An updated review of the scientific literature on the origin of SARS-CoV-2

Jose L Domingo

Universitat Rovira i Virgili Laboratory of Toxicology and Environmental Health, School of Medicine, 43201, Reus, Catalonia, Spain

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E-mail address: joseluis.domingo@urv.cat

ABSTRACT

More than two and a half years have already passed since the first case of COVID-19 was officially reported (December 2019), as well as more than two years since the WHO declared the current pandemic (March 2020). During these months, the advances on the knowledge of the COVID-19 and SARS-CoV-2, the coronavirus responsible of the infection, have been very significant. However, there are still some weak points on that knowledge, being the origin of SARS-CoV-2 one of the most notorious. One year ago, I published a review focused on what we knew and what we need to know about the origin of that coronavirus, a key point for the prevention of potential future pandemics of a similar nature. The analysis of the available publications until July 2021 did not allow drawing definitive conclusions on the origin of SARS-CoV-2. Given the great importance of that issue, the present review was aimed at updating the scientific information on that origin. Unfortunately, there have not been significant advances on that topic, remaining basically the same two hypotheses on it. One of them is the zoonotic origin of SARS-CoV-2, while the second one is the possible leak of this coronavirus from a laboratory. Most recent papers do not include observational or experimental studies, being discussions and positions on these two main hypotheses. Based on the information here reviewed, there is not yet a definitive and well demonstrated conclusion on the origin of SARS-CoV-2.

Keywords: COVID-19; SARS-CoV-2; zoonotic origin; laboratory leak; hosts

1. Introduction

How could it be otherwise, the world impact of COVID-19 has been tremendous and unprecedented. Obviously, it has included scientific research, which has been quantitatively the most important conducted to date in such a short period of time. To put the figures in context, on July 27, 2020, PUBMED included 279,690 results when COVID-19 was used as the search term, while 170,591 results were found using SARS-CoV-2. In turn, SCOPUS collected 343,925 and 153,183 documents, for COVID-19 and SARS-CoV-2, respectively, on the same date. For flu/influenza, as a comparative example, the number of documents found in PUBMED and SCOPUS were 157,209 and 199,484, respectively. Although this difference is quantitatively huge, the most significant is the time in which that information was generated; since the end of 2019-to date for COVID-19/SARS-CoV-2 (approx. 2.5 years), while those documents regarding flu/influenza began to be published more than 100 years ago.

In recent months, the advances in the questions/topics directly and indirectly related with COVID-19 have been very significant. They involve important areas such as diagnostic, prognostic factors, as well as the different possibilities of treatment and prevention, including vaccination, among the most relevant. However, in spite of the great scientific advances in the knowledge of the COVID-19, there are still some weak points on that knowledge, being the origin of SARS-CoV-2 one of the most notorious (Domingo, 2021a). One year ago, in a review of the topic (Domingo, 2021b) it was noticed that the available scientific literature regarding that origin was certainly scarce. It was especially relevant taking into account the tremendous amount of published information on COVID-19/SARS-CoV-2. That review-article summarized the information -published between January 1, 2020 and July 19, 2021- on the potential origins of SARS-CoV-2 (Domingo, 2021b). The analysis of the reviewed papers did not allow drawing clear and definitive conclusions on the origin of SARS-CoV-2. According to the available knowledge on that coronavirus, based on phylogenetic inferences, sequence analysis, and structure-function relationships of coronavirus proteins, Sallard et al. (2021) concluded that the data were not sufficient to firmly assert whether SARS-CoV-2 resulted from a zoonotic transfer or from a laboratory leak. Although most available documents mainly supported the hypothesis of a zoonotic origin, an unnatural origin of the SARS-CoV-2 could not be scientifically discarded (Domingo, 2021b). In fact, even right now there are only two main potential scenarios of how SARS-CoV-2 could initially infect humans. Firstly, a zoonotic transfer from wild animals, most likely bats or an intermediate animal, and secondly, a leak of this virus from a research laboratory.

