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Review Article

The zoonotic and natural foci characteristics of SARS-CoV-2

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ABSTRACT

The origin of SARS-CoV-2 is still an unresolved mystery. In this study, we systematically reviewed the main research progress of wild animals carrying virus highly homologous to SARS-CoV-2 and analyzed the natural foci characteristics of SARS-CoV-2. The complexity of SARS-CoV-2 origin in wild animals and the possibility of SARS-CoV-2 long-term existence in human populations are also discussed. The joint investigation of corona virus carried by wildlife, as well as the ecology and patho-ecology of bats and other wildlife, are key measures to further clarify the characteristics of natural foci of SARS-CoV-2 and actively defend against future outbreaks of emerging zoonotic diseases.

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1. Introduction

At present, the unprecedented pandemic of coronavirus disease 2019 (COVID-19) caused by novel coronavirus, severe acute respi-

ratory syndrome coronavirus 2 (SARS-CoV-2), is still rampant in the world, and remains a serious public health emergency of international concern. However, although the origin of SARS-CoV-2 is still a mystery, early evidence suggests bats as its origin.^{1,2} Understanding the zoonotic origins of SARS-CoV-2 is crucial for monitoring, preventing, and responding to both COVID-19 and future pandemic threats.³ In this study, we reviewed and combed the

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main literature examining SARS-CoV-2 in wild animals, analyzed the zoonotic and natural foci characteristics, and identified gaps in the literature that must be solved to confirm reservoir(s) and spillover origin. We also compiled relevant countermeasures for tracing the source of SARS-CoV-2 towards providing useful information for active prevention and control of SARS-CoV-2 pneumonia as well as other similar emerging zoonotic infectious diseases in the future.

2. The possible natural reservoir host of SARS-CoV-2

2.1. Bats as potential natural hosts of SARS-CoV-2

Bats are important natural hosts of many emerging infectious disease-causing pathogens and harbor a large diversity of coronaviruses,⁴ several of which are related to zoonotic pathogens that cause severe disease in humans, such as severe acute respiratory syndrome (SARS)-CoV, Middle East respiratory syndrome (MERS)-CoV, human CoVs NL63, and 229E.^{5,6} At present, RaTG13, which was found in *Rhinolophus affinis* in Yunnan Province, has the closest relationship with SARS-CoV-2, with 96.2% identity at the whole-genome level.¹ In addition, RmYN02 detected in *R. malayanus* in Yunnan was 97.2%, similar to that of SARS-CoV-2 in the non-structural protein gene ORF1ab.² Of note, ORF1ab contains natural insertions of three amino acids (PAA) at the S1/S2 cleavage site of the spike protein, resulting in a furin cleavage site similar to those of SARS-CoV-2, strongly indicating that such insertion events can occur naturally in animal beta-coronaviruses.² In addition, ZC45 and ZXC21 from *R. sinicus* in Zhejiang,⁷ RpYN06 from *R. pusillus* in Yunnan, China,⁸ RSHST200 and STT182 from *R. shameli* in Cambodia,⁹ RacCS203 from *R. acuminatus* in Thailand,¹⁰ and Rc-o319 from *R. cornutus* in Japan,¹¹ were recently found to be closely related to SARS-CoV-2, indicating that the distribution of SARS-CoV-2-related coronavirus is relatively wide, and bats are very likely to be the natural hosts of SARS-CoV-2.

Although RaTG13 is the bat coronavirus known to be the closest to SARS-CoV-2, its amino acid sequence consistency in the RBD of S gene is less than 90%.¹ The five key amino acid sites that bind the ACE2 receptor are also different from those of SARS-CoV-2, and the binding efficiency of the ACE2 receptor is far lower than that of

SARS-CoV-2.¹² Similarly, the RBD region RmYN02 and ZC45 coronaviruses also has a multi-segment deletion, resulting in the decreased ability to bind ACE2 receptors (Fig. 1), suggesting that these highly homologous bat coronaviruses are not direct ancestors of SARS-CoV-2, but a common sister group. Few coronaviruses related to SARS-CoV-2 have been reported thus far, limiting our understanding of the distribution and evolution of SARS-CoV-2 in the wild. According to geographical correlation and migration habits of bats, it is highly possible that similar viruses related to RaTG13 and RmYN02 already exist in bat populations in neighboring regions, including Southeast Asian countries. In addition, more extensive monitoring and investigation of the distribution and diversity of SARS-CoV-2-related coronavirus in Africa and Europe is also needed.

