The probable origin of SARS-CoV-2: A Scientific report

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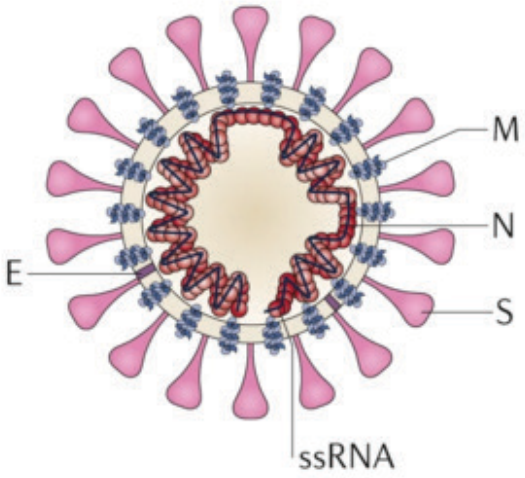
Introduction

The novel SARS-CoV-2, called corona virus that emerged in the city of Wuhan, China in December 2019, has since caused extraordinary scale COVID-19 epidemic, and spread to almost the entire world. On December 31st 2019, World Health Organization was alerted by China, of an outbreak of a novel strain of corona virus causing severe illness, which was subsequently named SARS-CoV-2. Worldwide it has infected more than a billion people, caused death ranging from 1-5% of the infected population and still on the rise. The killer virus (highly infectious and capable of causing death) is seen as a threat to human civilization and survival that challenges humans' ability to detect, understand and manage the unprecedented pandemic pathogen. This generated worldwide debate on its origin, molecular nature, mode of spread, and infectious behaviour inside the human body.

Corona viruses are a large family of viruses that can cause illnesses ranging widely in severity (Fig. 1). The first known severe illness caused by a corona virus emerged with the 2003 Severe Acute Respiratory Syndrome (SARS) epidemic in China (Andersen et al., 2020). A second outbreak of severe illness began in 2012 in Saudi Arabia with the Middle East Respiratory Syndrome (MERS).

Source of data

After the epidemic began in Wuhen, China, at first scientists from China sequenced the genome of SARS-CoV-2 and made the data available to researchers worldwide in public domain. After detection of the SARS-CoV-2 epidemic the number of COVID-19 cases has been increasing because of human to human transmission after a single introduction into the human population. Researchers have used this sequencing data to explore the origins and evolution of SARS-CoV-2 by focusing in on several tell-tale features of the virus (Wan et al., 2020; Letko et al., 2020). The scientists analyzed the genetic template for spike proteins, armatures on the outside of the virus that it uses to grab and penetrate the outer walls of human and animal cells. More specifically, they focused on two important features of the spike protein: the receptor-binding domain (RBD), a kind of grappling hook that grips onto host cells, and the cleavage site, a molecular can opener that allows the virus to crack open and enter host cells (Andersen et al., 2020).



The 3' terminus encodes structural proteins, including envelope glycoproteins spike (S), envelope (E), membrane (M) and nucleocapsid (N)

Fig. 1: Corona viruses form enveloped and spherical particles of 100–160 nm in diameter

Evidence for natural evolution

After detailed analysis scientists found that the RBD portion of the SARS-CoV-2 spike proteins had evolved to effectively target a molecular feature on the outside of human cells called ACE2, a receptor involved in regulating blood pressure. The SARS-CoV-2 spike protein was so effective at binding the human cells, in fact, that the scientists believe that it was the probably or as a result of natural selection and not the product of genetic engineering.

This evidence for natural evolution was supported by data on SARS-CoV-2's overall molecular structure. If someone were seeking to engineer a new corona virus as a pathogen, they would have constructed it from the backbone of a virus known to cause illness. But the scientists found that the SARS-CoV-2 backbone differed substantially from those of already known corona viruses and mostly resembled related viruses found in bats and pangolins. These two features of the virus, the mutations in the RBD portion of the spike protein and its distinct backbone, rules out laboratory manipulation as a potential origin for SARS-CoV-2 (Andersen et al., 2020). These findings are crucially important to bring an evidence-based view to the rumors that have been circulating about the origins of the virus (SARS-CoV-2) causing COVID-19. Thus it can be concluded that the virus is the product of natural evolution not deliberate genetic engineering.

