2020

Species Specificity and Cross-species Transition in Relation to SARS-CoV-2 Spike Proteins

Edrice Sediq

Seton Hall Biochemistry II Annals of Student Reviews
Vol 1. No. 3
2020

Species Specificity and Cross-species Transition in Relation to SARS-CoV-2 Spike Proteins

Author: Edrice Sediq
Reviewer/Editor: Dr. Gregory Wiedman

Introduction

Coronaviruses are known as envelope RNA viruses that are able to infect and manifest disease in various avian and mammalian species. They have the ability to participate in cross-species transmission as seen in the human coronavirus, Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in 2002. The most recent emergence of a novel coronavirus, SARS-CoV-2, has entered the world and presents similarities to known human coronaviruses. Mechanisms of viral entry and receptor interactions are key to understanding the process of transmission. Further elaboration will be presented on cross-species transmission and the role of viral proteins in spreading the virus.

1. Viral Structure and Function

Gaining an understanding of the viral entry mechanism will allow for further analysis of the spike proteins in relation to species, as well as cross species transmission. This concept is studied in the collaborative work of the Center for Infection and Immunity of Lille, France and the Department of Microbiology and Immunology of Cornell University into the mechanism for coronavirus cell entry through the analysis of the viral spike protein. This review focuses on the coronavirus entry mechanisms looking at the different triggers used by the virus to allow for the conformational change of the spike protein; "receptor binding, low pH exposure and proteolytic activation."[1] Before beginning to understand the species specificity and cross species transmission, viral entry must be examined. As an overview, viral entry is gained through interplay between the host cell and the virion which leads to infection. This happens once there is an interaction with said viral particle and cell surface receptors. The spike proteins play two roles during entry by both mediating receptor binding and membrane fusion. For fusion to occur there needs to be a large conformational change of the spike protein. This is the structure that is arranged in a trimer, which lends to its "crown-like" appearance. The 3 viral proteins on the virion envelope are (S) the spike protein, (M) the membrane protein and (E) the envelope protein, and while (M) and (E) focus on virus assembly it is the spike protein which is of main interest for viral entry.

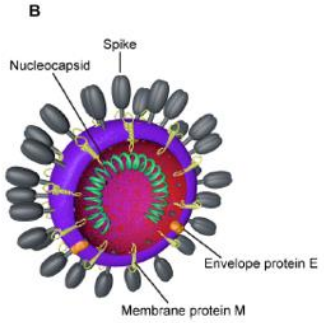

Figure 1. Coronavirus virion structure adapted from ref 1

There are 4 known species of coronaviruses: alphacoronavirus, betacoronavirus, gamacoronavirus, and deltacoronavirus. Media and current speculation place SARS-CoV-2 as originating from bats. Preliminary interpretation based on research data places the classification of the novel coronavirus as belonging to either the alpha or beta genus[1]. In a Features and Evaluation article the SARS-CoV-2 is placed as being a betacoronavirus due to its round or elliptic, often pleomorphic form and 60-140nm diameter in size. Common human coronaviruses (HCov-OC43, and HCov-HKU1) belong to the A lineage of betaCoV's and are primarily responsible for common colds, while in the B and C linage (SARS-CoV, SARS-CoV-2 and MERS-CoV) bring about respiratory and extra-respiratory manifestations[2]. By understanding the genus of this newly introduced coronavirus it allows for a better tracing of its origin. The Feature and Evaluation is comprehensive in reporting the standings of the novel coronavirus by presenting information provided by both the CDC and WHO.

2. Cross Species Genetic Similarities in Coronaviruses

Taking a look into recent media it was confirmed that another species has, as of what is know currently, contracted the SARS-CoV-2 virus. According to a New York times article and news segment by NBC news on their Today Show it was reported that a Bronx Zoo Tiger tested positive for COVID-19 (the disease resulting from infection with SARS-CoV-2). The tiger displayed symptoms of (i) Wheezing/labored breaths (ii) Persistent dry cough and (iii) Lack of appetite with the speculation that it was infected by an asymptomatic staff member[3,4]. This evidence lends to the possibility of cross-species transmission of SARS-CoV-2. In a research article from the Journal of Medical Virology titled *Cross-Species transmission of the newly identified coronavirus 2019-nCov,* Wei Ji and colleagues explore the transmission of the virus as many of the initial patients were open to exposure of wildlife animals at the Huanan seafood wholesale market where, it's stated, that poultry, snake, bats and other farm animals were sold. Through the results obtained it is suggested that the 2019-nCoV is a recombinant virus resulting between the bat coronavirus and an origin-unknown coronavirus. It appears that the recombination may have occurred within the receptor-binding glycoprotein (spike protein), which as examined earlier is primarily responsible for viral entry into the host cell. This adaptation of the spike protein caused the virus to move from presenting viral pneumonia and having limited capability of person to person spread to its current state of acquiring the capability to replicate more efficiently and spread more quickly with close person-to-person contact[5].

