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Origin of SARS-CoV-2: What Do We Know So Far

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A B S T R A C T

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is the latest coronavirus to infect humans. It has caused the present pandemic of COVID-19. Even after affecting more than 220 countries and territories, causing more than 220 million infections and more than 50 million deaths, the pandemic is continuing unabated. There are mutant strains of the virus emerging every few months that are more contagious than the previous ones, causing new waves of infection in different corners of our universe. Strong epidemiological evidence points towards bat origin of SARS-CoV-2, although the details of reservoir and intermediate hosts are still largely unknown.

Introduction

On December 31, 2019 Wuhan Health Commission in Hubei province of the Republic of China notified a cluster of 27 cases of pneumonia of unknown etiology to the National Health Commission, China Centre for Disease Control (CCDC) and World Health Organization (WHO).

On January 7, 2020 the CCDC announced the discovery of the etiological agent of this pneumonia- a betacoronavirus that had never been seen before and it was named novel coronavirus 2019 (2019-nCoV).

On February 11, 2020 the International Committee on Taxonomy of Viruses (ICTV) named 2019-nCoV as SARS-CoV-2. This name was selected because the virus was genetically related to the coronavirus (CoV) responsible for the SARS outbreak in 2003.

On the same day WHO announced Coronavirus Disease 2019 (COVID-19) as the name of the new disease that this virus produced (Ben Hu *et al.*, 2021). The high transmission efficiency of SARS-CoV-2 and the abundance of international travel enabled rapid spread of COVID-19 and on March 11, 2020 WHO declared COVID-19 a global pandemic (Carvalho *et al.*, 2021).

This is the first pandemic of 21st century. It has affected all aspect of our lives forcing us to change our daily habits, lifestyle, work, family and social cultures for indefinite period of time to come.

Human Coronaviruses

Coronaviruses have long been known to present a high pandemic risk. SARS-CoV-2 is the ninth documented coronavirus that infects humans and the seventh identified in the last two decades. All previous human coronaviruses (HCoV) have zoonotic origins (Holmes *et al.*, 2021).

SARS-CoV-2 belongs to the family Coronaviridae, of the order Nidovirales. Coronaviruses (CoV) are enveloped, positive sense, single-stranded RNA viruses with club-shaped spike projections emanating from the surface of the virion. This gives the virus particle the appearance of solar corona under electron microscope. CoVs are classified into four genera- Alphacoronavirus, Betacoronavirus, Gammacoronavirus and Deltacoronavirus. Alpha- & betacoronaviruses primarily infect mammals including humans (Machhi *et al.*, 2020). CoVs have relatively high rates of mutation and recombination frequency during RNA replication. The RNA genome of CoV is large (26 to 32 kilobases) exerting extra plasticity in genome modification for mutations and recombination (Asghari *et al.*, 2020). These genomic characteristics make them capable of adapting to new host and ecological niches easily. This property enhances the probability of interspecies co-evolution facilitating the emergence of novel CoV species when conditions become appropriate.

Origin of human coronaviruses

The emerging HCoVs of public health concern of 21st century- Severe Acute Respiratory Syndrome coronavirus (SARS-CoV), Middle East Respiratory Syndrome coronavirus (MERS-CoV) and SARS-CoV-2 belong to betacoronavirus family (Zi-Wei *et al.*, 2020). SARS-CoV caused the epidemic of SARS in 2003 and MERS-CoV caused MERS in 2012. No new cases of SARS have been reported after 2004. However, MERS has become endemic in the middle East. For both SARS-CoV & MERS-CoV bats are the natural hosts. The viruses enter the human population through intermediate hosts. For SARS, the prominent intermediate hosts are civet cats and for MERS dromedary camels.

