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Coronaviruses of the veterinary and socio-economic importance: Classification, pathogenicity, transmission, and evolution of the coronaviruses

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Abstract

Most of the coronaviruses are known because they are pathogens of veterinary and economic importance or of social importance. The current knowledge on the origin, diversity, evolution of coronaviruses, as well as treatment and prevention strategies, and their impact on animal industries are discussed in this paper. The contribution factors for the outbreak of pathogenic coronaviruses and the potential of spill over of zoonotic coronaviruses to humans are also highlighted in this review paper.

1. INTRODUCTION

Coronaviruses was well documented as causative agents for ranges of respiratory, enteric, and neurological diseases in animals and humans (ICTV, 2020). In general, the coronavirus infected a specific host, either animal or humans (de Wilde *et al.*, 2018; Fan *et al.*, 2019; Fung and Liu, 2019; Lim *et al.*, 2016). On the other hand, there are some coronavirus strains able to cause infection in both animal and humans (Gretebeck and Subbarao, 2015; Hasoksuz *et al.*, 2020; Menachery *et al.*, 2017). Extensive studies of various coronaviruses have not only led to a better understanding of coronavirus biology and ecology but also the origin and distribution of coronaviruses globally (Chen *et al.*, 2020; Cui *et al.*, 2019; Shereen *et al.*, 2020; Wang *et al.*, 2020).

In this review, we focused on the veterinary and social importance coronaviruses. Specifically, we emphasised more on the origin, ecological distribution, genetic diversity, evolution and interspecies transmission of coronaviruses. Thus this information can help in preparing counter measures against future emergence, re-emergence and spillover of these pathogenic coronaviruses.

2. CORONAVIRUS CLASSIFICATION AND DIVERSITY

Coronaviruses are named for the presence of crown-like spikes appearance on the surface of the virus. Coronaviruses are classified as a member of the subfamily Coronavirinae in the family Coronaviridae and the order Nidovirales (ICTV, 2020). The subfamily Coronavirinae consists of four genera namely *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus* and *Deltacoronavirus* based on their phylogenetic relationships and genomic structures (Payne, 2017; Perlman, 2020). The *Alphacoronaviruses* and *Betacoronaviruses* reported infect only mammals, whereas the *Gammacoronaviruses* and *Deltacoronaviruses* reported infect birds, but some of virus strains can also infect mammals (Figure 1).

Various coronaviruses species detected in different hosts including mammals, bats and birds are well described in Table 1.

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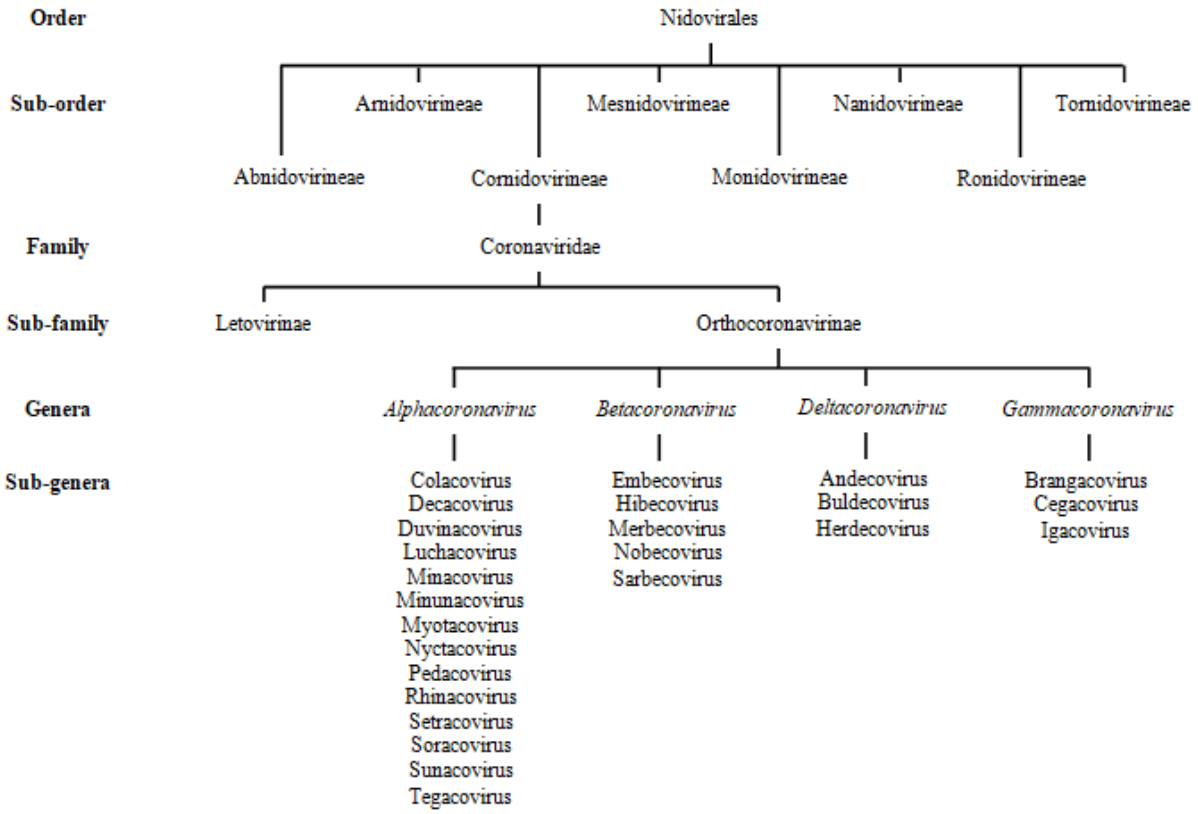