The researchers included a "maximum likelihood phylogenetic tree" diagram of the 2019-nCov which outlines the 272 near-complete genome sequences of the coronavirus grouped into 4 clades, being 2019 n-CoV, Clades A,B, and C as well as coronaviruses originating from different countries and regions which is represented below[5].

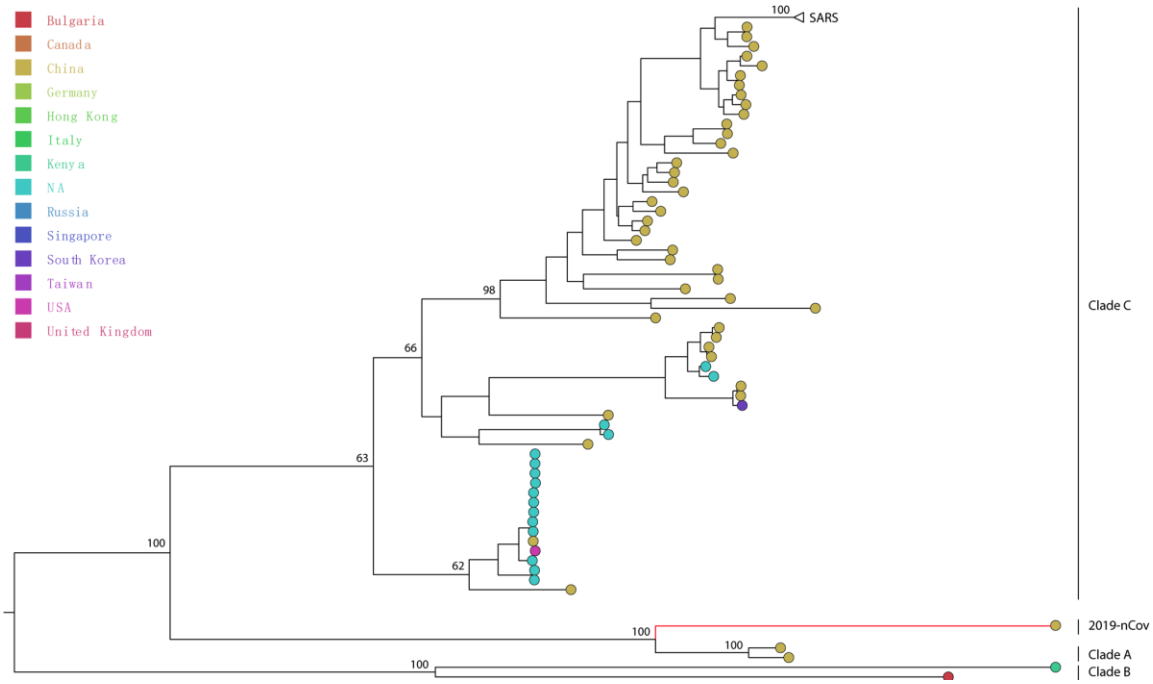

Figure 2. Maximum likelihood phylogenetic tree of 2019-nCoV adapted rom ref 5

By using these data the researchers were able to produce the similarity plot shown below in Figure 3. The similarity plot, focusing on the highlighted nucleotide position region of the spike glycoprotein, shows that a possible recombination may have occurred between strains of Clade A (bat-CoV) and an isolate of unknown origin located in the spike glycoprotein, which is responsible for mediating viral entry into the host cell. The analysis yields that the 2019-nCoV has similar genetic information to the bat coronavirus and most similar in codon usage bias with snake[5]. The principle of cross species transmission may relate to the homologous recombination of the viral receptor binding spike glycoprotein which may lend reason to the transmission of the virus to the Bronx Zoo tiger.

