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Previews

The continuing search for the origins of SARS-CoV-2

Erik A. Karlsson[1] and Veasna Duong[1,*]
[1]Virology Unit, Institut Pasteur du Cambodge, Phnom Penh, Cambodia
*Correspondence: dveasna@pasteur-kh.org
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Since the detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 2019, there has been a global hunt for the origin of the ongoing pandemic. Zhou et al. provide further evidence of coronavirus diversity, including four novel SARS-CoV-2-related viruses, in bat species in Yunnan province, China.

In the 1800s, English and German chemists discovered that mixing tartaric acid, bicarbonate of soda, and a large amount of sugar made an appealing effervescent drink. They named this fizzy concoction "sherbet." In 1854, several individuals indulged in sherbet at small cafes in London and, subsequently, became violently ill and died. Their deaths, along with hundreds of others, led an astute doctor to make a map, find and remove a simple water pump handle, stop an outbreak, and redefine the search for origins of disease. The pathogen, of course, was *Cholera vibrio*, and the man, Dr. John Snow.

Since the first cluster of unknown pneumonia cases at a seafood market, there has been a global race to determine the "water pump" equivalent for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). What have we learned so far? The origins of SARS-CoV-2 are more complicated than a pump handle. Evolution, environment, and humanity are critical factors in disease emergence. Ultimately, the cholera outbreak in London was not caused by the pump handle but rather by water sources contaminated with a macroscopic pathogen via industrialization and urbanization—an answer that took decades to be established and accepted. The origins of SARS-CoV-2 are likely just as complicated.

In this issue of *Cell*, Zhou et al. provide additional pieces to the puzzle (Zhou et al., 2021). Their work highlights the importance of accessible and affordable metagenomics in discovery of unknown pathogens and of using functional assays to determine zoonotic risk. Recent studies have identified viruses belonging to the RaTG13/SARS-CoV-2 lineage in rhinolophids in China, Cambodia, Japan, and Thailand (Hul et al., 2021; Wacharapluesadee et al., 2021). None perfectly match SARS-CoV-2. Zhou et al. add more depth and diversity to the understanding of the viral origins of SARS-CoV-2 beyond these studies, sequencing 411 bat samples from a small region in Yunnan collected between 2019 and 2020, leading to 24 full-length coronavirus (CoV) genomes, including three SARS-CoV and four novel SARS-CoV-2-related viruses in *Rhinolophus* bats. These four new possible "cousins" of SARS-CoV-2 cluster into two different groups: (1) RpYN06 is the second-closest known virus to SARS-CoV-2 (94.5% sequence identity by whole genome) and (2) RmYN04, RmYN05, and RmYN08 cluster closely to viruses detected in pangolins. In addition, they find 17 other novel alpha-CoV in *Rhinolophus* and other species.

CoVs are continually evolving and recombining. Their ability to jump the species barrier is uncanny. In the 20 years before coronavirus disease 2019 (COVID-19), beta-CoVs caused two deadly outbreaks and emerged as a seasonally circulating virus (Frutos et al., 2021). The origins of these viruses took years to uncover and remain unclear. Similarly, understanding how SARS-CoV-2 evolved within and escaped from its bat ancestors may be years away. One critical concern is the ability to jump from bats to humans. The beta-CoV detected by Zhou et al. present complex recombination patterns and variability in the spike gene, the key protein necessary for infecting human cells. Molecular characterization confirms this variability. On a functional level, while RpYN06 is closest to SARS-CoV-2 on a whole genome level, its spike could not bind to human ACE2 (hACE2) receptor. By contrast, although RmYN04 clusters more closely to viruses detected in pangolins, it has a spike that can bind to hACE2 to some degree. Overall, clear patterns in spike genetics are yet to emerge for accurate prediction of binding ability of bat viruses to the human receptor.

Humans have an obsession with origin. The world is desperate for answers about the origin of SARS-CoV-2. While Zhou and colleagues provide a greater understanding of CoV in bat species, including SARS-CoV-2, numerous questions still remain:

Will we ever find the closest ancestor?

Possibly, but it likely won't be where we think. Most zoonotic pathogens go through primary spillover into bridge/amplifier species before jumping into humans. To date, the closest SARS-CoV-2-related viruses detected in animals other than bats are from pangolins (Lam et al., 2020); however, pangolin CoV possibly arose through convergent evolution. All other human CoVs have a putative secondary host (Shereen et al., 2020). Therefore, it is highly likely that SARS-CoV-2 required an intermediate host(s) prior to spillover to humans.

Where did SARS-CoV-2 come from?

Based on everything we know: bats. Specifically, likely Horseshoe bats (*Rhinolophus sp*) somewhere in Southeast Asia. Due to their unique physiology, bats naturally harbor CoV. In addition, bats live together in large groups, often sharing viruses across species (Irving et al., 2021). To date, all SARS-CoV-2-related viruses from bats are detected in *Rhinolophus sp*, the majority in Southeast Asia. SARS-CoV-2-related

positive Rhinolophid species are diverse; however, their ranges and behaviors intertwine, promoting viral transmission, spread, and recombination (Hassanin et al., 2021). This viral diversity and prevalence, coupled with high population density and a richness of other potential bridge species, makes Southeast Asia a hotspot for emerging infectious diseases.

Will we ever find "bat zero" or "patient zero"?

Likely not. The bat itself probably was not even sick. Continual evolution, plasticity, and recombination of CoV make it harder and harder to determine origin. Viruses themselves do not exist in isolation. They exist as clouds of mutations called quasispecies. SARS-CoV-2 is no exception (Armero et al., 2021). A specific combination of genetics was advantageous for an individual virus at the right place at the right time. Apart from the original bat virus, it is likely that SARS-CoV-2 was circulating in humans, adapting and mutating, long before the first cases in the seafood market (Pekar et al., 2021).

Will there be another pandemic in the future?

Yes, indubitably. Three out of every four human diseases have an animal origin. Despite substantial impacts of zoonotic disease on global public health and economy, we still poorly understand them. The risks of new diseases emerging are accelerated by urbanization and environmental degradation through climate change.

Unfortunately, there may never be a COVID-19 pump handle, and we barely have an indication of the location of the well. We still know next to nothing. However, like Dr. Snow, we will continue the systematic search for answers. Zhou and colleagues add to our SARS-CoV-2 map. The global research community needs to keep searching for and mechanistically assessing potentially pandemic zoonotic pathogens, as well as mitigate risk of the next emergence through increases in biosafety, biosecurity, conservation, and reduction in environmental impact.

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Partners with a killer: Metabolic signaling promotes inflammatory cell death

Zhonghua Liu[1] **and Tsan Sam Xiao**[1,*]
[1]Department of Pathology, Case Western Reserve University, Cleveland, OH 44106, USA
*Correspondence: tsx@case.edu
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In this issue of *Cell*, Evavold et al. (2021) report that mTOR Complex 1 (mTORC1), a metabolic signaling complex, controls reactive oxygen species (ROS) production in mitochondria, which in turn promotes inflammatory cell death mediated by gasdermin D (GSDMD). This provides a new mechanistic connection between metabolic signaling and inflammatory cell death.

Pyroptosis is an inflammatory form of programmed cell death (Cookson and Brennan, 2001) implicated in both immune protection against infections and pathological inflammation from overexuberant immune response to infections or tissue damage (Liu et al., 2021). Gasdermin-D (GSDMD) is a key executioner of pyroptosis that drives cytolysis and inflammatory cytokine release by forming ~20 nm pores in the plasma membrane or organelle membranes (Aglietti et al.,