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Letter to the Editor General Surgery

Another perspective for COVID-19 pandemic: Angiotensin-converting enzyme 2 and ethnicity

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Angiotensin-Converting Enzyme 2 (ACE2) is a gene placed in the Xp22 region of the X chromosome containing 18 exons spanning 39.98 kb of DNA [1]. The ACE2 receptor is a captopril insensitive carboxypeptidase containing 805 amino acids with a 17-amino-acid N-terminal signal peptide and a C-terminal membrane anchor. ACE2 catalyzes the conversion of angiotensin-I into angiotensin 1–9 and angiotensin-II into angiotensin 1–7, which is a vasodilator. This phenomenon plays a main role in ensuring the homeostasis of blood pressure. Although the mRNA of ACE2 is found in all organs, a vast majority of the protein expression is made by lung alveolar epithelial cells, enterocytes, endothelial cells of arteries and veins, and arterial smooth muscle cells of the lungs [2]. The entrance of SARS-CoV-2 into the host cell is dependent on ACE2, which provides receptors to the viral spike glycoprotein, and on the serine protease TMPRSS2 genes, which allow the integration of the host cell membrane and viral membrane [3].

In addition to acting as a receptor for SARS-CoV-2, ACE2 also plays an significant role in the process of the pathophysiology of the virus in the lungs and other organs. ACE2 expression is affected at different levels by many diseases, such as hypertension, diabetes, cardiomyopathy and renal diseases. ACE2 plays a protective role in the kidney; accordingly, a decrease in ACE2 expression leads to the development of renal diseases. The presence of ACE2 in lung progenitor cells suggests that the virus may interfere with lung regeneration and cause damage to the lungs [4].

Various studies concluded that angiotensin-II was involved in interstitial fibrosis, endothelial dysfunction, strengthening inflammation, and increasing oxidative stress and coagulation. SARS-CoV-2 infection is thought to interfere with the adaptive immune system by activating macrophages and stimulating cytokines, such as IL-6 and TNF-alpha. ACE2 is believed to reduce the hazardous health consequences of angiotensin-II not only by breaking down angiotensin-II but also by promoting the formation of the anti-inflammatory angiotensin 1,7, which offers protection from fibrosis and provides an antithrombotic effect because of the release of NO and prostacyclin. There is evidence that SARS-CoV and SARS-CoV-2 enter cells by causing the internalization of the ACE2 receptor, thereby causing the down-regulation of the ACE2 receptor, which leads to increased

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lung damage. When interpreting the effects of ACE2 on SARS-CoV-2 infection, the immune system of the host, viral invasion, genetic predisposition, hyper-inflammation, and thrombosis should be evaluated together [5].

It is believed that the polymorphisms of ACE2 can play a role in susceptibility to infection and the overlapping of the infection with other diseases (such as hypertension). ACE2 polymorphism was associated with hypertension, diabetes mellitus, cerebral stroke, septal wall thickness, coronary artery diseases, and ventricular hypertrophy. Given that people living in the northern regions of China responded more strongly to the cold pressure test than those in the southern regions did, which helps detect the polymorphism of ACE2, this is perhaps proof that different weather conditions may play a role in the polymorphism of ACE2 through adaptive selection over generations. Although low ACE2 activity may seem to be a protective factor because it reduces the penetration of the virus into the cell in COVID-19 infection, critical losses in ACE 2 function are known to be correlated with cardiorespiratory insufficiency [2]. Studies show that ACE2 expression increases in people suffering from SARS-CoV, MERS-CoV, and H1N1 Influenza infections, which suggests that people suffering from these infections become more prone to COVID-19 infection [6].

When the genetic expression risk scores of 2,504 subjects from five different populations were calculated for ACE2 and TMPRSS2 genetic variants using the data from the 1000 Genomes Project, a significant difference was observed between these natives (ANOVA $P<0.0001$ for both male and female groups). The highest expression of the ACE2 gene was observed in South Asian and East Asian natives, while the lowest expression was found in African natives. These results suggest that the transmission, severity, course and prognosis of SARS-CoV-2 and the expressions of ACE2 and TMPRSS2 can be in different forms in different populations. The genetic predisposition of the African population to low expression of ACE and TMPRSS2, which are vital to the penetration of the virus into the human cell, may predict a lower number of COVID-19 cases in Africa. Howbeit, it should be noted that non-genetic factors were not assessed in this study [3].

A study comparing the polymorphisms in the ACE2 genes of Caucasians and Asians found four major missense variants, two of which were K26R and I468V, which significantly affect the penetration of the virus into the cell. The K26R variant was closely related to the peptidase domains, to which the spike glycoprotein (S protein) in the receptor binding zone of SARS-CoV-2 is directly linked. Caucasians tend to have the K26R mutation, while Asians tend to have the I468V mutation. In silico studies have shown that these two mutations may affect the connection among the S protein and ACE2 by slightly increasing the energy for free binding and slightly reducing the binding affinity. An examination of different populations revealed that the genetic diversity of ACE2 could vary among ethnic groups; however, because of the low percentage of such differences, the predisposition to COVID-19 infection and its effect on the severity of the disease is not yet clear. Although no significant difference was found in ACE2 expression between the sexes, men are known to have worse prognoses and complications than women do [7].

When examining the rate of ACE2 expression in the lung tissues of people with and without lung adenocarcinoma using data from the Cancer Genome Atlas, no correlation with race and sex was found, while a positive increasing correlation with age was found (Pearson correlation value $R=0.13$, $P=0.0003$, $N=835$). Researchers argue that the fact that older people are more affected by SARS-CoV-2 can be partly explained by this result. This study showed that the average ACE2 expression was not significantly different in Asians, Africans, and Europeans. This study suggests that the recurrent coronavirus outbreaks in China can be explained by the diversity of the coronaviruses in the region and the variety of their animal hosts or by the Chinese food culture [8].

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