected person, where infectious droplets and, in some cases, aerosols may come into contact with mucous membranes (Low, 2004; Deng and Peng, 2020). The spread by small droplet aerosols and droplet nuclei can also occur when much smaller and more numerous aerosol particles linger in the air and, when inhaled, can reach deep inside the lungs of a person; this has also been confirmed in recent studies for SARS-CoV-2 (Meselson, 2020; van Doremalen et al., 2020). This is thought to be a particularly important transmission route in enclosed rooms where large gatherings tend to take place (Stadnytskyi et al., 2020). Interestingly, the efficiency of transmission between individuals vary greatly between studies, and is likely associated with the degree of severity of illness and with the virulence of viral strains. Transmission through inanimate objects contaminated with infectious secretions occurs as CoVs remain viable for long periods on surfaces (Kampf et al., 2020), and has been a source of infection in healthcare settings (Bin et al., 2016; Gopalakrishna et al., 2004). These CoVs has also been detected in serum, feces and urine (Poissy et al., 2014). Increasing evidence also points to the possibility of, at least for SARS-CoV-2, transmission through contaminated feces. As an example, SARS-CoV-2 infected ferrets were found to have shed the virus in feces for up to 8 days after infection and is somewhat consistent with what was reported for some human studies (Wang et al., 2020d; Xiao et al., 2020a; Kim et al., 2020).

Laboratory diagnosis

Laboratory confirmation of pathogenic CoV infections has broadly included (i) molecular detection of CoV RNA; (ii) CoV antigen detection; or (iii) identification of a humoral response to previous infection (Mackay and Arden, 2015), often with varying degrees of success in terms of sensitivity and specificity.

During the SARS-CoV outbreak, a combination of serological and reverse transcription polymerase chain reaction (RT-PCR) assays was frequently used to confirm infection. Rapid diagnosis was most frequently made by RT-PCR using primers specific to the viral N-gene sequence. Throat, nasal, pharyngeal or serum samples were used to detect viral RNA by RT-PCR, as early as the first week of illness. During the second week of illness, stool and respiratory samples were also suitable for viral RNA assays. In rural areas, where expensive and complex molecular tests could not routinely be performed, enzyme immunoassays (EIAs) for viral N and S antigens were developed to screen suspected SARS cases (Bermingham et al., 2004; Chan et al., 2004). A positive real-time RT-PCR assay, targeting at least two different genomic regions of the MERS-CoV, can be used to confirm MERS. Probe and primer sets targeting the ORF1a and upstream of the E gene show the highest sensitivity and remain the most widely used for MERS-CoV confirmation assays (Corman et al., 2012). A single positive real-time RT-PCR test result, confirmed by gene sequencing, can also be considered positive for MERS-CoV infection (Chafekar and Fielding, 2018).

For a definitive COVID-19 diagnosis a combination of clinical manifestations, radiographical evaluations, and laboratory diagnosis, such as the detection of SARS-CoV-2 RNA (Zu et al., 2020), is required. SARS-CoV-2 viral RNA can be detected in a variety of samples, but it should be cautioned that not all samples are equally representative of the viral load, which could affect the diagnosis. Although SARS-CoV-2 can be detected in different parts along the respiratory tract, including from throat swabs, posterior oropharyngeal saliva, nasopharyngeal swabs, sputum, and bronchial fluid, samples from the lower respiratory tract contain a higher viral load since it is generally the target site of the virus (Zhou et al., 2020a; Pan et al., 2020; To et al., 2020b; Wang et al., 2020d; Han et al., 2020). Recommendations provided by the United States (US) Centers for Disease Control and Prevention (CDC) stipulate that BAL fluids, nasopharyngeal swabs (not throat swabs), and blood are all accepted clinical samples (CDC, 2020). However, when respiratory samples test negative, viral RNA can also be detected from the intestinal tract (Zhang et al., 2020). Since oral swabs commonly produce false positives, it is advised that multiple detection methods be used to confirm a COVID-19 diagnosis (Li, 2020; Xie et al., 2020). CT can be used in conjunction with laboratory testing to confirm a positive COVID-19 diagnosis. In Wuhan, when molecular detection services were overwhelmed, patients were screened for radiographic features of COVID-19. Features included bilateral multilobar ground-glass opacities along with peripheral or posterior distribution (Xie et al., 2020; Kanne, 2020). It is, therefore, recommended that patients who initially tested negative for viral RNA, but are strongly suspected of having COVID-19, receive chest CTs in conjunction with continued swab tests (Xie et al., 2020). Serological testing for the presence of pathogenic CoV-specific antibodies, such as those specific for the SARS-CoV-2 N or S protein, is another diagnostic method that proves useful for determining previous exposure to the virus. These tests can be used to quickly triage suspected cases of pathogenic CoV infection by confirming or ruling out infections *ex post facto*. It is, however, only useful in the later stages of the disease or even retrospective studies, after sufficient time has elapsed to mount an adaptive immune response (Zhang et al., 2020; Guo et al., 2020; To et al., 2020a). Of concern is that the extent and duration of the immune response can differ from patient to patient, and tests can vary in specificity and sensitivity (Bastos et al., 2020), possibly affecting the diagnosis. Nevertheless, good progress has been made regarding COVID-19 laboratory diagnostic methods, but the limitations warrant a combination of diagnostic methods to increase the reliability of a confirmed diagnosis. This, in turn, can help to accurately identify infected persons and consequently mitigate or limit the spread of SARS-CoV-2 (Lin et al., 2020).

