Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Respiratory Medicine 168 (2020) 105996

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: http://www.elsevier.com/locate/rmed

Review article

Severe respiratory SARS-CoV2 infection: Does ACE2 receptor matter?

Fabio Perrotta [a], Maria Gabriella Matera [b], Mario Cazzola [c,*], Andrea Bianco [d,**]

[a] Department of Medicine and Health Sciences "V. Tiberio", University of Molise, Campobasso, Italy
[b] Department of Experimental Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy
[c] Department of Experimental Medicine, University of Rome "Tor Vergata", Rome, Italy
[d] Department of Translational Medical Sciences, University of Campania "Luigi Vanvitelli"/Hosp. Monaldi, Naples, Italy

ARTICLE INFO

Keywords:
SARS-CoV-2
ACE2 receptor
ACE inhibitors
Renin-angiotensin inhibitors

ABSTRACT

SARS-CoV-2 is a novel virus of the Coronaviridiae family that represents a major global health issue. Mechanisms implicated in virus/host cells interaction are central for cell infection and replication that in turn lead to disease onset and local damage. To enter airway and lung epithelia, SARS-CoV-2 attaches to ACE2 receptors by spike (S) glycoproteins. Molecular mechanisms that promote interaction between SARS-CoV-2 virus and host with particular focus on virus cell entry receptor ACE2 are described. We further explore the impact of underlying medical conditions and therapies including renin-angiotensin inhibitors on modulating ACE 2, which is the major SARS-CoV-2 cell entry receptor.

1. Introduction

The Coronaviridae family comprises viruses with genetic heterogeneity that allow differentiation in four genera: α-coronavirus, β-coronavirus, γ-coronavirus, and δ-coronavirus. SARS-CoV-2, a novel virus belonging to the coronavirus family is causing the ongoing global pandemic. The coronavirus RNA genome (ranging from 26 to 32 kilobases in length) is the widest among all RNA viruses with a degree of variability.

Although several coronaviruses are potentially pathogenic for humans, most produce minimally symptomatic disease [1]. However, in 2002 and 2012 the outbreaks of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) respectively, resulted in relevant morbidity and mortality due to acute respiratory failure (ARF) [2,3].

An epidemic of respiratory disease caused by SARS coronavirus 2 (SARS-CoV-2) began in China and has spread to other countries. The novel coronavirus was originally named 2019-nCoV and subsequently SARS-CoV-2 by World Health Organization (WHO). The virus is a β-coronavirus belonging to the subgenus botulinum of Coronaviridae, and it is responsible for a zoonotic disease (coronavirus disease 2019 or COVID-19) which target airways and may severely involve lung airspaces [4]. When lung parenchyma is affected, in addition to fever, symptoms include dry cough, dyspnoea and, in more serious cases, potentially fatal ARF [5]. Mechanisms by which older age and underlying medical conditions negatively impact acute respiratory distress syndrome (ARDS) and concurrent cytokine storm require to be understood.

The SARS-CoV-2 is a single-strand positive-sense RNA genome identified by high-throughput sequencing and released through virological.org. The virus was originally discovered in humans. The animal reservoir remains unclear although growing data support that SARS-CoV-2 was a chimeric virus with high grade of affinity for genetic information of a bat coronavirus and elevated similarity in codon usage bias with snake [6]. Also the intermediate hosts of SARS-CoV-2 remain undetermined.

The interaction between viruses and host cells at entry site is crucial for disease onset and progression. In influenza A (H1N1), based on evidence in swine model, receptor binding domain on the host cells may also be used by intracellular bacteria both favouring the infection and enhancing the burden of symptoms [7]. For SARS-CoV and SARS-CoV-2 the virus tropism for the respiratory system is sustained by the attachment to angiotensin-converting enzyme 2 (ACE2). ACE2 is a membrane-anchored carboxypeptidase highly expressed by airway epithelial and type I and II alveolar epithelial cells, found to be the virus cell entry receptor previously during SARS-CoV outbreak [8].

