

Chapter 4

Transmission Cycle of SARS-CoV and SARS-CoV-2



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Abstract Severe acute respiratory syndrome (SARS) is a pandemic that has shocked the world twice over the last two decades caused by a highly transmissible and pathogenic coronavirus (CoV). It causes disease in the lower respiratory tract in humans that was first reported in late 2002 in Guangdong province, China, and later on in December 2019 in Wuhan, China. The two viruses designated as SARS-CoV and SARS-CoV-2, respectively, originated probably from the bat and infected humans via carrier animals. The constant recombination and evolution in the CoV genome may have facilitated their cross-species transmission resulting in recurrent emergence as a pandemic. This chapter intends to accumulate recent findings related to CoV transmission and tentative molecular mechanisms governing the process.

Keywords SARS · CoV · Zoonotic · Transmission · Infection · Virus · Host

4.1 Introduction

Severe acute respiratory syndrome (SARS) is a high-risk viral disease usually characterized by fever, headache, and severe respiratory symptoms such as coughing, shortness of breath, and pneumonia (Peiris et al. 2004; Hu et al. 2017). These viruses can infect the respiratory, gastrointestinal, hepatic, and central nervous system of humans, livestock, birds, bat, mouse, and many other wild animals (Wang

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et al. 2006; Ge et al. 2013; Chen et al. 2020a, b). It first emerged in southern China in late 2002 and due to its fast transmission rate among humans, it immediately led to a global pandemic in 2003. More recently it has created havoc around the globe from December 2019 onwards, spreading over 100 countries and affecting thousands of people (Remuzzi and Remuzzi 2020). For this reason, it has been considered as a major public health threat in the twenty-first century (Zhong et al. 2003; Cui et al. 2019).

The causative agent of SARS is a coronavirus (CoV), more accurately SARS coronavirus (SARS-CoV), has been previously assigned to group 2b CoV, and is now a member of the lineage B of genus Betacoronavirus in the family Coronaviridae and subfamily Coronavirinae (Drexler et al. 2014; Chen et al. 2020b; Kumar et al. 2020). It shares similar genome organization with other coronaviruses, but exhibits a unique genomic structure which includes several specific accessory genes, including ORF3a, 3b, ORF6, ORF7a, 7b, ORF8a, 8b, and 9b (Hu et al. 2017). SARS coronavirus (SARS-CoV) uses angiotensin-converting enzyme 2 (ACE2) as a receptor and primarily infects ciliated bronchial epithelial cells and type II pneumocytes (Li et al. 2003; Qian et al. 2013).

A recent outbreak of a new CoV strain during December 2019 in China has drawn huge attention throughout the world. The administrative and scientific communities of China still are working towards the etiology, prevention and control, and drug development for the epidemic. On January 12th, 2020, the World Health Organization provisionally named the new virus as 2019 novel coronavirus (2019-nCoV) that later on renamed as severe acute respiratory syndrome coronavirus 2, SARS-CoV-2 (Gorbalenya et al. 2020). The continuous evolution and transformation of CoVs lead to sudden outbreaks to the different parts of the world suggesting that it may pose a serious global health hazard in a very short period. In today's changing climate and ecological balance, and the human-animal interactions, there is an increased risk of CoV disease outbreaks. This makes an utter requirement to focus on efficient measures to fight against CoVs.

A disease that usually occurs among animals but can infect humans in specific conditions is known as a zoonotic disease. They have largely affected the human population for the past hundreds of years. However, with passing time they have changed in several perspectives concerning their occurrences and pathogenicity (Rodriguez-Morales et al. 2020). As for now, several proofs indicate that CoV transmission occurs via "zoonotic spillover," a term indicating the transmission of a pathogen from a vertebrate animal to a human host. Although the mechanism of such transmission is not very clear and therefore it is a matter of concern, certain factors determine zoonotic spillovers such as behavioral characteristics of CoV and the susceptibility of a human host (Plowright et al. 2017).

The upcoming sections present a collection of recent findings on CoV infection. Additionally, the different factors responsible for the varied transmission mode of CoVs among animals and humans and the possible mechanism behind the process have been discussed.

