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New Approaches in the Treatment of Covid-19 Virus

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Abstract

By increase the incidence of infection of coronavirus disease 2019 (COVID-19), diagnostic factors for early identification of high-risk individuals are important. On the other hand, more infections are in older patient, comorbidities, and male patients. Identification of components that related to severity of COVID-19 contributed to ACE2 and TMPRSS2 genes, which are critical for viral infection. It was found that adding enzyme copy, hrsACE2, lures the virus to attach itself to it instead of the actual cells… It inhibits the virus from infecting the cells in the lungs and other organs.

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HrsACE2

Using cell cultures, Scientists distinguished that by adding a recombinant product of ACE2, called human recombinant soluble angiotensin-converting enzyme 2 (hrsACE2), COVID-19 was inhibited to inter cells. this finding shows that hrsACE2 had a dose dependent effect of viral growth of SARS-CoV-2 and was able to reduce it by a factor of 1,000 to 5,000 in cell cultures [1].The researchers also used blood vessel and kidney organoids to demonstrate that SARS- CoV-2 can directly infect and multiply within these tissues, a possible cause of the multi-organ failures and cardiovascular damage seen in severe COVID-19 cases. The addition of hrsACE2 also reduced the SARS-CoV-2 infection in these organoids [1].

In cell cultures analyzed in the current study, hrsACE2 inhibited the coronavirus load by a factor of 1,000-5,000 [1]. "These studies have new aspect into how SARS-CoV-2 infects the cells of the body, including in blood vessels and kidneys [1]. It was believed that adding this enzyme copy, hrsACE2, lures the virus to attach itself to the copy instead of the actual cells… It distracts the virus from infecting the cells to the same degree and should lead to a reduction in the growth of the virus in the lungs and other organs." While the research has so far been limited to cell cultures and organoids, Aperion Biologics has showed that it plans to conduct a clinical pilot study on infected COVID-19 patients in China with its drug APN001, which contains hrsACE2 as an active substance. APN001 was designed and has been tested in Phase II trials for lung disease [2]. The researchers highlighted that their experiments have only examined the drug's effect during the primary stages of SARS-CoV-2 infection and that further research is needed to determine if it is also effective during later stages of disease development.

The expression levels of the SARS-CoV-2 spike protein receptor, angiotensin-converting enzyme 2 (ACE2) may also determine susceptibility to SARS-CoV-2-inflicted damage. Trans membrane serine protease 2 (TMPRSS2) primes the viral spike protein, allowing for the potent binding of ACE2. Both are known to be highly expressed in healthy epithelium, with lower levels in epithelial cells in the colon. It has been shown the mucosal ACE2 and TMPRSS2expression in the colon and ileum in IBD, and identify the critical determinants of altered expression [3].

ACE2 and TMPRSS2 Variants and Expression

Italy, Europe, and the entire world are facing one of the worst medical emergencies spanning centuries, the coronavirus disease 2019 (COVID-19) pandemic due to infection by SARS-CoV- 2 virus. The early identification of risk factors for COVID-19 is an urgent medical need to provide the appropriate support to patients, including access to intensive care units. Presently, Italy has one of the highest rate of SARS-CoV-2 infection in the world among large countries, with 143 cases per 100,000 people, the highest number of deaths and the highest mortality rate, 10.5% vs. an average value of 4.6% .These data may have different explanations, including: 1) the number of tests performed, 2) the structure of the population (Italy has the oldest population in Europe,) the percentage of smokers, even though no significant association was found between smoking and severity of COVID-19 in a very recent study on the Chinese population, the possible existence of a different virus strain, the concentration of severe cases in a limited region of the country, potentially overwhelming the available intensive care units, as well as differences in environmental factors (e.g. air pollution). However, there could also be some peculiar genetic characteristics of the Italian population that may have an impact on the susceptibility to viral infection, the disease severity, and the number of patients shedding huge amounts of virus. What is unquestionable is a more severe course of the disease associated with older age and high number of comorbidities and with the male sex (male:female ratio in case fatality rate among Italians 1.75, data from the Italian National Institute of Health a feature shared with the 2003 SARS epidemic and MERS.3-5 Indeed, while men and women have similar susceptibility to both SARS-CoV-2 and SARS-CoV, men are more prone to have higher severity and mortality, independently of age.[4] Among the many possible factors impacting on sex-related differences in disease manifestations, including the fact that females are known to mount a stronger immune response to viral infections compared to males due to more robust humoral and cellular immune [5]. It was recently demonstrated that both angiotensin I converting enzyme 2 (ACE2) and the

transmembrane protease, serine 2 (TMPRSS2) are crucial for SARS-CoV-2 entry into host cells.[5] While ACE2 is the main receptor for the spike (S) protein of bothSARS-CoV and SARS-CoV-2, mediating viral attachment to target cells, TMPRSS2 cleaves protein S at the S1/S2 and the S2 'sites, allowing fusion of viral and cellular membranes.[5] Both genes have been proposed to modulate susceptibility to SARS-CoV,19 and are good candidates to mediate sex-related effects: ACE2 is located on the X chromosome, while TMPRSS2 expression is responsive to androgen/estrogen stimulation. human pathogenic coronaviruses (severe acute respiratory syndrome coronavirus (SARS-CoV) and SARS-CoV-2) bind to their target cells through angiotensin-converting enzyme 2 (ACE2), which is expressed by epithelial cells of the lung, intestine, kidney, and blood vessels [5]. The expression of ACE2 is substantially increased in patients with type 1 or type 2 diabetes, who are treated with ACE inhibitors and angiotensin II type-I receptor blockers (ARBs). Hypertension is also treated with ACE inhibitors and ARBs, which results in an upregulation of ACE2.ACE2 can also be increased by thiazolidinediones and ibuprofen.These data suggest that ACE2 expression is increased in diabetes and treatment with ACE inhibitors and ARBs increases ACE2 expression [5]. Consequently, the increased expression of ACE2 would facilitate infection with COVID-19. therefore hypothesise that diabetes and hypertension treatment with ACE2-stimulating drugs increases the risk of developing severe and fatal COVID-19.

If this hypothesis were to be confirmed, it could lead to a conflict regarding treatment because ACE2 reduces inflammation and has been suggested as a potential new therapy for inflammatory lung diseases, cancer, diabetes, and hypertension. A further aspect that should be investigated is the genetic predisposition for an increased risk of SARS-CoV-2 infection, which might be due to ACE2 polymorphisms that have been linked to diabetes mellitus, cerebral stroke, and hypertension, specifically in Asian populations. Summarising this information, the sensitivity of an individual might result from a combination of both therapy and ACE2 polymorphism. We suggest that patients with cardiac diseases, hypertension, or diabetes, who are treated with ACE2-increasing drugs, are at higher risk for severe COVID-19 infection and, therefore, should be monitored for ACE2-modulating medications, such as ACE inhibitors or ARBs. And it was not found any evidence to suggest that antihypertensive calcium channel blockers increased ACE2 expression or activity, therefore these could be a suitable alternative treatment in these patients [6].

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