



SARS-CoV-2: no evidence of a laboratory origin

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SARS-CoV-2: no evidence of a laboratory origin

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3 The emergence and outbreak of a newly discovered acute respiratory disease in
4 Wuhan, China, has affected greater than 40,000 people, and killed more than 1,000 as
5 of Feb. 10, 2020. A new human coronavirus, SARS-CoV-2, was quickly identified, and
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7 the associated disease is now referred to as coronavirus disease discovered in 2019
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9 (COVID-19) (<https://globalbiodefense.com/novel-coronavirus-covid-19-portal/>).
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17 According to what has been reported [1, 2, 3], COVID-2019 seems to have similar
18 clinical manifestations to that of the severe acute respiratory syndrome (SARS) caused
19 by SARS-CoV. The SARS-CoV-2 genome sequence also has ~80% identity with SARS-
20 CoV, but it is most similar to some bat beta-coronaviruses, with the highest being >96%
21 identity [4, 5].
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31 Currently, there are speculations, rumors and conspiracy theories that SARS-CoV-2
32 is of laboratory origin. Some people have alleged that the human SARS-CoV-2 was
33 leaked directly from a laboratory in Wuhan where a bat CoV (RaTG13) was recently
34 reported, which shared ~96% homology with the SARS-CoV-2 [4]. However, as we know,
35 the human SARS-CoV and intermediate host palm civet SARS-like CoV shared 99.8%
36 homology, with a total of 202 single-nucleotide (nt) variations (SNVs) identified across the
37 genome; among these SNVs, 200 were in the coding sequences, and among the 128
38 nonsynonymous mutations, 89 led to predicted radical amino-acid changes [6]. Given that
39 there are greater than ~~1000~~ nt differences between the human SARS-CoV-2 and the bat
40 RaTG13-CoV [4], which are distributed throughout the genome in a naturally occurring
41 pattern following the evolutionary characteristics typical of CoVs, it is highly unlikely that
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3 RaTG13 CoV is the immediate source of SARS-CoV-2. The absence of a logical targeted
4 pattern in the new viral sequences and a close relative in a wildlife species (bats) are the
5 most revealing signs that SARS-CoV-2 evolved by natural evolution. A search for an
6 intermediate animal host between bats and humans is needed to identify animal CoVs
7 more closely related to human SARS-CoV-2. There is speculation that pangolins might
8 carry CoVs closely related to SARS-CoV-2, but the data to substantiate this is not yet
9 published (<https://www.nature.com/articles/d41586-020-00364-2>).
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21 Another claim in Chinese social media points to a Nature Medicine paper published in
22 2015 [7], which reports the construction of a chimeric CoV with a bat CoV S gene
23 (SHC014) in the backbone of a SARS CoV that has adapted to infect mice (MA15) and
24 is capable of infecting human cells [8]. However, this claim lacks any scientific basis and
25 must be discounted because of significant divergence in the genetic sequence of this
26 construct with the new SARS-CoV-2 (>5,000 nucleotides).
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38 The mouse-adapted SARS virus (MA15) [9] was generated by serial passage of an
39 infectious wildtype SARS CoV clone in the respiratory tract of BALB/c mice. After 15
40 passages in mice, the SARS-CoV gained elevated replication and lung pathogenesis in
41 aged mice (hence M15), due to six coding genetic mutations associated with mouse
42 adaptation. It is likely that MA15 is highly attenuated to replicate in human cells or patients
43 due to the mouse adaptation.
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3 When the original SARS-CoV was isolated, it was concluded that the S gene from bat-
4 derived CoV, unlike that from human patients- or civets-derived viruses, was unable to
5 use human ACE2 as a receptor for entry into human cells [10, 11]. ~~Civets were proposed~~
6 ~~to be an intermediate host of the bat CoVs, capable of spreading SARS CoV to humans~~
7 [6, 12]. However, in 2013 several novel bat coronaviruses were isolated from Chinese
8 horseshoe bats and the bat SARS-like or SL-CoV-WIV1 was able to use ACE2 from
9 humans, civets and Chinese horseshoe bats for entry [8]. Combined with evolutionary
10 evidence that the bat ACE2 gene has been positively selected at the same contact sites
11 as the human ACE2 gene for interacting with SARS CoV [13], it was proposed that an
12 intermediate host may not be necessary and that some bat SL-CoVs may be able to
