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Review Article

COVID-19: Zoonotic Origin, Interspecies Transmission, Virus-Host Interaction and Animals Susceptibility to SARS-CoV-2

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Abstract

The highly contagious coronavirus (now termed as COVID-19) outbreak started in Wuhan, China. It has affected several countries throughout the world and millions of lives are suffering of it. Coronavirus mainly causes respiratory tract infections like SARS (Severe Acute Respiratory Syndrome) and MERS (Middle-East Respiratory Syndrome). There are many debates regarding the origin of this deadly virus. Most promising and convincing view is that SARS-CoV-2 has zoonotic origin. Proper identification of the animal hosts is so crucial for the prevention of human diseases. SARS-CoV-2 has 96.2% nucleotide homology with a bat-CoV RaTG13 isolated from horseshoe bats (*Rhinolophus affinis*). In this review we focus on an overview of the zoonotic origins, phylogeny, interspecies transmission and animals susceptibility to HCoVs specifically SARS-CoV-2. We brief an idea about probable intermediate host (pangolin) for this deadly virus and host-virus interaction in relation to transmission. These novel pangolin CoV genomes show 85 - 92% homology in nucleotide sequence with SARS-CoV-2. In addition to that, their genome nucleotide sequence is about 90% identical to RaTG13. Transition of non-pathogenic state in their natural reservoir host to pathogenic state in a new host after interspecies transmission is also discussed in this review.

Keywords: *SARS-CoV-2; COVID-19; Zoonotic Origin; Reservoir Host; Intermediate Host*

Abbreviations

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2; nCoV: Novel Coronavirus; COVID-19: Coronavirus Disease 2019; HCoVs: Human Coronaviruses; BtCoV: Bat Coronavirus; MERS: Middle East Respiratory Syndrome Coronavirus; ORF: Open Reading Frame; RBD: Receptor-Binding Domain; WHO: World Health Organization; CDC: The Centers for Disease Control and Prevention; ACE2: Angiotensin-Converting Enzyme-2; TMPRSS2: Transmembrane Protease Serine 2; DPP4: Dipeptidyl Peptidase-4

Introduction

The 2019 novel coronavirus (2019-nCoV), which has subsequently been renamed SARS-CoV-2, is the causative agent of the ongoing pandemic of coronavirus disease 2019 (COVID-19), which has claimed more than 8,21,462 lives and infected more than 2,40,21,218 people as on 27th August 2020 [1]. India occupied the 3rd spot among affected countries with the highest number of reported COVID-19 cases in a short period. The total number of infected cases is 33,87,500 of which 61,529 are death as on 28th August 2020 [2]". Coronaviruses (CoVs) belong to the family *Coronaviridae*, which comprises a group of enveloped, positive-sensed, single-stranded RNA viruses

[3,4]. These viruses containing the largest genome of 26 - 32 kilobases amongst RNA viruses were termed "CoVs" because of their 'crown'-like morphology under electron microscope [4]. Around two thirds of the genome contain two large overlapping open reading frames (ORF1a and ORF1b), which encode the pp1a and pp1ab replicase polyproteins. The polyproteins are further processed to generate 16 non-structural proteins, designated nsp1~16. The remaining part of the genome contains ORFs which encode the structural proteins, including spike (S), envelope (E), membrane (M) and nucleoprotein (N) [4].

In this review we focus on an overview of the zoonotic origins, phylogeny, interspecies transmission and animals susceptibility to HCoVs specifically SARS-CoV-2. We brief an idea about probable intermediate host for this deadly virus and host-virus interaction in relation to transmission. Transition of non-pathogenic state in their natural reservoir host to pathogenic state in a new host after interspecies transmission is also discussed in this review.

