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LETTER TO THE EDITOR

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Covid-19 and Angiotensin Converting Enzyme 2(ACE2)

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ABSTRACT

Renin-angiotensin system (RAS) is a signaling pathway for regulation of blood pressure, blood volume, natriuresis, and other vascular functions. In coronavirus infection disease (Covid-19), SARS-CoV-2 binds ACE2 which is highly expressed by the epithelial cells of blood vessel, intestine and lung. The expression of ACE2 is augmented by angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), ibuprofen, statins, thiazolidinedione and by cigarette smoking. Pulmonary ACE2 is seems to be a protective defense pathway during acute respiratory distress syndrome (ARDS). Polymorphism of ACE2 has been associated with different cardio-metabolic disorders, thus implication of ACE2 and angiotensin receptor type 2 (ATR2) receptors in Covid-19-induced pneumonia should be considerably regarded with ACE2 polymorphisms. Covid-19 leads to significant lung injury through down-regulation of ACE2, which is attenuated by administration of angiotensin-receptor blockers (ARBs). Therefore, ACE2 receptors are protective against SARS-CoV-2 pathogenesis. Therefore, ACE2 is regarded as an important entry-point for SARS-CoV-2 and up-regulation of ACE2 by ACEIs, ARBs and during development of cytokine storm is regarded as a protective compensatory mechanism to overcome hyperinflammatory-induced ALI and ARDS.

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Background

Renin-angiotensin system (RAS) is a signaling pathway for regulation of blood pressure, blood volume, natriuresis, and other vascular functions. RAS consist of different effectors peptides that control the dynamic vascular functions [1]. Angiotensinogen from the liver is converted to angiotensin I (AngI), which is converted to angiotensin II (AngII) by Angiotensin converting enzyme 1(ACE1). AngII activates two types of receptors which are ATR1 (vasoconstrictor) 90% and ATR2 (vasodilator) 10%. The overall effect of AngII is vasoconstriction with sympathetic activation and aldosterone release. Excess of AngII is metabolized by ACE2 into vasodilator Ang (1-7) which act on specific receptor called MAS receptor [2].

In coronavirus infection disease (Covid-19), SARS-CoV-2 binds ACE2 which is highly expressed by the epithelial cells of blood vessel, intestine and lung. The expression of ACE2 is augmented by angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), ibuprofen, statins, and thiazolidinedione and by cigarette smoking [3].

Zhou et al found that the SARS-CoV-2 genome is 96% identical to the bat coronavirus (Cov), so; spike glycoprotein (SP) and receptor binding domain (RBD) of both SARS-CoV-2 and bat CoV bind ACE2, which might explain the cross-species transmission, from bat to human and vice versa [4]. In addition, the affinity of Covid-19-RBD to ACE2 is approximately 10-20 time more than of SARS-CoV.

The activity of RAS is highly functioning in the lung, which is the main source of circulating AngII due to higher expression of ACE. Lung ACE2 controls the balance of RAS activation through regulating AngII/Ang 1-7 ratio. Local pulmonary AngII provokes vascular permeability and causing pulmonary edema [5]. However, in acute respiratory distress syndrome (ARDS), activation of RAS is necessary to maintain oxygenation since' ACE2 knockout mice illustrated more sever pulmonary damage as compared with controls. Thereby, pulmonary ACE2 is seems to be a protective defense pathway during ARDS [6].

In addition, ACE2 has an important anti-inflammatory action

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and so; ACE2 therapy is effective in treatment of hypertension and diabetic nephropathy through attenuation of AngII-induced inflammation and oxidative stress [7]. Even so, recombinant ACE2 is effective in the management of animal model ARDS and inhibition of ACE2 may lead to the fatal outcomes due to reduction of vasodilator Ang1-7. However, chronic intravenous administration of Ang1-7 or MAS agonists leads to vasodilatation independent of circulating AngII levels [8].

Depending on these observations, different studies illustrate that RAS inhibitors might be of value in the reduction of ARDS, respiratory failure and acute pneumonia that are induced by SARS-CoV-2 [9]. Though, Wang confirm that RAS inhibitors increase risk of Covid-19 due to up-regulation of pulmonary ACE2, this study recommend stopping of RAS inhibitors during Covid-19 outbreak [10]. Nonetheless, all of recruited patients with Covid-19 developed ARDS without any evidence of acute kidney injury (AKI). Thus, RAS system mainly ACE2/Ang1-7 grows to be the focus and meeting point of different researches to implicate this pathway in the pathogenesis of Covid-19. This study undergone severe criticism and regarded as a flawed study. However, Zhuang et al. confirm that up-regulation of ACE2 by cytokine storm facilitate SARS-CoV-2 entry [11].

Moreover, expression of ACE2 is higher in renal tubules than in lung tissues, nevertheless Covid-19 leads to ARDS in much higher than that of AKI suggesting other mechanism other than ACE2 binding in the pathogenesis of Covid-19. AT2 receptor is activated by ACE2 and Ang1-7 that oppose the activity of AT1 receptor [12]. Similarly, AT2 receptors are highly expressed in lung epithelial cells compared with kidney tissues. Pulmonary AT2 receptors mediate lung injury through augmentation of pulmonary inflammation and vascular permeability as well as development of pulmonary fibrosis. Consequently, pulmonary AT2 receptors are regarded as a novel pathway in Covid-19-induced pneumonia and ARDS [13]. This finding does not rule out the responsibility of ACE2, since activation of ACE2 by SARS-Co-V causes considerable activation of pulmonary AT2 receptors [8].

Amide myriad literature survey, polymorphism of ACE2 has been associated with different cardio-metabolic disorders, thus implication of ACE2 and AT2 receptors in Covid-19-induced pneumonia should be considerably regarded with ACE2 polymorphisms. Furthermore, expression of ACE2 might not be necessary for Covid-19 pathogenesis as the absence of SARS-CoV-2 in some ACE2 expressing cell types as well, this infection was observed in some cell line lacking ACE2, suggesting a vague pathway and co-factors might be necessary for human infection [14]. Surprisingly, Gurwitz found that pulmonary Covid-19 infection leads to significant lung injury through down-regulation of ACE2, which is attenuated by administration of ARB [15]. This study suggests the protective role of RAS inhibitors in Covid-19-induced ARDS. Thus, according to the guideline for the management of hypertension, RAS inhibitors should be used irrespective of Covid-19 infection, as sudden withdrawal of these therapeutic regimens may increase the risk of deleterious outcomes in critically ill patients.

At the heart of the dilemma, extensive researches are recommended to explore the specific role of ACE2 and RAS inhibitors during precarious COVID-19 worldwide outbreak.

Conclusion

Therefore, ACE2 is regarded as an important entry-point for SARS-CoV-2 and up-regulation of ACE2 by ACEIs, ARBs and during development of cytokine storm is regarded as a protective compensatory mechanism to overcome hyperinflammatory-induced ALI and ARDS.

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