Taking the above into account, the present review was aimed at updating the information on the origin of SARS-CoV-2, based on the papers published since the previous review (Domingo, 2021b). Logically, the information now examined is bigger than that previously available. For example, 1675 and 2687 documents were found in PUBMED in July 19, 2021, and July 27, 2022, respectively. However, in both cases most documents can be considered as "*background noises*", being the real information on the specific origin of the coronavirus much more limited and focused on a reduced number of papers. For preparing the current review, the databases PUBMED (https://pubmed.ncbi.nlm.nih.gov/) and SCOPUS (https://www.scopus.com/) were used. The "origin of SARS-CoV-2" was again the search term. The collected information is next summarized. For each category (unnatural or zoonotic) the studies here reviewed are, in general terms, presented according to the dates of publication, from furthest to most recent.

2. Unnatural origin of SARS-CoV-2

It is evident that identifying the origins of zoonotic pathogens, understanding factors influencing disease transmission, and improving the diagnostic capacity of clinicians is basic in order to detect and prevent epidemics of zoonoses (Judson and Rabinowitz, 2021). The relevance of a better understanding of the origin of SARS-CoV-2 also relates to other aspects of science, such as 'theoretical' microbiology and biology, in addition to the clearly key point of preventing new epidemics. With respect to the origin of SARS-CoV-2, one of the most important pending questions is to establish how the virus that initiated the epidemic spread in Wuhan City, as well as to identify the missing links between the viruses circulating in bat populations and the human virus. Theories of accidental release from a lab and zoonotic spillover have been suggested and remain still as possible. Thus, the available evidence does not allow to draw a firm conclusion on that origin. It has been commented that the controversy over the epidemic origin has become part of a political debate, which is in turn a part of the problem. Independent reliable research and evidence are clearly needed to establish whether SARS-CoV-2 came directly from bats, or indirectly through intermediate hosts (Bloom et al., 2021; Vineis and Salmaso, 2021).

Regarding the origin of this coronavirus, in recent months an interesting debate has been maintained between two research groups. Initially, Segreto and Deigin (2021) reported that the genetic structure of SARS-CoV-2 did not rule out a laboratory origin, while an artificial origin of SARS-CoV-2 was not a baseless conspiracy theory. These authors suggested that SARS-COV-2 chimeric structure and furin cleavage site might be the result of genetic manipulation. Given the importance to establish the origin of SARS-CoV, these same researchers (Deigin and Segreto, 2021a) called for a careful reevaluation of RaTG13, MP789 and RmYN02 sequencing records and assembly methods. RaTG13, MP789 and RmYN02 are the strains closest to SARS-CoV-2, and their existence came to light only after the start of the current pandemic. Their genomes were used to support the natural origin of SARS-CoV-2. However, various issues were raised by these authors, including that the analysis of RaTG13 and RmYN02's metagenomic datasets found unexpected reads, suggesting a possible contamination. In response to this, Tyshkovskiy and Panchin (2021a) questioned the hypothesis raised by Segreto and Deigin (2021), who assumed an artificial chimeric construction of SARS-CoV-2 from a backbone of RaTG13-like CoV and receptor binding domain (RBD) of a pangolin MP789-like coronavirus, followed by serial cell or animal passage. Tyshkovskiy and Panchin (2021a) indicated that this hypothesis relied on incorrect or weak assumptions, not being in agreement with the results of comparative genomics analysis. Moreover, the comparative analysis of S-protein gene sequences suggested that the RBD of SARS-CoV-2 probably would represent an ancestral non-recombinant variant. For these authors, the hypothesis of a natural origin of the coronavirus would be more consistent with all available genetic and experimental data, than the hypothesis of a laboratory origin for SARS-CoV-2. The arguments raised by Tyshkovskiy and Panchin (2021a) were responded by Deigin and Segreto (2021b), who indicated that the main point of criticism of Tyshkovskiy and Panchin (2021a) was based on a false premise. More precisely, it was related to the fact that they claimed RaTG13 to be a direct progenitor of SARS-CoV-2. In addition, according to (Deigin and Segreto, 2021b) other points of criticism were not valid (based on flawed mathematical analysis), or were unrelated to their hypotheses. Therefore, Deigin and Segreto (2021b) concluded that the genetic structure of SARS-CoV-2 remained consistent with both, natural or laboratory origin. For these researchers, the zoonotic and the lab leak hypothesis should be investigated equally thoroughly. Another document suggesting that there was no evidence of SARS-CoV-2 laboratory origin was subsequently published by Tyshkovskiy and Panchin (2021b), who showed that neither the existence of a furin cleavage site in SARS-CoV-2, nor the presence of specific sequences within the nucleotide insertion encoding that site, evidenced an intelligent design. These researchers also discussed why existing genetic data, viral diversity and past human history, suggested that a natural origin of the virus would be the most probable scenario.

