Two hits to the renin-angiotensin system may play a key role in severe COVID-19

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Abstract
The spike glycoprotein on the virion surface docking onto the angiotensin-converting enzyme (ACE) 2 dimer is an essential step in the process of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in human cells—involves downregulation of ACE2 expression with systemic renin-angiotensin system (RAS) imbalance and promotion of multi-organ damage. In general, the RAS induces vaso-constriction, hypertension, inflammation, fibrosis, and proliferation via the ACE/Ang II/Ang II type 1 receptor (AT1R) axis and induces the opposite effects via the ACE2/Ang (1-7)/Mas axis. The RAS may be activated by chronic inflammation in hypertension, diabetes, obesity, and cancer. SARS-CoV-2 induces the ACE2 internalization and shedding, leading to the inactivation of the ACE2/Ang (1-7)/Mas axis. Therefore, we hypothesize that two hits to the RAS drives COVID-19 progression. In brief, the first hit originates from chronic inflammation activating the ACE/Ang II/AT1R axis, and the second originates from the COVID-19 infection inactivating the ACE2/Ang (1-7)/Mas axis. Moreover, the two hits to the RAS may be the primary reason for increased mortality in patients with COVID-19 who have comorbidities and may serve as a therapeutic target for COVID-19 treatment.

KEYWORDS
 coronavirush disease 2019, renin-angiotensin system, two hits

1 | INTRODUCTION

The first report related to the ongoing pandemic of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2), originated in Wuhan, China in early December 2019. Subsequently, COVID-19 rapidly spread across China and then globally within 2 months after the first confirmed COVID-19 case was reported outside of China, in Thailand, on 13 January 2020. The World Health Organization declared the outbreak to be a public health emergency of international concern on 30 January 2020, and then further elevated the level of emergency by recognizing it as a pandemic on 11 March 2020.1,2 Thus far, more than 3.5 million confirmed COVID-19 cases and more than 247 652 related deaths have been reported worldwide.2 Yan et al. reported that the trimer of the spike glycoprotein on the virion surface docking onto the angiotensin-converting enzyme (ACE) 2 dimer structure is an essential step in the attack by SARS-CoV-2 on human cells and leads to systemic organ injury.3,4 This SARS-CoV-2-ACE2 interaction has generated great interest in the development of renin-angiotensin system (RAS)-based therapeutic strategies for COVID-19.5

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2 | RAS

The RAS, a key hormone system, regulates blood pressure, fluid and electrolyte balance, and systemic vascular function particularly in maintaining plasma sodium concentration, arterial blood pressure, and extracellular volume. In most organs, RAS activation can result in hypertension, inflammation, cell proliferation, and fibrosis. Manipulating the RAS by stabilizing renin and angiotensin II (Ang II) levels and promoting ACE2 expression can prevent numerous chronic and acute diseases. The RAS signal transduction system is regulated by two main axes: (a) ACE/Ang II/Ang II type 1 receptor (AT1R) axis, which promotes vasoconstriction, hypertension, inflammation, fibrosis, and proliferation, and (b) ACE2/Ang (1-7)/Mas axis, which induces the opposite effects of ACE/Ang II/AT1R axis activation to inhibit any detrimental consequences (Figure 1).

3 | THE ROLE OF RAS IN COVID-19

Several studies have indicated that circulating Ang II levels are significantly higher in individuals infected with SARS-CoV-2 than in healthy individuals; thus, SARS-CoV-2 infection must cause tissue ACE2 downregulation with systemic RAS imbalance and thus promote multi-organ damage. SARS coronavirus (SARS-CoV) interacts with ACE2 via trimers of the SARS spike protein, a loop of which extends into a hydrophobic pocket of ACE2. In addition, the difference between SARS-CoV and SARS-CoV-2 is of only 380 amino acid substitutions, translating to differences only in five of the six important amino acids in the receptor-binding domain (RBD) of the viral spike protein. Both SARS-CoV-2 and SARS-CoV infect cells via viral spike protein-host ACE2 receptor contact, however, the RBD has significantly higher binding affinity to ACE2 receptors in SARS-CoV-2 than in SARS-CoV. Furthermore, the entry of SARS-CoV-2 into host cells induces ACE2 internalization and shedding, which increases Ang II and reduces Ang (1-7) levels, with a net increase in pro-inflammatory function relative to the anti-inflammatory function of RAS.

