Coronaviruses through time and species: analysis of coronaviruses in relation to the Covid-19 pandemic

Alexandria Zabiegala, Yunjeong Kim, and Kyeong-Ok Chang

Diagnostic Medicine and Pathobiology, College of Veterinary Medicine, Kansas State University. Manhattan, KS.

American Veterinary Medical Foundation

HELPING VETERINARIANS, HELP ANIMALS

Introduction

Coronaviruses, positive-sense, single stranded, RNA viruses, are a large group of viruses in the *Coronaviridae* family that cause a wide variety of diseases in humans and animals. From the avian IBV, the first coronavirus isolated from poultry with respiratory disease during 1930s to current SARS-CoV-2, coronaviruses continue to present challenges to animals and humans. Animal coronaviruses can cause asymptomatic to fatal infections in the respective target host including avian, porcine, bovine, canine, feline, or murine species.

Cross-species transmission of Coronaviruses have a long standing history in human and veterinary medicine. Cross-species transmission of coronaviruses became a major focus of study after the 2002-2004 Severe Acute Respiratory Syndrome (SARS) outbreak, in which the original hosts of the virus are believed to be bats. Bat populations are major reservoirs of coronaviruses and many different human strains identified today can be ancestrally linked to a bat origin[1]. These strains include the common cold (HCoV-229E and HCoV-NL63), Severe Acute Respiratory Syndrome (SARS), and Middle Eastern Respiratory Syndrome (MERS). While bats are a common source of coronavirus reservoirs, there are several strains of common cold (HCoV-HKU1 and HCoV-OC43) which do not appear to have an ancestral linkage to bats and appear to be linked to rodents. Cross-species transmission of coronaviruses are thought to be facilitated by high viral recombination and mutation rates, and increasing human disturbance on wild animal habitats. Currently, Covid-19 (SARS-CoV-2) is suspected to have originated in bats[2] since there is a high homology to SARS-related (SARSr) coronaviruses which have been found in bat populations throughout the past 15 years[3]. One strain in particular RATG13[4], appears to be the closest related ancestor with approximately 96% homology. It is also implicated that the pangolin serves as an intermediate host[5].

The S protein is involved in cellular attachment and entry, which makes it a major focus of study on cross-species transmission, tissue tropism, and virulence of coronaviruses. The S protein genome is similar among coronaviruses, with an S1 and S2 region (Figure 1). S1 is variable between strains and contains the N-terminal domain (NTD) typically responsible for viral adherence to sialic acids and a C-terminal domain (CTD) typically responsible for viral attachment to the functional receptor. So far, well characterized functional receptors for coronaviruses includes dipeptidyl peptidase-4 (DDP4) Aminopeptidase N (APN), angiotensin-converting enzyme (ACE2), carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) (Table 1). The S2 region contains the necessary proteins for envelope fusion to the cellular membrane or the endosome and is highly conserved. The currently available information suggests that the NTD of the S protein of SARS-CoV-2 adheres to sialic acids present on the cell surface, followed by the binding of the CTD to ACE2 (Figure 2), a mechanism typically seen with many other coronaviruses. This literature review analyzes the S protein's cellular receptors in the NTD and CTD of S1 and the structural changes involved in the protein binding to the cell for various coronaviruses.

Materials and Methods

Data Source and Analysis: Peer-reviewed articles on the S protein, cell receptors, and viral-cell interactions of coronaviruses in the PubMed database (Approximately 150 articles and years from 1963 to 2020) were reviewed in this study. Crystallographic structures of coronavirus S proteins were obtained from Protein Data Bank and analyzed using PyMol (Schrödinger Inc., New York) and Chimera (University of California, San Fransisco) software. Protein alignment was created using CLC Sequence Viewer 8 (Quiagen, Hilden, Germany).

Results

Various animal and human coronaviruses are summarized in Table 1. Receptor interaction with subdomains of S protein and tissue tropisms were highlighted in the Table 1. The structures of coronavirus S protein is shown in Figure 1.

