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## Spotlight

Pangolins Harbor  
SARS-CoV-2-Related  
CoronavirusesGuan-Zhu Han<sup>1,\*</sup>

**The pandemic of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 has posed a severe threat to global public health. Yet, the origin of SARS-CoV-2 remains mysterious. Several recent studies (e.g., Lam et al., Xiao et al.) identified SARS-CoV-2-related viruses in pangolins, providing novel insights into the evolution and diversity of SARS-CoV-2-related viruses.**

The outbreak of coronavirus disease 2019 (COVID-19) has been spreading rapidly throughout the globe, resulting in ~0.8 million confirmed infections as of March 31, 2020. On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a positive-sense single-stranded RNA virus that belongs to the genus *Betacoronavirus* within the family *Coronaviridae* [1,2]. Yet, the origin and evolution of SARS-CoV-2 remains largely unclear. Several recent studies identified SARS-CoV-2-related viruses in Malayan pangolins (*Manis javanica*), providing new insights into the host distribution and evolution of SARS-CoV-2-related viruses [3–7].

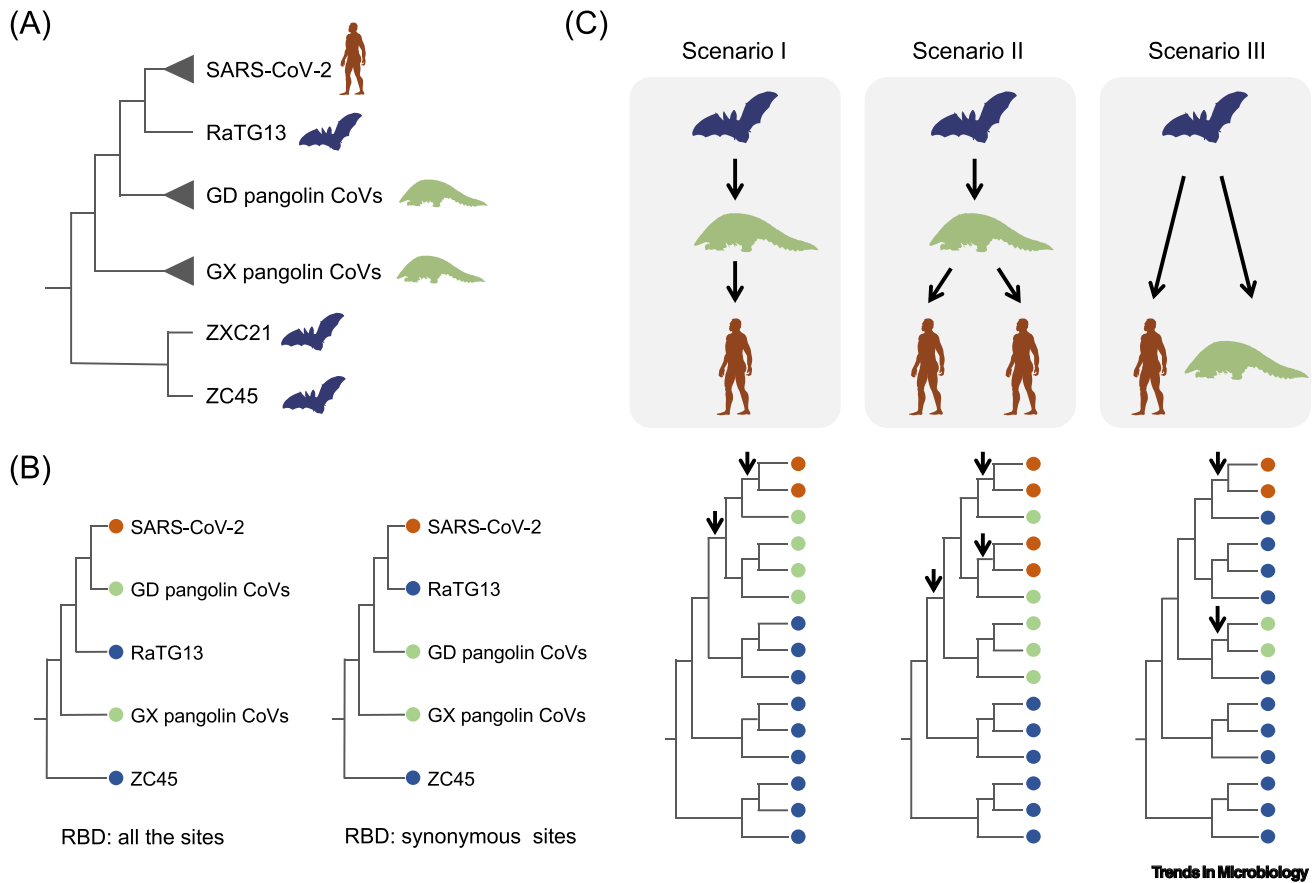
Sharing ~80% nucleotide identity, SARS-CoV and SARS-CoV-2 are closely related to each other [1]. SARS-CoV and SARS-CoV-2 have been taxonomically classified into a single viral species, *Severe acute respiratory syndrome-related coronavirus* [8]. A large number of SARS-related coronaviruses (SARSr-CoV) have been isolated from bats. Therefore, it has been

widely thought that bats are the natural reservoirs of SARSr-CoV. SARS-CoV-2 is closely related to multiple SARSr-CoVs of bats; for example, a bat CoV, BatCoV RaTG13, detected in *Rhinolophus affinis* from the Yunnan province of China, exhibits very high nucleotide identity (96.2% at the genome level) with SARS-CoV-2. These findings suggest a probable bat origin of SARS-CoV-2 [1,2]. Whereas SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), two highly contagious CoVs that emerged in humans during the past two decades, might ultimately have bat origins, both of them were introduced into human populations through intermediate hosts [9]. It is possible that SARS-CoV-2 entered human populations through intermediate host(s). However, few SARS-CoV-2-related viruses have been described in mammals other than bats and humans.