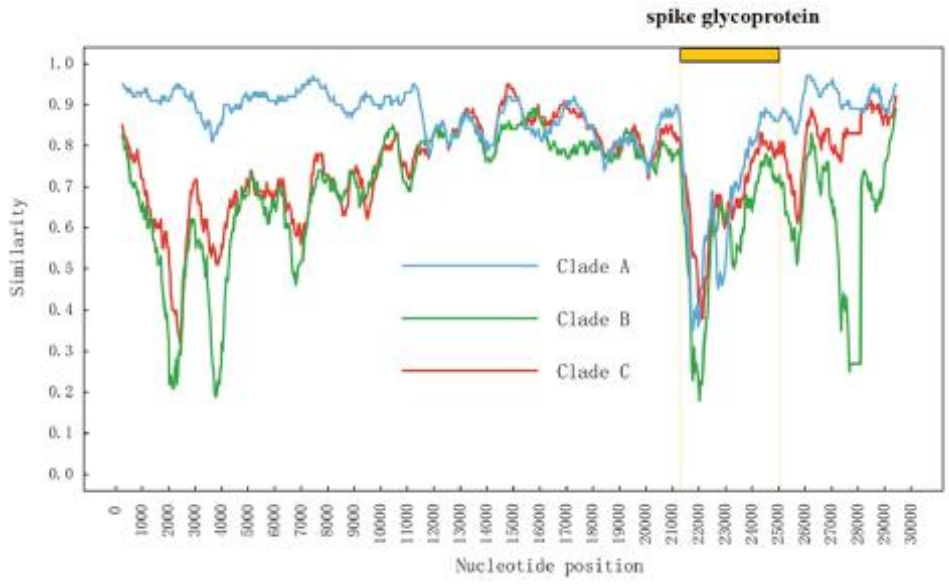

Figure 3. Similarity plot analysis of Clades A, B and C adapted from ref 5

The research presented by Wei Ji and colleagues in the Journal of Medical Virology is an initial step into understanding the origin and transmission patterns of the virus. The diagram shown in Figure 3, although key in comparing the spike glycoprotein amongst different virus clades, is missing the comparison of each clade with 2019-nCov to better match the recombination of the viral spike glycoprotein. The phylogenetic tree in Figure 2 shows that 2019-nCoV is most similar to Clade A which are coronaviruses derived in the city of Nanjing, China between 2015 and 2017. Clade B is representative of coronaviruses found form bats in Bulgaria and Kenya and Clade C being of 276 coronavirus strains. This tree allows for one to better understand the similarity of the novel coronavirus and its relation to known strains which further add conviction to it being a part of the beta-CoV genus.

3. Lessons from other Cross-Species Transmitting Viruses

Apart from human coronaviruses there are other virus forms that circulate amongst different classes of animals. The Avian Influenza Virus (H5N1) is one that can occur naturally amongst wild aquatic birds and are known to infect domestic poultry and other birds and animal species. Normally, this virus is not known to infect humans. There are, however sporadic infections which have occurred[6]. Referring to the CDC, there are known cases of transmission of H5N1 to humans although the clusters are, "limited, non-sustained person-to-person spread of avian influenza A viruses." The CDC lists human-to-human transmission as ranging from occasional, limited, non-sustained without further spread ("dead-end transmission"), to efficient and sustained transmission (ongoing transmission)[7]. Of the listed cases provided by the CDC the transmission of H5N1 from birds to humans while although possible cannot be sustained enough to spread. On the Contrary, SARS-CoV and the current SARS-CoV-2 belong to the class of human coronaviruses that spread with sustained human-to-human transmission. There appears to be an emerging pattern of sustained spreading of coronaviruses amongst organisms of the same animal class, meaning that spreading amongst mammals is more prominent than from birds to humans for example. Inter-class transmission of coronaviruses appears not to be sustained unlike those transmitting amongst the mammalian class, proposing the speculation that SARS-CoV-2 may not transmit to other organisms such as birds or pest organisms.

Zoonotic origins of SARS-CoV and SARS-CoV-2 provide insight into their relation and amongst other human coronaviruses. As previously highlighted the current SARS-CoV-2 shows similarity between the bat CoV and another of unknown origin which alters the spike glycoprotein. From the *International Journal of Biological Sciences*, Zi-Wei Ye *et at al*, report further information on SARS-CoV-2 and its relationship with other human coronaviruses. SARS-CoV-2 shares 96.2% nucleotide homology with the bat CoV RaTG13 isolated from *Rhinolophus*

affinis bats. This analysis currently cannot be assigned as a parental relationship as there is a significant sequence divergence from the two. This suggests that something with origin has to played a role in the development of SARS-CoV-2. Although SARS-CoV and SARS-CoV-2 are similar with a 82% nucleotide sequence homology, they cluster into different branches of the phylogenetic tree[8,9]. Its comparison to the other six human coronaviruses, they are of great interest into further understanding. The incubation period and duration of infection are comparable to the human coronavirus diseases.. The list of symptoms lies between SARS-CoV and the four community human coronaviruses (HCoV-229E, HCov-OC43, HCoV-HKU1 and HCoV-NL63) as well as the transmission patterns of SARS-CoV-2. Although it compares to the transmissibility of community-acquired human coronaviruses, it has not yet been verified if transmissibility of SARS-CoV-2 decreases after passages in humans as was experienced with SARS-CoV and MERS-CoV. Lastly, it was determined that SARS-CoV-2 can be detected in fecal samples as with other human, which lends to possibility of fecal-oral transmission as in the case of SARS-CoV. Although similarities exist between the human coronaviruses and the new emerged SARS-CoV-2 its patterns of transmission may contain an "origin-unknown" component as examined during this time.