Already in the current (2002) year, in a document focused on the dilemma on the origin of the coronavirus, Ruiz-Medina et al. (2022) concluded that although there was stronger evidence supporting a zoonotic transfer, unfortunately, a lack of transparency had been given way to maintain the laboratory leak hypothesis still alive. Consequently, for these researchers, both scenarios are still plausible, which means that in-depth investigations are needed to establish the origin of SARS-CoV-2. In contrast, Borsetti et al. (2022) recently concluded that even if suspicions by some about the possibility of lab-leak hypothesis still remain, the consensus view is that the pandemic probably started from a natural source. In a recent meta-analysis to explain unknown causes of the origins of SARS-CoV-2, Coccia (2022) reported that natural spillover of novel viral agents, which generated more than 6.00 M deaths worldwide in about two years (such as SARS-CoV-2 from February 2020 to March 2022) would have a remote probability of occurrence (using an analogy with the probability of natural disasters generating a lot of fatalities). However, science advances on hazardous viral agents and consequential lab accident would have a higher probability of occurrence; about 13-20% like in manifold lab accidents.

3. Natural/zoonotic origin of SARS-CoV-2

Colombo et al. (2021) analyzed the scientific literature of the SARS-related viruses generated in the laboratory -over the years-, which were used to study the evolution of coronaviruses and to generate drugs for their treatment. By means of analysis of restriction site (RS), these authors showed that SARS-CoV-2 contained neither peculiar

RS, nor other markers, which could suggest a manipulation deriving from the recombinant viruses known in the literature. In turn, Li et al. (2021) reviewed the available studies examining SARS-CoV-2 in wild animals. The zoonotic and natural foci characteristics were also analyzed and the potential gaps in the literature, which should be solved in order to confirm reservoir(s) and spillover origin, were identified. In general terms, it was noticed that bats, pangolins, felines, minks, ferrets and rabbits were susceptible to SARS-CoV-2, which suggest their potential as hosts. Li et al. (2021) recommended to conduct systematic and in-depth studies including international cooperation and joint investigations on the presence of coronavirus in cross-border wildlife. However, it was also concluded that the risk of direct transmission of virus -including SARS-CoV-2- from natural hosts, minks, and other domestic animals to humans through contact clearly exists. In an interesting review-article published one year ago by Mitra (2021), it was noted that although SARS-CoV-2 was quite unlikely "*to be creation of an evil human mind*", doubtless that deforestation and illegal wildlife might be prime drivers for this viral spillover. Based on the published literature, Mitra (2021) remarked that although the genome of SARS-CoV-2 was similar to that of viruses found in bats, there were genomic stretches showing notable similarity with those of viruses identified from other animals. The warnings and advice of scientists, who have investigated the origins of SARS-CoV-2 strongly recommending to reduce the risk of future outbreaks by limiting exposure to animal pathogens as much as possible, was also highlighted.

In July 2021, Speciale (2021) published a commentary on a paper published by Rahalkar and Bahulikar (2020) on lethal pneumonia cases detected in Mojiang miners, which could give potential important clues to explain the origin of SARS-CoV-2. After a careful analysis of the documents on this topic, Speciale (2021) commented that taking into account the hypotheses to explain the origin of SARS-CoV-2, and given the global health implications, it was critical that scientific inquiry into the origin of SARS-CoV-2 not be stifled by sociocultural or ideological factors. In a similar line, Bloom et al. (2021) had previously suggested that hypotheses involving natural and lab spillover should be equally considered. On the other hand, Lytras et al. (2021) reported that SARS-CoV-2 animal-to-human transmission associated with infected live animals would be the most likely cause of the COVID-19 pandemic, being now humans, the dominant SARS-CoV-2 host species. For these researchers, an additional danger would be that SARS-CoV-2 might spread from humans to other animal species, termed reverse zoonosis. The promiscuous infection of various host species by sarbecoviruses would mean that future spillovers of SARS-CoVs from wildlife would be very likely. In turn, Khadka and Gupta (2021) reported conserved molecular signatures in the spike protein, which provides evidence indicating the origin of SARS-CoV-2 and a Pangolin-CoV (MP789) by recombination(s) between specific lineages of Sarbecoviruses