2.2. Pangolins as potential natural hosts of SARS-CoV-2

Before and after the outbreak of COVID-19, some research groups successively found highly homologous SARS-CoV-2 from smuggled Malayan pangolins (*Manis javanica*), including coronavirus PRJNA573298¹³ and multiple lineages of coronaviruses (homology as high as 85.5–92.4%).^{14,15} One study also found evidence that circulating antibodies against pangolin-CoV reacted with the S protein of SARS-CoV-2,¹⁵ suggesting that pangolin may have the potential to act as an intermediate host of SARS-CoV-2. Further reinvestigation of published data confirmed that pangolin coronavirus is homologous with SARS-CoV-2, but it does not support the theory that SARS-CoV-2 directly derives from the pangolin variant, indicating that pangolin is a natural reservoir of coronavirus.^{16,17}

Unlike RaTG13, the S1 protein, especially the five key amino acid residues of Pangolin-CoV, is more closely related to SARS-CoV-2 than to RaTG13,¹⁶ suggesting that Pangolin-CoV has a higher utilization efficiency for human ACE2. However, it is necessary to systematically compare the biological characteristics, cross-species transmission, and pathogenic mechanisms of the three virus strains to better understand the role of pangolins in coronavirus disease ecology. Furthermore, pangolins have similar pathological features in their lungs and other organs, suggesting that pangolins are less likely to be intermediate host, but are still

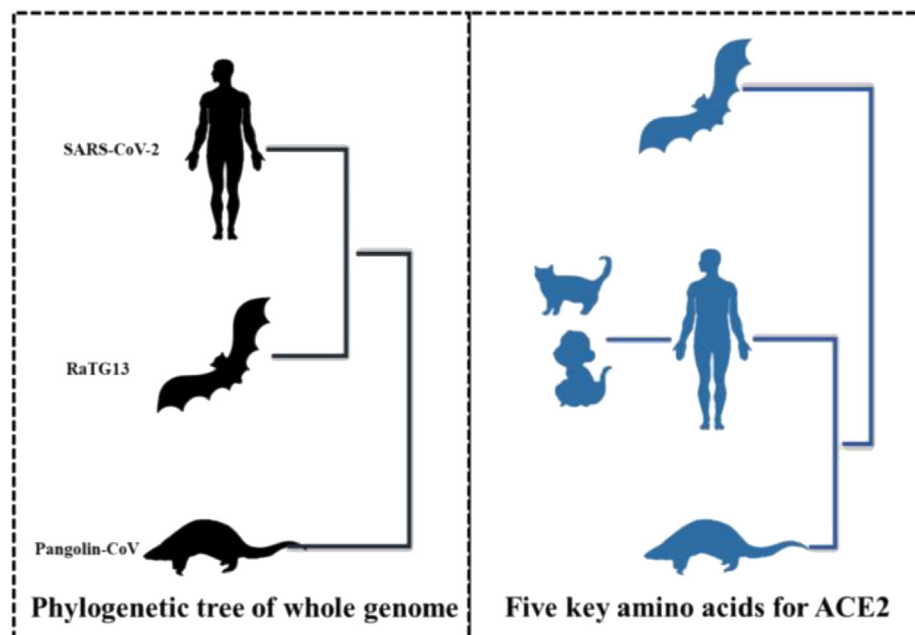


Fig. 1. The distance between the genome of coronavirus and key amino acids of ACE2 from humans, bats, and pangolins, respectively.

susceptible to infection. Regardless, the chain of evidence to support or refute the role pangolins play in coronavirus emergence remains incomplete and warrants further investigation.