Focus of this review is to dissect the knowledge on ACE2 receptor on airway and lung epithelium and attempt to understand whether

* Corresponding author. Department of Experimental Medicine, University of Rome "Tor Vergata", Via Montpellier, 1 – 00133, Rome, Italy.
** Corresponding author. Department of Translational Medical Sciences University of Campania "L Vanvitelli", Hosp Monaldi, Via L Bianchi, 80131, Napoli, Italy.
E-mail addresses: mario.cazzola@uniroma2.it (M. Cazzola), andrea.bianco@unicampania.it (A. Bianco).

https://doi.org/10.1016/j.rmed.2020.105996
Received 19 March 2020; Received in revised form 22 April 2020; Accepted 24 April 2020
Available online 25 April 2020

underlying diseases or therapies are able to modulate expression affecting SARS-CoV-2 cell entry and infectivity.

2. Coronaviruses and ACE2 receptor: molecular interaction and damage associated pathways

A large spike (S) protein that forms homotrimers protruding from the viral surface mediates coronaviruses attachment and adhesion to human target cells. In most avian and mammalian coronaviruses, S protein is cleaved into two smaller proteins although this has not been reported in SARS-CoV. However, two different functional regions have been described, S1 and S2 [9].

The S1 subunit consists of four core domains, S1A to S1D. The distal S1 domain mediates receptor association and stabilization, whereas the S2 domain promotes structural rearrangements and finally membrane fusion. Coronaviruses use different regions of S1 domain to interact with specific binding receptors.

Acetylated sialoside attachment receptors expressed by glycoproteins and glycolipids on the host cell are the target of endemic human coronaviruses OC43 and HKU1 while non-acetylated sialoside attachment receptors bind the A domain (SA) of MERS-CoV. For SARS-CoV and SARS-CoV-2, a small fragment of the S1 region, receptor binding domain (RBD), is necessary for binding to the peptidase domain of ACE2. This represents the critical site for virus/host cell interaction [10].

SARS-CoV-2 has low homology to S-protein of SARS-CoV with patches of sequences in the RBD domain. Walls et al. reported that SARS-CoV-2 S-protein has a boundary between the S1 and S2 subunits site presumably due to furin cleavage in the Golgi compartment [11].

In particular, SARS-CoV and SARS-CoV-2 present more conserved S2 fusion machinery than the S1 subunit with the highest divergence found within SA and SB [12]. These changes in SARS-CoV-2 result in a functional advantage as the ectodomain S attaches to ACE2 with ~15 nM affinity, which is approximately 10- to 20-fold higher than that of SARS-CoV [13] These findings have been proposed as the rationale for elucidating the efficient transmission of SARS-CoV-2 in humans.

ACE2 expression is widely represented in type II lung alveolar cells, oesophageal epithelial cells, enterocytes, cholangiocytes, myocardial cells, kidney proximal tubule cells, and bladder urothelial cells [14].

Single-nucleotide ACE2 polymorphisms are not associated with SARS susceptibility or outcomes [15]. Furthermore, in experimental models, the binding of the S protein to ACE2 is not altered by the addition of a specific ACE2 inhibitor, confirming the inability of this inhibitor to block SARS infection [16]. Conversely, SARS-CoV2 S-mediated entry into target was enabled in mice immunized with a stabilized SARS-CoV S-protein.

These data support a role for SARS-CoV neutralizing antibodies in preventing receptor engagement [12]. While ACE2 has been extensively discussed as receptor for entry into the host alveolar cell, in a murine ARDS model ACE2 protected lungs from severe acute injury [17,18]. Impaired tissue repair mechanisms, increased vascular permeability, fluid accumulation in extra-alveolar spaces and oxidant/antioxidant imbalance have been described in relation to ACE2 deficiency [19–21]. After attachment and virion membrane fusion, ACE2 expression is downregulated resulting in excessive production of angiotensin (Ang) enhancing oxidative stress mechanisms [22] in contrast to what happens during other viral infections.