Phylogeny of SARS-CoV-2

CoVs are classified into four genera (alpha-CoV, beta-CoV, gamma-CoV and delta-CoV) based on the difference in protein sequences. Among which the beta-CoV genera contains most HCoVs and is further subdivided into four lineages (A, B, C and D) [4,5]. Phylogenetic evidence has shown that bats and rodents serve as the gene source of most alpha-CoVs and beta-CoVs [4]. SARS-CoV-2 is the seventh coronavirus infective to humans. Among these CoVs, HCoV-229E and HCoV-NL63 are alpha-CoVs. The remaining five CoVs including HCoV-OC43, HCoV-HKU1, severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-2 belong to beta-CoVs group [4-6]. HCoV-229E, HCoV-OC43, HCoV-HKU1 and HCoV-NL63 are associated with mild symptoms [7]. In contrast, SARS-CoV, MERS-CoV and the newly-identified SARS-CoV-2 are highly pathogenic, causing severe respiratory infection like pneumonia is one of the most severe symptoms and can progress rapidly to acute respiratory distress syndrome [8]. Phylogeny analysis suggested that the earliest zoonotic spillover event might have occurred at the end of November 2019 [7,9]. Zhang., *et al.* 2020; well picturise the evolution of two major lineages of SARS-CoV-2 (clades I and II) from their data analysis of 326 SARS-CoV-2-infected people in Shanghai, China. Most probably they evolved independently from a common ancestor, but the important thing is that their ancestry in terms of how they are related or not to each other is undecided, because they vary at only two genomic sites. No significant differences are observed in clinical features, mutation rate between patients infected with two lineages clade I or II virus [9].

Transmission

The main route of transmission of SARS-CoV-2 is respiratory droplet [10]. It can also be transmitted via airborne droplets (aerosols) to the nasal mucosa in closed environments, crowded area and through close contact (within 1 metre) between people, unwashed hands and indirectly through touching contaminated surfaces. The virus begins to replicate locally in ciliated epithelial cells, consequently damage cells and results inflammation [11]. Multiple evidences strongly suggest that this deadly virus can pass from one person to other in tiny droplets (aerosols) which drift through the air and accumulate over time [12]. The possible modes of transmission for SARS-CoV-2, as mentioned by WHO, includes contact, droplet, airborne, fomite, fecal-oral, bloodborne, mother-to-child, and animal to human transmission [13]. However, we should not forget the importance of asymptomatic carriers which may play a critical role in the transmission process [14].

Zoonotic origin of SARS-CoV-2

All seven HCoVs have a zoonotic origin from bats, mice or domestic animals [4,15]. Multiple lines of evidence support an evolutionary origin of all HCoVs from bats, where viruses are well adapted and non-pathogenic but show great genetic diversity [8]. Bats have been identified as the natural reservoirs for a number of pathogenic viruses such as Rabies, Hendra, Marburg, Nipah, Ebola virus etc [16]. Bats are also reservoir hosts of coronaviruses. Alpha-CoV (α-CoV) and beta-CoV (β-CoV) have been detected in bats in greater part of the world [17].

SARS-CoV-2 shares 96.2% nucleotide sequence homology with a bat CoV RaTG13 isolated from *Rhinolophus affinis* bats [18]. Severe acute respiratory syndrome (SARS)-CoV-2 causing the current pandemic [CoV disease 2019 (COVID-19)] is also a member of the same genus and found to be similar to bat-derived CoV strain RaTG13 [7]. It has been reported that at the whole genome level, SARS-CoV-2 is 96% identical to BtCoV and related viruses which were identified in the previously sampled bat population in China [18]. Bats are reservoirs for viruses with human pathogenic potential [19]. Yadav., *et al.* 2020; hypothesized a possible link for this virus to their intraspecies transmission due to the global distribution of bats, along with the different types of cell receptors present within them which favours virus replication. They also suggested that the interspecies spread out of a BtCoV to humans might occur through intermediate host, in which the virus replicates through yet completely unidentified routes. Recent report of pathogenic human viruses from two species of bat in India demands enhanced methods to monitor human exposure to various bat species [20].