13 directly infect human hosts. To directly address this possibility, the exact S gene from bat
14 coronavirus SL-SHC014 was synthesized and used to generate a chimeric virus in the
15 mouse adapted MA15 SARS-CoV backbone. The resultant SL-SHC014-MA15 virus
16 could indeed efficiently use human ACE2 and replicate in primary human airway cells to
17 similar titers as epidemic strains of SARS-CoV. While SL-SHC014-MA15 can replicate
18 efficiently in young and aged mouse lungs, infection was attenuated, and less virus
19 antigen was present in the airway epithelium as compared to SARS MA15, which causes
20 lethal outcomes in aged mice [7].
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47 Due to the elevated pathogenic activity of the SL-SHC014-MA15 chimeric virus
48 relative to the SARS-MA15 CoV in mice, such experiments with SL-SHC014-MA15
49 chimeric virus were later restricted as gain of function (GOF) studies under the US
50 government-mandated pause policy (<https://www.nih.gov/about-nih/who-we-are/nih->
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3 [director/statements/nih-lifts-funding-pause-gain-function-research](#)). The current COVID-
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5 2019 epidemic has restarted the debate over the risks of constructing such viruses that
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7 could have pandemic potential, irrespective of the finding that these bat CoVs already
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9 exist in nature. Regardless, upon careful phylogenetic analyses by multiple international
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11 groups [5, 14], the SARS-CoV-2 is undoubtedly distinct from SL-SHC014-MA15,
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13 with >6,000 nucleotide differences across the whole genome. Therefore, once again there
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15 is no credible evidence to support the claim that the SARS-CoV-2 is derived from the
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17 chimeric SL-SHC014-MA15 virus. Finally, we note that the synthetic and chimeric panels
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19 of bat and SARS-like CoV led to the identification of remdesivir as a broad spectrum
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21 inhibitor of all group 2b SARS-like coronaviruses tested in vitro or in vivo [15, 16],
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23 providing critical pre-clinical data that has led to the ongoing clinical trials in China and is
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25 critical for the future development of universal vaccines for all the SARS-like
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27 coronaviruses.
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35 There are also rumors that the SARS-CoV-2 was artificially, or intentionally, made by
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37 humans in the lab, and this is highlighted in one manuscript submitted to BioRxiv (a
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39 manuscript sharing site prior to any peer review), claiming that SARS-CoV-2 has HIV
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41 sequence in it and was thus likely generated in the laboratory. In a rebuttal paper led by
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43 an HIV-1 expert Dr. Feng Gao, they used careful bioinformatics analyses to demonstrate
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45 that the original claim of multiple HIV insertions into the SARS-CoV-2 is not HIV-1 specific
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47 but random (Gao et al., [EMI paper 2/12/2020 in press](#)). Because of the many concerns
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49 raised by the international community, the authors who made the initial claim have already
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51 withdrawn this report.
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3 Evolution is stepwise and accrues mutations gradually over time, whereas synthetic
4 constructs would typically use a known backbone and introduce logical or targeted
5 changes instead of the randomly occurring mutations that are present in naturally isolated
6 viruses such as bat CoV RaTG13. In our view, there is currently no credible evidence to
7 support the claim that SARS-CoV-2 originated from a laboratory-engineered CoV. It is
8 more likely that SARS-CoV-2 is a recombinant CoV generated in nature between a bat
9 CoV and another coronavirus in an intermediate animal host. More studies are needed to
10 explore this possibility and resolve the natural origin of SARS-CoV-2.
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