



Review on SARS- CoV-2 Transmission, Infection and Pathogenesis in Animals

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Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

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ABSTRACT

Coronavirus are single stranded, positive sense, enveloped virus that belongs to the order Nidovirales. Coronavirus consists of pathogens of many animal species and humans including the current severe acute respiratory syndrome coronaviruses (SARS-CoV). This review considers the transmission, pathogenesis and diagnosis of coronavirus in animal. Transmission of coronavirus is by inhalation of aerosol or droplets containing the virus via respiratory system and close contact with infected patients. Clinical signs exhibited by coronavirus infected animals are; coughing, sneezing, diarrhea, fever and gastrointestinal symptoms. Coronavirus pathogenesis involves viral attachment or entry, replication, transcription, translation, assembly and eventual release. Polymerase chain reaction is the most modern and acceptable method for coronavirus detection because of its sensitivity and accuracy, though, several other methods abound. The PCR amplifies a specific region of a DNA strand; employs thermal cycling and the main agents are primers and a DNA polymerase. The process of denaturation, annealing and elongation constitutes a single cycle. Multiple cycles are required to amplify the target DNA to millions of copies.

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1. INTRODUCTION

Coronaviruses (CoV) belongs to the family, enveloped, single stranded RNA viruses. It is of medical and veterinary importance infecting mammals and birds, causing respiratory diseases [1]. CoVs are members of the subfamily Coronavirinae in the family Coronaviridae and Nidovirales. The unique features of Coronaviridae is that it has the largest genome size among all RNA viruses (26.4-31.7kb in length) with a Guanine to cytosine ratio content varying from 32 to 43% [2]. The avian infectious disease virus was isolated for the first time, from an outbreak of chicken flocks in 1937, since then, several viral isolation have been seen in rodents, domestic animals and humans [3].

Taxonomically, the name of the Coronavirus family comes from the spiky crown (or corona, in Latin) on its outer surface when viewed through an electron microscope. The order, family, genus and species are globally used to organize all diversity of virus in hierarchical system in current taxonomy [4]. Viruses are classed to a taxonomic position based on genome characteristic, virion structure, replication formats of the viruses and comparative evaluation of selected properties [5]. The various animal Coronavirus diseases are Feline CoVs, Canine CoVs, Porcine CoVs, Bovine CoVs, Dromedary Camel CoVs and Birds CoVs. The Feline Enteric Coronavirus is a virulent biotype in domestic cats and is a hyper virulent precursor of Feline Infections Peritonitis viral viruses (FIPV) that causes fatal disease in cats. The diseases have two forms, dry and wet sarcoidosis [6]. The epithelial cells of the pharynx and the intestinal tract are sites of replication.

Canine Coronavirus is related to Porcine and Feline Coronavirus genetically. Canine CoVs is grouped into two genotypes, CCoV type-1 and CCoV type-11 [7]. Here, the main predilection site of this virus is the gastrointestinal tract. High morbidity and low mortality is a feature of Canine Enteric Coronavirus infection. The major route of viral transmission is the oral route [8]. Porcine Coronavirus; Porcine Respiratory Virus (PRCoV) is a variant of Transmissible Gastroenteritis Virus (TGEV) that binds to the lungs, causing antigen aggregation in pneumocytes and alveolar macrophages, which results in interstitial pneumonia [9].

Bovine Coronaviruses (BCoVs) infects the respiratory and gastrointestinal tracts. This

infection is associated with high mortality [10]. Dromedary Camel Coronaviruses have a predilection site of upper respiratory tract, especially in the epithelium of the nasal turbinate where it replicates [11]. The review arises due to the recent outbreak of Coronavirus in human that is ravaging the entire world and the need to re-evaluate the earlier observations about this virus in animals and to improve upon the knowledge of the present Coronavirus outbreak in humans.