Figure 1: Family tree of coronaviruses (adapted from International Committee on Taxonomy of Viruses, 2020).

Table 1: Different coronavirus species classification based on four coronavirus genera by International Committee on Taxonomy of Viruses (2020).

Coronavirus genera	Coronavirus species	Host
Alphacoronavirus	Bat coronavirus CDPHE15	Bat
	Bat coronavirus HKU10	Bat
	Rhinolophus ferrumequinum alphacoronavirus HuB-2013	Bat
	Human coronavirus 229E	Bat/Alpacas/Human
	Lucheng Rn rat coronavirus	Rat
	Mink coronavirus 1	Mink
	Miniopterus bat coronavirus 1	Bat
	Miniopterus bat coronavirus HKU8	Bat
	Myotis ricketti alphacoronavirus Sax-2011	Bat
	Nyctalus velutinus alphacoronavirus SC-2013	Bat
	Pipistrellus kuhlii coronavirus 3398	Bat
	Porcine epidemic diarrhea virus	Pigs
	Scotophilus bat coronavirus 512	Bat
	Rhinolophus bat coronavirus HKU2	Bat/Pigs
	Human coronavirus NL63	Bat/Human
	NL63-related bat coronavirus strain BtKYNL63-9b	Bat
	Sorex araneus coronavirus T14	Shrew
	Suncus murinus coronavirus X74	Shrew
	Alphacoronavirus 1	Cats/Dogs/Pigs
Betacoronavirus	Betacoronavirus 1	Cattle/Human
	China Rattus coronavirus HKU24	Rat
	Human coronavirus HKU1	Rat/Human
	Murine coronavirus	Murine
	Myodes coronavirus 2JL14	Bank vole
	Bat Hp-betacoronavirus Zhejiang2013	Bat
	Hedgehog coronavirus 1	Hedgehog
	Middle East respiratory syndrome-related coronavirus	Bat/Dromedary camel/Human
	Pipistrellus bat coronavirus HKU5	Bat

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	Tylonycteris bat coronavirus HKU4	Bat
	Eidolon bat coronavirus C704	Bat
	Rousettus bat coronavirus GCCDC1	Bat
	Rousettus bat coronavirus HKU9	Bat
	Severe acute respiratory syndrome-related coronavirus	Bat/Civet/Human
Gammacoronavirus	Goose coronavirus CB17	Goose
	Beluga whale coronavirus SW1	Whale
	Avian coronavirus	Chicken
	Avian coronavirus 9203	Chicken
	Duck coronavirus 2714	Duck
Deltacoronavirus	Wigeon coronavirus HKU20	Wild bird
	Bulbul coronavirus HKU11	Wild bird
	Common moorhen coronavirus HKU21	Wild bird
	Coronavirus HKU15	Pigs
	Munia coronavirus HKU13	Wild bird
	White-eye coronavirus HKU16	Wild bird
	Night heron coronavirus HKU19	Wild bird

3. GENOME ORGANISATION, GENE AND PROTEINS OF DIFFERENT CORONAVIRUSES

Naturally, coronavirus is round to pleomorphic, an enveloped virus with prominent spike glycoprotein which can be seen in a form of club-shaped projection on the surface of the virus (Tyrrell and Myint, 1996). The average size of coronaviruses is measured in range of 80-120 nm and the club-shaped structures emanated on the surface measured about 20 nm (Guy *et al.*, 2001; Maier *et al.*, 2015). The schematic diagram of coronavirus structure is shown in Figure 2.