Wu CI et al. (2021) elaborated an Insight piece on the biological origin of SARS-CoV-2, which -according to the authors- was strictly based on scientific principles. In response to previous papers (Sallard et al., 2021; Segreto and Deigin, 2021) in which the hypothesis was that SARS-CoV-2 could not have evolved in nature, Wu CI et al. (2021) wrote textually: "*since no known natural law prohibits the SARS-CoV-2 genome to evolve to its current state, the claim of non-natural origin of SARS-CoV-2 is moot*". These authors especially recommended to focus research efforts on the natural processes in relation to the SARS-CoV-2 origin, taking into account that there have been already three coronavirus epidemics in the last two decades.

In an extensive review paper, Goraichuk et al. (2021) examined the known properties and the existing gaps in the scientific knowledge on the zoonotic (animal-to-human) and reverse zoonotic transmissibility of SARS-CoV-2. These authors noticed that epidemiological surveillance studies of SARS-CoV-2 were mainly focused on human populations, being certainly limited the number of SARS-CoV-2 molecular and serological surveillance studies conducted on animals worldwide. Based on this, Goraichuk et al. (2021) concluded that the surveillance of wild, domestic, laboratory, zoo, and companion animals is a key issue to determine the SARS-CoV-2 intermediate host. Doubtless, this could help to prevent secondary zoonotic events and possible reverse zoonosis. Another interesting article on the COVID lab-leak hypothesis was published by Maxmen and Mallapaty (2021), who carefully reviewed what scientists do and do not know on that hypothesis.

Maclean et al. (2021) reported that SARS-CoV-2 carried signs of positive selection, being already adapted to humans prior to the emergence of COVID-19. It was concluded that SARS-CoV-2 had already acquired this human adaptation in bats. In relation to this, Frutos et al. (2021a) proposed an alternative model to the spillover model (used by Maclean et al., 2021) to explain the emergence of SARS-CoV-2: the circulation model. This model states that the virus causing the disease in human populations did not exist yet in the wild, evolving in humans following primo-infection by a circulating proximal virus. According to this, adaptation to humans would have occurred in people after primo infection. In a subsequent review by the same research group (Frutos et al., 2021b), the hypotheses on the origin of SARS-CoV-2 were reviewed: a) the man-made virus theory, b) the bat-pangolin recombinant virus theory, and c) a naturally occurring virus. The transmission of SARS-CoV-2 to humans was also object of that review: a) the conspiracy theory of SARS-CoV-2: the voluntarily release from a laboratory, b) a laboratory accident, and c) a contamination from rural and wild environments. Regarding this, the authors remarked that the spillover model was considered as the main explanation to zoonotic emergence, but it did not match the virus dynamics. Frutos et al. (2021b) concluded proposing a change of paradigm and model, which should introduce the circulation model for explaining the various aspects of the dynamic of SARS-CoV-2 emergence in humans.