2.3. Mink and other wild animals as potential natural hosts of SARS-CoV-2

There is now evidence that SARS-CoV-2 has spilled over from humans into other animal hosts, especially minks (mustelids), which exhibit a higher susceptibility to the virus.¹⁸ Mustelids comprise approximately 60 different species and are widely distributed across diverse habitats, including aquatic (marine and freshwater) and terrestrial (prairies, steppes, tundra, and forests). If SARS-CoV-2 spills into wild mustelids, there is serious concern that mustelids have the potential to become permanent reservoirs and maintenance hosts of disease, spreading infection to other animal species, and possibly causing unprecedented zoonotic transmission.¹⁹ This is further supported by experiments demonstrating that non-human primates, cats, ferrets, hamsters, rabbits, and bats can be infected by SARS-CoV-2. Virus replication in mice, mink, hamsters, and ferrets resembled subclinical human infection, indicating that these mammals may serve as potential hosts.²⁰ SARS-CoV-2 RNA has also been detected in felids, minks, and dogs outside laboratory settings.^{21,22} These animals have a high risk of exposure during the pandemic period, most likely pandemic period, most likely due to passive infection after coming into contact with confirmed patients. What is most alarming is that the whole genome sequencing of outbreaks on 16 mink farms provided evidence of animal to human transmission of SARS-CoV-2 within mink farms.²² Artificial intelligence (AI), machine learning (ML), and deep learning (DL) technologies recently determined that ACE2 in rhesus monkeys, rabbits, pangolins, cats, and other animals has a strong binding affinity with the RBD of SARS-CoV-2.^{23,24} However, there are insufficient evidences to confirm that these animals will become the hosts (Fig. 2).

2.4. The possibility for SARS-CoV-2 to be transmitted to marine animals, specifically in Arctic and Antarctic regions

A second reported outbreak of COVID-19 in China occurred in June 2020, which was associated with the Xinfadi Seafood Market

in Beijing. Multiple experiments have demonstrated that SARS-CoV-2 can survive for more than one week at 4 °C attached to fish,²⁵ suggesting long-term survival of SARS-CoV-2 on salmon as a potential source for international transmission. However, none of the seven coronaviruses that can infect humans has been found in fish, and there have been no reports of fish infection with any coronavirus. In addition to mammals, only amphibians, which are closely related to fish, have been found to carry coronavirus-like viruses.²⁶ Thus, fish are unlikely to be the hosts, but are instead contaminated sources of infection. Nevertheless, the pathogen has spread rapidly worldwide, even in Antarctica. The concerns of potential human introduction of SARS-CoV-2 into Arctic and Antarctic wildlife, such as cetaceans and penguins, or then being sealed in an iceberg forever, have been expressed.²⁷

In general, bats, pangolins, felines, minks, ferrets, and rabbits were all susceptible to SARS-CoV-2 (Table 1),²⁰ indicating their potential as hosts. Focused investigations and additional epidemiological studies of these wild animals in their natural environments are urgently needed.

3. Epidemiological evidence for animal origin of SARS-CoV-2 is needed

SARS-CoV-2-related coronavirus undergoes frequent recombination and exhibits spatially structured genetic diversity on a regional scale, which makes it difficult to determine the origin of SARS-CoV-2.²⁸ By reconstructing the evolutionary history of SARS-CoV-2-related coronavirus, one cooperative research group revealed that the SARS-CoV-2 lineage has been circulating unnoticed in bats for decades, and the virus lineage of SARS-CoV-2 was differentiated from other bat viruses about 40–70 years ago. The RBD on the spike protein enables the virus to recognize and bind to receptors on the surface of human cells, which means that other viruses that can infect human beings may also be spreading in bats. Whether these viruses can jump directly from bats to humans remains unknown. It has been reported that key evolutionary changes occurred in pangolins. However, there is no evidence that pangolin infection is a necessary prerequisite for bat virus to infect human beings, nor has other close bat coronavirus been detected in pangolins.²⁹

The migratory behavior of bats increases the difficulty of tracing the origin of coronavirus. RaTG13 was found in border areas in Yunnan,¹ where the bat population exists and frequently crosses borders with Laos, Thailand, Cambodia, and Vietnam. SARS-CoV-2-related coronaviruses in these areas and their role in the origin and transmission of SARS-CoV-2 are worthy of further study.