Although SARS-CoV and SARS-CoV-2 are quite similar due to high (82%) nucleotide sequence homology, they cluster into different branches in the phylogenetic tree [5]. Ye., *et al.* 2020; observed and well demonstrated few important similarities and dissimilarities between SARS-CoV-2 and the other/rest six HCoVs. Firstly, the incubation period and the duration of the course of SARS-CoV-2-infected disease follows the general trend of the other six HCoVs. Secondly, the severity of symptoms of COVID-19 lies between SARS-CoV and the four community-acquired HCoVs (i.e. HCoV-229E, HCoV-OC43, HCoV-HKU1 and HCoV-NL63)-infected diseases. Apart from it, the transmission of SARS-CoV-2 follows almost the same patterns characteristic of both community-acquired HCoVs and SARS-CoV. It has been reported that SARS-CoV-2 follows the same cell entry receptor ACE2 as SARS-CoV to infect humans [21]. SARS-CoV-2 can be detected in fecal samples which are same as the other HCoVs [22]. The characters of SARS-CoV-2 including its transmissibility, pathogenicity and spreadability after passages in human body will be significant on the final fate of the ongoing outbreak of COVID-19 [23].

Intermediate host determinants of SARS-CoV-2

Most probably, the intermediate animal hosts of SARS-CoV-2 should be among the wildlife species sold and killed at the Huanan Seafood Wholesale Market, which indicates a probable animal-to-human transmission event [24]. Metagenomic sequencing data obtained by various group of researchers suggested that an endangered mammal, pangolin (*Manis javanica*) could also harbors ancestral beta-CoVs related to SARS-CoV-2 [25]. These novel pangolin CoV genomes show 85 - 92% homology in nucleotide sequence with SARS-CoV-2. In addition to that, their genome nucleotide sequence is about 90% identical to RaTG13 [25].

It has been reported from an earlier study that the lung samples of some diseased pangolins contain viral contigs, which is quite related to SARS-CoV-2 [26]. Altogether these data suggest the possibility that pangolin is one of the intermediate animal hosts of SARS-CoV-2 [25]. To trace the zoonotic origin of SARS-CoV-2, we need to establish the evolutionary pathway of SARS-CoV-2 in bats, pangolins and other mammals first. It has been found that the RBDs (receptor-binding domains) of SARS-CoV-2 share highest sequence homology with pangolin SARS-CoV-2-related beta-CoVs. It is highly tentative that the high degree of similarity between the RBDs of pangolin SARS-CoV-2-related beta-CoVs and SARS-CoV-2 is driven by selectivity-mediated convergent evolution. However, there is another possibility too which is a recombination between a pangolin SARS-CoV-2-related beta-CoV and RaTG13 in the third wild animal species. As a driving force in evolution, recombination is widespread among beta-CoVs [27].

Particularly, pangolin beta-CoVs are highly pathogenic in pangolins. They might be a dead-end host for SARS-CoV-2-related beta-CoVs, similar to civets in the case of SARS-CoV. There are numerous aspects for interspecies transmission of SARS-CoV-2 from animals to humans which need further clarifications. Ye., *et al.* 2020; proposed some unavoidable clues regarding the zoonotic origin of SARS-CoV-2 which are (1) Bats could be the reservoir host of a SARS-CoV-2-related virus almost identical to SARS-CoV-2. Humans might share the ecological niche with bats through butchering or coal mining. (2) Pangolins could be one of intermediate amplifying host to which a SARS-CoV-2-related virus had been newly introduced. Ye., *et al.* 2020; assumed the possibility that humans might contract the virus through butchering and consumption of game meat. In parallel to it, many mammals including domestic animals are susceptible to SARS-CoV-2.

An active continuous survey of domestic and wild animals for antibodies is necessary. (3) Recombination and adaptation of SARS-CoV-2 might have occurred in a third species that has contact with both bats and pangolins [23].