4 | ROLE OF RAS IN COVID-19 DEVELOPMENT IN PATIENTS WITH COMORBIDITIES

RAS activation induced by chronic inflammation stimulates pro-inflammatory and anti-inflammatory cytokine production in immune cells, which in turn upregulates the expression of RAS components and accelerates the formation of systemic and local Ang II. Blood Ang II levels are elevated in patients with chronic inflammatory diseases, such as pulmonary arterial hypertension, diabetes, and obesity. Moreover, elevated plasma Ang II levels are correlated with shortened survival in patients with cancer cachexia. In addition, senescent T cells are more sensitive to Ang II stimulation and have adverse effects on the target organ, in which senescent T-cell-derived IFN-γ may play a key role. These findings indicate that chronic inflammation and aging have complex but close relationship with activation of the ACE/Ang II/AT1R axis.

Patients with COVID-19 develop acute inflammatory diseases, such as SARS-CoV-2-induced acute respiratory distress syndrome. These patients, particularly those aged >65 years or with hypertension, diabetes, cardiovascular disease, chronic respiratory disease, low immune status, cancer, or obesity, have poor prognosis and may develop multiple organ failure. Furthermore, increased levels of obesity-related inflammatory cytokines possibly increase COVID-19 morbidity. Finally, patients with cancer might have an increased COVID-19 risk because they generally have systemic immunosuppression due to the malignancy and the administered anticancer treatments.

**FIGURE 1** Steady-state of the RAS under normal physiological conditions. The RAS signal transduction system is activated via the ACE/Ang II/AT1R axis; this promotes vasoconstriction, hypertension, inflammation, fibrosis, and proliferation. Studies on the biological functions of AT2R, a receptor of Ang II, are scant. Although AT2R activation induces the effects opposite to those of AT1R activation, AT2R expression is lower than AT1R expression in most adult tissues. Most functions of Ang II are performed via AT1R. The ACE2/Ang (1-7)/Mas axis induces the opposite effects to suppress the harmful effects of the ACE/Ang II/AT1R axis induction.
A recent cohort study on 45,000 confirmed cases in China reported a considerably increased mortality rate in patients with COVID-19 who had cardiovascular disease (10.5%), diabetes (7.3%), or hypertension (6.3%) compared with those who did not have these comorbidities (0.9%). In addition, an analysis of the medical records of 355 patients who died due to COVID-19 in Italy revealed that only 0.8% of these patients had no comorbidities. Moreover, of all 355 patients, approximately half had at least three comorbidities, approximately one-quarter had two comorbidities, and approximately one-quarter had one comorbidity; moreover, approximately 73.8% had hypertension, approximately 33.9% had diabetes, and approximately 30.1% had heart disease.

Therefore, we hypothesize that the higher mortality rate in patients with COVID-19 who have comorbidities may be attributable to the two hits to the RAS: The first hit originates from chronic inflammation activating the ACE/Ang II/AT1R axis, and the second hit originates from the COVID-19 infection inactivating the ACE2/Ang (1–7)/Mas axis. These two hits increase tissue damage and multiple organ failure risks in patients with SARS-CoV-2 infection (Figure 2).

**Figure 2** Two hits to the RAS by chronic inflammation and COVID-19 infection. The ACE/Ang II/AT1R axis of the RAS is activated through chronic inflammation, including hypertension, diabetes, obesity, and cancer. Furthermore, SARS-CoV-2 induces ACE2 internalization and shedding, which lead to inactivation of the ACE2/Ang (1–7)/Mas axis. Therefore, the two hits to the RAS may be the primary reason for the mortality rate being high among patients with COVID-19 who have comorbidities. In brief, the first hit originates from chronic inflammation activating the ACE/Ang II/AT1R axis, and the second hit originates from the COVID-19 infection inactivating the ACE2/Ang (1–7)/Mas axis.

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**CONCLUSION**

Regulation of the RAS may serve as a therapeutic target for COVID-19 treatment, and therefore, the underlying mechanism of its effects requires urgent clarification.

**CONFLICT OF INTEREST**

The authors declare no potential conflict of interest.
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