2. TRANSMISSION

The transmission of Middle East respiratory syndrome Coronavirus (MERS-CoV) to dromedaries was identified through the detection of specific antibodies against the virus in these animals [12]. According to Corman et al (2014), MER-CoV has been circulating in dromedaries for over 20years. It is assumed that bats are reservoirs for several coronaviruses, including SARS-CoV, MER-CoV and SARS-CoV-2. [13]. Though SARS-CoV-2 is closely related to SARS-CoV [14], the similarity between the genome was about 80% [15]. Understandably, SARS CoV-2 most likely originated from bats, the intermediate host which serves as reservoir and contributes to the evolution of the virus before the spill to humans occur is yet to be ascertain. Animal transmission to humans does not seem likely, though, the identity between nucleotides and amino acids of the spike protein, transmission between animals seem possible. This is because it has a similar genome to other animal coronaviruses. SARS-CoV-2 may have undergone nucleotide mutation when transmitted to animals, expressing amino acids that increased its pathogenicity in animals, especially those related to spike protein [16]. One of the most probable intermediate hosts for SARS-CoV-2 is a Pangolin. Pangolin CoV has 91.02% and 90.55% identity to SARS-CoV-2 and BatCoV RaTG13 respectively [15]. Furthermore, the SARS-CoV-2 spike protein RBD resembles closely Malayan pangolin CoV (Pangolin-CoV) [17]. These finding suggests that pangolins can be intermediate host for SARS-CoV-2 transmission.

Transmission from animal to man; for places where coronavirus prevalence is high across the pet population, it is important we examine the impact of this virus. Canine respiratory coronaviruses often occur in dogs. Ownership of an infected pet can lead to the transmission of the viruses from animal to humans. [18] At the

beginning of the SARS CoV-2 outbreak, it was thought that pets were not susceptible to the SARS-CoV-2. However, a natural infection of a cat was reported in Belgium with traces of the virus identified in the collected samples by PCR. The cat showed clinical features of respiratory difficulty, vomiting and diarrhea which were suggestive of viral replication inside the animal (14). In another study carried out by Shi et al., it was shown that cats could not only be infected with SARS-CoV-2, but it was observed that adult cats artificially inoculated with the virus presented severe histological lesions and died. [19]. There have been reports that shows that SARS-CoV can infect ferrets and cats [20] and this implies that ferrets and cats may also be susceptible to SARS- Cov-2. This variable may be responsible with cases of SARS-CoV-2 transmission in animals [21]. Based on the spread or epidemiology of SARS-CoV, the COVID-19 pandemic raises the alarm that animals may become infected and therefore potential transmitters to human. The fear that griped people of the possibility of transmission of animals to humans, made many people to abandon their animal since there were not quarantined [14]. In China for instance, the authorities in Hunan and Zhejiang provinces stated that, they will commence killing of pets found in public to prevent transmission and this was effective in February 2020. [22]. It has been shown by some researchers that cats could naturally be infected with other coronaviruses like feline coronavirus, just as canines can be infected with canine coronavirus [23]. It is suspected that these animals probably got infected once the virus binds to the receptor [24].

In a research conducted in France, a group of 18 veterinary students investigated the spread of the new coronavirus, in 21 pets made up of 9cats and 12dogs. Eleven cases showed symptoms compatible with COVID-19 while only two confirmed positive for the new coronavirus. However, the presence of specific antibodies to SARS-CoV-2 was not established by RT-PCR [23]. In a separate study conducted by some researcher, it was observed that cats infected with SARS-CoV-2 could transmit the virus to naïve cats that comes into contact with them [25].