Treatment and prevention

For the vast majority of pathogenic hCoV infections, supportive care, which includes rest, taking in fluids and analgesics are used, and mainly depends on the provision of organ support and management of complications. At times, broad-spectrum antibiotics, antivirals, IFNs and/or antifungals are prescribed to minimize the risk of co-infection with opportunistic pathogens (Momattin et al., 2013).

Ribavirin and corticosteroid treatment of SARS-CoV proved largely ineffective, since corticosteroids suppress the humoral and cellular components of the immune system (Ferron et al., 2018). Other drugs, like pentoxifylline, were promising therapeutic candidates for treating SARS-CoV on account of its anti-inflammatory, antiviral, immunomodulatory, and bronchodilatory effects, but it proved largely unsuccessful in the clinical treatment of SARS-CoV infection (Bermejo Martin et al., 2003). Many antioxidant compounds demonstrate anti-SARS-CoV activity by inhibiting 3C-like protease (3CLpro), an enzyme vital to the replication of SARS-CoV (Jo et al., 2020). Accordingly, several studies of antioxidant compounds, including quercetin and quercetin-related compounds, reported the efficient inhibition of 3CLpro, in some cases reducing SARS-CoV replication (Ryu et al., 2010).

For MERS-CoV, monitoring epidemic patterns and investigating the spread of infection allows efficient identification, control, and prevention of possible pandemics. Combined treatment of MERS-CoV with ribavirin and IFN-α2b was proposed as an early treatment since a combination of ribavirin and IFNs. could inhibit MERS-CoV replication in vitro and improve clinical outcomes in MERS-CoV-infected non-human primates (Falzarano et al., 2013). The limited effective therapeutic window of MERS-CoV infections might also limit the efficacy of broad-spectrum antivirals when treating severe MERS-CoV patients (Widagdo et al., 2017). Alisporivir, a non-immunosuppressive cyclosporin A-analogue, inhibited MERS-CoV replication in vitro and could be

further potentiated by ribavirin, underpinning the potential use of cyclophilin inhibitors as host-directed, broad-spectrum inhibitors of CoV replication (de Wilde et al., 2017). However, since none of these potential anti-MERS-CoV candidates have demonstrated a significant benefit to treating acute MERS-CoV infections in a consistent and controlled manner, supportive management adapted from SARS-CoV guidelines has formed the basis for MERS-CoV treatment (Modjarrad, 2016). Various MERS-CoV vaccines have been designed, of which one has been progressed to clinical trials. Current MERS-CoV vaccines have been shown to induce effective protection in a few animal models (see review by Chafekar and Fielding, 2018).

Both researchers and pharmaceutical manufacturers are conducting large-scale clinical trials to evaluate a variety of COVID-19 treatment options. Some drugs, such as umifenovir (Arbidol), aim to block the binding of SARS-CoV-2 to the ACE2-receptor to prevent entry, but its efficacy is not yet established (Wang et al., 2020e; Zhu et al., 2020c; Li et al., 2020b; Lian et al., 2020). Camostat mesylate can also block the entry of SARS-CoV-2 into human lung cells (Hoffmann et al., 2020), but clinical data to support its efficacy is insufficient (Kawase et al., 2012; Zhou et al., 2015). Specific monoclonal antibodies (mAbs), recombinant human ACE2 receptors, or fusion inhibitors targeting the S protein have also been considered, but lack the required safety and efficacy parameters for clinical trials (Monteil et al., 2020; Tian et al., 2020; Xia et al., 2020b). SARS-CoV-2 viral replication inhibitors lopinavir and ritonavir (3CLpro inhibitors), and remdesivir, favilavir, and ribavirin (targets RdRp) have also been investigated (Wang et al., 2020c; Tahir ul Qamar et al., 2020; Williamson et al., 2020; Grein et al., 2020; Cai et al., 2020; Cao et al., 2020; Hung et al., 2020).