SARS-CoV-2 internalization is promoted through hemagglutinin cleavage operated by the transmembrane serine protease 2 (TMPRSS2), a cell-surface protein expressed by epithelial cells within the airway and alveolar spaces [8,23]. Viral priming mechanisms, TMPRSS2 dependent, were demonstrated during previous coronaviruses and influenza A H1N1 outbreaks [8,24,25] (Fig. 1). TMPRSS2 involvement in SARS-CoV-2 is currently under investigation based on in vitro data of camostat mesylate, an inhibitor of the protease activity of TMPRSS2, demonstrating SARS-CoV-2 entry cell inhibition [8]. A phase I/II study with camostat mesylate (NCT04321096) and a phase II/III study with nafamostat, an extremely potent TMPRSS2 inhibitor, (NCT04352400) are ongoing [26,27]. Preliminary results are expected by 2021.

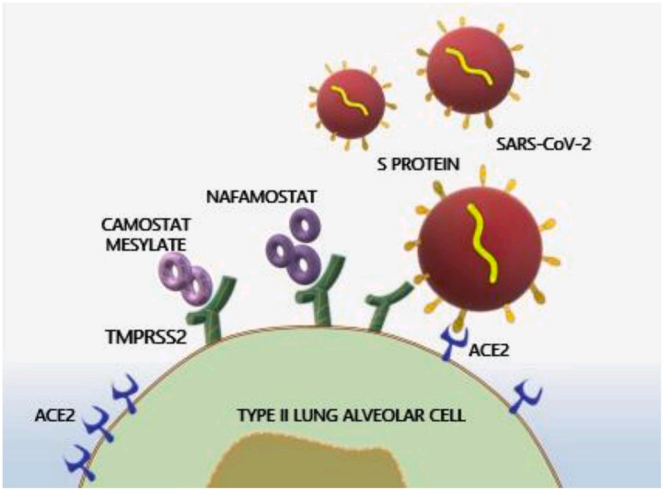

Fig. 1. Postulated mechanisms modulating SARS-CoV-2 attachment and fusion machinery on human host cells.

3. ACE and ACE2 expression in pre-existing chronic pulmonary diseases

ACE is a type 1 transmembrane monomeric glycoprotein expressed in lungs, intestine, kidneys, brain, aorta, and adrenal medulla; it cleaves two amino acids from Ang I to produce Ang II. ACE2 conversely cleaves single amino acid from Ang II to generate Ang-(1–7) [28].

In human lungs, elevated Ang II/Ang-(1–7) ratio favours vascular permeability and extra-alveolar fluid accumulation. Conversely, elevated levels of Ang-(1–7) though Mas receptor (Mas1) activation, which is widely present on endothelial cells, exert vasodilatory, anti-inflammatory and anti-fibrotic effects [29]. Most importantly, ACE2 differs from ACE for not being inhibited by ACE inhibitors (ACE-I) [30].

In a rat model, ACE2 mRNA expression is significantly reduced in COPD rat lung compared to wild type animals [31]. Likewise, ACE2 overexpression through intratracheal injection of Ad-ACE2 significantly attenuated the lung function deteriorations and pathological manifestations of COPD, supporting a pathogenetic ACE/ACE2 imbalance in COPD [32]. Similarly, an increment in ACE/ACE2 ratio has been reported in the murine model of asthma. However, administration of ACE2 activator counteracts the cytokine storm (IL-1β, IL-4, NF-κB, BCL2, p-AKT, p-p38) in asthmatic rat model [33].

To an uncertain extent, smoking may play a role in ACE2 modulation. Lungs from rats chronically exposed to cigarette smoke exhibited significant reduction in ACE2 expression as well as an increase of ACE. Based on data independently reported by Guan et al. [34] and Zhang et al. [35], incidence of SARS-CoV-2 appears to be lower in patient with smoking history. By contrast, smoking seems to be associated with adverse outcome. These mechanisms need to be fully explored.

Previous data highlighted that viral infections might amplify local inflammation in chronic respiratory conditions. In atopic subjects, HRV and allergen exposure singularly increased ICAM-1 expression resulting in migration of immune effector cells into the airways [36]. Conversely, in SARS-CoV2 infection, the presence of comorbid chronic respiratory disorders is not associated with enhanced risk for developing infection compared to other common clinical conditions. However, COVID could evolve in more severe clinical outcomes in COPD subjects [34].