The first known animal transmission of non domesticated animal in the United States occurred in a 4 year Malayan tiger and was confirmed by all the agencies responsible for animal health. This Tiger was infected from the COVID-19 workers at the Bronx Zoo. Similarly, a new case was reported in Russia, in the town Moskva of Moskaovskya State, where a 5year-old cat tested positive for SARS CoV-2. In this test, samples from throat and nasal swabs were used. The test conducted using real-time RT-PCR and electrophoresis, detected amplicons that show 100% identity with analyzed fragment of N gene ORF1ab of the SARS-CoV-2 [26]. The ways through which SARS-CoV-2 is transmitted from infected humans to animals is still not properly clear. The possibility of transmission may occur through contact with the nose or mouth by infected hands contaminated with respiratory droplets [27]. Infected humans through sneezing, coughing and talking can spread respiratory droplet which in turn transmits the virus to animals [28].

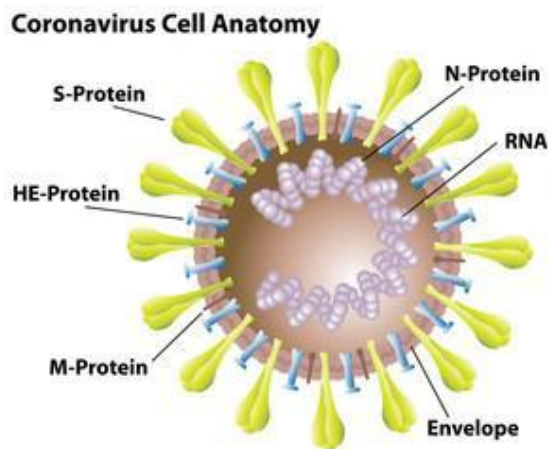


Fig. 1. www.shutterstock.com 1684060378

2.1 Coronavirus Pathogenesis

Coronavirus on entry into an animal host attaches to specific cellular receptor sites through the spike proteins and this triggers a conformational change in the spike which mediates fusion between the viral and cell membranes resulting in the release of the nucleocapsid into the cell [29]. On entry of the viral particle into the cell, the 5' end of the genome RNA, ORFs 1a and 1b, are translated into pp 1a and pp 1b; pp 1b is translated via a frame-shift mechanism, which occurs at high frequency [30]. It should be noted that there are 2 major lineage of SARS-CoV-2. Lineage A and B. Lineage A are Wuhan/WH04/2020 sequence and possess 2 nucleotides {position 8,782 The ORF 1a and 28,144 in ORF8) with the closest known bat viruses (RATG 13 and RmYN02). Different nucleotide are present at those sites in viruses assigned to lineage B, which is represented by the Wuhan-Hu-1 strain [31] encodes one or two papain-like proteases and a picornavirus 3C-like protease (3CLpro), which functions to process pp 1a and pp 1ab into the mature replicase proteins [32]. Similarly, within the X domain of the ORF 1a is an ADP-ribose 1-phosphatase [33]. ORF 1b is encoded and processed from pp 1ab and RNA independent RNA polymerase (RdRp) and a helicase [34] as well as other activities of enzymes and this includes (putative) 3'-to-5' exonuclease (ExoN), poly (U)- specific endonuclease (XendoU) and (putative) S-adenosylmethionine-dependent ribose 2-o-methyltransferase [35].

More putative enzymatic activity, cyclic phosphodiesterase, is encoded downstream in ORF 2a. Several multiples of enzymatic activities are suspected to play important roles in metabolism of coronavirus RNA.

When there is a coronavirus infection, like all other RNA viruses, the genome is replicated and the transcription of mRNA will occur. Genome replication is associated with synthesis of a full-length negative strand RNA that is present at low concentration and this serves as template for full-length genomic RNA. There are several overlapping 3' –co-terminal sub-genomic RNAs which serves as mRNA, as it does in full-length genomic RNA. The mRNA possess a sequence at its 5' end obtained from 5' end of genomic RNA [36]. The process by which positive and negative-strand RNAs are synthesized is unclear, but it is suspected to be regulated by transcription –regulating sequence, found in the genome RNA [37]. The viral proteins are