Another study supporting the natural origin of SARS-CoV-2 was performed by Shan et al. (2021). These researchers used a computational strategy specifically developed for detecting *de novo* mutations in SARS-CoV-2 from the transcriptome of virus-infected cell lines. Subsequently, a phylogenetic tree for SARS-CoV-2 and related coronaviruses was constructed, being identified hundreds of mutations, which accumulated in its genome before jumping to human hosts. These authors also investigated whether the accumulation of these mutations was compatible with other viruses in the phylogenetic tree that are reported to have a natural origin. Similarities between the mutation spectra of SARS-CoV-2 and the bat coronavirus RaTG13 suggested that SARS-CoV-2 evolved in a host cellular environment highly similar to that of bats. It before its zoonotic transfer into humans. Thus, the results of Shan et al. (2021) also supported a natural origin of SARS-CoV-2. In a similar line, Lytras et al. (2022) conducted a comprehensive phylogenetic investigation on SARS-CoV-2 and all the related bat and pangolin sarbecoviruses sampled so far. It was found that horseshoe bats, *Rhinolophus*, were the likely reservoir species for the SARS-CoV-2 progenitor. However, it was also noted that a direct proximal ancestor to SARS-CoV-2 had not been yet sampled. For Lytras et al. (2002), it is essential to pinpoint the exact origins of SARS-CoV-2's animal progenitor, as well the intermediate species (if any) that facilitated transmission from bats to humans.

One of the best analyses on the origin of SARS-CoV-2 carried out in 2020-2021 is the critical review by Holmes et al. (2021). After a careful analysis of the data existing when that review was published, the authors stated that while as for the vast majority of human viruses, the explanation for the origin of SARS-CoV-2 is a zoonotic event, there is no clear evidence that SARS-CoV-2 has a laboratory origin. The authors also stated that although the possibility of a laboratory accident could not be entirely dismissed, at the time of publication of their review there was substantial body of scientific evidence supporting a zoonotic origin. This, although the animal reservoir for SARS-CoV-2 had not been identified, and the key species might not have been tested yet. In another recent review on the topic, Voskarides (2022) indicated that while a number of findings support a bat origin for SARS-CoV-2, the results are not highly convincing. There is evidence that the progenitor of SARS-CoV-2 had already the capability to bind strongly to the human *ACE2* receptor. This could be an indicator that many other animal viruses would be capable to jump to humans, having already affinity for a human receptor. As conclusion, Voskarides (2021) strongly recommended zoonotic disease surveillance over the world. Recently, Cattaneo (2022) reviewed the findings on the polypeptide sequence of SARS-CoV-2 S-protein in order to stimulate further questions about the origins of this virus and its most closely related ancestral bat coronavirus RaTG13. When reviewing the investigations on the origins of the amino acid insertions within the SARS-CoV-2 S-protein (Cattaneo, 2022), the most plausible hypothesis suggested that a homologous recombination within the viral spike glycoprotein (S-protein) gene could have occurred between RaTG13 and a coronavirus with unknown origins involving possibly infection of an intermediate animal host. On the other hand, in order to understand how SARS-CoV-2 emerged, Huang et al. (2021) investigated the probable intermediate hosts and the allergenicity of that coronavirus. It was concluded that SARS-CoV-2 (also SARS-CoV) was naturally originated from bats and it might be transmitted to humans through rodents. It was shown by performing a comprehensive amino acid sequence analysis and comparison of sliding sequence fragments of SARS-CoV-2 with all sequences from mammals available in the NCBI database.

Frutos et al. (2022a, b) have recently contributed to the debate on the origin of SARS-CoV-2. These authors showed that according to the clinical reports, the Mojiang miners did not develop COVID-19 (or even SARS), not being infected by SARS-CoV-2. Based on the analyses of those clinical reports, Frutos et al. (2022a) dismissed the Mojiang mine as the origin of SARS-CoV-2. As a consequence of it, the Mojiang mine theory (Rahalkar and Bahulikar, 2020) would leave the laboratory leak hypothesis without the necessary scientific support. In another article of the same research group (Frutos et al., 2022b), it was concluded that there is not any specific origin of SARS-CoV-2. The authors suggested that there is not a determined origin to viruses, simply (as it happens for any animal or plant) an evolutionary and selective process, in which chance and environment play a key role. Thus, the evolutionary process that gave rise to SARS-CoV-2 would still be ongoing with regular emergence of novel variants, which would be more adapted than the previous ones. In turn, Chakraborty et al. (2022) analyzed the appearance and re-appearance of zoonotic disease during the COVID-19 pandemic. They concluded that long-term monitoring and analysis of zoonosis is essential to confirm the animal origin of SARS-CoV-2 (as well as that of the monkeypox). Policymakers are urged to pay more attention in that direction in order to stop the emerging and reemerging zoonotic diseases (Chakraborty et al., 2022). In one of the most recent studies on the topic of the current review, Desingu et al. (2022) showed evidence that the SARS-CoV-2 virus originated with novel Type-I-S1-NTD in its spike protein. The presence of different S1-NTDs in SARS-CoV-2-related-bat-CoVs (except RaTG13 and BANAL-20-52, which displays Type-I-S1-NTD), was also shown. The potential for various genetic recombinations in SARS-CoV-2-related-bat-coronavirus, especially in the S1-NTD regions of the spike gene, was also demonstrated, whereas the possibility that the spike gene of the common precursor SARS-CoV-2/RaTG13/BANAL-20-52-like viruses could have evolved by recombination was also suggested.