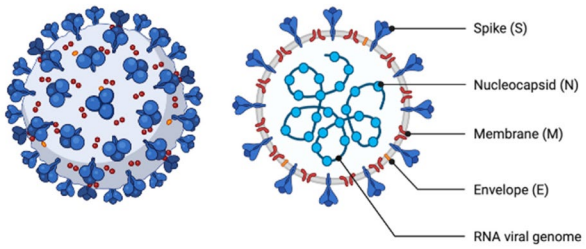

Figure 2: A schematic diagrams of coronavirus structures (adapted from Won and Lee, 2020).

The genome of coronavirus is linear positive-sense single stranded RNA, with size in range of 27-31 kb and contains 5' and 3' un-translated regions (Brian and Baric, 2005). A general characteristic of coronaviruses is as listed in Table 2. In general, the genomic organisation of coronavirus arranged in the order of 5'-1ab-S-E-M-N-3' (Domanska-Blicharz *et al.*, 2020; Lai, 1990). The virus genome is separated into several open reading frames (ORFs) that encodes the virus structural and non-structural proteins (Qiu and Xu., 2020; Rohaim *et al.*, 2020). These include two large overlapping ORF (1a and 1b) identified at the first two-third of the genome, and the remaining one-third of the genome encodes four structural proteins and accessory proteins (Michel *et al.*, 2020).

Table 2: General features of coronaviruses (adapted from Cavanagh, 2005)

Features	Descriptions
Enveloped	+
Linear positive-sense ssRNA genome with poly(A) tail	+
5' polymerase gene-structural protein genes 3'	+
3' co-terminal nested set of ≥4 subgenomic mRNAs	+
Only the 5' unique region of an mRNA is translated	+
Polymerase gene has two ORFs, 1a and 1b	+
The 1b ORF is translated after ribosomal frameshifting	+
M protein has three membrane-spanning sequences	+
Virion formation at internal membranes	+
Genome size (kb)	27-31
5' leader sequence	+
Core shell	+
Nucleocapsid (RNA plus N protein)	Helical
Prominent S glycoprotein	+
Coiled-coil structure in S protein	+

+, the feature present in the virus

Proteins encoded by ORF 1a and 1b produce large polyprotein 1ab which associated with RNA replication and transcription (Fang *et al.*, 2008; Naqvi *et al.*, 2020). The polymerase coding region is located at the 5'-end of the genome which encodes the RNA-dependent RNA polymerase (RdRp) that is responsible for replicating the virus genome as well as for carrying out transcription (Gao *et al.*, 2020; Venkataraman *et al.*, 2018; Wilkinson *et al.*, 2020). The next four ORFs encode for four main structural proteins namely spike glycoprotein (S), envelope protein (E), membrane glycoprotein (M) and nucleocapsid protein (N), however, some *Betacoronavirus* ORFs encode haemagglutinin-esterase protein (HE) as described in Table 3.

Table 3: Virion-associated proteins of coronaviruses (adapted from Enjuanes *et al.*, 2000).

Protein	Size (kDa)
Spike glycoprotein (S)	28-220
Integral membrane protein (M)	23-35
Small envelope protein (E)	9-12
Haemagglutinin-esterase protein (HE)	65
Nucleocapsid protein (N)	50-60

Among the virus structural proteins, the coronavirus S protein is the most studied (Chen *et al.*, 2020; Hasoksuz *et al.*, 2020; Li, 2016; Wickramasinghe *et al.*, 2014). Generally, the S protein is usually cleaved into distinct S1 and S2 polyproteins (Cavanagh, 1983). The S1

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subunit forms the globular head (N-terminal), whereas the S2 subunit forms the base-like structure (C-terminal) (Cavanagh, 1983). The N-terminal S1 subunit encodes for epitopes that can induce neutralisation, haemagglutination inhibition and serotype-specific antibodies (Cavanagh, 1995). On the other hand, the C-terminal S2 subunit is responsible in helping the infectious bronchitis virus (IBV) in the cell attachment and virus-cell membrane fusion (de Groot *et al.*, 1987).

