

Review Article:

COVID-19: A natural phenomena or laboratory-based origin?

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Abstract :

The novel coronavirus, otherwise known as COVID-19 has fast become a major health concern. The current pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the third coronavirus outbreak, following severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronaviruses. Since the initial cases of a pneumonia of unknown aetiology, which was later identified as COVID-19 in Wuhan, Hubei province, China, there has been much debate and speculation regarding the origins of this novel virus. This review aims to provide an insight into the origin of SARS-CoV-2 by reflecting on genomic data gathered thus far. Identifying the origins of SARS-CoV-2 can lead to better understanding of hidden viral reservoirs that may exist and pose a threat to society as well as allow greater understanding of the mechanisms by which these viruses have successfully achieved cross species transmission. Greater knowledge in regard to this can lead to the development of strategies which can aid in preventing future outbreaks of this scale.

Keywords: Severe acute respiratory syndrome coronavirus-2, SARS-CoV-2, COVID-19, coronavirus, SARS-CoV-1, MERS-CoV, origins

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Introduction

On 31 December 2019, a significant number of cases were reported to be suffering from a viral pneumonia of unknown cause in Wuhan Hubei Province, China¹. This particular pneumonia was identified as the novel coronavirus and is now labelled as COVID-19. Not long after its discovery, the International Committee on Taxonomy of Viruses renamed the virus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)². As of 30 January 2020, the World Health Organisation declared a global health emergency in regard to the growing number of cases both in China and international locations. At present the Wuhan coronavirus pandemic has spread globally with more than 200 countries being affected². Despite media outlets identifying the original source of SARS-CoV-2 as the Huanan seafood markets, there are speculations that the SARS-CoV-2 is of laboratory

origin. Therefore, this article aims to investigate the origins of this novel virus.

Coronaviruses are enveloped, single stranded large RNA viruses, approximately 26 to 32 kilobases in length, that have primarily been identified in animals but have been known to also infect humans². There are four sub-families of coronaviruses: alpha, beta, gamma and delta. Alpha and beta coronaviruses are primarily associated with mammals such as bats whereas gamma and delta are more commonly associated with pigs and birds. Different families of coronavirus vary in terms of the severity of disease that they cause. The International Committee for the Taxonomy of Viruses has approved the naming of approximately more than 40 coronaviruses, with the majority only shown to infect animals. However, the SARS-CoV-2 outbreak has increased the number of identified coronaviruses that infect humans to seven.

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Four of these, 229E and NL63 (alpha coronaviruses), OC43 and HKU1 (beta coronaviruses) are community acquired and have continuously circulated through the human population. These subtypes are also typically associated with the common cold. Among the subtypes that can infect humans, beta coronaviruses tend to cause more severe disease and fatalities and have thus far been identified as the only family to lead to viral outbreaks³. SARS-COV-2 is a new viral strain that belongs to beta- coronavirus⁴. SARS-COV-2 has not previously been identified in humans, however there have been previous outbreaks of different versions of beta coronaviruses including severe acute respiratory (SARS-CoV-1) and Middle East respiratory syndrome (MERS-CoV)⁴.

Viruses can only exert their pathological influence once they have invaded a cell. The first step for a viral infection is recognition. In order to invade a cell, the virus needs to possess a special surface molecule that allows it to bind to receptors on the host cell membrane. In the case of SARS-CoV-2, recent reports have shown that human-to-human transmissions occurs via the binding between the surface molecule virus spikes, otherwise known as the S protein (specific part that can make coronaviruses transmittable to humans) and the cellular receptor which has now been identified as angiotensin-converting enzyme 2 (ACE2) receptor. Once attached to a host cell, viruses have the ability to enter and infect host cells. Many reports have highlighted that the novel coronavirus is a result of cross species transmission, where a foreign virus has been introduced into human species from another host species. However, the exact species this new virus has evolved from is yet to be determined which has raised many questions regarding its origin⁵.