4. The continuing search for the origin of SARS-CoV-2

An important number of the above examined documents on the origin of SARS-CoV-2, are comments, notes, and review papers, rather than scientific observational and experimental studies. In addition to those documents, in the last 12 months a number of authors have called for the need for studies focused on searching the origins of this coronavirus, which is currently a critical juncture (Koopmans et al., 2021). Vezzoni et al. (2022) wonder where does the coronavirus come from, indicating that the controversy on that origin is an excellent opportunity to investigate mechanisms underlying the endorsement of conspiracy theories. The hypothesis that SARS-CoV-2 might have originated in a lab has been considered a debunked conspiracy theory, but some experts are still revisiting it, and therefore, new and more thorough investigations are still necessary (Thacker, 2021). Zhou et al. (2021) have provided evidence of coronavirus diversity, including four novel SARS-CoV-2-related viruses in bat species from Yunnan province (China). Although for Karlsson and Duong (2021), these findings provide a greater understanding of coronavirus in bat species, the important impacts of zoonotic disease on global public health and economy are still poorly understood. However, it seems obvious that the risks of new diseases are accelerated by urbanization and environmental degradation through climate change. Battacharya et al. (2021) wonder if the origin and emergence of SARS-CoV-2 is ingenuous, while Wu Z et al. (2021) recommended that the origin of SARS-CoV-2 should be investigated worldwide for pandemic prevention, and Gronwall (2021) remarked that even in the best circumstances, the search for the origin of an infectious disease outbreak -such as the current one- is certainly complicated, slow and full of uncertainties. In a similar line, Wang et al. (2021) concluded that the origins of SARS-CoV-2 remain elusive. Therefore, understanding how, when and where SARS-CoV-2 was transmitted from its natural reservoir to human beings, is crucial for preventing potential future coronavirus outbreaks. Wang et al. (2021) noticed that the origin-tracing progress has long been hindered by politicization, unfounded slander and widespread laboratory leakage hypothesis. Consequently, starting the real global search for sarbecoviruses in the potential locations to identify the origins, intermediate hosts, and transmission paths of SARS-CoV-2 should not be postponed.

5. Conclusions

The available scientific information on the origin of SARS-CoV-2 -published in the last 12 months- has been here reviewed. The novelties regarding to my previous review (Domingo, 2021) are certainly scarce, being the two main hypothesis on that origin still subject of debate. As above indicated, most documents published in the scientific literature again do not correspond to scientific observational and experimental studies, being mainly discussions and positions on the two theories explaining the origin of SARS-CoV-2 (Friedman et al., 2022; Frutos et al., 2021c; Gabarron et al., 2021; Himmel and Frey, 2022; van Helden et al., 2021). Based on the information here reviewed, the only true facts are that, nowadays, there is not a definitive and well demonstrated conclusion on the origin of SARS-CoV-2. Although most data certainly point to a natural origin, the intermediate host has not been found, and the hypothesis of a laboratory-leak has not been yet scientifically discarded. As suggested by many scientists, the continuing search for the origin of SARS-CoV-2 is currently an essential issue in order to prevent and/or being more prepared to respond to further potential coronavirus pandemics. In relation to this, the characterization of the periodic nature of the demographic spread of SARS-CoV-2 variants in various countries might contribute to the identification of the origin of SARS-CoV-2 (Hassan et al., 2022).

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