4.2 Coronavirus Transmission Cycle

A coronavirus (SARS-CoV) is considered as the etiological agent of SARS. Further investigation proved that the first transmission of the virus to human hosts occurred probably in southern China in Guangdong province, from zoonotic reservoirs, including bats, Himalayan palm civets (*Paguma larvata*), and raccoon dogs (*Nyctereutes procyonoides*), the latter two of which are sold in exotic animal markets (Graham and Baric 2010).

Studies from the past suggest that SARS-CoV may also have a broad host range besides humans. SARS-CoV was transmitted directly to humans from market civets and is thought to have originated in bats (Cui et al. 2019).

Earlier, genetically similar CoVs were isolated from civet cats and raccoon dogs (Guan et al. 2003). Studies show that SARS-CoV has the ability to infect and produce disease in macaques and ferrets too, while did not produce any readily observable symptoms in cats (Fouchier et al. 2003; Martina et al. 2003). A recent study reports about 80% gene similarity between SARS-CoV-2 and SARS-CoV (Gralinski and Menachery 2020; Xu et al. 2020). Correspondingly, one more study reports a 96% sequence similarity between SARS-CoV-2 and the CoV isolated from *Rhinolophus affinis* indicating bats as virus source (Zhou et al. 2020). To date, there is not much clarity about SARS-CoV-2 host and it is reported to be snakes, minks, or other animals (Ji et al. 2020).

Figure 4.1 represents the tentative transmission path from a natural host to a human. The natural host of the CoV is considered as a bat (Li et al. 2020). While the species differ, CoV can still manage to migrate from its natural host to humans via intermediate host depending on its ability to access the host cell (Rodriguez-Morales et al. 2020). Since the last few decades, CoV has evolved to adapt to bind the receptors to enter inside the host's cells through its surface glycoproteins. These

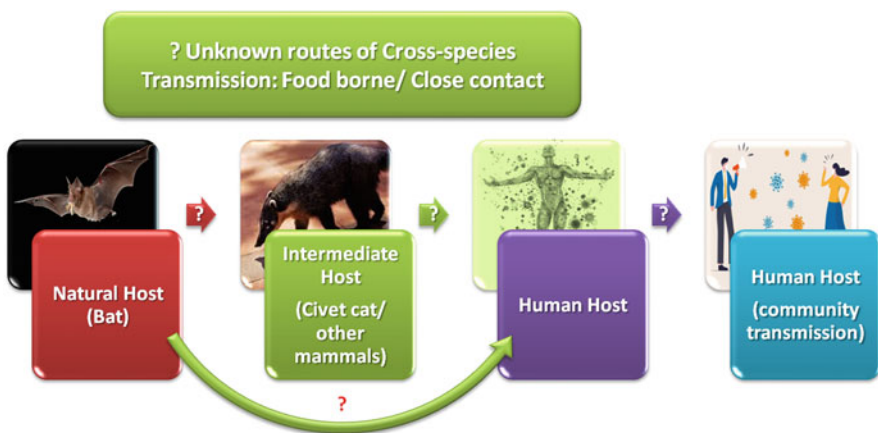


Fig. 4.1 The probable transmission path of SARS-CoV and SARS-CoV-2 from natural hosts to various hosts

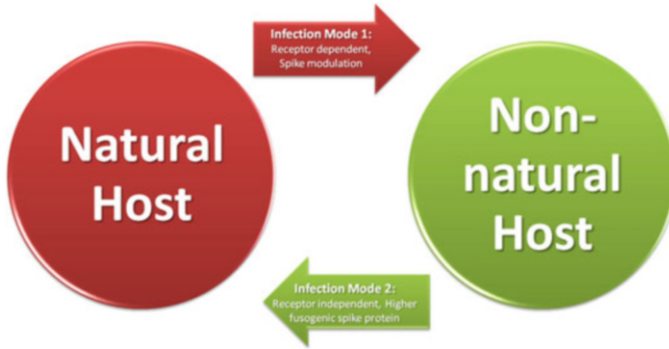


Fig. 4.2 Potential cross-species transmission mechanism from natural host to non-natural hosts (other animals and humans)

surface glycoproteins show significant variations that allow the virus to bind to varied mammalian host species (Rothan and Byrareddy 2020).