4. ANTIGENICITY, VARIABILITY OF CELLULAR BINDING RECEPTORS AND TROPISM

The S protein contains several key functional domains namely (i) receptor-binding domain (RBD) for virus attachment to the host cell, (ii) cleavage site between S1 and S2 subunits, and (iii) fusion peptide and heptad repeats which facilitates entry of the virus into the host cell as well as (iv) trans-membrane domain and cytoplasmic tail that anchors spike to the viral membrane (Li, 2016; Stevenson-Leggett *et al.*, 2019). The RBD sites within the S1 region of a coronavirus S protein vary depending on the virus; some have the RBD at the N-terminus and others have the RBD at the C-terminus (Hasoksuz *et al.*, 2020). Cell surface molecules that act as receptors have been identified for several known coronaviruses as listed in Table 4.

Table 4: Cellular binding receptors of several known coronaviruses.

Viruses	Cellular binding receptors of S protein	References
Infectious bronchitis virus (IBV)	α2,3-linked sialic acid	Wickramasinghe *et al.* (2014)
Turkey coronavirus (TCoV)	poly-LacNAc	Wickramasinghe *et al.* (2015)
Porcine transmissible gastroenteritis virus (TGEV)	pAPN	Delmas *et al.* (1994)
Porcine epidemic diarrhea coronavirus (PEDV)	pAPN	Liu *et al.* (2015)
Porcine respiratory coronavirus (PRCV)	pAPN	Peng *et al.* (2020)
Porcine haemagglutinating encephalomyelitis coronavirus (PHEV)	Neu5, 9Ac2	Tortorici *et al.* (2019)
Bovine coronavirus (BCoV)	Neu5,9Ac2	Schultze and Herrler (1994)
Canine respiratory coronavirus (CRCoV)	α2,3-linked sialic acid	Szczepanski *et al.* (2019)
Canine enteric coronavirus (CECoV)	cAPN	Haake *et al.* (2020)
Feline enteric coronavirus (FECV)	fAPN	Haake *et al.* (2020)
Feline infectious peritonitis virus (FIPV)	fAPN	Haake *et al.* (2020)
Human coronavirus-NL63	hACE2	Milewska *et al.* (2018)
Human coronavirus-229E	hAPN	Yeager *et al.* (1992)
Severe acute respiratory syndrome coronavirus (SARS-CoV)	hACE2	Li *et al.* (2003)
Middle East respiratory syndrome coronavirus (MERS-CoV)	DPP4	Raj *et al.* (2013)
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	hACE2 & TMPRSS2	Letko *et al.* (2020), Hoffmann *et al.* (2020)
Mouse hepatitis coronavirus (MHV)	CEACAM	Williams *et al.* (1991)

cAPN, Canine aminopeptidase N; CEACAM, Carcinoembryonic antigen-related cell adhesion molecule 1; DPP4, Dipeptidyl peptidase 4; fAPN, Feline aminopeptidase N; hACE2, Human angiotensin-converting enzyme 2; hAPN, Human aminopeptidase N; pAPN, Porcine aminopeptidase N; Neu5 9Ac2, N-acetyl-9-O-acetylneuraminic acid; Poly-LacNAc, Poly-N-acetyllactosamine; TMPRSS2, Transmembrane serine protease 2

The S protein is responsible in activating the fusion of viral envelope with cellular membrane to release the viral RNA into the cytoplasm (Belouzard *et al.*, 2012). The cleavage site of S protein has been identified important for entry of virus into cells associated with endocytic pathway of the virus that requires cellular proprotein convertase during viral binding and uptake into the cells. Several proprotein convertase of coronaviruses have been identified for cleaving such as serine protease (Millet and Whittaker, 2015), furin (Ming and Qiang, 2020; Ord *et al.*, 2020), chymotrypsin-like cysteine 3C-like peptidase ($3CL^{pro}$) (Pislar *et al.*, 2020), and papain-like protease (PL^{pro}) (Barretto *et al.*, 2005). Even though the cleavage site is a key determinant of virus tropism (Hulswit *et al.*, 2016) and virus replication (Pislar *et al.*, 2020), however it is reported not associated with coronavirus serotype and pathogenicity.