Immunomodulatory agents are used to mitigate the excessive inflammatory response induced by SARS-CoV-2. Dexamethasone reduced the mortality of COVID-19 hospitalized patients who received invasive mechanical ventilation by 1/3 and by 1/5 for patients who received oxygen support, but no benefit was found in patients who did not require oxygen support for COVID-19 treatment (RECOVERY, 2020; The Recovery Collaborative Group, 2020). Tocilizumab and sarilumab, antibodies (Abs) specific for the interleukin-6 receptor (IL-6R), were effective in treating severe COVID-19 by attenuating the cytokine storm (Xu et al., 2020). Preliminary results using eculizumab, a mAb which inhibits the proinflammatory complement protein C5, showed potential for treating severe COVID-19 cases by decreasing inflammatory markers and C-reactive protein (CRP) levels (Diurno et al., 2020). SARS-CoV-2 is reportedly more sensitive to type I IFN than SARS-CoV, making it a promising candidate in the early treatment of COVID-19 (Mantlo et al., 2020).

The Food and Drug Administration (FDA) approved convalescent plasma treatment as an adjunctive therapy for COVID-19 and preliminary results suggest that patients improved after treatment, but there are possible adverse effects (Duan et al., 2020; Shen et al., 2020). Conversely, mAbs can neutralize the SARS-CoV-2 infection both in vitro and in vivo and has an advantage over convalescent plasma therapy since it can be produced in much larger quantities to meet clinical demands (Wang et al., 2020a; Wu et al., 2020; Zost et al., 2020).

Several vaccines are currently being developed against SARS-CoV-2—recombinant vectors, DNA vaccines, mRNA in lipid nanoparticles, live-attenuated viruses, and protein subunit-based vaccines (Smith et al., 2020; Zhu et al., 2020b; Gao et al., 2020). Several of these are being tested in phase II trials and some have already advanced to phase III trials (Hu et al., 2020). An adenovirus type 5-vectored vaccine expressing the SARS-CoV-2 S protein produces a considerable humoral and cellular immune response in most recipients after a single immunization and has proven safe (Zhu et al., 2020a). An initial dose of the lipid nanoparticle-formulated mRNA vaccine candidate encoding the pre-fused SARS-CoV-2 S protein (mRNA-1273) induces a robust neutralizing antibody response in a dose-dependent manner, increasing after the second dose (Jackson et al., 2020). A whole virus, inactivated vaccine induces the production of neutralizing antibodies effectively and reported a low rate of adverse reactions (Xia et al., 2020a). These vaccine candidates show promise toward preventing and controlling the spread of SARS-CoV-2, but their safety and immunogenicity will need to be evaluated first with the aim of protecting healthy populations from the SARS-CoV-2 infection.

Until a successful, effective vaccine is produced and distributed, public health measures are the most effective at limiting the spread of SARS-CoV-2 and, to some extent, MERS-CoV. The ability of SARS-CoV-2 to remain viable on inanimate surfaces validates the need for proper sanitation through regular hand washing or the use of hand sanitisers with at least 70% ethanol. Despite some controversy over the efficacy of masks in reducing SARS-CoV-2 transmission, their mere presence acts as a physical barrier that can, in the least, minimize the spread of potentially virus-laden respiratory droplets from one person to another or onto surfaces.

Conclusions

Since the intermediary hosts for the pathogenic hCoVs have not been conclusively identified, there is always a likelihood that these CoVs could pose a problem, even after they are removed from the human population. Also, with no effective, ubiquitous therapeutic available for infections caused by the pathogenic hCoVs, the development of a vaccine remains a priority. Some of the challenges faced when developing a safe and effective CoV vaccine, include (1) host immunity to CoVs often wanes rapidly; (2) individuals requiring protection include the elderly and those with chronic co-morbidities; and (3) vaccines could instead of protect, worsen lung immunopathology (Enjuanes et al., 2008).

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