translated from individual mRNAs, from the 5' ORF only. Hence, the replicase is translated from the 5' end of the genomic RNA. It is suspected that the translation of ORF 5'b is mediated by an internal ribosome entry site [38]. The M and E membrane proteins are localized to the Golgi intracellular membranes near the endoplasmic reticulum, which is suspected to be the real site of budding [39]. Besides, there exist other factors needed to determine the site of budding. The expression of M and E proteins in the absence of other viral proteins and viral RNA are sufficient to produce virus-like particles [40]. The spike protein which is distributed on the intracellular and plasma membrane interacts with the trans-membrane region of the M protein during assembly [41]. Nucleocapsid protein interacts with the genome RNA forming helical structures. The interaction of N and M protein results in budding into vesicles [42]. The virus is later transported to the cell surface from where it exits the cell.

The coronavirus protein is a type 1 glycoprotein that forms the peplomers on coronavirus particles. Most coronavirus spike cleaves into two subunits by a furin-like enzymatic activity during processing in the Golgi. The amino-terminal S1 subunit, which forms the head of the mature protein, contains a receptor binding domain (RBD) within the first 330 amino acids [43]. Spikes are also found in S1, although not at the amino terminal. S1 of MHV contains downstream of the RBD, a hypervariable domain (HVR) that varies in length among strains. Coronavirus attaches to specific cellular receptor through the spike protein. The first known coronavirus receptor was CEACAM 1, utilized by MHV [44]. Viral attachment triggers a conformational change in the spike protein that promotes the fusion of viral and cellular membranes [45]. The coronavirus spike play important role in viral entry, cell to cell spread and in determining tissue tropism. Besides, the virus uses plasma route, endosomal route of entry has also been implicated [46]. Entry of SARS-CoV is inhibited by lysosomotropic agents, suggesting endosomal route [32]. The treatment by protease of virus that has attached to the cell eliminates inhibition. The understanding that infection is blocked by inhibitors of the PH and sensitive endosomal protease, suggests that there is a requirement for cleavage of the SARS-CoV spike during entry through the endosomes [47]. It should be stated that entry at the plasma membrane after protease treatment is more efficient than entry by the endosomal route [46].

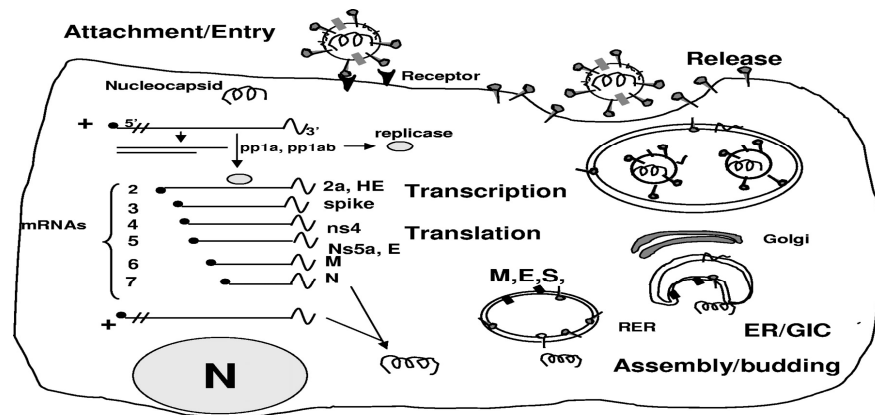


Fig. 2. Model of coronavirus replication[9]

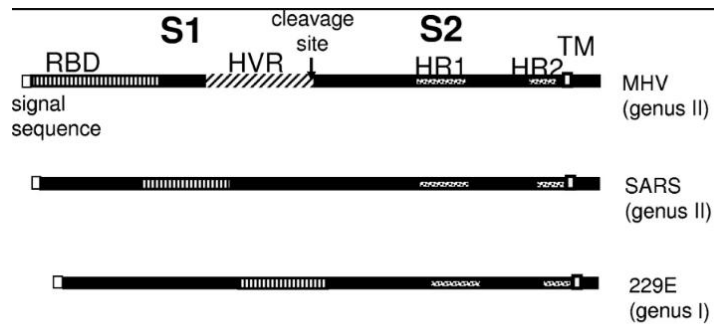


Fig. 3. Schematic of coronavirus spike proteins[9]