It has been known for decades that CoVs occasionally avoid the receptor-dependent entry into the host cell. The murine coronavirus strain JHM (MHV-JHM or MHV4) that codes for an extremely fusogenic spike protein may accomplish the infection via cell-to-cell spread mechanisms by giving up the known receptor-dependent entry route (Gallagher et al. 1992, 1993). In another study, MHV-JHM was found to infect CEACAM^{-/-} (carcinoembryonic antigen-cell adhesion molecule) mice severely, a phenotype that was mapped specifically to the JHM strain spike protein (Miura et al. 2008). Based on these results, it can be assumed that there is an existence of a receptor-switching mechanism in CoVs leading to spike modularity and its tendency for recombination. Another speculation can be derived here about the higher fusogenic potential of the spike protein that minimizes its dependency on receptor-based cell entry (Nakagaki and Taguchi 2005; Graham and Baric 2010). The SARS-CoV and SARS-CoV-2 may have followed one of these mechanisms as depicted in Fig. 4.2.

4.3 Transmission Among Animals

In 2005, two individual research groups reported novel coronaviruses associated with human SARS-CoV, which were named SARS-CoV-related viruses or SARS-like coronaviruses, in horseshoe bats (genus *Rhinolophus*) (Lau et al. 2005; Li et al. 2005). Based on these studies it was understood that bats may have played a natural host for SARS-CoV while civets acted only as an intermediate. One more study exposed the coexistence of varied SARSr-CoVs in bat populations inhabiting one cave of Yunnan province, China, that was also the first information regarding human ACE2 (angiotensin-converting enzyme 2) as a receptor for bat SARS-like coronavirus (Ge et al. 2013; Hu et al. 2017). Further, it has already been known that the coronavirus genome frequently undergoes recombination (Lai and Cavanagh 1997),

suggesting the high possibility of the emergence of new SARS-CoV through recombination of bat SARS-CoVs existing in same or another bat caves. Cui et al. (2019) speculated the production of SARS-CoV direct progenitor via recombination within bats, and thereafter it passed on to the farmed civets and other mammals leading to virus infection to civets by fecal-oral transmission. These virus-contained civets transported to the Guangdong market where they infected market civets and further mutated before affecting humans.

The phylogenetic investigation of novel CoVs suggests the existence of several cross-species transmission events; however, most of these events were transient spillover. The high recombination frequency of CoVs in bats suggests bats being a vital reservoir for CoV recombination and evolution (Banerjee et al. 2019).

4.4 Transmission from Animals to Human

The zoonotic origin of SARS-CoV-2 in Wuhan, China, can be strongly associated with the wet animal market since a large number of people who got an infection in the beginning were more or less exposed to it (Rothan and Byrareddy 2020). Several attempts were made to confirm the primary host or intermediary carriers from which the infection may have transmitted to humans.

Current research confirms more than 95% genomic similarity between SARS-CoV-2 and bat coronavirus, indicating bats as the most probable host of the former (Perlman 2020; Zhou et al. 2020). Besides bat, several other animal hosts were reported as a virus reservoir. Ji et al. (2020) demonstrated snakes as a possible virus reservoir for human infection while Lam et al. (2020) identified SARS-CoV-2-related coronaviruses in pangolins (*Manis javanica*). Stated the possibility of minks being intermediate hosts for SARS-CoV-2.

One more remarkable phenomenon observed for SARS-CoV was that the human strain recovered at the time of epidemic retained efficient hACE2/cACE2 recognition; however, the in vitro adapted civet strains quickly achieved hACE2 recognition (Sheahan et al. 2008). These data indicate the competent human/civet ACE2 recognition as a key factor to support SARS-CoV in human populations, offering an animal reservoir for continual persistence.

The main culprit for SARS-CoV and SARS-CoV-2 in humans is considered as bats since they are known to contain a wide variety of coronaviruses, although the mechanism for virus zoonotic spillover is still unclear. The pieces of evidences suggest the occurrence of recombination events among SARS-CoVs exist in the neighbouring bat population. Such phenomena may be responsible for the series of recombination within the S gene and around ORF8 leading to the origin of SARS-CoV direct progenitor. Moreover, it is expected that from here the spillover took place from bats to civets and later on to the people residing near the location or due to indulgence in wildlife trade of infected animals (Hu et al. 2017; Ahmad et al. 2020; Lu et al. 2020).

