Research Open

Journal of Molecular Genetics
Volume 3 Issue 2

Perspective Article

Does a commensal relationship exist between coronaviruses and some human populations?

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Received: March 31, 2020; **Accepted:** April 13, 2020; **Published:** April 20, 2020

Abstract

Coronaviruses enter lung tissue via the ACE2 receptor, which varies structurally among human populations. In particular, the Chinese population has fewer variants that bind weakly to the coronavirus S-protein. This global variation suggests that the ACE2 receptor has coevolved with different environments, some of which have favored susceptibility to infection of lung tissue by coronaviruses. It has been argued that respiratory viruses boost the immune response of lung tissue and thereby prevent more serious pulmonary diseases, like tuberculosis, pneumonia, and pneumonic plague. This preventive effect has been shown with other viral pathogens, notably γherpesvirus 68 and cytomegalovirus. Some human populations may have therefore gained protection from severe respiratory infections by becoming more susceptible to mild respiratory infections, such as those normally caused by coronaviruses. This commensal virus-host relationship would have been especially adaptive wherever respiratory pathogens could easily propagate, i.e., in crowded environments, where many people live in proximity not only to each other but also to animal sources of infection. In regions that have long had crowded environments, natural selection may have favored susceptibility to infection by coronaviruses, which are normally mild in their effects, as a means to maintain a strong immune response to deadly pulmonary diseases.

Keywords: *ACE2, China, coronaviruses, respiratory viruses, tuberculosis*

Coronaviruses were not considered highly pathogenic until the emergence of SARS in 2002. Although previous strains could be highly infectious, the infection itself was normally mild, i.e., a common cold. The current "novel" strain has raised concern because it is as contagious as the common cold but much more pathogenic.

Coronaviruses infect lung tissue via the ACE2 receptor. This receptor varies structurally among human populations, notably in its ability to bind to such viruses and facilitate their entry into lung tissue. A study of 1,700 alleles in the *ACE2* gene region found major differences in allele frequency not only between Asians and other human groups but also between different Asian groups. In particular, the Chinese population has fewer alleles that code for weak binding to the coronavirus S-protein [1]. Different *ACE2* alleles are also associated with differences in susceptibility to diabetic retinopathy, an eye disease with a distinct global pattern of prevalence: 22% in Italy, 23% in China, 30% in the United Kingdom, and 40% in the United States [2].

Chinese lung tissue may therefore be especially susceptible to coronavirus infection, although the evidence remains controversial. One study, after identifying certain cells with high concentrations of the ACE2 receptor, showed that such cells were over five times more numerous in the lung tissue of an Asian donor than in the lung tissue of Euro American or African American donors; however, the entire sample had only one Asian donor [3]. Another study failed to find significant differences in *ACE2* gene expression between Asian and Caucasian lung tissue [4]. Both studies suffer from the broadness of the term "Asian," which covers a wide range of populations that differ from each other in many ways, notably in the structure of the ACE2 receptor.

Ethnic differences are also suggested by data on the prevalence of bronchiectasis, which is often caused by respiratory viruses [5]. In the United States, the prevalence is 2.5 to 3.9 times higher among Asian Americans than among Euro or African Americans [6]. Again, the term "Asian" is problematic. A high prevalence has likewise been found in Korean adults [7].

While it is not surprising that some human populations have adapted to the presence of certain pathogens by becoming more resistant, the population in this case has become less resistant, as if it actually benefits from infection by respiratory viruses. Some immunologists have suggested that such viruses boost the immune response of lung tissue and thereby prevent more serious pulmonary diseases, like tuberculosis, pneumonia, and pneumonic plague [8]. This preventive effect has been shown with other viruses. When mice are infected with γherpesvirus 68, which is similar to Epstein-Barr virus, there is production of large quantities of IFN-γ and activation of macrophages that protect against subsequent infection by *Listeria monocytogenes*, *Mycobacterium tuberculosis*, and *Yersinia pestis* [9,10]. Infection with cytomegalovirus likewise protects against *Listeria monocytogenes* and *Yersinia pestis* [9]. Other viruses may have similar commensal relationships with human hosts, but little is still known

about the benefits the host would gain from their presence [11,12]. Recent work suggests that commensal viruses contribute to intestinal health [13].

Some human populations may have therefore gained protection from severe respiratory infections by becoming more susceptible to infection by coronaviruses, which are normally mild in their effects. This commensal virus-host relationship would have been especially adaptive wherever respiratory pathogens posed a major threat to health. As one team of researchers suggested: "human γHV-infection may be an important but unrecognized factor which modifies TB [tuberculosis] outcome, particularly in high TB burden countries where most children acquire EBV [Epstein-Barr virus] by 3 years of age" [10].

Tuberculosis has historically caused much mortality, particularly in crowded social environments:

> Crowd diseases are generally highly virulent and depend on high host population densities to maximize pathogen transmission and reduce the risk of pathogen extinction through exhaustion of susceptible hosts. Many crowd diseases emerged during the Neolithic Demographic Transition (NDT) starting around ten thousand years ago (kya), as the development of animal domestication increased the likelihood of zoonotic transfer of novel pathogens to humans, and agricultural innovations supported increased population densities that helped sustain the infectious cycle. The marked expansion of MTBC [*Mycobacterium tuberculosis* complex] during the NTD, but not during earlier human expansion events, suggests that the success of this pathogen was primarily driven by increases in human host density, which is typical of crowd diseases [14].

Tuberculosis became prevalent at an early date in China, approximately six to eleven thousand years ago [14]. This time frame is consistent with China's expansion of agriculture, domestication of animals for food, and emergence of large communities. In a crowded environment, where many people live in proximity not only to each other but also to animal sources of infection, natural selection would favor different ways to boost the immune response of lung tissue. One way would be to increase susceptibility to mild respiratory infections, such as those normally caused by coronaviruses. This commensal relationship may explain why China was less affected by the Spanish flu of 1918-1920 [15]. Since that time, the Chinese population may have unknowingly become less resistant to severe respiratory infections because mild respiratory infections have become less prevalent, through improvements in public health and reduction of household size.

This kind of gene-culture coevolution probably happened not only in China but also in other regions with a long history of animal domestication and crowded environments, such as the Indo-Gangetic Plain, the Fertile Crescent of the Middle East, and the Mediterranean Basin [16]. In all of these regions, natural selection may have increased susceptibility to infection by coronaviruses, as a means to maintain a strong immune response to deadly respiratory pathogens.

Perhaps this commensalism explains why COVID-19 has been more severe in southern Europeans than in northern Europeans. One might expect the opposite: the severity of infection would increase with increasing latitude. After all, a respiratory virus should be more contagious under conditions of lower temperature, lower humidity, and lower solar UV. Northern Europeans, however, have coevolved with animal domestication and crowded environments for a shorter time. The virus may be more contagious among them, but its entry into lung tissue is not facilitated to the same extent.

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Citation:

Peter Frost (2020) Does a commensal relationship exist between coronaviruses and some human populations? *J Mol Genet* Volume 3(2): 1-2.