The use of recombinant coronaviruses, including MHV and TGEV [48] has shown that the spike is a main determinant of tropism and pathogenicity. In TGEV, the replacement of the spike gene of an attenuated respiratory strain of TGEV with the spike gene from a virulent enteric strain renders the virus enterotropic [49]. Pathological findings suggest that SARS-CoV-2 can widely spread in epithelial lining of the respiratory tract, digestive tract, distal convoluted tubules of the kidney, the sweat glands of the skin and testicular epithelium including spermatogonia and sertoli cells [50]. Histopathological findings shows the affected animal with lungs that appear congested, with patches of haemorrhagic necrosis, alveolitis with atrophy, vacuolar degeneration, proliferation, desquamation and squamous metaplasia of alveolar epithelial cells with presence of exudative monocytes and macrophages are prominent features microscopically [50].

2.2 Methods for Detection of Coronavirus

Many techniques are used for detection of virus including coronavirus and this is dependent on

the type of virus and the size of the viral particles. The different methods have their advantage and disadvantages. Of all the technique, Polymerase Chain Reaction (PCR) appears to gain more universal acceptance.

2.3 Polymerase Chain Reaction

The PCR technique involves copies of one DNA template made using primers, enzymes and graded temperature range [51]. However, to increase the sensitivity of the PCR, Real-time PCR was developed and this play a key role where antibody could not be used [52].

3. PROCEDURE

Sample often used in animal is swab from the nasal cavity and oral cavity. Typical Polymerase Chain Reaction (PCR) consist of a series of 20-40 repeated temperature changes, called thermal cycles, with each made up of two or three discrete temperature steps. The cycling commences with a single temperature step at a high temperature (>90°C), followed by a hold

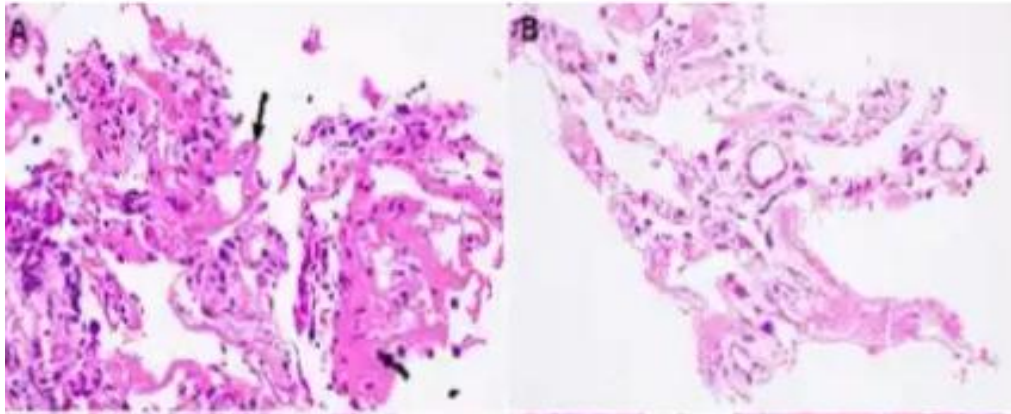


Fig. 4. Histopathological changes in lungs of Covid-19 patients (A) and (B) ultrastructure of an epithelial cells of bronchiole. (Tian et al.2019)

and the final product extension. The temperature used and the length of time they are applied in each cycle depend on a several factors: enzyme used for DNA synthesis, the concentration of bivalent ions and dNTPs in the reaction and the melting temperature (T_m) of the primers [53]. Steps common to most PCR methods include Initialization. This step is only needed for DNA polymerases that require heat activation by hot – start PCR [54]. It involves heating the reaction chamber to a temperature of 94-96^oC, or 98^oC, if extremely thermostable polymerases are used, which is then held for 1-10minutes. Denaturation: this is the first regular cycling and is made up of heating the reaction chamber to 94-98^oC for 20-30seconds. It melts the DNA (denaturation) of the double stranded DNA template by breaking the hydrogen bonds between the complimentary bases, thereby producing two single stranded DNA molecules.

