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Overview of pharmacotherapy targeting COVID-19 disease based on ACE-2: current challenges and future directions

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Abstract

The new Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) triggered the pandemic of COVID-19, which is currently still ongoing. In 2021 a worldwide vaccine campaign was launched, and in parallel the lines of research are continuing to target the most effective drug therapies for the treatment of COVID-19 disease. SARS-CoV-2 enters host cells via glycoprotein angiotensin-converting enzyme 2 (ACE-2), which plays a major role in renin–angiotensin system interactions and undergoes changes in expression during metabolic and viral diseases, including COVID-19. It seems that the severe lung damage that occurs in several cases of COVID-19 disease may be connected to a deregulated expression of ACE-2. In this manuscript we focus on the line of research that studies the pharmacological modification of ACE-2 expression, a promising weapon to counter the severe harms caused by COVID-19.

Keywords
Pandemic · Pharmacology · Immune System · Infectiology · Virology

Background

SARS-CoV-2

The COVID-19 pandemic to date has caused about 550 million infections and over 6 million deaths [1–3]. Although an intense and extensive worldwide vaccination campaign has been launched for over 1 year [4], research is continuing to examine and evaluate the best possible pharmacological treatments that can be used for the care of patients with COVID-19. The infection often has a slightly symptomatic or even asymptomatic course. Coughing, dyspnea, loss of smell, fatigue, and fever are the most common clinical symptoms of COVID-19 [5–7]. In more serious cases, lung tissue damage may occur, including to the heart, generated by an abnormal and uncontrolled response of the inflammatory/immune system, induced by a rapid release of pro-inflammatory mediators such as cytokines and chemokines [8–11]. Research has not yet selected a specific antiviral cure against SARS-CoV-2. Some therapeutic treatments for COVID-19 have been proposed to date, including antivirals drugs indicated for other pathologies, anticoagulant medicines, convalescent plasma, and anti-inflammatory/immunomodulatory agents [12–16]. SARS-CoV-2 exploits the widespread presence of angiotensin-converting enzyme 2 (ACE-2) glycoprotein in the different tissues of the human body to penetrate human cells [17–19]. Indeed, ACE-2 plays a major role in the interaction with the renin–angiotensin system (RAS).

Availability of data and materials
Full availability of data and materials

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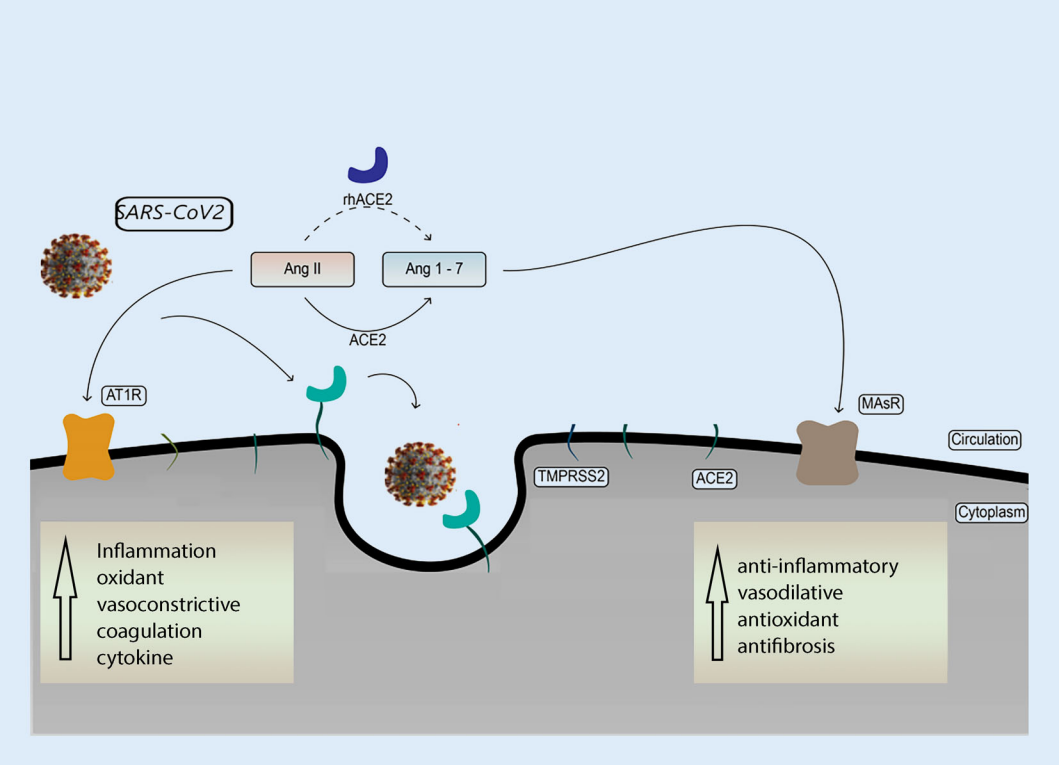