The epidemiology of emergence of SARS-CoV-2 has close resemblance to that of SARS-CoV. SARA-CoV spilled over into humans in Foshan, Guangdong province, China in November 2002, and again in Guangzhou, Guangdong province in 2003 (Xu *et al.*, 2004). Both these SARS-CoV emergence events were associated with markets selling live animals and involved species, particularly civets and raccoon dogs (Zi-Wei *et al.*, 2020).With SARS, live-animal markets continued to sell infected animals for many months, allowing zoonotic spillover to be established as the origin and revealing multiple independent jumps from animals into humans (Worobey, 2021). The WHO-China report and other epidemiological investigations have found that one-third to two-thirds of early symptomatic cases of COVID-19 had link to Huanan live-animal market specifically its western section where raccoon dogs were kept caged (Xiao *et al.*, 2021). Civets and raccoon dogs are known to be susceptible to SARS-CoV-2 infection (Freuling *et al.*, 2020). Unfortunately, no live mammals collected from Huanan market or any other live-animal market in Wuhan has been screened for SARS-CoV-2-related viruses and Huanan market was closed and disinfected on January 1, 2020. Nevertheless, the extraordinary preponderance of the earliest cases of COVID-19 in close proximity to Huanan market provides strong evidence for a live-animal market origin of the pandemic. The fact that so many of more than hundred COVID-19 cases from December 2019 with no identified epidemiologic link to Huanan market nonetheless lived in its direct vicinity is notable and provides compelling evidence that community transmission started at the market (WHO, 2021). SARS-CoV-2 also shows similarities to the four endemic HCoVs: human coronavirus OC43 (HCoV-OC43), human coronavirus-229E (HCoV-229E), human coronavirus-HKU1 (HCoV-HKU1), and human coronavirus NL63 (HCoV-NL63). These viruses have zoonotic origins, and the circumstances of their emergence are unclear. In direct parallel to SARS-CoV-2, HCoV-HKU1,

which was first described in a large Chinese city (Shenzhen, Guangdong) in the winter of 2004, has unknown animal origin, contains a furin cleavage site in its spike protein and was originally identified in a case of human pneumonia (Woo *et al.,* 2005).

Samples from the earliest COVID-19 patients in Wuhan have been sequenced, and two distinct SARS-CoV-2 lineages, A and B, have been identified. If lineage A had a separate animal origin from lineage B, both most likely occurring at Huanan market, this phylogenetic pattern is suggestive of multiple spill-over events as potentially infected or susceptible animals were moved into or between Wuhan markets via shared supply chains and sold for human consumption (Worobey, 2021).

No bat reservoir or intermediate animal host for SARS-CoV-2 has been identified to date. The animal origins of many well-known human pathogens, including Ebola virus, hepatitis C virus, poliovirus, and the HCoVs HCoV-HKU1 and HCoV-NL63, are yet to be identified. It took over a decade to discover bat viruses with more than 95% similarity to SARS-CoV and able to use human ACE-2 as a receptor (Hu *et al.,* 2017).

SARS-CoV-2: natural or manmade virus?

Two intriguing facts regarding the origin of SARS-CoV-2 has led to several speculations. First, even after two years into the pandemic, any close relative of SARS-CoV-2 still has not been found in an animal and second, SARS-CoV-2 was found in a place where a top laboratory studying coronaviruses, the Wuhan Institute of Virology (WIV), is located. Some of the speculations are- the virus is a man-made bioweapon generated by gene modifications, an accidental laboratory leak leading to the outbreak and the virus was unintentionally introduced by scientists during field work (Zheng-Li Shi, 2021). There is currently no evidence that SARS-CoV-2 has a laboratory origin. For example, it doesn't carry any genetic markers that one might expect from laboratory experiments. Under any laboratory escape scenario, SARS-CoV-2 would have to be present in a laboratory prior to the pandemic, yet there is no evidence that the WIV possessed or worked on a progenitor of SARS-CoV-2 prior to the pandemic (Holmes *et al.,* 2021). Considerable attention has been devoted to claims that SARS-CoV-2 was genetically engineered or adapted in cell culture or "humanized" animal models to promote human transmission. Yet, since its emergence, SARS-CoV-2 has experienced repeated sweeps of mutations in the receptor binding domain of its spike protein which have helped improve its human adaptation by increasing infectivity and ACE2 binding affinity (Deng *et al.,* 2021; Otto *et al.,* 2021; Simmonds *et al.,* 2020). Almost all the laboratory escapes documented to date have almost exclusively involved viruses brought into laboratories specifically because of their known human infectivity. Moreover, epidemiological investigations have not provided any link of early cases of COVID-19 in Wuhan to the WIV (Worobey, 2021; Holmes *et al.,* 2021).

