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Letter to the Editor

The role of angiotensin-converting-enzyme 2 in the age- and sex related poor prognosis of COVID-19. A comment on recent findings on novel coronavirus infection by SARS-CoV-2

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1. INTRODUCTION

Recent epidemiological reports on actual coronavirus epidemic showed that elderly and male patients presented the worst prognosis. Because of many similarities, pathophysiological studies on SARS were very important in understanding the mechanisms of the current epidemic. In particular, several Authors highlighted the central role of angiotensin-converting enzyme (ACE2), both as a gateway to the virus and for disease progression.

2. AIM

In this letter, we wanted to investigate the pathogenetic role of ACE2 in the various stages of coronavirus infection, showing the similarities between SARS and current COVID-19. Despite the lack of evidences, we also suggested the link between COVID-19 and negative prognosis in male and elderly patients, analyzing animal model studies.

3. MATERIAL AND METHODS

We analyzed recent epidemiological reports to evaluate clinical factors associated with a poor prognosis in COVID-19. We collected available evidence regarding the role of ACE2 in coronavirus infection, analyzing analogies between SARS and current COVID-19. Due to the scarcity of clinical studies, we analyzed animal models to evaluate pathogenesis of ACE2 in all phases of coronavirus infection, and to understand its behavior in categories associated with a poor prognosis.

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4. DISCUSSION

Novel coronavirus disease (COVID-19) identifies the recent betacoronavirus epidemic, named Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2), which began in China at the end of December 2019, promoted by the World Health Organization as a pandemic at the time the article is composed.

Recent epidemiological reports on the Chinese population provided clinical and laboratory characteristics of patients affected by COVID-19, highlighting the centrality of symptoms such as fever, respiratory disorders, leukopenia and an increase in transaminases and lactate dehydrogenase (LDH).[1,2] Severity of current infection is evidenced by high need for hospitalization, and in particular, the need for intensive care unit (ICU) admission.[1,2] Other reports also outlined a risk profile for the patient with a severe course; in particular, Authors underlined the worst prognosis of elderly and male patients, as well as a high incidence of infection among hypertensive patients.[3] Pathophysiological studies on COVID-19, outlined significant similarities with the previous SARS pandemic, caused by betacoronavirus, named SARS-CoV.[4] In particular, researchers highlighted that both pathogens use angiotensin-converting enzyme (ACE) 2 as a vector for entry into the cell.[5]

ACE2 is a type I membrane-anchored zinc carboxypeptidase, a human homologue of ACE, which is an important regulator of the renin-angiotensin system.[6] The enzyme is part of the ACE2/angiotensin (1–7)/ Mas receptor (ACE2/Ang (1–7)/Mas receptor) pathway, an alternative to the ACE/angiotensin II/ angiotensin receptor 1 (ACE/Ang II/AT1R) cascade, which produces beneficial vasoactive peptides, and counterbalances the negative effects of ACE/Ang II/AT1R cascade.[7] Virus binding site was identified in a densely glycosylated spike (S) protein, a trimeric class I fusion protein, which undergoes significant structural changes at the time of the union between the cell wall and the virus[8]. Harmful action of the virus on the infected tissue can be at least partially explained by the downregulation of the ACE2 and the blockage of the cascade that follows. Distribution of the enzyme is ubiquitous in the body; In particular, expression in alveolar epithelium, bronchiolar epithelium, endothelium and smooth muscle cells of pulmonary vessels, may take into account a large part of the symptoms related to SARS-CoV-2 infection.[9] Age and gender-related changes in expression and activation of the ACE2 may contribute to explain different clinical responses to coronavirus infection. Evidence showed that advanced age and male sex have been associated with a worse outcome of COVID-19. Previous studies on SARS, performed on animal models, could provide valuable clues. Xie et al. showed that levels of ACE2 are reduced with advancing age, describing a significant age-specific decline of ACE2 expression in male and female rat lung; although the concentration of ACE2 does not vary significantly between the two genders in young and middle-aged mice, males experienced a more rapid and significant decline in old age, and especially in lung tissue.[10] Similar data from a study conducted on F344 rats by Nagata et al. confirmed previous results.[11] Social dynamics could explain the high incidence of infection in younger people, described in some reports, rather than the high levels of ACE2.[12] Furthermore, the reduced functionality of ACE2 is associated with an increase in the inflammatory response through the cytokines interleukin 6 (IL-6), interferon (IFN)-γ, TNF (tumor necrosis factor)-α and interleukin (IL)-1 β. An early and explosive cytokine response was described in elderly animal models, and it was associated to both greater severity and a worse prognosis; a similar uncontrolled inflammatory response has not been demonstrated in younger subjects. If the downregulation of ACE2 contributes to directly damage the infected tissue, inflammatory hyper-response extends the damage also to non-directly infected tissues. The role of S-glycoprotein in relation to the virulence of the pathogen has been deeply investigated; a variability in tropism and functionality was associated to advancing age, and related to disease severity.[13] The notion that hyper-expression of ACE2 may hinder, rather than promote, coronavirus infection seems paradoxical. However, previous evidences from human immunodeficiency virus (HIV) studies reported that increase in expression levels of the HIV binding sites CCR5 and CD4 protect from, rather than stimulate, HIV virulence. Michel et al. identified that the early gene product Nef was able to elevate viral replication in vivo and thus promotes AIDS pathogenesis, reducing the expression of the receptor complex (14). However, further studies are needed to understand if the current mechanism is also valid for coronavirus.

5. CONCLUSION

Animal model data demonstrate the centrality of ACE2 alterations in the pathogenesis of SARS, and given the similarity with SARS-CoV-2, these data could also be valid for COVID-19. In particular, the worst clinical course and the poor prognosis associated with old age and male sex could be the consequence of these variables on the ACE2 enzyme. Better understanding how to restore the balance between ACE and ACE2, could provide a therapeutic opportunity. Due to the lack of direct human model data, further studies are needed both to understand in depth the pathogenesis of COVID-19 damage, and to indicate therapeutic strategies.

Conflict of interest

None.

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