Alphacoronavirus					
Name	**Year Identified**	**Species**	**Tissue Tropism**	**NTD Receptor**	**CTD Receptor**
Common Cold (HCoV-229E)[8,9]	1965	Human	Upper Respiratory		hAPN
Common Cold (HCoV-NL63)[8,10]	2002	Swine	Upper Respiratory		ACE-2
Transmissible Gastroenteritis Virus (TGEV) [8,11]	1946		Enteric		pAPN
Swine Hemagglutinating Encephalomyelitis (Vomiting and Wasting Disease) [12,13]	1959	Swine	Enteric CNS		NCAM
Feline Coronavirus (FCoV)[14,15]	1963	Feline	Enteric (FECoV) Systemic (FIP)		Serotype 1: unknown Serotype 2: fAPN
Betacoronavirus					
Disease Name	**Year Identified**	**Species**	**Tissue Tropism**	**NTD Receptor**	**CTD Receptor**
Mouse Hepatitis Virus (MHV)[16,6]	1949	Mouse	Liver Enteric CNS	CEACAM-1	
Bovine Enteritis and Respiratory Disease (BCoV)[17]		Bovine	Enteric Lower Respiratory	Sialic Acids	HLA-1
Common Cold (HCoV-OC43)[16,17]	1967	Human	Upper Respiratory CNS	Sialic Acids	
Common Cold (HCoV-HKU1) [16,17]	2005	Human	Lower Respiratory	Sialic Acids	HLA-1
Severe Acute Respiratory Disease (SARS/SARS-CoV-1) [16,18]	2002	Human	Lower respiratory		ACE-2
Covid-19 (SARS-CoV-2)[19,20]	2019	Human	Lower Respiratory		ACE-2
Middle Eastern Respiratory Syndrome (MERS)[21,22]	2012	Human	Lower Respiratory		DDP4
Canine Respiratory Disease (CRCoV)[23,17]	1971	Canine	Upper and Lower Respiratory	Sialic Acids	HLA-1
SARS-like Coronaviruses (SARSr-CoV)[24]		Bat	Enteric		ACE-2
HKU4[25,26]	2006	Bat	Enteric		DPP4
Gammacoronaviruses					
Disease Name	**Year Identified**	**Species**	**Tissue Tropism**	**NTD Receptor**	**CTD Receptor**
Infectious Bronchitis Virus (IBV)[27,28]	1930	Poultry	Upper Respiratory	Sialic Acids	

Table 1: Comparisons of various coronaviruses by their species and tissue tropism, and their functional receptor. Table arranged by genus displaying viruses by the year identified, species afflicted, tissues affected, and known receptors. Blank boxes indicate ambiguity or lack of data.

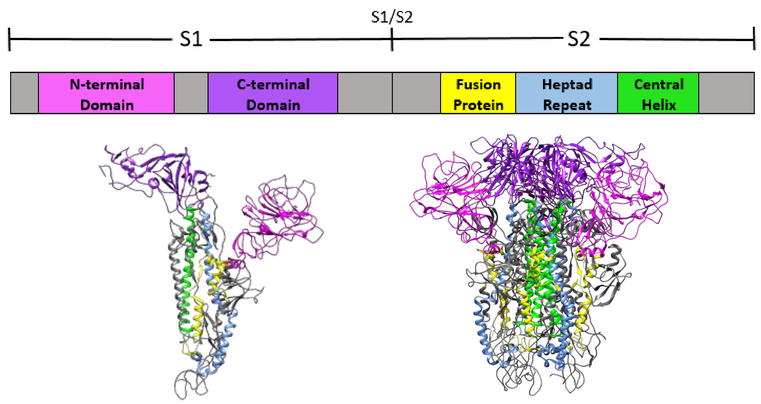

Figure 1: Arrangement of the coronavirus spike protein. Protein domains and structural arrangement of the monomer (left) and functional trimer (right) S protein of MHV (PDB: 6VSJ).

SARS-CoV2 S protein interactions with ACE2 have been reported, which include several 3D structures with or without receptor bindings (Figure 2). These detailed information regarding interactions have been utilized for vaccine and therapeutic development. Figure 3 shows the S1/S2 junction of S proteins from various human and animal coronaviruses.

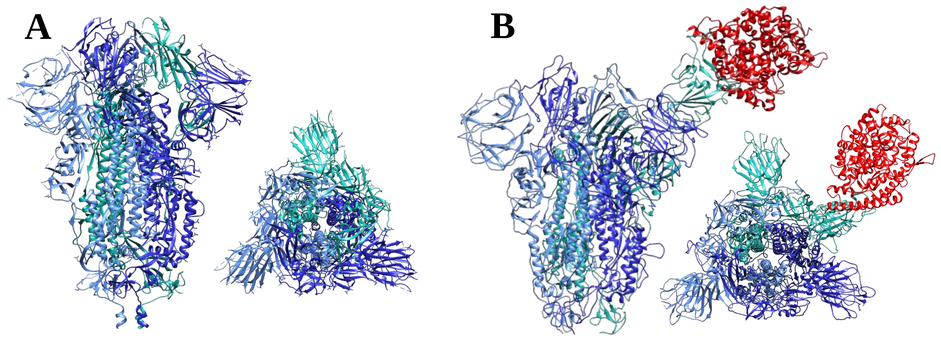

Figure 2: Three dimensional structure of SARS-CoV-2 S protein bound to receptors. (A) SARS-CoV-2 spike protein in unbound, "closed" positon (PDB: 6VXX). (B) SARS-CoV-1 spike protein (blue) in "open" positon (PDB: 6ACK) bound to functional receptor ACE-2 (red) at the CTD of S1. This view is representative of the conformation of most coronavirus S proteins when bound to their functional receptors.