Bats have been recognized as a “container” for the cultivation of multiple ‘super viruses’ including 11 viral families.^{30,31} A large number of viruses have been detected in bats from these regions,^{32,33} including Nipah virus in Thailand, Malaysia, Bangladesh, and other countries,^{34,35} which is another emerging virus that warrants more attention. According to the analysis and prediction of the relationship between virus and host, the history of animal virus diseases, and the emerging pattern of viruses, it is estimated that there are 630,000–820,000 kinds of viruses in mammals that can infect and cause human diseases.³⁶

4. Can SARS-CoV-2 become seasonal like its common human coronavirus sisters?

It remains unclear whether SARS-CoV-2 will co-exist in the human population after the pandemic. In the historical evolution, the natural foci for pathogens of infectious diseases are constantly changing due to adaptation to new biological environments. Natural focus diseases are constantly evolving from animals to humans.

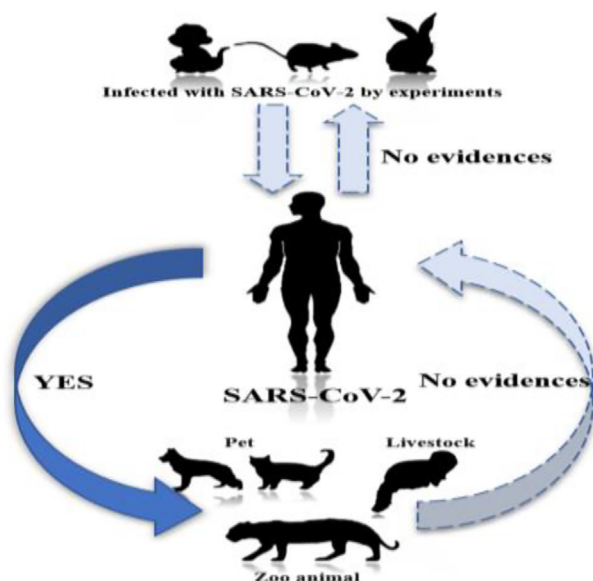


Fig. 2. Enough evidences needed to confirm these animals will become the hosts.

Table 1
The animals carried SARS-CoV-like coronaviruses and infected with by SARS-CoV-2.

Wild Animal	Scientific name	Virus name	Location	Reference	
Bats	<i>Rhinolophus affinis</i>	RaTG13	Yunnan, China	1	
	<i>R. malayanus</i>	RmYN02	Yunnan, China	2	
	<i>R. pusillus</i>	RpYN06	Yunnan, China	8	
	<i>R. stheno</i>	RpYN04	Yunnan, China		
	<i>R. malayanus</i>	RpYN05, RpYN08	Yunnan, China		
	<i>R. shameli</i>	RSHSTT182,200	Cambodia	10	
	<i>R. acuminatus</i>	RacCS203	Thailand	10	
	<i>R. cornutus</i>	Rc-o319	Japan	11	
	<i>R. sinicus</i>	ZC45,ZXC21	Zhejiang, China	7	
	Pangolins	<i>Manis javanica</i>	PRJNA573298	Unknown	13
		<i>M. javanica</i>	GX/P1E,GX/P2V,GX/P3B, GX/P4L, GX/P5E and GX/P5L	Unknown	14
<i>M. javanica</i>		Pangolin-CoV	Unknown	15	
Susceptible animals Ferrets, Ats, Dogs, Minks, Rabbits		SARS-CoV-2	NA	20,21,22,24	

