Proximal Origin paper

On March 17, 2020, a paper Lipkin co-authored, titled *The proximal origins of SARS-CoV-2*, was published in *Nature Medicine*.[63] The premise of the paper was that SARS-CoV-2 arose through a process of natural evolution and therefore had not leaked from a laboratory. It was widely cited by media outlets throughout the world.[64][65][66][67][68][69][70]

Wet market/pangolin theory

The paper proposed that horseshoe bats, possibly from Yunan, infected Malayan pangolin, which were smuggled into Guangdong, then transported to the Huanan Seafood Wholesale Market in Wuhan, where they were slaughtered for sale. Before their death, the bat virus is theorized to have mutated in the pangolin until it became infectious to humans. Countering the notion that the virus may have leaked from a research facility, the authors write: "...pangolins...provide a much stronger and more parsimonious explanation" of how the virus originated through natural selection.[71]

This Wuhan wet market narrative, concurred with the initial explanation of Chinese authorities,[72] [73] although a paper published on Jan 26 by Chinese researchers reported that 13 of the first 41 cases had no epidemiological link with the market, including the first known case.[74]

Regarding the mutations in pangolin, the Proximal Origin authors remarked: "For a precursor virus to acquire both the polybasic cleavage site and mutations in the spike protein suitable for binding to human ACE2, an animal host would probably have to have a high population density (to allow natural selection to proceed efficiently)."[75] (authors' brackets) Although Wikipedia describes pangolin as "solitary animals, meeting only to mate", *Proximal Origins* inferred that the 'high-population density' threshold may have been met during transportation or at the market. A *Nature* article noted, "pangolins were not listed on an inventory of items sold at the market", but didn't dismiss the idea that they may have been sold there illegally.[76] As of January 2021, no evidence had emerged that pangolin were sold at the market.

On May 26, Chinese media reported that Gao Fu (George F. Gao), director of the Chinese Center for Disease Control and Prevention, had announced that, "no viruses were detected in the animal samples" collected from the Wuhan market in early January.[77] Lipkin referred to Gao Fu as a "close friend" who he consulted with on his investigative trip to China from Jan 29-Feb 4.

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On June 3, 2021, Freedom of Information obtained emails, dated Feb 1, 2020, from lead author Kristian Andersen to Anthony Fauci, stated:

"I should mention that after discussions earlier today, Eddie (Holmes), Bob, Mike, and myself all find the genome inconsistent with expectations from evolutionary theory. But we have to look at this much more closely and there are still further analyses to be done, so those opinions could still change.

"The unusual features of the virus make up a really small part of the genome (<0.1%), so one has to look really closely at all the sequences to see that some of the features (potentially) look engineered."[78]

Andersen responded that upon further analysis and discussion, it was decided the virus wasn't engineered, hence the Proximal Origin paper. The authors stand by the paper's conclusion that the virus did not originate from an Wuhan lab.[79]

Natural origins

The *Proximal Origins* paper stated: "Our analyses clearly show that SARS-CoV-2 is not a laboratory construct or a purposefully manipulated virus" and presents "strong evidence" that SARS-nCoV-2 was the result of natural selection.[63] In an interview with India Today, Lipkin re-emphasized this point: "There is no evidence whatsoever that there was an effort to create anything of this sort. There is no evidence that there are animals in which it was passaged to create this problem."[80]

However, a 2008 paper published in *Journal of Virology*, titled *Difference in Receptor Usage between SARS and SARS-Like Coronavirus of Bat Origin,* did detail a purposeful manipulation of a bat virus (SL-CoV S). A 'gain-of-function' experiment was performed to make the virus more infectious to humans. They wrote: "A series of S chimeras was constructed by inserting different sequences of the SARS-CoV S into the SL-CoV S backbone." In terms of Ace2-binding, or enhancing the ability of the virus to infect human cells, the experiment was successful: "ACE2-binding activity of SL-CoVs was easily acquired by the replacement of a relatively small sequence segment of the S protein from the SARS-CoV S sequence." The paper concluded: "It remains to be seen whether a recombinant SL-CoV containing a CS protein (e.g., CS14-608) will be capable of infecting experimental animals and causing disease."[81] An additional paper from WIV scientists and Peter Daszak in 2016 detailed "the construction of WIV1 (a bat virus) mutants."[82] According to a co-author of *Proximal origins,* Edward C. Holmes, the closest known virus was RaTG13 (96.2% identical) which was held at WIV.[83]