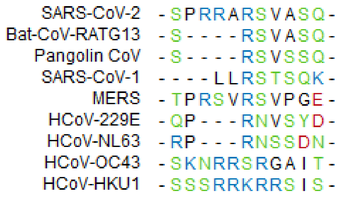

Figure 3: Alignment of S1/S2 cleavage site in various coronavirus strains. The S1/S2 cleavage site aligned at Arginine (R) residues of human coronaviruses and Bat-CoV-RATG13 and pangolin CoV thought to be linked to the Covid-19 outbreak.

Discussion

From the economic impacts in the swine, poultry, and beef industry, to the devastation witnessed by small animal veterinarians and pet owners with cases of FIP, to the current pandemic we are all experiencing, coronaviruses have a history of shaping the past, present, and future. While the SARS-CoV-2 outbreak was a shock to the general public, the emergence of another SARS-related coronavirus has been predicted by researchers for years since SARS outbreaks. The SARS-CoV-2 has been a devastating pandemic for several reasons; like SARS-CoV and MERS, it primarily affects the lower respiratory tissues and can induce severe pneumonia, unlike SARS-CoV and MERS, it has markedly higher transmissibility between humans. This higher transmissibility of SARS-CoV-2 seems to be associated with high levels of viral replication and shedding from the upper respiratory tract, and a higher binding affinity to the receptor ACE2. This high binding affinity is thought to be due to the cleavage of S1 and S2 by host furin as a result of the presence of a multibasic arginine residue cleavage site (Figure 3), facilitating the protein from the closed to the open conformation where it can bind to ACE2[7] (Figure 2).

Currently there is extensive research involved in vaccine development for the novel SARS-CoV-2 virus, and most of approach is targeting S protein including viral vectors, DNA or RNA expressing S protein, subunit S protein (such as full S trimer in the "closed" conformation)[29,30]. Because antibodies against S protein could neutralize coronavirus infection by interfering receptor binding, S protein is excellent target for therapeutics. Numerous neutralizing monoclonal antibodies (Mab) have been developed for the COVID-19 treatment[31]. Understanding this fundamental biology should help find solutions for preventive and therapeutic measures for current and future coronavirus pandemics.

Acknowledgement

This work was funded by the National Institutes of Health (R01AI130092). We also thank the American Veterinary Medical Association/American Veterinary Medical Foundation for their generous scholar support through the 2nd Opportunity Scholarship.

References

[1]Corman et al. (2018). *Adv Virus Res,100*. [2]Benvenuto et al. (2020). *J Med Virol*, *92*(4). [3]Hu et al. (2017). *PLoS Pathog*, 13(11). [4]Lau et al. (2020). Emerg Infect Dis, 26(7). [5]Wong et al. Preprint (2020). bioRxiv. [6]Shang et al. (2020). *PLoS Pathog, 16*. [7]Hoffman et al. (2020) *Mol Cell*, *78*(4). [8]Decaro. (2011). Alphacoronavirus¹. In: Tidona C., Darai G. (eds) The Springer Index of Viruses. Springer, New York, NY. [9]Li et al. (2019). *Elife*, *8*. [10]Hofmann et al. (2005). *Proc Natl Acad Sci USA*, *102*(22). [11]Delmas et al. (1992). *Nature*, *357*(6377). [12]Mora-Díaz et al. (2019). *Front Vet Sci*, *6*(53). [13]Dong et al. (2015). *Intervirology*, *58*(2). [14]Tekes et al. (2016) *Adv Virus Res*, *96*. [15]Holzworth. (1963). *Cornell Veterinarian*, *53*. [16]Decaro. (2011). Betacoronavirus¹. In: Tidona C., Darai G. (eds) The Springer Index of Viruses. Springer, New York, NY. [17]Szczepanski et al. (2019). *Viruses*, *11*(4). [18]Prabakaran et al. (2004). *Biochem Biophys Res Commun*, *314*(1). [19]World Health Organization. Novel coronavirus. Available from: https://www.who.int/westernpacific/emergencies/novel-coronavirus. [20]Letko et al. (2020). *Nat Microbiol*, *5*(4). [21]World Health Organization. Middle East respiratory syndrome coronavirus (MERS-CoV). Available from https://www.who.int/en/news-room/fact-sheets/detail/middle-east-respiratory-syndrome-coronavirus-(mers-cov). [22]Raj et al. (2013). *Nature*, *495*(7440). [23]Pratelli. (2006). *Vet Res*, *37*(2). [24]Menachery et al. (2020). *Nat Med*, *26*(7). [25]Woo et al. (2006). *Virology*, *351*(1). [26]Yang et al. (2014). *Proc Natl Acad Sci U S A*, *111*(34). [27]Decaro. (2011) Gammacoronavirus¹. In: Tidona C., Darai G. (eds) The Springer Index of Viruses. Springer, New York, NY. [28]Wickramasinghe et al. (2011). *J Virol*, *85*(17). [29]Pandey et al. (2020). *Life Sci,256*. [30]Tian et al. (2020). [31]Zost et al. (2020). *Nature,10*.