Results obtained from the study of Ji., *et al.* 2020; suggested that SARS-CoV-2 shares similarities in terms of genetic information with bat coronavirus. In addition to that, they also suggested a homologous recombination might occur within the viral receptor-binding spike glycoprotein, which might decide cross-species transmission [8]. It has been reported that Pangolin beta-CoVs strikingly homologous to SARS-CoV-2, supporting the view that pangolins might serve as one of intermediate hosts or pangolin beta-CoVs could contribute gene fragments to the final version of SARS-CoV-2 [23].

Interspecies transmission

Before becoming a zoonotic disease, SARS-CoV-2 has to cross species barriers to exist in different types of hosts. There are some factors which may make them capable. First of all, comparatively high mutation rate of this RNA-virus with an average substitution rate being $\sim 10^{-4}$ substitution per year per site approximately [4]. Second most important thing is their large RNA genome which exerts extra plasticity in genome modification for mutations and recombination, thereby increasing the probability for interspecies co-evolution, which is beneficial for the emergence of novel CoVs when the environments become suitable [28]. Rapid mutation and genetic recombination also drive HCoVs evolution and serve as two important steps in this process [4]. RNA viruses such as SARS-CoV-2 achieve mutations easily and most of these are deleterious. There are several subtypes have been identified from different isolates across the globe [29]. Among those types, the ancestral type (O) was first reported from China at the end of December 2019. Few months later, another type (A2a), which was also first reported from China on 24th January 2020. It has been assumed that this type spread rapidly and extensively across Europe and North America [GISAID: https://www.gisaid.org/ and Nextstrain: https://nextstrain.org/] outcompeting the ancestral (O) type [30,31].

Considerable modification of viral phenotypes is due to the acquisition or loss of novel protein-coding genes. Among SARS-CoV accessory proteins, ORF8 has been thought to be important in adaptation to humans, as SARS-CoV-related bat viruses encoded divergent ORF8 proteins [32]. At the beginning of the human epidemic, a 29-nucleotide deletion characteristic of SARS-CoVs has been found in isolated strains. The occurrence of deletion splits the ORF8 into ORF8a and ORF8b. Therefore, host switching of these viruses is may be due to this adaptive mutation [33].

Virus-host interaction in relation to transmission

Generally, the RBD in the S (spike) protein of a CoV interacts with the cellular receptor and is intensely selected by the host antibody response. In SARS-CoV, the RBD is in the 318th to 510th amino acids on the S1 fragment, which binds to the human ACE2 as well as its co-receptors for viral entry [34]. According to Zhou., *et al*. 2020; the RBD of SARS-CoV is capable of recognizing the ACE2 receptors of various animals, including bat, civet, mouse and raccoon dog, which allow the virus's interspecies transmission. It is notable that SARS-CoV-2 shares the same cellular receptor with SARS-CoV [18]. A 30% difference between SARS-CoV-2 and SARS-CoV in the S1 unit of the S protein implicates higher binding affinity of SARS-CoV-2 S protein with human ACE2 (10- to 20-fold higher affinity of this binding) as supported by the recent cryo-EM study [5,35].

It is questionable now how bats remain asymptomatic or show only mild symptoms when infected with CoVs. Calisher., *et al.* 2006; exposed the fact of mutual adaptation between CoVs and bats [19]. It has been found that bats are well adapted to CoVs anatomically and physiologically. Bats are capable to reduce the pathology triggered by CoVs due to their defects in the activation of proinflammatory response and also reduce the immune response to a virus [36,37]. Another important immunological phenomenon such as upregulation of inhibitory natural killer cell receptor NKG2/CD94 suppresses the natural killer cell activity in bats. Besides, low expression level of major histocompatibility complex class I molecules is also noticed [38]. Apart from these, due to high metabolic activity of bats, production of increased level of reactive oxygen species (ROS) could suppress CoV replication as well as affects proofreading by exoribonuclease [39],

thus providing the selection pressure for the emergence of virus strains highly pathogenic when introduced into a new host. According to Calisher., *et al.* 2006; more pathogenic CoV strains might also evolve by recombination which leads to the acquisition of novel proteins for host adaptation [19]. Now-a-days, the researchers assume that studying bats' immune systems will provide new therapeutic targets to fight various human diseases and aging. As bats are capable to mutate or completely eliminate several genes involved in inflammation, so scientists can develop drugs to inhibit these genes in humans and to regulate our immune system more like a bat [37].