Looking back at the spike glycoprotein, the key component in viral entry, it is determined that SARS coronaviruses use the spike glycoprotein to bind to ACE2 for docking and entry. The SARS spike protein can recognize and interact with different ACE2 receptors:dogs, civet, mouse and racoon dog. This indicates a movement along receptor ortholog networks to transition between different species. The role of the different ortholog proteases used by the coronavirus spike glycoprotein for cleavage and viral entry are still undefined. The Receptor Binding Domain (RBD) provides further insight into specificity of the host receptor. Pertaining to SARS-CoV, which is similar in nucleotide sequence homology to SARS-CoV-2, only requires a minimum of 1-2 substitutions in the RBD to allow the virus to change the host receptor specificity. The plasticity of the spike glycoprotein has been examined and determined to accommodate mutations and deletions of up to 681 nucleotides[10]. The plasticity of the spike protein and specificity of the receptor binding domain may offer reasons as to the rapid rate of transmission of SARS-CoV-2 and its ability to move interspecies and intraspecies.

Conclusions

Overall, the current outbreak of SARS-CoV-2 can be traced to the beta coronavirus genus and have similar genetic information with bat coronaviruses mixed with an origin unknown source. The spike glycoprotein plays a prominent role in viral entry and a homologous recombination of this protein is noted in SARS-CoV-2 and may determine cross-species

transmission, along with the ability to implement different ACE2 cell receptors. Although there do exist other coronaviruses amongst other classes of organisms, they are unable to maintain sustained spreading when interacting with humans. The Receptor Binding Domain provides further information into the specificity of the host receptor. Further study should be explored into the frequency of virus transmission amongst species of the mammalian class to see if there is data to suggest the cause and reason behind the rapid transmission and cross species transmission capability seen in known and the current human coronaviruses. Transmission of coronaviruses from other classes of organism are unable to sustain themselves when interacting with humans and thus do not spread as compared to SARS-CoV-2 and the other human coronaviruses. The spike glycoprotein of SARS-CoV-2 must be identified and examined to see where there may be substitutions in its receptor binding domain.

References

(1) Belouzard, S., Millet, J. K., Licitra, B. N., and Whittaker, G. R. (2012, June) Mechanisms of coronavirus cell entry mediated by the viral spike protein. *Viruses*. MDPI.
(2) Cascella, M., Rajnik, M., Cuomo, A., Dulebohn, S. C., and Di Napoli, R. (2020, April 6) Features, Evaluation and Treatment Coronavirus (COVID-19). *StatPearls*. StatPearls Publishing.
(3) Goldstein, J. (2020, April 6) Bronx Zoo Tiger Is Sick With the Coronavirus. *The New York Times*. The New York Times.
(4) NBC News, 2020. *Bronx Zoo Tiger Tests Positive: Could You Get Coronavirus From Your Pets? | TODAY*. [image] Available at: <https://www.youtube.com/watch?v=2kN-pJQvx9A> [Accessed 11 May 2020].
(5) JJi, W., Wang, W., Zhao, X., Zai, J., and Li, X. (2020, February 19) Cross-species transmission of the newly identified coronavirus 2019-nCoV. *Wiley Online Library*. John Wiley & Sons, Ltd.
(6) (2017, April 10) Bird Flu Basics. *Centers for Disease Control and Prevention*. Centers for Disease Control and Prevention.
(7) (2017, April 10) Examples of Human Infections with Avian Influenza A Viruses with Possible Limited, Non-Sustained Human-to-Human Transmission. *Centers for Disease Control and Prevention*. Centers for Disease Control and Prevention.
(8) Ye, Z.-W., Yuan, S., Yuen, K.-S., Fung, S.-Y., Chan, C.-P., and Jin, D.-Y. (2020, March 15) Zoonotic origins of human coronaviruses. *International journal of biological sciences*. Ivyspring International Publisher.
(9) Chan, J. F.-W., Kok, K.-H., Zhu, Z., Chu, H., To, K. K.-W., Yuan, S., and Yuen, K.-Y. (2020, January 28) Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerging microbes & infections*. Taylor & Francis.
(10) Bolles, M., Donaldson, E., and Baric, R. (2011, December) SARS-CoV and emergent coronaviruses: viral determinants of interspecies transmission. *Current opinion in virology*. Elsevier B.V.