Fig. 1 ◀ Schematic representation of the correlation between SARS-CoV-2 and angiotensin-converting enzyme 2 (*ACE-2*): SARS-CoV-2 penetrates cells through binding of the viral spike protein (spike; S) ACE-2. ACE-2 converts angiotensin (*Ang*)-II into Ang 1–7, which has biological effects mediated by Mas receptor (*MAsR*) activation (antifibrotic, antioxidant, and antihypertrophic) opposed to Ang-II mediated by angiotensin receptor (AT1) (pro-oxidant, hypertrophic, vasoconstrictive, hyperinflammatory)

The role of ACE-2 in COVID-19

Angiotensin-converting enzyme 2 is used as a receptor-binding domain for intracellular penetration by the SARS-CoV-2 virus [20]. The RAS is regulated by ACE-2. Furthermore, ACE-2 receptors are substantially ubiquitous, although they are particularly abundant in the lung, precisely in type 2 pneumocytes, small cylindrical cells very close to the pulmonary capillaries and producing alveolar surfactant, which facilitates gas exchange [21, 22]. Moreover, ACE-2 is also expressed as a coreceptor in intestinal epithelial cells where it plays a mediating role in the absorption of nutrients [23]; ACE-2 is found expressed on cell membranes and in the circulation in a soluble form. The role that ACE-2 plays in the various stages of COVID-19 disease is not yet entirely clear. Some evidence suggests that there is modulation of the variation of RAS and ACE-2 during the different phases of the infection. The severity of the infection can occur as a result of the link between ACE-2 and the entry of SARS-CoV-2 into target cells, due to the dispersion of the host ACE-2 receptors, capable of impacting the homeostasis of the RAS tissue. A viral protein (spike protein), called "protein S," located on the outer surface of the virus binds to the ACE-2 receptor. Binding appears to occur between residues 272 and 537 of the viral protein S 16 [24]. Protein S of the SARS-CoV-2 virus is structurally identical to protein S of the SARS-CoV and Middle East Respiratory Syndrome-Coronavirus (MERS-CoV) viruses by as much as 76.5% [25]. The entry of the virus into the cell through the ACE-2 receptor would be much slower and more difficult if it were not "helped" by some proteases. In fact, many studies suggest that some proteases located on the cell surface, in very close proximity to the ACE-2 receptor, facilitate the entry of the virus into the cell [26, 27]. During viral infection, ACE-2 appears to have a protective role in the lungs, suggesting the use of pharmacological treatments focused on this target. The conversion of angiotensin (Ang)-I to Ang 1–9 and Ang-II to Ang 1–7 is mediated by ACE-2 (◘ **Fig. 1**). The biological action of Ang-II mediated by AT1 receptors has several effects: vasoconstrictor, proinflammatory hypertrophy, increased oxidative stress, and coagulation. Such effects, if they occur uncontrollably, may aggravate the course of COVID-19 infection. Furthermore, across the development of interleukin (IL)-6, Ang-II can generate increased phlogosis, tumor necrosis factor (TNF)-α, and other inflammatory cytokines [28–30]. The degradation of Ang-II and the synthesis of Ang 1–7 is promoted by ACE-2. Through Mas receptor (MAsR) and Angiotensin II type 2 (AT2) receptor, Ang 1–7 exhibits biological effects opposed to Ang-II, such as antiplatelet, antihypertrophic, anti-inflammatory, and antifibrotic effects. This description could suggest the use of pharmacological treatments that focus on ACE-2 targets [31, 32].

Focus on ACE2-based pharmacotherapy in the treatment of COVID-19

In the treatment of COVID-19, an increase in the ACE-2 expression may demonstrate therapeutic benefits. As RAS-modulating pharmacological agents, ACE inhibitors increase the expression of ACE-2, while the use of angiotensin receptor blockers leads to a greater expression of the activity of ACE and ACE-2 [33, 34]. In the advanced stages of the disease, the increase of ACE-2 could be useful in opposing the hyperinflammatory and hyperfibrotic state at