The S1 subunit is highly variable because of nucleotide insertion, deletions and/or substitutions, and recombination events that occurred during virus replication cycle (Abolnik, 2015; Krishnamoorthy *et al.*, 2020). In addition, the amino acid changes in the N-terminal of S1 subunit which resulted from nucleotide variations are commonly detected in different serotype and variants of coronaviruses (Abolnik, 2015). The antigenic determinants of coronaviruses are contributed by the frequent point mutations and evolutionary fitness specifically within the hypervariable regions of the S1 gene (Ismail *et al.*, 2020). Hence, the S gene is referred to as the index of coronavirus genetic diversity and evolution because of its high variability and close genotype or serotype correlation (Anthony *et al.*, 2017; Cui *et al.*, 2019; Toro *et al.*, 2012).

Different coronaviruses reported display diverse host range and tissue tropism (Hulswit *et al.*, 2016; ICTV, 2020). Changes in the S glycoprotein are largely responsible for the host variety of coronaviruses and the variety in tissue tropism (Chen *et al.*, 2020).

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5. REPLICATION CAPACITY

Coronaviruses enter cells by binding of S protein to cellular specific receptors (Belouzard *et al.*, 2012). Upon attachment, the virus is taken up via receptor-mediated endocytosis by clathrin- or caveolin-dependent pathways (Burkard *et al.*, 2014). In order to release the genome into the cytoplasm, the coronaviral envelope must fuse with a host cell membrane. This fusion event is played by regions in the S2 subunit, C-terminal part of the S protein, following the attachment mediated by S1 subunit (Schoeman and Fielding, 2019).

After entering the cell, the replication event of coronavirus is taking place within the cell cytoplasm. The virus manipulates and exploits host cellular components and pathways to facilitate various steps of their replication cycle (Figure 3). Generally, after the virus enters the host cell and uncoats, the genome is transcribed and then translated. Once the genomic RNA released from virions early in the infection, it will acts as an mRNA for translation of gene 1, to produce the polymerase, RdRp. The RdRp is reported to play a pivotal role in viral replication and transcription (Robson *et al.*, 2020). RdRp catalyses the synthesis of a nascent RNA strand by adding ribonucleotide units to the 3'-hydroxyl terminus, building the RNA molecule in the 5' to 3' direction (Picarazzi *et al.*, 2020). Thereafter this generates mRNAs from the other genes, from which all the other proteins are made. The proteins are assembled at the cell membrane and the genomic RNA forms mature particle by budding from the internal cell membranes to produce the new viral particles (Alsaadi and Jones, 2019; Artika *et al.*, 2020).

6. PATHOGENICITY

Coronaviruses cause wide range of acute and chronic respiratory, enteric, and neurological diseases (Enjunaes *et al.*, 1995; Farcas *et al.*, 2005). The expression and tissue distribution of entry receptors consequently influence viral tropism and pathogenicity of coronaviruses (Gallagher and Buchmeier, 2001). A study by Saif (2004) has demonstrated that porcine coronavirus, transmissible gastroenteritis virus (TGEV) infects epithelial cells of the piglet small intestines, leading to a potentially fatal gastro-enteritis; however mild disease is reported in adult pigs. In other study, the porcine respiratory coronavirus (PRCV) infects lung epithelial cells (type I and II pneumocytes) as well as alveolar macrophages, causes interstitial pneumonia in pigs (Jabrane *et al.*, 1994). The porcine epidemic diarrhoea virus (PEDV), a porcine enteric coronavirus appeared in Europe in 1970's and some part of Asia in 2000's causing lethal watery diarrhoea in neonatal pigs, leading to significant losses within the porcine industry (Koonpaew *et al.*, 2019). On the other hand, the IBV reported causes a highly contagious disease in chickens and considered as one of the economic importance disease to the poultry industry. The virus reported replicates in upper respiratory tissues, however some IBV strains able to cause systemic infections, replicating in extra pulmonary tissues, including the kidney, oviduct, and the intestinal tract (Bande et al., 2016). The bovine coronavirus (BCoV) is a ubiquitous virus worldwide causing both respiratory and enteric disease, including calf diarrhoea, winter dysentery in adults, and respiratory disease in cattle (Cho et al., 2001; Ellis, 2019; Gomez et al., 2017). The feline coronaviruses are composed of two biotypes; FECV and FIPV. FECV usually asymptomatic, whilst the FIPV causing severe and lethal disease to the cat. FIPV initially replicates in the pharyngeal respiratory or intestinal epithelial cells, and then leads to viraemia and systemic spread to the abdominal and thoracic cavities causing ocular and neurological disorders (Addie, 2004; Sharif et al., 2010).

