AMA

THE STRAIN OF **SARS-COV-2**

Federal AMA Vice President

Dr Chris Zappala

Thoracic Physician

24 April 2020

THE STRAIN OF SARS-COV-2

SARS-CoV-2 is the third documented spill over of an animal coronavirus to humans in the last two decades. There is an enormous number of viruses circulating in the environment which have never been fully characterised. The genome sequence is all that is known for the majority of these viruses and it is on this basis that viruses are named[1].

Evolution

The SARS-CoV and MERS-CoV pathogens are zoonotic in origin – both deriving from bats as the animal host source, and mask palm civets and camels to be the intermediate animal hosts (between bats and humans), respectively[2]. Recent reports suggest SARS-CoV-2 is 96 per cent identical at the genome level to previously detected bat coronaviruses, which belongs to the SARS-related coronavirus species. Although bats could be the original host for SARS-CoV-2 also, the virus may initially have been transmitted to an intermediate animal host at the Wuhan Huanan Seafood Wholesale Market[2].

Given the similarity of SARS-CoV-2 to bat SARS-CoV-like coronaviruses, it is likely that bats also serve as reservoir hosts for its progenitor[2]. Although RaTG13, sampled from a Rhinolophus affinis bat, is approximately 96 per cent identical overall to SARS-CoV-2, its spike diverges in the receptor binding domain (RBD), which suggests that it may not bind efficiently to human ACE2 (refer previous Covid fact sheet). Malayan pangolins (Manis javanica) illegally imported into Guangdong province contain coronaviruses similar to SARS-CoV-2. Some pangolin coronaviruses exhibit strong similarity to SARS-CoV-2 in the RBD, including all six key RBD residues. This strongly suggests that the SARS-CoV-2 spike protein optimised for binding to human-like ACE2 is the result of natural selection[3].

In such situations where a virus jumps from one animal host to another species—which is probably how this coronavirus initially infected humans—most mutations are detrimental to or have no effect on the virus, and selection pressure may improve survival in the new host. Therefore, we predict that one or more mutations may be selected and sustained during the 2019-nCoV outbreak as the virus adapts to human hosts and possibly changes virulence[4], as reported in the previous study. Thus mutation can be both useful or destructive for the virus over time, but also may be structurally/functional silent[5].

The host clearly exerts evolutional pressures in virus mutation[6]. In SARS-CoV, there was positive selection during interspecies transmission events (from civets to humans) with rapid adaptation and mutation at the receptor binding domain of the S protein. The receptor binding domain of SARS-CoV is capable of recognising the ACE2 receptors of various animals – but key mutations increase the affinity of the interaction of the spike protein of the RBD with human ACE2 receptor i.e. these mutations are critical to viral adaptation to humans[6].

Varying mutations with dubious significance

When genomic datasets from COVID-19 virus isolated in China, Thailand, and the USA were analysed, increasing genetic divergence of SARS-CoV-2 in human hosts was noted[2]. RNA viruses have a high mutation rate due to the lack of proofreading activity of polymerases[6,7]. Consequently, RNA viruses are prone to evolve resistance to drugs and escape from immune surveillance.

The mutation rate of SARS-CoV-2 is still unclear, but is believed to be slightly lower than SARS-CoV (0.80-2.38 x 10-3 nucleotide substitutions per site per year)[7].

THE STRAIN OF SARS-COV-2

This mutation rate also results in high levels of intra-host variants. The median number in a recent trial was found to be 4 (range 0 to 51), which is similar to Ebola. Although the authors did not find any mutation hotspot genes in either polymorphism or intrahost variants, the observation of shared intra-host variants among different individuals implied the possibility of adaptive evolution of the virus in patients, which could potentially affect the antigenicity, virulence, and infectivity of the virus[7]. By investigating a person-to-person spread event between two members of the one household, however, there was no evidence found for transmission of intra-host variants[7].

In another study analysing genetic variants among 95 complete sequences, there was a strong association between the time of sample collection, location of sample, and accumulation of genetic diversity. 116 mutations were found, with unknown functional consequence[8].