Lipkin maintained that the types of changes observed in SARS-CoV-2 that differentiate it from RaTG13 "would not have occurred... unless it was being passed somehow either in animals or in people" and that "if it had been modified in the Wuhan Institute of Virology, they would have used a different sequence for that purpose because this was not obvious." Lipkin lamented that “rumors have their own life - there doesn’t seem to be any good way to choke them."[84]

Reaction

Lipkin's paper was widely cited by media outlets as evidence debunking growing "conspiracy theories" that the virus may have accidentally escaped from an Wuhan lab.[85][86][87][88] In China, the tabloid CCP controlled *Global Times* said, "US scientists, such as the world's leading "virus hunter" W. Ian Lipkin, have been sticking to the facts and insisting on scientific integrity when it comes to research and cooperation with China."[89] The China Daily praised Lipkin as an "intellectual giant" who had "shared profound insights and lessons".[90] A spokesperson for the Chinese Consulate General in Sydney referenced *Proximal Origins* and WHO experts, saying "the novel coronavirus originated through natural processes and was not manipulated or produced in a laboratory." It noted: "The scientific community has ...reported that the virus is possibly related to bats and pangolins."[91]

Other international experts also agreed with Lipkin's analysis. Maureen Miller, an epidemiologist who had cooperated with WIV researchers, said the idea the virus may have escaped from a lab was an "absolute conspiracy theory",[92] while disease ecologist Peter Daszak, who had also collaborated with WIV, branded any accidental escape scenario as "pure baloney".[93] WHO emergencies chief Michael J. Ryan said WHO had "listened again and again to numerous scientists" and "(w)e are assured that this virus is natural in origin."[94] Researchers from Duke University, which operates a joint research institute with Wuhan University,[95] also agreed with the Proximal Origins' pangolin premise, stating that "SARS-CoV-2 appears to be a hybrid between bat and pangolin viruses."[96]

In addition, a Lancet petition written by Peter Daszak[97], president of EcoHealth Alliance, with links to *Proximal Origins,* was circulated through the scientific community. It stated: "The rapid, open, and transparent sharing of data (by China) on this outbreak is now being threatened by rumours and misinformation around its origins. We stand together to strongly condemn conspiracy theories suggesting that COVID-19 does not have a natural origin. We support the call from the Director-General of WHO to promote scientific evidence and unity over misinformation and conjecture."[98]

There was some dissent, however. Professor Richard Ebright of Rutgers University's Waksman Institute of Microbiology, said the paper provided "no basis to rule out a lab accident" and was itself just conjecture. Ebright pointed out that bat viruses collected by WIV researchers were also studied at the less secure Wuhan Center for Disease Control, a BSL-2 facility, "which provides only minimal protections against infection of lab workers". He cautioned that "Virus collection, culture, isolation, or animal infection at BSL-2 with a virus having the transmission characteristics of the outbreak virus, would pose substantial risk of infection of a lab worker, and from the lab worker, the public."[99] With regard to the authors' claim that the virus's 'signature' showed no signs of human intervention, thereby proving its non-lab origin, Ebright noted that WIV and US scientists had previously "constructed a series of novel chimeric viruses ...using 'seamless ligation' procedures that leave no signatures of human manipulation."[100]

Similarly, in Nov 2020, Rossana Segreto and Yuri Deigin suggested that, "genetic manipulations (may) have been performed in order to evaluate pangolins as possible intermediate hosts for

bat-derived CoVs that were originally unable to bind to human receptors." They noted that "Both cleavage site and specific RBD could result from site-directed mutagenesis, a procedure that does not leave a trace."[101]

In July 2020, researchers from the Broad Institute of MIT and the University of British Columbia cast further doubt on the hypothesis that the virus evolved naturally in pangolin. In a review of the literature related to different pangolin CoV genomes, they discovered that researchers had all relied on the same 2019 dataset sourced from a single pangolin by Liu et al.[102]

In August 2020, a collective of scientists writing on the ResearchGate platform questioned the conclusions of Proximal Origins, saying "Although based on phylogenetic analysis SARS-CoV-2 seems to be related to BatCoVs RaTG13 or RmYN02 ...(t)he host tropism pattern has major discrepancies compared to other CoVs, raising questions concerning the proximal origin of SARS-CoV-2. "[103]

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