Almost as soon as the novel coronavirus came to light, there was speculation that SARS-CoV-2 was a result of a leak from a laboratory studying coronaviruses. In 2010, scientists at this laboratory found that the ACE2 proteins of different bat species conferred variable susceptibility to SARS-CoV entry, thus identifying the capacity for coronavirus transmission across species⁶. Not long after in October 2013, another scientific report by the same group of scientists claimed that they had successfully isolated 3 viruses from bats, one of which had an S protein that fused with the ACE2 protein on human cells. This integration enabled SARS- like viruses to exhibit direct human to human transmission without the need for an intermediate host⁷. In 2015, another paper was published which discussed the creation

of a synthetic virus, which was a self-replicating chimeric virus. This new virus demonstrated the powerful ability of cross species infection⁸. The above reports indicate the possibility of generating a laboratory-based virus, which has the ability to self-replicate and capable of infecting human cells without the need of an intermediate host and thus a laboratory origin of COVID-19 does not seem like an unlikely theory.

However, in a recent publication entitled 'The proximal origin of SARS-CoV-2', scientists analysed the genetic template for spike proteins. They specifically focused on a specific section of the protein known as the receptor-binding domain (RBD), a hook like region that attaches to host cells allowing the virus to enter inside the cells. The results showed that the novel coronavirus contained unique adaptations in its spike protein, one of which proved the virus had enhanced ability to bind to the human ACE2 protein. Moreover, computational analysis showed that the sequences present in the genetic template of SARS-CoV-2 were different from what was predicted to be optimal for receptor binding, thus providing evidence that the enhanced binding of the SARS-CoV-2 spike protein to human ACE2 is likely the result of natural selection on a human or human-like ACE2. Furthermore, the overall molecular structure of SARS-CoV-2 has been analysed and the backbone of the novel coronavirus's genome has been found to closely resemble a bat coronavirus however, the RBD region of the spike protein is similar to the spike protein found in pangolins⁹. Additionally, through genomic analysis a second study found that SARS-CoV-2 was more closely related to two bat-derived SARS -like coronaviruses, bat-SL-CoVZC45 and bat-SL-CoVZXC21 as it exhibited approximately 88% similarity. However, the genome of SARS-CoV-2 was found to be more distant from SARS-CoV and MERS-CoV, with similarity being approximately 79% and 50% respectively¹⁰. These findings show the possibility of SARS-CoV-2 acquiring such sequences through the process of recombination or mutation. Bats may be the original host of this novel virus, however an animal sold at the Wuhan seafood market may represent an intermediate host which enabled the transmission of the virus into human. Thus, providing further evidence that the novel coronavirus responsible for this COVID-19 pandemic may have originated in nature. Despite the fact that the precise origins of SARS-CoV-2 is still undetermined, two possible scenarios regarding its origin have been proposed. The first scenario

hypothesises that COVID-19 evolved from its natural host, thus allowing it to effectively bind to the human ACE2 receptor. This scenario seems to follow the trend of previous coronavirus outbreaks, such as SAR-CoV-1 which emerged from cat like civets and MERS- CoV which emerged from camels. On the other hand, in the second scenario, it has been proposed that the coronavirus transmitted from animals into humans a long time before it became capable of causing human disease. The virus then became pathogenic to humans as a result of gradual evolutionary changes over years and even perhaps decades⁹.

Conclusion

As it stands, despite the controversial claims that the novel coronavirus is of a laboratory origin, the evidence is unsubstantial and hence further studies are required to determine the exact origin of SARS-CoV-2. Till date, the research strongly favours the argument that SARS-CoV-2 is of natural origin, which in itself highlights the hidden viral reservoir that currently exist in wild animals and further highlights their potential to transfer into human populations. Understanding the origins of SARS-

CoV-2 can lead to better understanding of such hidden viral reservoirs, which will in essence allow the prediction of future epidemics that may arise. Additionally, it will also provide an insight into how SARS-CoV-2 successfully achieved cross species transmission, understanding the mechanisms at play can lead to implementations of strategies that can ultimately aid in preventing future outbreaks of this scale.

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FS and MTN have designed the study, gathered data, written, and reviewed the manuscript. MTN has approved the final draft and submitted the manuscript.

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