However, it is recognised that a down regulation of ACE2 following infection does promote lung injury [19]. In lung, reduced ACE2 levels prompt reduce Ang-(1–7) levels, which promotes protective tissues regeneration and reduces reactive oxygen species (ROS) [28,32]. COVID

outbreak makes ACE2 regulation in lung epithelial cells a crucial area of research interest.

4. Role of pharmacological agents in ACE2 modulation

COVID-19 exhibits more severe clinical course in patients with hypertension, cardiovascular disease and diabetes [35,37]. Renin-angiotensin system (RAS) inhibitors are the cornerstone of therapy of many cardiovascular and renal diseases. These drugs are widely used for reducing blood pressure in hypertensive patients. Experimental and clinical models show different responses from administration of agents interfering with this regulatory axis: angiotensin-receptor blockers (ARB) and mineralocorticoid-receptor blockers seem to increase the levels of ACE2 gene expression and cardiac ACE2 activity [38,39], whereas ACE-I are associated with elevated cardiac ACE2 activity but not cardiac ACE2 mRNA [40]. An early study documented increased cardiac ACE2 expression after myocardial infarction in rats treated with agents blocking the Ang II receptors when compared to placebo [41]. Similarly, higher urinary ACE2 levels were observed in hypertensive patients treated with olmesartan, an Ang II type 1 (AT1) receptor antagonist [42]. Furthermore, administration of losartan, another AT1 receptor antagonist, counterbalanced smoke-induced decrease of ACE2 and restored to some extent the ACE/ACE2 ratio in the lung [43].

In a small cohort study, levels of Ang II were found markedly increased in COVID-19 plasma samples [44]. These results are in accordance with previous studies which reported high Ang II levels in mice infected with SARS [17] and with experiments in H7N9 viruses showing that Ang II levels were related to worse clinical outcomes [45].

RAS may represent a double-edged sword. Its positive impact in upregulating ACE2 has been demonstrated [41], suggesting a potential role against lung damage in SARS-CoV-2 infected patients [22]. However, risk of increase susceptibility to infection linked to ACE2 upregulation due to RAS inhibitors remains uncertain and needs to be clarified. Fang et al. based on higher prevalence of hypertension, diabetes mellitus and chronic cardiovascular diseases among patients who died from COVID-19 postulated that ACE-I or ARBs might favour severe disease progression [46]. However, more recently, in a multicentre retrospective study including 1,128 COVID-19 inpatients with hypertension, the use of ACE-I/ARBs was associated with lower all-cause mortality (adjusted HR, 0.42; 95% CI, 0.19–0.92; P = 0.03) and septic shock (adjusted HR, 0.36; 95% CI, 0.16–0.84; P = 0.01) compared with ACE-I/ARB non-use. Unfortunately, the study was not designed to detect differences between ACE-I and ARBs and overall the patient number in ACE-I/ARB group was limited (188/1128; 16.6%) [47]. These data support the statements of European Society of Cardiology [48], American Heart Association, the Heart Failure Society of America and the American College of Cardiology [49], International Society of Hypertension [50], Italian Society of Pharmacology [51] and European Society of Hypertension [52] that recommend against ACE-I or sartans discontinuation in light of the current evidences.

However, a recent comment by Phadke et al. [53], based on unpublished observational data, supports the use of losartan or telmisartan, which block AT1 receptor more avidly than valsartan, to potentially prevent the virus spread.

Finally, data about non-steroidal anti-inflammatory drugs (NSAIDs) are still far from being clarified. Earlier evidences in rat models suggest that ibuprofen and thiazolidinediones may upregulate ACE2 expression [54–56]. It has yet to be established whether these observations may objectively influence the clinical scenario in patients with SARS-Cov-2 infection.

5. Conclusions

There is sufficient evidence to support the concept that one of the main battles in the war on COVID will be played at the level of ACE2, the receptor for viral cell entry. In healthy individuals, ACE2 promotes lung homeostasis through the production of Ang-(1–7). In chronic respiratory conditions, ACE2 down-regulation may prevent SARS-CoV-2 host cell interaction. However, patients with pre-existing COPD who are infected with SARS-CoV-2 may experience poor clinical outcomes most likely due to reduced respiratory reserve.