Li et al reported there were three phylogenetic clusters and three transmission clusters when the genetic distance between the 2019-nCoV strains was less than 0.001 per cent substitutions/site[2]. This identification of three central variants has been replicated[9], distinguished by amino acid changes – named A, B and C. A is the ancestral type according to the bat outgroup coronavirus. The A and C types are found in significant proportions outside East Asia i.e. Europe and the Americas, but the B type is most common in East Asia. The B type ancestral genome appears not to have spread outside East Asia without first mutating into derived B types, pointing to founder effects or immunological/environmental resistance against this type outside Asia[9] i.e. it must first mutate to overcome resistance outside East Asia.

An earlier study found many mutations and deletions on coding and non-coding regions of SARS-CoV-2.11. Of note, three mutations (D354, Y364, and F367) located in the spike surface glycoprotein receptor-binding domain. The spike surface glycoprotein plays an essential role in binding to receptors on the host cell and determines host tropism. It is also the major target of neutralising antibodies. Mutations in the spike surface glycoprotein might induce its conformational changes, which probably led to the changing antigenicity[10].

Interpretation of genome-driven virus evolution has remained difficult because the published data still refer to a relatively low number of viral isolates. One group examined all available SARS-CoV-2 sequence with the aim of mapping structural variations and the patterns for selection of viral protein genes[5]. Clustering of sequence presenting amino acidic mutations did not indicate a geographical/epidemiological link with the patients from whom SARS-CoV-2 was isolated[5].

In particular, two key mutations were discovered affecting the non-structural protein 6 (NSP6) and the open reading frame 10 (ORF10). These authors went one step further, however, and examined the structure of the proteins encoded by the mutated genes in an attempt to gain some insight into the biologic significance. Amino acid change stability analysis suggests both mutations could confer lower stability of the protein structures[5]. In the case of the NSP6 mutation, it is hypothesised that the presence of the mutation produces several phenylalanine residues in the outer membrane region of the NSP6 and this favours the affinity between this region and the endoplasmic reticulum, thereby compromising the ability of autophagosomes to deliver viral components to lysosomes for degradation, thus conferring a possible viral advantage[5,6].

THE STRAIN OF SARS-COV-2

Coronaviruses have a proof-reading exoribonuclease which checks against the high mutation rate in coronaviruses[6]. Deletion of this results in very high mutability and attenuation or even unviability. Interestingly, the nucleotide analogue, remdesivir, emerging as a potential therapeutic agent in SARS-CoV-2, is known to suppress replication through inhibition of this exoribonuclease and the RNA-dependent polymerase.

Conclusions

Compared to SARS-CoV, the mutation rate of SARS-CoV-2 is apparently lower, suggestive of a higher level of adaptation to humans[6]. This may have resulted from adaptation to another host close to humans[6]. Thus both viral factors, and the influence with the host as outlined above, are influential.

An increased level of viral diversity was found in some SARS-CoV-2 infected patients, suggesting that the virus has begun to adapt to the human environment and its genomes have begun to evolve in the population[11]. While mutation is common, there still remains very high similarly between SARS-CoV-2 strains with few variable genomic regions[12].

This virus's comparative lower mutation rate (compared to SARS-CoV and Influenza) is perhaps related to its high infectivity i.e. it is not under any evolutionary pressure to evolve. This means, therefore, that it is perhaps less likely to spontaneously evolve into a more deadly variant. Supporting this hypothesis various scientific commentators have observed that the virus mutations don't seem to be any more infectious or fatal than the original strain that appeared in Wuhan, China, in late December.

There remains a very rare chance a virus could mutate to be more aggressive, but if anything, RNA viruses are more likely to mutate into a weaker version. Time and further study will tell …

References

1. Coronaviridae Study Group of the ICTV. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nature Microbiology 2020 5:536-544.
2. Li X, Wang W, Zhao X, Zai J, Zhao Q, Li Y, Chaillon A. Transmission dynamics and evolutionary history of 2019-nCoV. Journal of Medical Virology 2020 May; 92)5):510-511.
3. Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF. The proximal origin of SARS-CoV-2. National Medicine. 2020 Apr; 26(4):450-452.
4. Muth D, Corman VM, Royj H, et al. Attenuation of replication by a 29-nucleotide deletion in SARS-coronavirus acquired during the early stages of human-to-human transmission. Scientific Reports 2018; 8.
5. Benvenuto D, Angeletti S, Giovanetti M, Bianchi M, Pascarella S, Cauda R, Ciccozzi M, Cassone A. Evolutionary analysis of SARS-CoV-2: how mutation of non-structural protein 6 (NSP6) could affect viral autophagy. Journal of Infection. 2020 Apr 10. [Epub].
6. Ye ZW, Yuan S, Yuen KS, Fung SY, Chan CP, Jin DY. Zoonotic origins of human coronavirus. International Journal of Biologic Science. 2020 Mar 15; 16(10):1686-1697.

