

The Role of the Renin-Angiotensin System in Severe Acute Respiratory Syndrome-CoV-2 Infection

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The scientific world has brought to the fore angiotensin-converting enzyme 2 (ACE2) for its pivotal role in the pathogenesis of novel coronavirus infectious disease (COVID-19). ACE2 is part of the renin-angiotensin system (RAS), an intricate interlinked system of regulatory mediators involved in the control of blood pressure and hemostasis of several organs. RAS has been implicated in the regulation of inflammatory pathways in models of lung injury and pulmonary vascular disease. Recently, physicians have suggested a possible concerning effect of ace inhibitors and angiotensin II (Ang II)-receptor blockers with the COVID-9 outbreak, as ACE2 is the host receptor required for cellular entry of severe acute respiratory syndrome (SARS)-CoV-2, the etiological agent of the current SARS.

ACE2 was discovered 46 years after [1] the first description of this enzyme by Skeggs et al. [2]. ACE is a protein produced in the endothelium of somatic tissues that catalyzes the

conversion from angiotensin I (Ang I) to Ang II, a potent vasoconstrictor, and degrades bradykinin, an inflammatory mediator with vasodilator propriety (Fig. 1a) [3].

ACE2 is both a membrane associated and secreted enzyme able to cleavage Ang I to 1–9 and Ang II to Ang 1–7. ACE2 has partial analogy with ACE. Analysis of the human genomic sequence shows that the metalloprotease catalytic domain of ACE2 is identical to ACE for 42% [1]. This evidence supports the hypothesis that the 2 genes may derive from a common ancestor. Similar to ACE, the expression of ACE2 has been found in many organs including the lung, heart, kidney, and testis [1]. However, vasopressor activity and response to commercially available antihypertensive drugs appear different in these two enzymes, despite their homologous catalytic domain. ACE2 is a counter-regulator of ACE and participates in the regulation of blood pressure decrease with the formation

of non-vasoactive Ang 1–9 and vasodilator Ang 1–7. In addition, ACE2 activity is not inhibited by ACE inhibitors [1, 4].

The key role of ACE2 in SARS-CoV-2 infection was established in 2003 during the first coronavirus outbreak in China. S1 domain of the SARS-CoV-2 (protein S1) mediates the entry of the virus into target host cells after binding with the transmembrane ACE2 receptor [5]. The virus has marked tropism for the respiratory tract, bowel, and heart cells, where the ACE2 expression is well-represented.

Data show that the severity of SARS-CoV-2 is unpredictable, and the clinical manifestations, especially respiratory symptoms, can quickly worsen even in paucisymptomatic subjects [6]. Initial data from Italy document that the infection is severe and carries high morbidity and mortality [7]. Lung involvement is the most severe complication, often evolving in acute respiratory distress syndrome