Possible origins of the virus

It is observed that the RBD of SARS-CoV-2 is optimized for binding to human ACE2 with an efficient solution different from those previously predicted virus (Wan et al., 2020; Letko et al., 2020). If genetic manipulation had been performed, it would have been easy to use one of the several reverse-genetic systems available for beta corona viruses (Cui et al., 2019). However, the genetic data conclusively show that SARS-CoV-2 is not derived from any previously used virus backbone. There could be two scenarios that can plausibly explain the origin of SARS-CoV-2: (i) natural selection in an animal host before zoonotic transfer; and (ii) natural selection in humans following zoonotic transfer.

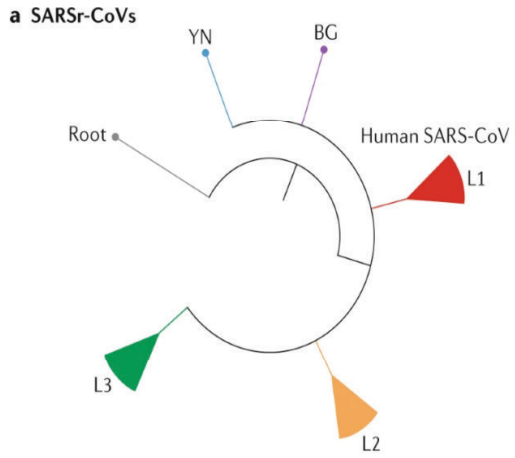
In one scenario, the virus evolved to its current pathogenic state through natural selection in a non-human host and then jumped to humans. This is how previous corona virus outbreaks have emerged, with humans contracting the virus after direct exposure to civets (SARS) and camels (MERS). The researchers proposed bats as the most likely reservoir for SARS-CoV-2 as it is very similar to a bat corona virus (Zhou et al., 2020). There are no documented cases of direct bat-human transmission, however, suggesting that an intermediate host was likely involved between bats and humans.

In this scenario, both of the distinctive features of SARS-CoV-2's spike protein the RBD portion that binds to cells and the cleavage site that opens the virus up would have evolved to their current state prior to entering humans. In this case, the current epidemic would probably have emerged rapidly as soon as humans were infected, as the virus would have already evolved the features that make it pathogenic and able to spread between people.

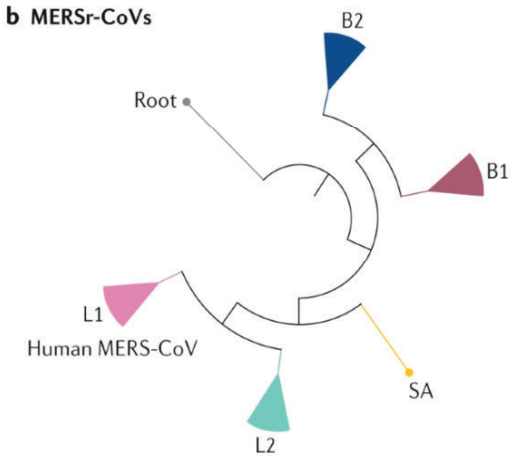
In the other proposed scenario, a non-pathogenic version of the virus jumped from an animal host into humans and then evolved to its current pathogenic state within the human population. For instance, some corona viruses from pangolins, armadillo-like mammals found in Asia and Africa, have an RBD structure very similar to that of SARS-CoV-2 (Zhang et al., 2020). A corona virus from a pangolin could possibly have been transmitted to a human, either directly or through an intermediary host such as civets or ferrets. Then the other distinct spike protein characteristic of SARS-CoV-2, the cleavage site, could have evolved within a human host, possibly via limited undetected circulation in the human population prior to the beginning of the epidemic. The researchers found that the SARS-CoV-2 cleavage site, appears similar to the cleavage sites of strains of bird flu that has been shown to transmit easily between people. SARS-CoV-2 could have evolved such a virulent cleavage site in human cells and soon kicked off the current epidemic, as the corona virus would possibly have become far more capable of spreading between people.