7. Shen Z, Xiao, Y, Kang L, Ma W, Shi L et al. Genomic diversity of SARS-CoV-2 in Coronavirus Disease 2019 patients. Clinical Infectious Disease. 2020 Mar 4 [Epub]

8. Khailany RA, Safdar M, Ozaslan M. Genomic characterisation of a novel SARS-CoV-2. Gene Reports. 2020 Apr 16 [Epub].

9. Forster P, Forster L, Renfrew C, Forster M. Phylogenetic network analysis of SARS-CoV-2 genomes. Proceedings of the National Academy of Science USA. 2020 Apr 8 [Epub].

10. Phan T. Genetic diversity and evooution of SARS-CoV-2. Infection, Genetics, Evolution. 2020 Feb 21; 81. [Epub].

11. Li C, Yang Y, Ren L. Genetic evolution analysis of 2019 novel coronavirus and coronavirus from other species. Infection, Genetics, Evolution. 2020 Mar 10; 82. [Epub].

12. Ceraolo C, Giorgi FM. Genomic variance of the 2019-nCoV coronavirus. Journal of Medical Virology. 2020 May; 92(5):522-528.

Contact Information

AMA FEDERAL
842 Macquarie Street, BARTON ACT 2600
Postal: PO Box 6090, KINGSTON, ACT, 2604
Phone: 02 6270 5400
Fax: 02 6270 5499
Email: ama@ama.com.au
Website: ama.com.au

AMA ACT
Ground Floor, AMA House
42 Macquarie Street, BARTON, ACT
Postal: PO Box 560, CURTIN, ACT, 2605
Phone: 02 6270 5410
Fax: 02 6273 0455
Email: reception@ama-act.com.au
Website: act.ama.com.au

AMA NSW
AMA House, Level 6, 69 Christie St,
St Leonards, NSW, 2065, Australia
Postal: PO Box 121 St Leonards NSW 1590
Phone: 02 9439 8822
Fax: 02 9439 3760
Email: enquiries@amansw.com.au
Website: amansw.com.au

AMA NORTHERN TERRITORY
Unit 2/25 Parap Road, Parap, NT, 0820
PO Box 2299, Parap, NT, 0804
Phone: 08 8981 7479
Fax: 08 8941 0937
Email: amant@amant.com.au
Website: nt.ama.com.au

AMA QUEENSLAND
88 L'Estrange Terrace
Kelvin Grove, Queensland, 4059
Post: PO Box 123, Red Hill, QLD 4059
Phone: 07 3872 2222
Fax: 07 3856 4727
Email: amaq@amaq.com.au
Website: qld.ama.com.au

AMA SOUTH AUSTRALIA
Level 2, AMA House, 161 Ward Street,
North Adelaide, South Australia
Phone: 08 8361 0101
Fax: 08 8267 5349
Email: admin@amasa.org.au
Website: sa.ama.com.au

AMA TASMANIA
AMA HOUSE, 147 Davey St, Hobart, TAS 7000
Phone: 03 6223 2047
Email: ama@amatas.com.au
Website: tas.ama.com.au

AMA VICTORIA
AMA VICTORIA HOUSE
293 Royal Parade
Parkville, Victoria, 3052, Australia
Postal: PO Box 21 Parkville Victoria 3052
Telephone: 03 9280 8722
Facsimile: 03 9280 8786
Email: amavic@amavic.com.au
Website: amavic.com.au

AMA WESTERN AUSTRALIA
14 Stirling Highway, Nedlands, WA 6009
Postal: PO Box 133, Nedlands, WA 6909
Phone: 08 9273 3000
Fax: 08 9273 3073
Email: mail@amawa.com.au
Website: amawa.com.au