Coronavirus is a common pathogen that causes respiratory diseases. Besides SARS-CoV, MERS-CoV, and SARS-CoV-2, there are four other human coronaviruses, HCoV-229E, HCoV-NL63, HCoV-HKU1, and HCoV-OC43, which can cause relatively mild symptoms of upper respiratory tract infection. Based on the diversity and evolutionary analysis of mammalian coronaviruses, it is very likely that human CoV NL63 is a recombinant between NL63-like viruses circulating in Triaenops bats and 229E-like viruses circulating in Hipposideros bats, with the breakpoint located near the 5' and 3' ends of the spike (S) protein gene.⁶ These coronaviruses are widely distributed and circulated among humans, causing seasonal epidemics. At present, a large proportion of asymptomatic COVID-19-infected persons, ranging from 1% to 90%, varied by region,³⁷ which provides sufficient conditions for long-term existence and maintenance in the population. However, asymptomatic infected persons likely contribute less to the spread of the epidemic,³⁸ but they can pass on the virus and the role in transmission is complicated and challenging.³⁹ The higher the number of infected individuals with SARS-CoV-2, the more likely mutations and novel variants will emerge, leading to concern of long-term 'seasonal' outbreaks. Thus, it is equally important to monitor asymptomatic infections and the role they play in disease maintenance and transmission.

5. Summary

SARS-CoV-2 should be of natural origin, based on the recent emergence of bat-borne and pangolin-borne zoonotic viruses with high homology, the discovery of furin cleavage site similar to SARS-CoV-2 in RmYN02, virus infection experiments, and genetic evolution analysis of the binding ability of ACE2 to the RBD of S protein in many potential animals. However, the evolutionary pathways of CoVs remain elusive, and more attention should be paid to the risk of interspecies recombination, which plays an important role in CoV evolution and the emergence of novel CoVs with zoonotic potential (Fig. 3). The risk of direct transmission of virus from natural hosts, minks, and other domestic animals to humans through contact still exists (Fig. 1). These infected animals store pathogens that might form small local foci and gradually act as hosts, leading to the spread of the virus. A large number of asymptomatic SARS-CoV-2 infections have led to the long-term existence of SARS-CoV-2 in the population. All of them need systematic and in-depth investigation and more sufficient evidence, including international cooperation and joint investigations on the presence of coronavirus in cross-border wildlife, as well as in Europe, the Americas, and Africa, where COVID-19 has been detected earlier. In addition, prospective and systematic prospective investigations of future

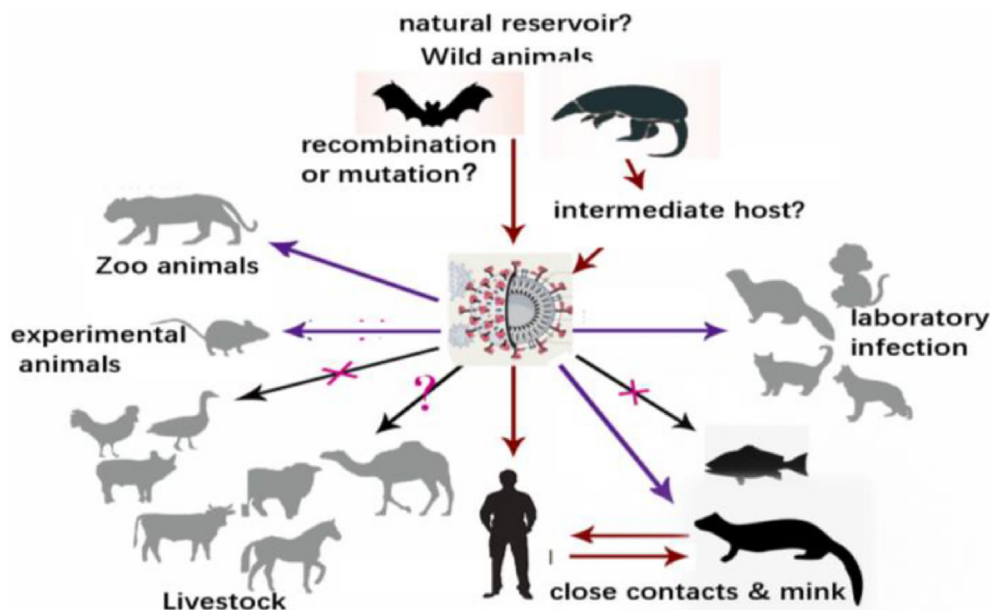


Fig. 3. Potential natural reservoir and susceptibility of wild or domestic animals to SARS-CoV-2.

pathogens in other important wildlife, as well as macroecology, migration characteristics, population dynamics, and pathogen ecology of bats and other wildlife are urgently needed.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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