The spillover proceeds via several consecutive events that facilitate CoVs to establish infection in humans. The probability of animal-to-human transmission is ruled by various factors such as the dynamics of disease in an animal host, level of virus exposure, and the susceptibility of human population. All these factors can be summarized into three major stages that depict the way of virus transmission. The primary stage defines the pathogen pressure on human host, i.e., the amount of virus interacting with humans at a particular instant regulated by virus prevalence and dispersal from the animal host, followed by its survival, development, and distribution outside the animal host. In the next stage, the behavior of humans and vector defines the chances of viral exposure, the route of entry, and the dose of the virus. The last stage is influenced by genetics, the physiological and immunological status of the human host along with stage two factors determining the possibility and severity of infection (Plowright et al. 2017). The aforementioned stages create a barrier for transmission of the virus to the next level, and spillover necessitates the virus to surpass all barriers to establish an infection in the upcoming host.

4.5 Transmission Among Humans

Data from various studies so far implicate the zoonotic origin of SARS-CoV and SARS-CoV-2, and its fast spread among humans confirms person to person transmission. Many research works present added information on such modes of transmission. SARS being an airborne virus, transmit via the same way as cold and flu do. The virus spreads by an infected person on coughing or sneezing leaving small droplets in the air or by stool. So the person who inhales such droplets or touches the infected surfaces may also get infected.

In recent works, live SARS-CoV-2 has been detected in the stool of patients evidencing the subsistence of SARS-CoV in the gastrointestinal tract justifying the gastrointestinal symptoms, probable recurrence, and transmission of the virus via fecal-oral route (Gu et al. 2020; Holshue et al. 2020). However, it is not sure whether the consumption of virus-contaminated food may cause infection and transmission (Wu et al. 2020).

Ghinai et al. (2020) found that person-to-person transmission of SARS-CoV-2 may occur due to prolonged and unprotected exposure with the infected person suggesting constant pathogen pressure leading to infection and disease.

A case of SARS-CoV-2 transmission along four successive generations has been studied. Such incidence produces an example of sustained human to human transmission (Phelan et al. 2020; WHO 2020). So far the SARS-CoV-2-infected person acted as a major infection source and respiratory droplets as the main route of transmission, along with aerial droplets and close contact (Jin et al. 2020).

The virus infection commences via binding specific host receptors then fusing with the cell membrane. Reports state that the receptor-binding domain (RBD) of

virus spikes binds with ACE2 receptor of the potential host cell in case of SARS-CoV human-to-human transmission (Jaimes et al. 2020; Wan et al. 2020). The most interesting feature is that SARS-CoV-2 and SARS-CoV spikes share RBD sequence similarity strongly suggesting their common route of entry into the host cells via the ACE2 receptor (Wan et al. 2020). Currently, there is inadequate information on the transmission of SARS-CoV and SARS-CoV-2 from pet animals like dog and cat to the human; however in a fast-evolving situation it is difficult to predict the future.

Executive Summary

- The recurrent emergence of pathogenic CoVs indicates the disturbances in their ecological niche.
- There is still no clarity on the potential animal reservoir for the virus.
- The alleged zoonotic origin and cross-species transmission of SARS-CoV and SARS-CoV-2 need further attention to confirm the underlying adaptation-evolution mechanism.
- Understanding the molecular basis for ACE2 receptor usage by different SARS-CoV strains is vital to obtain clarity on cross-species transmission and check on possible future disease outbreaks.

4.6 Conclusions

Numerous viruses have existed in nature for years without affecting the human population, and their recurrent spillover on other animals and humans is the consequence of man-made activities. Therefore, the best way to keep them away is to keep a barrier between their natural reservoirs and civilization.

4.7 Future Perspectives

There is a need to scrutinize more animal models for infection and transmission of SARS among animals and humans. We need to study the effect of ethnic and cultural differences on CoV transmission and pathogenesis.

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