Several recent studies reported the identification of SARS-CoV-2-related viruses in Malayan pangolins, native in Southeast Asia, that were smuggled into Southern China [3–7]. Pangolins (or scaly anteaters) are mammals that belong to the order of Pholidota, with one extant family (Manidae) and three genera (*Manis*, *Phataginus*, and *Smutsia*) [10]. As a source of food and traditional Asian medicines, pangolins are among the most illegally traded mammals in the world [10]. A number of pangolin species have been assessed to be endangered or critically endangered by the International Union for Conservation of Nature (IUCN) Red List of Threatened Species. Two distinct clusters of SARS-CoV-2-related viruses were identified in pangolin samples obtained by anti-smuggling operations in the Guangxi (GX) and Guangdong (GD) provinces of China (Figure 1A). Interestingly, the GD pangolin CoVs have a higher amino acid identity (97.4%) with SARS-CoV-2 than does the bat CoV RaTG13 (89.2%) in the receptor-binding domain (RBD) [3–7]. In the remainder of the genome, RaTG13

exhibits a higher sequence identity with SARS-CoV-2 than do the GD pangolin CoVs. This pattern can be explained by either recombination or convergent evolution [3–7]. Phylogenetic analysis based on the synonymous sites of RBD, whose evolution is less likely to be influenced by natural selection, shows that RaTG13 is more closely related to SARS-CoV-2 than are the GD pangolin CoVs (Figure 1B), indicating that the high amino acid similarity between the GD pangolin CoVs and SARS-CoV-2 in the RBD might be due to convergent evolution [3].

What is the relationship between the pangolin CoVs and SARS-CoV-2? It has been widely circulated that pangolins potentially serve as the intermediate host of SARS-CoV-2 (<https://www.nature.com/articles/d41586-020-00364-2>). SARS-CoV-2 might be of ‘probable pangolin origin’ [4]. Alternatively, the pangolin CoVs might represent ‘trivial’ SARS-CoV-2-related viruses that are cryptically circulating in the wild and are not the direct source of SARS-CoV-2. Different scenarios of cross-species transmission will exhibit different phylogenetic patterns (Figure 1C). If pangolins act as the intermediate host (spillover to humans once [scenario I] or multiple times [scenario II]), SARS-CoV should fall within the diversity of pangolin CoVs. If SARS-CoV-2-related viruses independently entered into humans and pangolins (scenario III), and pangolin CoVs are not the direct source of SARS-CoV-2, then SARS-CoV-2-related viruses in humans and pangolins should form distinct clusters that nest within the diversity of bat CoVs. Therefore, based on the analysis of the genome regions other than RBD, it can be concluded that these known pangolin CoVs are not the direct source of SARS-CoV-2. Based on the analysis of RBD, we cannot conclude that pangolins are the intermediate host of SARS-CoV-2. It is also possible that the GD pangolin CoVs derived from cross-species transmission from bats (or from other animals) [3]. Clearly, SARS-



**Figure 1. The Evolution of Pangolin Coronaviruses (CoVs).** (A) The phylogenetic relationship among SARS-CoV-related viruses at the genome level. (B) The phylogenetic relationship among SARS-CoV-related viruses based on all the sites (left panel) or the synonymous sites (right panel) of the receptor-binding domain (RBD). (C) Cross-species transmission scenarios and their expected phylogenetic patterns. Pangolin CoVs might ultimately originate from cross-species transmission from bats. Pangolins serve as the intermediate host, and SARS-CoV-2 arose through spillover from pangolins to humans once (scenario I) or multiple times (scenario II). SARS-CoV and pangolin CoVs originated independently through cross-species transmission from bats (scenario III). Black arrows indicate cross-species transmission events.

CoV-2-related viruses are still poorly sampled in mammals (even in bats) to reach a conclusion. The identification of two distinct viral clusters in pangolins indicates that SARS-CoV-2-related viruses might be more widely distributed in wild mammals than expected. Further surveillance of SARS-CoV-2-related viruses in mammals might help to clarify the origin of SARS-CoV-2.

The high similarity between the Guangdong pangolin CoVs and SARS-CoV-2 in the RBD raises concern that these viruses might be readily transmitted to human populations. More work is needed to explore the pathogenicity and diversity of

CoV-2-related viruses in pangolins. Nevertheless, due to their status of being endangered, and the risk of causing future CoV outbreaks, the hunting, handling, and trafficking of pangolins should be strictly prohibited.

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