the level of the lung tissue. Additionally, an increase in ACE-2 expression suggests the possibility of a greater increase in bradykinin degradation, further preventing pro-oxidant, profibrotic, and pro-inflammatory effects [18]. Treatment with a soluble rhACE-2 form of ACE-2 could be used as a bait effect for SARS-CoV2, with the consequence of hindering the cellular entry of the virus [35]. Recombinant soluble human ACE-2 showed effectiveness when administered to patients affected by acute respiratory distress syndrome [36]. At the pharmacological–molecular level of the RAS system, rhACE-2 when administered stimulates the non-classic synthesis pathway of Ang 1–7 and Ang 1–9, by lowering the levels of Ang II and the concentrations of pro-inflammatory cytokines. It has been shown that soluble recombinant human rhACE-2 does not allow SARS-CoV-2 to enter cells [37], counteracting the early stages of infection and increasing the effectiveness of remdesivir activity, when taken together [38, 39]. Furthermore, clinical studies on the administration of Ang peptide 1–7 are also ongoing, representing another promising line of research. In addition, it has emerged that the administration of vitamin D increases the levels of ACE-2, potentially providing an additional weapon in the fight against complications related to COVID-19 infection [40]. Further approaches to increase the expression of ACE-2 in vivo in the central and peripheral nervous systems involve viral release systems that use adenovirus, adeno-associated viruses, or lentivirus. Furthermore, the compounds called "ACE-2 activators," used to amplify the expression of ACE-2, are the subject of research [41].

Finally, a promising pharmacological tool could be allosteric modulation. Drugs that act by allosteric modulation, such as allosteric enzymes, bind to sites other than the active site and often alter the shape of the active site itself and its affinity. It is hypothesized that SARS-CoV-2 may lose the ability to infect new host cells due to an allosterically altered interaction between the ACE-2 receptor and viral receptor binding domain (RBD): In fact, in the case that the biophysical properties of the ACE-2 receptor are altered, viral RBD can reduce or increase the degree of affinity toward the ACE-2 receptor [42]. This process may be possible due to the allosteric binding of the drug, which could disrupt the interactions between ACE-2 and SARS-CoV-2 RBD. There is some evidence that the binding of a drug to the allosteric site of the ACE-2 receptor can decrease biophysical interactions of ACE-2 and viral RBD [43]. At the same time, binding of a drug to an allosteric site of ACE-2 may also decrease the conversion of the angiotensin-I and -II enzyme substrate [42]. In conclusion, amending the biophysical properties of the ACE-2 receptor by modulating an allosteric site of ACE-2 could be a promising strategy against COVID-19, but this aspect will have to be studied in detail.

Conclusion

A therapeutic approach aimed at increasing angiotensin-converting enzyme 2 (ACE-2) can have several positive effects. On the one hand, it can reduce the harmful actions that angiotensin (Ang) 2 is able to induce by stimulating AT1r; on the other hand, it can increase the benefits that occur when Ang 1–7 and Ang 1–9 stimulate the Mas receptor. These benefits are potentially useful to counteract COVID-19 by reducing the risk of grave complications, such as tissue hyperfibrosis and the hyperinflammatory state. Moreover, they can help to significantly reduce lung injury as well as renal and cardiac damage caused by the virus. More clinical evidence is needed with new data to support and intensify this promising line of research.

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Declarations

Conflict of interest. A. Vitiello, A. Zovi, U. Trama and F. Ferrara declare that they have no competing interests. Consent to Publish: The authors consent to the publication of the manuscript. All authors declare that the opinions expressed are of a personal nature and their administrations are not responsible for this.

For this article no studies with human participants or animals were performed by any of the authors. All studies mentioned were in accordance with the ethical standards indicated in each case. Ethical Approval and Consent to Participate: Not applicable.

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Zusammenfassung

Übersicht über Pharmakotherapie auf der Basis von ACE-2 bei COVID-19-Erkrankung: aktuelle Herausforderungen und zukünftige Entwicklungen

Das neue Coronavirus SARS-CoV-2 hat die COVID-19-Pandemie ausgelöst, die zzt. immer noch anhält. Im Jahr 2021 wurde eine weltweite Impfkampagne gestartet, und parallel dazu laufen Forschungsansätze, um die wirksamsten medikamentösen Therapien zur Behandlung der COVID-19-Erkrankung herauszufinden. SARS-CoV-2 dringt über das Glykoprotein Angiotensin-Converting-Enzym 2 (ACE-2) in Wirtszellen ein, das eine wesentliche Rolle bei Interaktionen mit dem Renin-Angiotensin-System spielt und bei dem sich im Verlauf metabolischer und viraler Erkrankungen, einschließlich COVID-19, die Expression verändert. Es scheint, dass die schwerwiegende Schädigung der Lunge, die in vielen Fällen einer COVID-19-Erkrankung auftritt, mit einer deregulierten Expression von ACE-2 zusammenhängt. In der vorliegenden Arbeit liegt der Schwerpunkt auf Forschungsansätzen zur pharmakologischen Modifikation der ACE-2-Expression, einer vielversprechenden Strategie gegen die schweren Schäden durch COVID-19.

Schlüsselwörter
Pandemie · Pharmakologie · Immunsystem · Infektiologie · Virologie

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