It has been reported that the number of asymptomatic subjects infected with SARS-CoV-2 are increasing and might contribute to its rapid spreading around the world. Another important secret needs to be explored that is why asymptomatic carriers are seen, how they cope up and what causes the severe cases in human infection. According to Ye., *et al.* 2020; the severe symptoms arise mainly due to the hyperactivation of immune response and the cytokine storm wherein the stronger the immune response, the more severe the lung damage. In contrast, the immune response has been de-coupled from CoV replication in asymptomatic carriers. The strong interferon response in bats may protect them from corona virus infection [23].

Susceptibility of animals to SARS-CoV-2

It has been reported that ferrets and cats are highly susceptible to SARS-CoV-2 but dogs have low susceptibility. Other domesticated animals such as pigs, chickens, and ducks are not susceptible to the virus. The most important fact obtained from the study of Shi., *et al.* 2020; is that SARS-CoV-2 replicates competently in the upper respiratory tract of ferrets which makes them a candidate animal model for evaluating the efficacy of drugs or vaccines against COVID-19 [40]. SARS-CoV-2 also capable to replicate efficiently and is transmissible to naïve cats. Cats in Wuhan have been reported to be sero-positive for SARS-CoV-2 [41]. Therefore, in addition to ferrets, proper surveillance for SARS-CoV-2 in cats should be considered for eradication of COVID-19 in humans [40].

Discussion

The origin of SARS-CoV is still enigmatic. SARS-CoV virus has been identified in many animals such as palm civets, raccoons, dogs and Chinese ferret-badgers, which are claimed to be intermediate hosts found in live animal markets from Guangdong, China. Several bats species (for e.g. horseshoe bats) which are the reservoir host/primary host of coronaviruses [42,43]. There is contradictory view too. Few scientific findings have explained that several bat Coronaviruses are capable of infecting human cells without passing through intermediate host [44,45]. However, on the basis of recent phylogenetic data it is not unlikely that SARS-CoV-2 passed directly from bats to humans without the intermediate host [46]. Earlier study suggested that the recombination of SARS in the spike glycoprotein genes might have mediated the initial cross-species transmission event from bats to other mammals [34]. Ji., *et al.* 2020; also pointed out that the ancestral origin of the 2019-nCoV was more likely from divergent host species rather than SARS-CoV. The fact is that we paid attention on these viruses when they made epidemic or pandemic such as SARS, MERS, and 2019-nCoV [8]. To understand the molecular mechanism of SARS-CoV-2 cross-species spread, it is vital to determine the animal reservoir of the 2019-nCoV [34].

Coronaviruses usually do not produce clinical symptoms in their natural reservoir host bats. Accidental transmission of these viruses to human beings and other animals may result in several respiratory, enteric, hepatic or neurologic diseases of variable intensity. It needs to decipher why only certain CoVs can infect human beings. Current world-wide situation demands continuous active and unprecedented surveillance of zoonotic infections in bats. Proper detection and identifications of such aetiological agents will provide leads for the development of diagnostic and therapeutic along with preparedness and readiness to deal with such emerging novel viruses with pandemic potential. Yadav., *et al.* 2020; also emphasized on cross-sectional antibody surveys (human and domestic animals) in localities where the viruses have been detected [20].