The receptor binding domain (RBD) sites within the S1 region of a coronavirus S protein was listed in Table 4. The RBD is varying, and depending on the virus, that, some have the RBD at the N-terminus and others have the RBD at the C-terminus of the S protein (Hulswit *et al.*, 2016). However, the evolution of the genomic of the coronavirus cause changes to the ability of the virus attachment to the cellular surface molecules that act as receptors, and host range expansion (Li, 2016). The coronavirus S proteins are prone to accumulate mutations and can easily recombine (Masters, 2006). Hence, the RBD regions have been identified as mutational and recombination hotspots (Li, 2015). By investigating the evolutionary of coronavirus-receptor interactions, the dynamic nature and diverse array of coronaviruses can be gathered to elucidate the complex evolutionary of coronavirus adaptation to new environment as well as new hosts, and offer insights into how the novel coronaviruses emerge, cross species barriers and conquer entirely new host populations (Millet *et al.*, 2021).

7. DISTRIBUTION AND DYNAMIC

Members of the coronavirus group are widely distributed in nature and show a variety of tissue and species tropisms. Animals and humans are susceptible to coronavirus infection, and the diseases is caused by virus multiplication and cytopathogenicity in various tissues such as upper and lower respiratory tracts (Enjuanes et al., 1995), kidneys (Cavanagh, 2005), genital tract (Zhang et al., 2020), small and large intestines (Cho et al., 2001; Zappulli et al., 2020), brain (Arbour et al., 2000), and salivary glands (Liu et al., 2011). In addition, it appears likely that some coronaviruses able to infect multispecies animals causing wide range of diseases (Menachery et al., 2017). Moreover, studies reported that spillover of the pathogenic coronavirus from animal to human cause zoonotic diseases (Cui et al., 2019; Fung and Liu, 2019; Raj et al., 2013; V'kovski et al., 2020).