Genetic evidence suggests that SARS-CoV-2 is a natural virus that probably originated in animals, although there is no conclusive evidence to know as to when and where the virus first entered humans (Ben Hu *et al.,* 2020). WIV discovered a virus sequence (RaTG13) that shows a 96.2% genomic sequence identity match with the SARS-CoV-2 genome, in its archived bat samples collected in 2013 (Zhou *et al.,* 2020). This bat coronavirus was isolated from Chinese horseshoe bats (*Rhinolophus affinis*) found in Yunnan province (Ben Hu *et al.,* 2020). Phylogenetic analysis confirms that SARS-CoV-2 closely clusters with RaTG13. The high genetic similarity between SARS-CoV-2 and RaTG13 supports the hypothesis that SARS-CoV-2 likely originated from bats (Paraskevis *et al.,* 2020). There are three other bat coronaviruses- RmYN02, RpYN06, and PrC31 that are closer in most of the virus genome and thus share a more recent common ancestor with SARS-CoV-2 (Li *et al.,* 2021; Lytras *et al.,* 2021; Zhou *et al.,* 2021). None of these three closer viruses were collected by the WIV and all were sequenced after the pandemic had begun.

There are several other bat CoVs detected in horseshoe bat (*Rhinolophus pusillus*) from Eastern China that fall into the SARS-CoV-2 lineage of the subgroup Sarbecovirus. The discovery of diverse bat CoVs closely related to SARS-CoV-2 suggests that bats are possible reservoirs of SARS-CoV-2. But, the sequence diversion between these bat CoVs and SARS-CoV-2 is too great to assign parental relationship. Phylogenetic analysis suggests this evolutionary relationship to be at least twenty years old (Ben Hu *et al.,* 2020).

Beyond bats, pangolins are another wildlife hosts probably linked with SARS-CoV-2(Ben Hu *et al.,* 2020). Multiple SARS-CoV-2 related viruses have been identified in the tissues of Malayan pangolins (*Manis javanica*) smuggled from Southeast Asia into Southern China between 2017 and 2019. These pangolin CoVs belong to two distinct sub lineages. Out of these the Guangdong strains exhibit 92.4% sequence similarity with SARS-CoV-2 and their receptor binding domain (RBD) has 97.4% amino acid sequence similarity with RBD of SARS-CoV-2.

The receptor binding motif (RBM) of these viruses has only one amino acid variation from SARS-CoV-2, and it is identical to that of SARS-CoV-2 in all five critical residues for receptor binding (Xiao *et al.,* 2020).

However, unlike bats, which carry CoVs healthily, the infected pangolins showed clinical signs and histopathological changes, including interstitial pneumonia and inflammatory cell infiltration in multiple organs. This suggests that pangolins are unlikely to be reservoir host of these viruses and appear to have acquired the viruses after spill over from the natural hosts (Ben Hu *et al.,* 2020).

The available evidence is insufficient to assign pangolins as intermediate hosts of SARS-CoV-2 and there is no evidence to suggest that pangolins were directly involved in the emergence of SARS-CoV-2. It is possible viral RNA recombination among different related CoVs was involved in the evolution of SARS-CoV-2 (Ben Hu *et al.,* 2020).

Bat CoVs

Bats are highly diversified and are the group of mammals having the second largest number of species. Presence of various cell types and receptors facilitate bats to be potential host for a large number of viruses.

Bats have several qualities that make them ideal virus spreaders- widespread distribution, capable of sustained flight, long-life, resident in densely-packed colonies and keeping close social interactions (Wong *et al.,* 2019). Bats are direct source of human pathogenic viruses including rabies virus and other lyssaviruses, Hendra virus, Nipah virus and Ebola virus (Wong *et al.,* 2019). Before the SARS epidemic, bats were not known to host CoV. Research over the last 15 years has led to genomic sequencing of more than 30 bat-CoVs and isolation of many more if genetic sequencing is not considered. Bats are now considered to be the mammals harbouring the largest number of CoVs. Among the four genera of CoVs, only alphaCoVs and betaCoVs have been found in bats (Wong *et al.,* 2019).

Horseshoe bats (*Rhinolophus genus*) have been found to be reservoirs of SARS-like and MERS-like CoVs. Molecular epidemiology studies have revealed that the largest population of completely sequenced bat SARS-like CoVs are found in Chinese horse-shoe bats (*Rhinolophus sinicus*) (Lau *et al.,* 2010; Hu B *et al.,* 2017).