Several studies in different parts of the world emphasized on the concept of zoonotic origin of SARS-CoV-2 and suggest that COVID-19 is a zoonotic disease. However, Zhang., *et al.* 2020; mentioned some ambiguity about the origin of the virus, SARS-CoV-2. According to

the Chinese authorities, the first infection case was reported on December 31, 2019 and many of the initial cases were linked directly to Huanan seafood market in Wuhan, in the Hubei province [47]. Till now, the hypothesis which is suggested to be most likely and convincing one that the outbreak originated at the market, with its initial transmission from live animals to human beings followed by rapid human-to-human transmission. However, another recent study claimed that the first patient, diagnosed on December 1, 2019, was never exposed to the market [24]. Thus, origin of the disease still remains an enigma unresolved. Proper identification and subsequent elimination of the zoonotic source appears to be the most crucial and demanding task at present to prevent further events of viral spill over at the animal-human interface [48]. Zhang., *et al.* 2020; suggested some significant thumb-rules to trace the source of the virus which are: (1) Tracing back the viral emergence at the Huanan seafood market. Animal sampling can be done directly from the market before selling. (2) SARS-CoV-2 detection test in wild animals. Although viruses isolated in pangolin and bats [18,49] have been reported to genetically relate to SARS-CoV-2, larger number of samples would be required for the purpose of detecting and profiling the exact animal source. (3) Clinical samples collected before December 2019 in Hubei Province, especially in Wuhan must undergo serum antibody detection. It appears urgent to specifically identify as who is "patient zero" for the outbreak at least to address the complex riddles as how, when and why the virus emerged. To unravel the enigmatic origin of novel coronavirus, detection and profiling of antibodies against it in the sera of human individuals before December, 2019, present in Wuhan hospital might present scopes to determine as when the event of viral transmission to human population had originally occurred [48]. The search for the animal origins of SARS-CoV-2 is still going on. Proper identification of the animal hosts is so crucial for the prevention of this pandemic infectious disease.

Apart from it, animal health surveillance systems (especially those animals are suspected) play an important role in making an idea to control this outbreak and should be integrated with human public health surveillance systems parallelly [50]. In addition to the adaptation, evolution, and virus spread among humans and possible intermediate animals and reservoirs; potential routes of transmission and subclinical infection should be taken into considerations. There are some basic questions which include details about what is the testing rate in a SARS-CoV-2-infected country, what is the frequency of spreading infection, how many becomes positive in a single day, whether this rate remains constant or variable along with identification of asymptomatic patients are need to be addressed as early as possible.

Name of the Coronavirus	Place of Origin	Probable Reservoir Hosts	Probable Intermediate Hosts	Cell Receptors involved for entry
SARS-CoV-2	Wuhan, Hubei province, China	Bats (*Rhinolophus affinis*)	Pangolin (*Manis javanica*)???	ACE2, TMPRSS2
SARS-CoV	Guangdong province, South China	Chinese Horseshoe Bats	Masked Palm Civets (*Paguma larvata*)	ACE2
MERS	Saudi Arabia	Bats or Rodents	Dromedary Camels (*Camelus dromedarius)*	DPP4 or CD26

Table 1: *Comparison of animal hosts of SARS-CoV-2, SARS-CoV and MERS (Reference: Ye., et al. 2020; Contini., et al. 2020).*

Conclusion

From several scientific research and evidences, it is understandable that bats provide a rich pool of virus species for interspecies exchange of genetic fragments and interspecies transmission. To be an ideal 'virus spreader', bats fulfill all the important criteria such as longevity, densely packed colonies, close social interaction and strong ability to fly. SARS-CoV-2 is capable for cross-species transmission and pangolin may act as intermediate host for this virus. Lastly, tracing the evolution of SARS-CoV-2 is quite essential for informing the public-health policies required to limit this COVID-19 spread.

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Conflict of Interests

Author declares there is no conflict of interests exists.

Author Contributions

I solely have planned the idea for the review article, performed all the literature search and data analysis, and finally drafted and critically revised the work.

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