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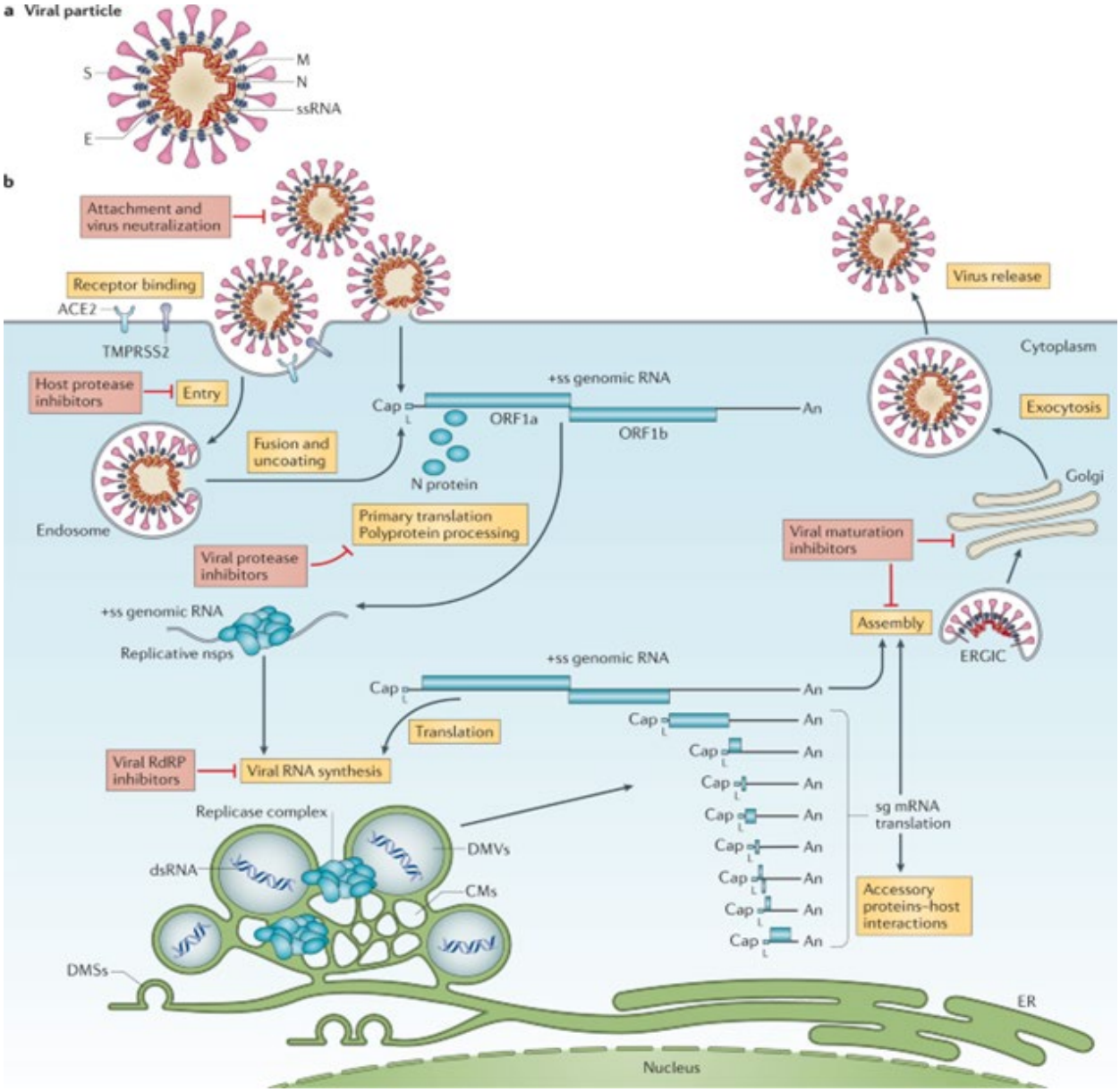

Figure 3: Diagram of the coronavirus virion and life cycle (adapted from V'kovski *et al.*, 2020). The replication of coronavirus started with virus particles bind to cellular attachment factors and specific S interactions with the cellular receptors, together with host factors, promote viral uptake and fusion at the cellular or endosomal membrane. Following entry, the release and uncoating of the incoming genomic RNA subject it to the immediate translation of two large open reading frames, ORF1a and 1b. The polyproteins pp1a and pp1ab are translated into the individual non-structural proteins (nsps) that form the viral replication and transcription complex. Concordant with the expression of nsps, the biogenesis of viral replication organelles consisting of characteristic perinuclear double-membrane vesicles (DMVs), convoluted membranes (CMs) and small open double-membrane spherules (DMSs) create a protective microenvironment for viral genomic RNA replication and transcription of sub-genomic mRNAs (sg mRNAs). Translated structural proteins translocate into endoplasmic reticulum (ER) membranes and transit through the ER-to-Golgi intermediate compartment (ERGIC), where interaction with N-encapsidated, newly produced genomic RNA results in budding into the lumen of secretory vesicular compartments. Finally, the matured virions are secreted from the infected cell by exocytosis/budding process.

8. TRANSMISSION

Transmission of coronaviruses is usually via contaminated airborne droplets or hands to the nasal mucosa or eyes (Tyrell and Myint, 1996), where the virus invades the respiratory tract via the nasal cavity. Direct contact was found to be the most efficient route of coronaviruses transmission. Coronaviruses within the bioaerosols are transmitted during speaking, sneezing and coughing is the main mode for the transfer of the infected aerosolised droplets to the surroundings that cause of the

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respiratory disease (Aliyu *et al.*, 2021; Chan *et al.*, 2020; de Vries *et al.*, 2021). Aerosols created during sneezing can reach up to 7-8 meters, while coughing can reach up to 2 meters horizontally (Kirubananthan *et al.*, 2021). Hence, the exhaling events able to push the respiratory droplets up to 1 meter horizontally (Jayaweera *et al.*, 2020). Within the respiratory tract, the virus replicates locally in cells of the ciliated epithelium, causing cell damage and inflammation (Gallagher and Buchmeier, 2001). However, some coronaviruses species reported to have the ability to replicate in extra pulmonary tissues causing systemic infections (Bande *et al.*, 2016).