Data on ACE2 modulation from RAS inhibitors is inconclusive. Whilst subjects chronically exposed to these agents appear to have hypothetically higher availability of cell receptors within lung, it remains uncertain whether this may influence the susceptibility to developing SARS-CoV-2 infection. However, ACE2 upregulation may also result in enhanced host defence mechanisms that counteract ACE2 virus-induced downregulation.

Dissecting the pathways of the major cell receptor for SARS-CoV-2 will let us understand both the mechanisms of viral induced direct lung injury and the effects of perturbation of ACE2 on their function. Manipulation of ACE2 receptor expression and its implication on viral cell entry has the potential to be a major target for therapy.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] S. Su, G. Wong, W. Shi, J. Liu, A.C.K. Lai, J. Zhou, et al., Epidemiology , genetic recombination , and pathogenesis of coronaviruses, Trends Microbiol. 24 (2016) 490–502, https://doi.org/10.1016/j.tim.2016.03.003.
[2] M. Chan-Yeung, R.-H. Xu, SARS: epidemiology, Respirology 8 (Suppl) (2003) S9–S14, https://doi.org/10.1046/j.1440-1843.2003.00518.x.
[3] A.M. Zaki, S. van Boheemen, T.M. Bestebroer, A.D.M.E. Osterhaus, R.A. M. Fouchier, Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia, N. Engl. J. Med. 367 (2012) 1814–1820, https://doi.org/10.1056/NEJMoa1211721.
[4] N. Zhu, D. Zhang, W. Wang, X. Li, B. Yang, J. Song, et al., A novel coronavirus from patients with pneumonia in China, 2019, N. Engl. J. Med. 382 (2020) 727–733, https://doi.org/10.1056/NEJMoa2001017.
[5] N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, et al., Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, Lancet (London, England) 395 (2020) 507–513, https://doi.org/10.1016/S0140-6736(20)30211-7.
[6] W. Ji, W. Wang, X. Zhao, J. Zai, X. Li, Cross-species transmission of the newly identified coronavirus 2019-nCoV, J. Med. Virol. 92 (2020) 433–440, https://doi.org/10.1002/jmv.25682.
[7] A. Giannattasio, L. Brunese, G. Ripabelli, G. Mazzarella, A. Bianco, Coinfections with influenza virus and atypical bacteria: implications for severe outcomes? Clin. Res. J 12 (2018) 366–367, https://doi.org/10.1111/crj.12510.
[8] M. Hoffmann, H. Kleine-Weber, S. Schroeder, N. Krüger, T. Herrler, S. Erichsen, et al., SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor, Cell S0092–8674 (20) (2020) 30229–30234, https://doi.org/10.1016/j.cell.2020.02.052.
[9] F. Li, W. Li, M. Farzan, S.C. Harrison, Structure of SARS coronavirus spike receptor-binding domain complexed with receptor, Science 309 (2005) 1864–1868, https://doi.org/10.1126/science.1116480.
[10] W. Li, C. Zhang, J. Sui, J.H. Kuhn, M.J. Moore, S. Luo, et al., Receptor and viral determinants of SARS-coronavirus adaptation to human ACE2, EMBO J. 24 (2005) 1634–1643, https://doi.org/10.1038/sj.emboj.7600640.
[11] A.C. Walls, Y.-J. Park, M.A. Tortorici, A. Wall, A.T. McGuire, D. Veesler, Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein, Cell (2020), https://doi.org/10.1016/j.cell.2020.02.058.
[12] C.-S. Glycoprotein, A.C. Walls, Y. Park, M.A. Tortorici, A. Wall, A.T. Mcguire, et al., Structure , function , and antigenicity of the SARS- structure , function , and antigenicity of the SARS-CoV-2 spike glycoprotein, Cell (2020) 1–12, https://doi.org/10.1016/j.cell.2020.02.058.
[13] X. Xu, P. Chen, J. Wang, J. Feng, H. Zhou, X. Li, et al., Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission, Sci. China Life Sci. 63 (2020) 457–460, https://doi.org/10.1007/s11427-020-1637-5.
[14] H. Xu, L. Zhong, J. Deng, J. Peng, H. Dan, X. Zeng, et al., High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa, Int. J. Oral Sci. (2020) 1–5, https://doi.org/10.1038/s41368-020-0074-x.
[15] R.W.K. Chiu, N.L.S. Tang, D.S.C. Hui, G.T.Y. Chung, S.S.C. Chim, K.C.A. Chan, et al., ACE2 gene polymorphisms do not affect outcome of severe acute respiratory syndrome, Clin. Chem. 50 (2004) 1683–1686, https://doi.org/10.1373/clinchem.2004.035436.

