Latest updates on SARS-CoV-2 (Corona Virus)

Chapter 1

Ace2 As Enzyme, Gateway and Therapeutic Target For The Covid-19

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1. Introduction

The ACE2 (angiotensin-converting enzyme 2) has become especially important in the development of COVID-19, which became the 2020 pandemic that has made it difficult for the world to deal with it. ACE2 began to have relevance since 2002, with the cases presented by the SARS-CoV [1] [2], in this coronavirus outbreak, ACE2 was identified as the gateway for this virus, then MERS was presented, in which ACE2 also had an important role in enabling this virus to generate its infectious process [2]. As for ACE2, other functions have been attributed to it, different from those it performs in the cardiovascular system [3], now in 2020, ACE2 has become more important, since it is a key factor for SARS-CoV-2 to fuse to the membrane of human cells and to be able to introduce its genetic material [4] [5]. Today, it is challenging to be able to target drugs to specific regions and to be selective for ACE2 [6], so ACE2 will have to be studied from different perspectives, trying not to alter the functions it performs in the human organism.

2. ACE2

ACE2 is found in the cell membrane of different cell tissues, mainly in the lung, heart, kidney, brain, and gut. The functions of ACE2 are mainly in the cardiovascular system, as a vasoconstrictor and cardioprotector [7], of the main functions of ACE2 is its participation in the renin-angiotensin-aldosterone system (RAAS); ACE2 degrades Ang II, a peptide with multiple actions that promote manly vasoconstriction, and generates Ang-(1-7) [7] [8].

Currently the use of anti-RAAS and statins drugs for the regulation of ACE2 has been related to COVID-19, there are reports of effects that cause the decrease of ACE2 functions

in the human organism, the loss of ACE2 in the brainstems may facilitate an increase in sympathetic drive, alterations in the baroreflex and exacerbation of hypertension [9] [10]. A loss of pulmonary ACE2 may exacerbate hypertension, respiratory distress and fibrosis post-viral infection [10]. Cell surface diminution of ACE2 may contribute to widespread inflammation observed with COVID-19. As already extensively studied, SARS-CoV-2 infection is triggered by the binding of the virus spike protein to ACE2, which is highly expressed in the heart and lungs, SARS-CoV-2 mainly invades epithelial cells alveolar, which produces respiratory symptoms [3] [11] [12].

3. ACE2 as receptor to SARS-CoV-2

The affinity of SARS-CoV-2 with ACE2 has been determined to be up to 20 times higher than that reported in SARS-CoV in 2002, which may help explain why the complications that develop are more serious, and the probability of contagion is greater, having a great impact on the health of the population [13]. It was determined that in SARS-CoV, ACE2 plays a very important role so that it can cross the cell membrane and be able to replicate the SARS-CoV; taking into account that SARS-CoV-2 also interacts with ACE2, an important protein for the interaction of ACE2 with SARS-CoV2, the TMPRSS2, was identified; where it is demonstrated that if it is limited to this protein, the interaction of the virus with the cell can be affected [14]. This viral infection dependent on cellular entry of the virus that utilize the cellular machinery of the host to replicate multiple viral copies that are subsequently shed by the host cell. Coronaviruses such as SARS-CoV and SARS-CoV-2 are now known to utilize the host protein ACE2 as a co-receptor to gain intracellular entry in the cells [4] [5] [14]. ACE2 is a membrane-bound peptidase that is expressed in essentially all tissues, with increased activity in the ileum and kidney, adipose tissue, the heart, the brainstem, the lung, blood vessels, the stomach, and the liver [3].

4. ACE2 as Therapeutic Target against COVID-19

The development of drugs and vaccines against covid-19 is a work in progress around the world, proposing specific therapeutic targets against SARS-CoV-2 is what could result in an effective medicine, since this pandemic has been treated in different ways. Forms and with treatments that were previously designed for other diseases.

Some works for the development of new drugs against SARS-CoV-2, propose epitopes as potential sites of interaction [15], as well as using docking and compound libraries [17], as well as looking for a repositioning of drugs [16], to search for compounds that interact with some SARS-CoV-2 region and thus be able to prevent interaction with ACE2. Recently, new antivirals have been developed, focusing on RNA-Dependent RNA Polymerase (RdRp) (Remdesivir, Ribavirin and Favipiravir) [18], Polyproteins (3CLpro and PLpro) (Lopinavir and Darunavir) [19-21], Spike Protein (S-Protein) [19, 22], membrane fusion inhibitors (HR1 and

HR2 of S-Protein) from SARS-CoV-2 [16, 23, 24] and against ACE2 [6]. Without a treatment that demonstrating an advantage therapeutic yet, which demonstrates the urgent need for the development of specific drugs against a selective target that alters the evolution of this disease. A drug that was proposed to interact in ACE2, is Arbidol, but was reported the crystallographic structure and demonstrated that Arbidol interacts in S-protein (domain S2) from SARS-CoV-2 [25].