Majority of bat SARS-like CoVs in Yunnan province share 90-95% genome nucleotide identity to human & civet SARS-CoVs compared to only 77-90% in those found in Southeast China, Korea & Europe. Yunnan province in Republic of China is an ecological niche where many different species of horseshoe bats reside. It is also the geographical region where the highest diversity of bat SARS-like CoV is observed, with many recombination events taking place among the various strains of bat SARS-like CoV (Hu B *et al.,* 2017; Lau *et al.,* 2015; Wu *et al.,* 2016). SARS-like CoV are well-adapted and

non-pathogenic in bats making bats the ideal reservoir hosts for CoVs. Bat CoVs show great genetic diversity and serve as gene pool for HCoVs. Bats act as petri-dish, mixing up CoVs from humans and other species leading to evolution of novel CoVs (Wang *et al.,* 2019). It is not by chance that three novel HCoVs have emerged in the past two decades.

Interspecies Transmission of SARS-CoV-2

Although several pieces in the puzzle of the zoonotic origin of SARS-CoV-2 are missing, strong epidemiologic and phylogenetic evidence supports that SARS-CoV-2 has a bat origin and is transmitted to humans via intermediate hosts.

Interaction between various bat species, between bats and other animals as well as between bats and humans are important for interspecies transmission of CoVs (Ben Hu *et al.,* 2020). To complete the spill over chain, susceptible recipient hosts need to be present within the viral shedding area. Host susceptibility mainly depends on the availability of the specific receptors on recipient tissue to interact with the spike protein of CoVs for viral entry-angiotensin-enzyme 2 (ACE2) for SARS-CoV and SARS-CoV-2 and dipeptidyl peptidase-4 (DPP4) for MERS-CoV. Similarly, recipient hosts which share similar receptor identity to human are potential candidates as intermediate hosts in interspecies jumping events. CoV transmission from bats to intermediate hosts allows for multiple rounds of replication and mutations before human transmission (Wong *et al.,* 2019).

Events like habitat destruction, climate change, coal mining and wildlife trafficking are bringing humans and animals closer (Zheng-Li Shi, 2021). CoV is just an example of a string of pathogens that have come from wildlife trafficking, including SARS, Ebola, Bird Flu, HIV, and many more(Wong *et al.,* 2019). In the wildlife trafficking and poaching, animals are hunted, trapped and taken to markets to be sold for traditional medicines, food and the pet trade. The wild animals can harbor diseases that can make other animals, including humans, sick. Trapping and keeping different animal species together in an enclosed space like a farm or a cage in wildlife trade markets brings them in prolonged contact with each other which is not possible in their natural habitats. This facilitates interspecies viral transmission and also emergence of virulent strains of pathogens. A common phenomenon observed in both SARS-CoV and Swine acute diarrhea syndrome coronavirus (SADS-CoV) outbreaks was that the outbreaks involved caged or farmed animals which were restricted in defined areas with bats residing around (Wong *et al.,* 2019). Human capture of wildlife and incursion into natural wildlife habitats allow viruses to jump the species barrier and infect humans (Zheng-Li Shi, 2021). Addressing the legal trade and illegal trafficking of wild animals is vital to help stop the spread of zoonotic pathogens in human population. Recent shutting down of all wild-life animal markets in China is one such step in this direction. Many viruses have existed in our planet for ages. They stay in their own natural reservoirs. The most effective way to prevent viral zoonosis is for humans to stay away from the ecological niches of the natural reservoirs of the zoonotic viruses. Extensive and long-term surveillance for viruses carried by wild animals would be another vital prophylactic strategy that needs to be adapted by governments and organizations worldwide to rapidly identify and limit spread of emerging pathogen at the very early stage and prevent the next pandemic from emerging. There is substantial body of scientific evidence supporting a zoonotic origin of SARS-CoV-2. Although the possibility of a laboratory accident cannot be entirely ruled out, this conduit of emergence is highly unlikely vis-a-vis the numerous and repeated human-animal contacts that occur routinely in the wildlife trade. There is pressing need for collaborative and carefully coordinated studies for comprehensive understanding of zoonotic origin of the present pandemic so that we can take measures to save the world from future pandemics arising from the same human activities that have repeatedly put us on a collision course with novel viruses.

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