[16] F. Li, Receptor recognition and cross-species infections of SARS coronavirus, Antivir. Res. 100 (2013) 246–254, https://doi.org/10.1016/j.antiviral.2013.08.014.

[17] Y. Imai, K. Kuba, S. Rao, Y. Huan, F. Guo, B. Guan, et al., Angiotensin-converting enzyme 2 protects from severe acute lung failure, Nature 436 (2005) 112–116, https://doi.org/10.1038/nature03712.

[18] K. Kuba, Y. Imai, J.M. Penninger, Angiotensin-converting enzyme 2 in lung diseases, Curr. Opin. Pharmacol. 6 (2006) 271–276, https://doi.org/10.1016/j.coph.2006.03.001.

[19] K. Kuba, Y. Imai, S. Rao, H. Gao, F. Guo, B. Guan, et al., A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury, Nat. Med. 11 (2005) 875–879, https://doi.org/10.1038/nm1267.

[20] R.P. Marshall, P. Gohlke, R.C. Chambers, D.C. Howell, S.E. Bottoms, T. Unger, et al., Angiotensin II and the fibroproliferative response to acute lung injury, Am. J. Physiol. Lung Cell Mol. Physiol. 286 (2004) L156–L164, https://doi.org/10.1152/ajplung.00313.2002.

[21] F. Fyhrquist, O. Saijonmaa, Renin-angiotensin system revisited, J. Intern. Med. 264 (2008) 224–236, https://doi.org/10.1111/j.1365-2796.2008.01981.x.

[22] D. Gurwitz, Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics, Drug Dev. Res. (2020), https://doi.org/10.1002/ddr.21656.

[23] K.H. Stopsack, L.A. Mucci, E.S. Antonarakis, P.S. Nelson, P.W. Kantoff, TMPRSS2 and COVID-19: serendipity or opportunity for intervention? Canc. Discov. (2020) https://doi.org/10.1158/2159-8290.CD-20-0451.

[24] S. Matsuyama, N. Nagata, K. Shirato, M. Kawase, M. Takeda, F. Taguchi, Efficient activation of the severe acute respiratory syndrome coronavirus spike protein by the transmembrane protease TMPRSS2, J. Virol. 84 (2010) 12658–12664, https://doi.org/10.1128/JVI.01542-10.

[25] E. Böttcher, T. Matrosovich, M. Beyerle, H.-D. Klenk, W. Garten, M. Matrosovich, Proteolytic activation of influenza viruses by serine proteases TMPRSS2 and HAT from human airway epithelium, J. Virol. 80 (2006) 9896 LP–9898, https://doi.org/10.1128/JVI.01118-06.

[26] ClinicalTrials.gov Identifier: NCT04321096 the Impact of Camostat Mesilate on COVID-19 Infection (CamoCO-19) n.D. https://clinicaltrials.gov/ct2/show/NCT04321096. (Accessed 21 April 2020).

[27] NCT04352400 C go I. Efficacy of Nafamostat in Covid-19 Patients (RACONA Study) (RACONA) (n.d).

[28] R.R. Gaddam, S. Chambers, M. Bhatia, ACE and ACE2 in inflammation: a tale of two enzymes, Inflamm. Allergy - Drug Targets 13 (2014) 224–234, https://doi.org/10.2174/1871528113666140713164506.

[29] A.R. Hemnes, A. Rathinasabapathy, E.A. Austin, E.L. Brittain, E.J. Carrier, X. Chen, et al., A potential therapeutic role for angiotensin-converting enzyme 2 in human pulmonary arterial hypertension, Eur. Respir. J. 51 (2018), https://doi.org/10.1183/13993003.02638-2017.