Annealing: In this third step, the temperature is reduced to 50-65^oC for 20-40 seconds, enabling annealing of the primers to each of the single stranded DNA templates. Two different primers are typically included in the reaction mixture: one for each of the two single –stranded complements containing the target region. The primers are single-stranded sequences themselves, however, are shorter than the length of the target region, complementing only very short sequences at the 3' end of each strand.

Extension/elongation: The temperature here depends on the DNA polymerase that was used. The optimum activity temperature for the thermostable DNA polymerase of taq polymerase is approximately 75-80^oC [55]; however, a

temperature of 72^oC is often used with enzymes. The DNA polymerase synthesizes a DNA strand complementary to the DNA template strand by adding free dNTPs from the reaction mixture that is complementary to the template in the 5'-to-3' direction, condensing the 5-phosphate group of the dNTPs with the 3'-hydroxyl group at the end of the elongating DNA strand. The precise time required for elongation depends both on the DNA polymerase used and on the length of the DNA target region to amplify. At optimum temperature, most DNA polymerase polymerizes thousand bases per minute. Hence, the number of DNA target sequences is doubled, with each successive cycles, the original template strands in addition to newly generated strands become template strands for the next round of elongation, leading to geometric amplification of the specific DNA target region.

3.1 Immunofluorescence Method

This is a rapid technique for detection of viral antigens and could be completed within 3hours. The sensitivity and specificity of this method is great. This technique encompasses the indirect fluorescent-antibody assay (IFA) [56]. No researcher ideally want to perform a test that will take a long time as seen in the use of enzyme linked immunosorbant assay (ELISA), though, easy to perform and sensitive, a lot of time is consumed in anti-sera production [57].

3.2 Nucleic Acid Amplificton Test

Clinical samples could be used together with cell culture supernatants through specific nucleic acid probes. This probes compliments target viral

DNA or RNA sequence or by use of Nucleic acid amplification probes [58].

3.3 Isothermal Amplification

This technique is based on separating two strands of the template via non-thermal methods, like helicase dependent amplification and Recombinant Polymerase Amplification [59].

3.4 Electron Microscopy

This is one of the main virus detection methods. It captures live images of cells and tissues with high resolution. The morphological evaluation in terms of the size, shape and stability could lead to immediate conclusion of enveloped or naked virus. For enveloped viruses, the extra-outer cover is distinct, while the naked viruses possess rigid capsid that is capable of surviving desiccation and maintain their spherical structure [60].

3.5 Next Generation Sequencing NGS

This is use in the identification of new viruses via pyro-sequencing and this approach can make a difference in costs, ease of sequence assembly and identification. [61]

3.6 Cell Culture

This makes available large numbers of cells as hosts for the virus and help decrease the use of experimental animals, thereby reducing the risk of contamination. Hence, viruses are able to attain high titers in the cells which could be subjected to microscopic examinations [56].

3.7 Nanoelectromechanical Devices

Nanoelectromechanical systems (NEM) of high frequency are considered as new sensors and devices [62]. It has been proved that the selective molecular binding to the surface of nano-mechanical oscillators may lead to detecting pathogens viral binding through observing their effects on the natural frequency shift of NEMS devices [62].

4. CONCLUSION

Coronavirus has caused devastating effect in animals and humans resulting in several mortalities. The mechanism of action of this disease is quite unique and transmission is very astronomical. Since the disease spread is by

aerosol and close contact, the need to observe appropriate ventilation and spacing becomes necessary. Further study and review is advised to rule out the cross transmission of coronavirus from animal to humans as alleged by some researchers, though unverified.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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