Proposing ACE2 as a therapeutic target has not been very popular, since, as we know, ACE2 works as a gateway for this virus, so we would be thinking of a drug that helps antiviral treatment, in order to make entry more difficult or even, prevent entry of the virus, and thus prevent the infectious process of SARS-CoV-2. An important point is to determine what would happen if a drug directed at ACE2 could cause some loss of the classic functions of ACE2, mainly in the cardiovascular system. Side effects of anti-hypertensive drugs such as losartan, are already known [26, 27], as well as other drugs like lisinopril, ramipril, olmesartan, losartan, valsartan, candesartan, telmisartán, atorvastatin, Fluvastatin, among others [27-32], that they can have an effect on the functions of ACE2 and the infectious process of COVID-19, therefore, using ACE2 as a therapeutic target may have disadvantages.

To assess the effect that a drug against COVID-19 would have that is directed towards ACE2, and the RBD of SARS-CoV-2 has to be addressed, 20 compounds have recently been published that are directed to prevent the interaction between ACE2 and RBD from S-Protein [33], with which a drug could be developed to prevent entry to this type of virus (Figure 1, the site reported as a therapeutic target in ACE2 is in amino acids:Gln24, Asp30, His34, Tyr41, Gln42, Met82, Lys353 and Arg357 [33]).

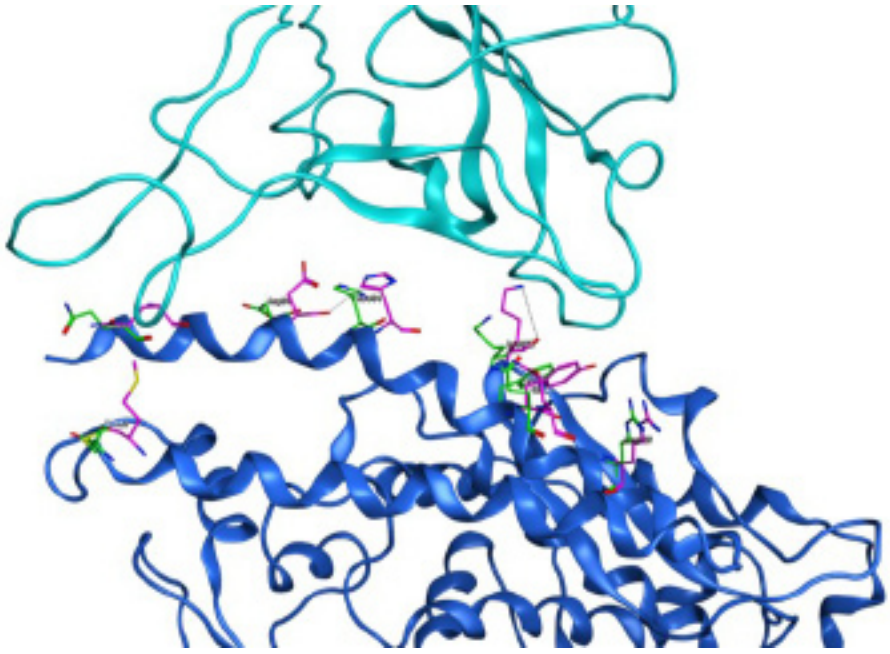

Figure 1: ACE2 (Blue) shows residues Gln24, Asp30, His34, Tyr41, Gln42, Met82, Lys353 and Arg357 (Green) and region binding domain (RBD of S-Protein in Cyan).

5. **Conclusions**

ACE2 has a very important role in the development of the infectious process of SARS-CoV-2, understanding the changes that may occur due to the drugs currently used as anti-hypertensives are still being studied, and now, proposing ACE2 as a therapeutic target for COVID-19, it requires more attention. Using ACE2 for drug development should be evaluated, check the efficacy of compounds directed towards ACE2 and their effect on the infectious process of COVID-19 [33], through *in vivo* assays, and assess the risk/benefit of the effects of these compounds that could generate in humans.

References

1. F. Li, W. Li, M. Farzan, and S. C. Harrison, "Structure of SARS coronavirus spike receptor-binding domain complexed with receptor.," Science, vol. 309, no. 5742, pp. 1864–8, Sep. 2005.