[30] M.J. Huentelman, J.L. Grobe, J. Vazquez, J.M. Stewart, A.P. Mecca, M.J. Katovich, et al., Protection from angiotensin II-induced cardiac hypertrophy and fibrosis by systemic lentiviral delivery of ACE2 in rats, Exp. Physiol. 90 (2005) 783–790, https://doi.org/10.1113/expphysiol.2005.031096.

[31] H. Jia, Pulmonary angiotensin-converting enzyme 2 (ACE2) and inflammatory lung disease, Shock 46 (2016) 239–248, https://doi.org/10.1097/SHK.0000000000000633.

[32] T. Xue, N. Wei, Z. Xin, X. Qingyu, Angiotensin-converting enzyme-2 overexpression attenuates inflammation in rat model of chronic obstructive pulmonary disease, Inhal. Toxicol. 26 (2014) 14–22, https://doi.org/10.3109/08958378.2013.850563.

[33] V.S. Dhawale, V.R. Amara, P.A. Karpe, V. Malek, D. Patel, K. Tikoo, Activation of angiotensin-converting enzyme 2 (ACE2) attenuates allergic airway inflammation in rat asthma model, Toxicol. Appl. Pharmacol. 306 (2016) 17–26, https://doi.org/10.1016/j.taap.2016.06.026.

[34] W.-J. Guan, Z.-Y. Ni, Y. Hu, W.-H. Liang, C.-Q. Ou, J.-X. He, et al., Clinical characteristics of coronavirus disease 2019 in China, N. Engl. J. Med. (2020), https://doi.org/10.1056/NEJMoa2002032.

[35] J.-J. Zhang, X. Dong, Y.-Y. Cao, Y.-D. Yuan, Y.-B. Yang, Y.-Q. Yan, et al., Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China, Allergy (2020), https://doi.org/10.1111/all.14238.

[36] A. Bianco, S.C. Whiteman, S.K. Sethi, J.T. Allen, R.A. Knight, M.A. Spiteri, Expression of intercellular adhesion molecule-1 (ICAM-1) in nasal epithelial cells of atopic subjects: a mechanism for increased rhinovirus infection? Clin. Exp. Immunol. 121 (2000) 339–345, https://doi.org/10.1046/j.1365-2249.2000.01301.x.

[37] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (2020) 497–506, https://doi.org/10.1016/S0140-6736(20)30183-5.

[38] S. Keidar, A. Gamliel-Lazarovich, M. Kaplan, E. Pavlotzky, S. Hamoud, T. Hayek, et al., Mineralocorticoid receptor blocker increases angiotensin-converting enzyme 2 activity in congestive heart failure patients, Circ. Res. 97 (2005) 946–953, https://doi.org/10.1161/01.RES.0000187500.24964.7A.

[39] J.-C. Zhong, J.-Y. Ye, H.-Y. Jin, X. Yu, H.-M. Yu, D.-L. Zhu, et al., Telmisartan attenuates aortic hypertrophy in hypertensive rats by the modulation of ACE2 and profilin-1 expression, Regul. Pept. 166 (2011) 90–97, https://doi.org/10.1016/j.regpep.2010.09.005.

[40] C.M. Ferrario, J. Jessup, M.C. Chappell, D.B. Averill, K.B. Brosnihan, E.A. Tallant, et al., Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2, Circulation 111 (2005) 2605–2610, https://doi.org/10.1161/CIRCULATIONAHA.104.510461.

[41] Y. Ishiyama, P.E. Gallagher, D.B. Averill, E.A. Tallant, K.B. Brosnihan, C. M. Ferrario, Upregulation of angiotensin-converting enzyme 2 after myocardial infarction by blockade of angiotensin II receptors, Hypertension (Dallas) 43 (2004) 970–976, https://doi.org/10.1161/01.HYP.0000124667.34652.1a.