The human behaviour may contribute to the virus transmission. Touching the contaminated fomites is one of the indirect transmissions of the coronaviruses. The coronavirus able to remain on the fomites ranging from a few hours to days depending on the viral load, environmental conditions, and the nature of the surface of the object (Goldman, 2020). As a comparison, the SARS-CoV-2 can remain viable in aerosols for more than 3 hours with the half-life projected about 1.1 hours, however, the viable virus can remain up to 72 hours on plastic surface with the average half-life about 6.8 hours (van Doremalen *et al.*, 2020). The virus transmitted by fomite mode is more likely due to self-inoculation in the mouth, nose, or eye following contact with the environment (Kirubananthan *et al.*, 2021).

9. EVOLUTION OF CORONAVIRUSES

The emerging coronaviruses have caused significant global morbidity and mortality. The virus demonstrates great potential for interspecies transmission, including zoonotic outbreaks (Cui *et al.*, 2019). Therefore, in order to prevent further outbreaks, it is crucial to understand the ecology and evolution of coronaviruses, particularly how these factors relate to animal and human health (Vijayakrishna *et al.*, 2007).

For better understanding the evolution of coronaviruses S gene is the most studied because of its nucleotide insertion, deletions and/or substitutions, and recombination events that occurred during virus replication cycle (Abolnik, 2015; Adachi *et al.*, 2020; Krishnamoorthy *et al.*, 2020). Furthermore, the S gene sequence of different types of coronaviruses have been exploited for epidemiological and evolutionary studies (Bidokhti *et al.*, 2012; Martinez *et al.*, 2012; Woo *et al.*, 2012).

Like many other positive-sense RNA viruses, coronaviruses show high rates of recombination (Bobay *et al.*, 2020; Lai, 1992; Zhu *et al.*, 2020). The mechanisms involved in viral RNA recombination are diverse and may even extend to non-replicating systems (Gallei *et al.*, 2004). The mechanism to produce 5′ leader-containing segmented mRNAs represents a prime example for copy-choice RNA recombination guided by complex RNA-RNA interactions (Bujarski, 2008). Hence, the transcription-regulating sequence core sequences and likely requires additional interactions of viral proteins with specific RNA signals (Simon-Loriere and Holmes, 2011). In the vast majority of cases, recombination results in defective RNA (dRNA) copies that lack essential *cis*-active elements and thus cannot be replicated. In other cases, defective interfering RNAs (DI-RNAs) may be produced. These defective DI-RNAs contain all the *cis*-acting elements required for efficient replication by a helper virus polymerase and, therefore, represent parasitic RNAs that compete for components of the viral replication/transcription complex with non-defective viral RNAs (Pathak and Nagy 2009).

translation of gene 1, to produce the polymerase, RdRp. The RdRp is reported to play a pivotal role in viral replication and transcription (Robson *et al.*, 2020). RdRp catalyses the synthesis of a nascent RNA strand by adding ribonucleotide units to the 3'-hydroxyl terminus, building the RNA molecule in the 5' to 3' direction (Picarazzi *et al.*, 2020). Thereafter this generates mRNAs from the other genes, from which all the other proteins are made. The proteins are assembled at the cell membrane and the genomic RNA forms mature particle by budding from the internal cell membranes to produce the new viral particles (Alsaadi and Jones, 2019; Artika *et al.*, 2020).

10. FUTURE PERSPECTIVES

The advent of pathogenic coronaviruses served as a reminder of an important aspect that we already knew about coronaviruses, namely that their host range and transmission is greater than was often supposed.

The coronaviruses replicate, at least initially, in either or both of the respiratory or enteric tracts (Millett *et al.*, 2021). Within a coronavirus species, some strains may have a tropism for the respiratory tract, others for the enteric region, though usually causing pathology in one or both of these regions (Jonsdottir and Dijkman, 2016; Weiss and Navas-Martin, 2005). Hence, some coronaviruses strains that may have tropism in extra-pulmonary and -enteric regions need also to be considered (Al-Sharif *et al.*, 2020).

The origins and evolutionary dynamics of coronaviruses are being traced worldwide; however, many questions remained unanswered. For better understanding the ecology and evolution of coronaviruses, information such as disease susceptibility, transmission and driving factors causing coronavirus infections need also to be elucidated.

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