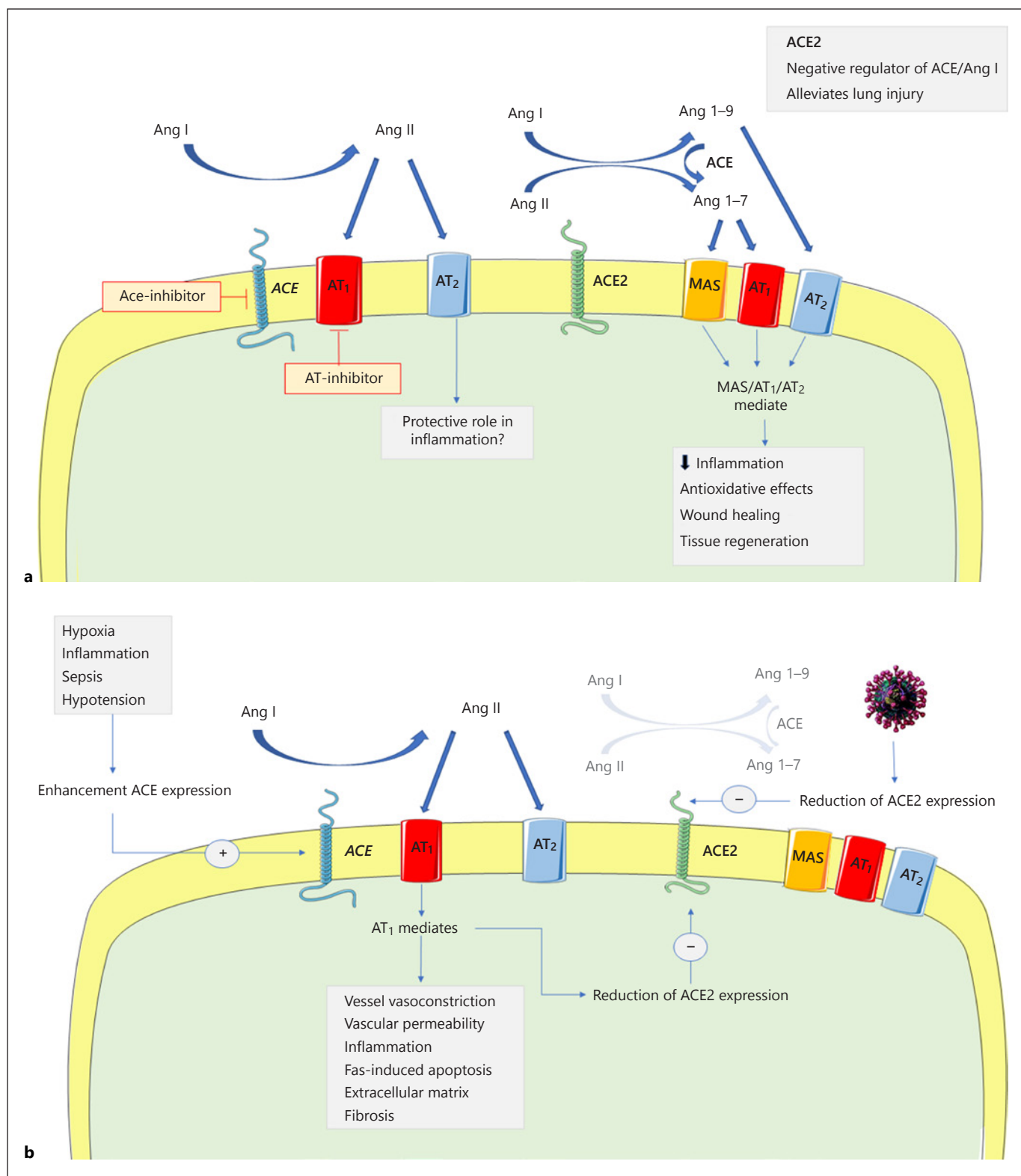


Fig. 1. a Representation of the RAS homeostasis in the lung. **b** Pathologic modulation of the RAS in SARS-CoV-2 infection. ACE, angiotensin-converting enzyme; Ang I, angiotensin I; Ang II, angiotensin II.

(ARDS), a devastating clinical syndrome with a high mortality rate (30–60%) [8]. There is a consensus that ACE2 is a key protective molecule in the development and maintenance of lung injury (Fig. 1b) [9]. An elegant experiment in mice showed that the loss of ACE2 expression resulted in lung edema, inflammatory cell infiltration, and hypoxia in different models of acute lung injury. Damage of the lungs led to an increase in the level of AngII that, in turn, drove downregulation of ACE2 through receptor AT1a. The authors also demonstrated that infusion of recombinant ACE2 significantly ameliorated lung injuries, findings that emphasized the protective role of ACE2 in the lungs [10].

We believe that multiple factors are implicated in the battle of the host against SARS-Cov-2 including immune response, comorbidities, early respiratory support, and modulation of inflammation. Regarding this latter variable, understanding the physiological regulation of the ACE2 pathway can help physicians for the management of SARS-CoV-2 infection. Variability of RAS activation in patient subgroups might explain the enormous variability in clinical manifestations.

ACE2 plays a twofold role in SARS-CoV-2 infection. The protective role of ACE2 from acute lung failure is antagonized by its crucial role in virus entry. Hence, the reduced expression of transmembrane ACE2, which theoretically minimizes the spread of the virus among cells, could negatively balance an augmented risk of ARDS in the infected people. It is not surprising that the disruption of ACE2 signaling pathway in lung cells is the main determinant of SARS-CoV-2 virulence. The targeted injury of fundamental respiratory epithelial cells involved in immunomodulation (Clara cells) and

maintaining of a functional environment and tissue regeneration (type II alveolar cells) probably supports the high prevalence of severe lung involvement complicated by ARDS.