[42] M. Furuhashi, N. Moniwa, T. Mita, T. Fuseya, S. Ishimura, K. Ohno, et al., Urinary angiotensin-converting enzyme 2 in hypertensive patients may be increased by olmesartan, an angiotensin II receptor blocker, Am. J. Hypertens. 28 (2015) 15–21, https://doi.org/10.1093/ajh/hpu086.

[43] Y.-M. Yuan, L. Luo, Z. Guo, M. Yang, R.-S. Ye, C. Luo, Activation of renin-angiotensin-aldosterone system (RAAS) in the lung of smoking-induced pulmonary arterial hypertension (PAH) rats, J. Renin-Angiotensin-Aldosterone Syst. JRAAS 16 (2015) 249–253, https://doi.org/10.1177/1470320315576256.

[44] Y. Liu, Y. Yang, C. Zhang, F. Huang, F. Wang, J. Yuan, et al., Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury, Sci. China Life Sci. 63 (2020) 364–374, https://doi.org/10.1007/s11427-020-1643-8.

[45] P. Yang, H. Gu, Z. Zhao, W. Wang, B. Cao, C. Lai, et al., Angiotensin-converting enzyme 2 (ACE2) mediates influenza H7N9 virus-induced acute lung injury, Sci. Rep. 4 (2014) 7027, https://doi.org/10.1038/srep07027.

[46] L. Fang, G. Karakiulakis, M. Roth, Correspondence hypertension and increased risk for, Lancet Respir 8 (2020) e21, https://doi.org/10.1016/S2213-2600(20)30116-8.

[47] P. Zhang, L. Zhu, J. Cai, F. Lei, J.-J. Qin, J. Xie, et al., Association of inpatient use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19, Circ. Res. (2020), https://doi.org/10.1161/CIRCRESAHA.120.317134.

[48] European Society of Cardiology (ESC), Position Statement of the ESC Council on Hypertension on ACE-Inhibitors and Angiotensin Receptor Blockers, 2020 n.d, https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang. accessed March 18, 2020.

[49] American Heart Association (AHA), Heart Failure Society of America (HFSA) and American College of Cardiology (ACC). Patients Taking ACE-I and ARBs Who Contract COVID-19 Should Continue Treatment, unless Otherwise Advised by Their Physician, 2020 (n.d).

[50] International Society of Hypertension, A Statement from the International Society of Hypertension on COVID-19, 2020 n.d).

[51] G. Trifirò, S. Crisafulli, G. Andò, G. Racagni, F. Drago, Should patients receiving ACE inhibitors or angiotensin receptor blockers be switched to other antihypertensive drugs to prevent or improve prognosis of novel coronavirus disease 2019 (COVID-19)? Drug Saf. (2020) https://doi.org/10.1007/s40264-020-00935-2.

[52] European Society of Hypertension, Statement of the European Society of Hypertension (ESH) on Hypertension, Renin Angiotensin System Blockers and COVID-19 March 19th 2020, 2020 n.d).

[53] M.A. Phadke, S. Saunik, Use of angiotensin receptor blockers such as Telmisartan, Losartsan in nCoV Wuhan Corona Virus infections – novel mode of treatment, BMJ 368 (2020) m406, https://doi.org/10.1136/bmj.m406.

[54] W. Qiao, C. Wang, B. Chen, F. Zhang, Y. Liu, Q. Lu, et al., Ibuprofen attenuates cardiac fibrosis in streptozotocin-induced diabetic rats, Cardiology 131 (2015) 97–106, https://doi.org/10.1159/000375362.

[55] R.M. Ali, M.Y. Al-Shorbagy, M.W. Helmy, H.S. El-Abhar, Role of Wnt4/beta-catenin, Ang II/TGFbeta, ACE2, NF-kappaB, and IL-18 in attenuating renal ischemia/reperfusion-induced injury in rats treated with Vit D and pioglitazone, Eur. J. Pharmacol. 831 (2018) 68–76, https://doi.org/10.1016/j.ejphar.2018.04.032.

[56] W. Zhang, C. Li, B. Liu, R. Wu, N. Zou, Y.-Z. Xu, et al., Pioglitazone upregulates hepatic angiotensin converting enzyme 2 expression in rats with steatohepatitis, Ann. Hepatol. 12 (2013) 892–900.