On the other hand, it needs to be recorded that basic research involving passage of bat SARS-CoV-like coronaviruses in cell culture and/or animal models has been ongoing for many years in biosafety level 2 laboratories across the world and there are documented instances of laboratory escapes of SARS-CoV (Lim et al., 2004). Therefore, it is utmost necessary to examine the possibility of an inadvertent laboratory release of SARS-CoV-2. In theory, it is possible that SARS-CoV-2 acquired RBD mutations during adaptation to passage in cell culture, as has been observed in studies of SARS-CoV (Sheahan, et al., 2008). The finding of SARS-CoV-like corona viruses from pangolins with nearly identical RBDs, however, provides a much stronger and more

parsimonious explanation of how SARS-CoV-2 acquired these via recombination or mutation (Cui et al., 2019).



The figure shows a simplified phylogenetic tree of severe acute respiratory syndrome-related corona viruses (SARSr-CoVs) from bats. SARSr-CoVs cluster into three lineages, L1–L3, and human severe acute respiratory syndrome corona viruses (SARS-CoVs) embed in L1. Two individual SARSr-CoVs do not cluster into these lineages



Middle East respiratory syndrome-related corona viruses (MERSr-CoVs) form two major viral lineages, L1 and L2. L1 is found in humans and camels, and L2 is found only in camels. Two small clusters, B1 (bat 1) and B2, and one single virus, SA, from South Africa, were found in bats.

(Source : Cui et al., 2019)

Fig. 2: Phylogenetic analysis of SARSr-CoVs and MERSr-CoVs

If the SARS-CoV-2 entered humans in its current pathogenic form from an animal source, it raises the probability of future outbreaks, as the illness-causing strain of the virus could still be circulating in the animal population and might once again jump into humans. The chances are lower of a non-pathogenic corona virus entering the human population and then evolving properties similar to SARS-CoV-2.

Treatment

There is no specific treatment for disease caused by a novel corona virus. However, many of the symptoms can be treated and therefore treatment based on the patient's clinical condition. While some western, traditional or home remedies may provide comfort and alleviate symptoms of mild COVID-19, there are no medicines that have been shown to prevent or cure the disease. WHO does not recommend self-medication with any medicines, including antibiotics, as a prevention or cure for COVID-19. There is no strong evidence that the Bacille Calmette-Guérin vaccine (BCG) protects people against infection with COVID-19 virus. Two clinical trials addressing this question are underway meanwhile WHO continues to recommend neonatal BCG vaccination in countries or settings with a high incidence of tuberculosis.

Most people (about 80%) recover from the disease without needing special treatment and some other with symptoms are treated systematically for which protocols are developed. Around 1 in every 5 people who are infected with COVID-19 develops difficulty in breathing and requires hospital care. People who are aged over 60 years and people who have underlying medical conditions such as diabetes, heart disease, respiratory disease or hypertension are among those who are at greater risk.

Conclusions

The entire world is now focused on how to bring down the human casualty to COVID-19 curtailment of its further spread to non-infected population through all possible measures. Given the level of damage it has caused to the human life in the modern day, it is not surprising to see the active involvement of scientists from various institutions across the globe trying to design a

vaccine and complete the required test as early as possible to bring the vaccine to the public use. At this juncture, detailed understanding of how an animal virus jumped species boundaries to infect humans so productively will help in the prevention of future zoonotic events. In addition, identifying the closest viral relatives of SARS-CoV-2 circulating in animals will greatly support studies of viral function. Indeed, the availability of the RaTG13 bat sequence helped to unlock the RBD mutations and the polybasic cleavage site.

Based on the observations of available information on SARS-CoV-2 features, including the optimized RBD and polybasic cleavage site, it is unlikely that SARS-CoV-2 is a purposefully manipulated virus in laboratories. However it is currently impossible to prove or disprove the other theories of its origin described here. More scientific data could swing the balance of evidence to favor one hypothesis over another.

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