Animal studies have demonstrated that SARS-CoV infection downregulates the expression of ACE2 in the lungs. The binding of circulating S protein to ACE2-expressing cells aggravates the model of lung injury resulting in severe acute respiratory failure [11]. Likewise, the SARS-CoV-2-mediated downregulation of ACE2 in humans could be the causative factor of the severe lung pathology. The evidence coming from clinical practice reports that the duration of illness in patients with lung involvement lasts much longer than the time necessary to mount an adequate host immune response against the virus. In this way, an excessive inflammatory respiratory response triggered by SARS-CoV-2 and maintained by dysregulation of the RAS system may be the principal pathologic mechanism in this infection and partly account for the disparity in the rate of morbidity and mortality of subjects affected by SARS-CoV-2. The high prevalence of elderly and the slightly higher incidence in males than women among subjects with worse outcomes [12] may be explained by dysregulation of ACE/ACE2 secondary to an imbalance in sex steroid hormones with age. Experiments conducted in organs other than lungs reported that a low level of testosterone has been associated with low ACE2 activity in heart tissue in rats [13, 14] and vice versa and estrogen increased myocardium expression of ACE2 in humans [15]. The high prevalence of diabetes status, constantly present among severely affected subjects [6, 16], could be determined by the imbalance in ACE and ACE2 production in the lungs [17]. Studies on diabetic animal mod-

els documented a decrease in ACE2 expression in the lungs and a reduced ACE2 to ACE ratio, which lowers Ang1–7 concentration and enhances AngII accumulation. Besides the age- and gender-associated variability, genomic variants of ACE/ACE2 may further explain the different outcomes seen in COVID-19 outbreak [18].

ACE-inhibitors and Ang II-receptor blockers have been associated with a high risk of infection through upregulation of ACE2 expression that, in turn, would facilitate SARS-CoV-2 infection [19]. The lack of clinical data in support of this hypothesis has led the most representative cardiologist groups to declare to continue ACE inhibitors or angiotensin-receptor blockers. Moreover, some evidence in animals shows that these drugs might be rather protective against serious lung complications. Indeed, ACE inhibitors reduce the level of deleterious AngII and increase expression of the protective of ACE2, whereas Ang II-receptor blockers may attenuate the inflammatory response driven by the AT1a pathway [10, 20].

It is worth noting that the management of hypertension raises questions about the appropriate treatment in symptomatic patients with SARS-CoV-2 infection. Based on reports from clinical practice, blood pressure is notably variable and showed a tendency to difficult-to-control hypertension after withdrawing antihypertensive drugs. Patients with fever, hyperventilation, diarrhea, loss of appetite, and a reduction of fluid intake due to continuous oxygen therapy (mask, helmet) are prone to become severely dehydrated. In this setting, antihypertensive drugs such as diuretics, ace inhibitors, and Ang II-receptor blockers must be withdrawn to prevent acute kidney injury [21]. Treatment with beta-blockers should be accurately

assessed in patients with severe hypoxemia and hemodynamic instability due to sepsis. The beneficial effects of beta blockers in protecting against myocardial ischemia and hypoxia-induced arrhythmia should be balanced with a concrete risk of worsening of lung function, especially with nonselective beta blocker (propranolol, carvedilol) [22]. Therapy with nonselective beta blocker needs to be converted to the minimum effective dose of more selective agents (nebivolol, bisoprolol), and dose should be modulated on heart rate and respiratory performance. To note, tachycardia should not be completely corrected, as it acts as a compensatory mechanism for maintaining hemodynamics and peripheral oxygenation. Instead, treatment with calcium channel blockers, peripheral alpha antagonist, and central agonists of alpha 2-adrenergic receptors appears to have a good safety profile in this cohort of patients.

In summary, there is no scientific evidence supporting an aggravation of lung injury in patients treated with RAS blockers who develop pneumonia. The apparent beneficial effect of RAS modulation and the use of ace

inhibitor and Ang II-receptor blockers in these patients warrant the conduction of further clinical trials [23], to elucidate the underlying pathophysiological mechanism of this concerning infectious disease and provide information on its best management.

Statement of Ethics

This article does not contain any studies or data on human participants or animals performed by any of the authors.

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Author Contributions

G.A.: conceptualization, methodology, writing – original draft, writing – data curation, review, and editing. G.G.: conceptualization. A.F.: data curation, review, and editing. F.F.: writing, review, and editing. C.M. and G.C. supervision, review, and editing. R.M.: supervision.

Appendix

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