2. E. de Wit, N. van Doremalen, D. Falzarano, and V. J. Munster, "SARS and MERS: recent insights into emerging coronaviruses.," Nat. Rev. Microbiol., vol. 14, no. 8, pp. 523–34, 2016.

3. R. A. S. Santos et al., "The ACE2/Angiotensin-(1–7)/MAS Axis of the Renin-Angiotensin System: Focus on Angiotensin-(1–7)," Physiol. Rev., vol. 98, no. 1, pp. 505–553, Jan. 2018.

4. M. Hoffmann et al., "SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor," Cell, Mar. 2020.

5. R. Yan, Y. Zhang, Y. Li, L. Xia, Y. Guo, and Q. Zhou, "Structural basis for the recognition of the SARS-CoV-2 by full-length human ACE2," Science (80-.)., p. eabb2762, Mar. 2020.

6. C. G. Benítez-Cardoza and J. L. Vique-Sánchez, "Potential inhibitors of the interaction between ACE2 and SARS-CoV-2 (RBD), to develop a drug," Life Sci., p. 117970, Jun. 2020.

7. M. José Soler, J. Lloveras, and D. Batlle, "Enzima conversiva de la angiotensina 2 y su papel emergente en la regulación del sistema renina-angiotensina," Med. Clin. (Barc)., vol. 131, no. 6, pp. 230–236, Jul. 2008.

8. A. M. South, D. I. Diz, and M. C. Chappell, "COVID-19, ACE2, and the cardiovascular consequences," Am. J. Physiol. Circ. Physiol., vol. 318, no. 5, pp. H1084–H1090, May 2020.

9. D. I. Diz et al., "Injections of angiotensin-converting enzyme 2 inhibitor MLN4760 into nucleus tractus solitarii reduce baroreceptor reflex sensitivity for heart rate control in rats," Exp. Physiol., vol. 93, no. 5, pp. 694–700, May 2008.

10. N. Alenina and M. Bader, "ACE2 in Brain Physiology and Pathophysiology: Evidence from Transgenic Animal Models," Neurochem. Res., vol. 44, no. 6, pp. 1323–1329, Jun. 2019.

11. M. C. Chappell, A. C. Marshall, E. M. Alzayadneh, H. A. Shaltout, and D. I. Diz, "Update on the Angiotensin Converting Enzyme 2-Angiotensin (1–7)-Mas Receptor Axis: Fetal Programing, Sex Differences, and Intracellular Pathways," Front. Endocrinol. (Lausanne)., vol. 4, 2014.

12. W. Guan et al., "Clinical Characteristics of Coronavirus Disease 2019 in China," N. Engl. J. Med., p. NEJMoa2002032, Feb. 2020.

13. A. C. Walls, Y.-J. Park, M. A. Tortorici, A. Wall, A. T. McGuire, and D. Veesler, "Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein," Cell, Mar. 2020.

14. M. Hoffmann et al., "SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor," Cell, Mar. 2020.

15. A. Grifoni, J. Sidney, Y. Zhang, R. H. Scheuermann, B. Peters, and A. Sette, "A Sequence Homology and Bioinformatic Approach Can Predict Candidate Targets for Immune Responses to SARS-CoV-2," Cell Host Microbe, Mar. 2020.

16. C. Wu et al., "Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods," Acta Pharm. Sin. B, vol. 10, no. 5, pp. 766–788, May 2020.

17. A.-T. Ton, F. Gentile, M. Hsing, F. Ban, and A. Cherkasov, "Rapid Identification of Potential Inhibitors of SARS-CoV-2 Main Protease by Deep Docking of 1.3 Billion Compounds," Mol. Inform., p. minf.202000028, Mar. 2020.

18. M. Wang et al., "Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro," Cell Res., vol. 30, no. 3, pp. 269–271, Mar. 2020.

19. J. Huang, W. Song, H. Huang, and Q. Sun, "Pharmacological Therapeutics Targeting RNA-Dependent RNA Polymerase, Proteinase and Spike Protein: From Mechanistic Studies to Clinical Trials for COVID-19," J. Clin. Med., vol. 9, no. 4, p. 1131, Apr. 2020.

20. T. P. Sheahan et al., "Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV," Nat. Commun., vol. 11, no. 1, p. 222, Dec. 2020.

21. G. Li and E. De Clercq, "Therapeutic options for the 2019 novel coronavirus (2019-nCoV)," Nat. Rev. Drug Discov., vol. 19, no. 3, pp. 149–150, Mar. 2020.

22. P. Calligari, S. Bobone, G. Ricci, and A. Bocedi, "Molecular Investigation of SARS–CoV-2 Proteins and Their Interactions with Antiviral Drugs," Viruses, vol. 12, no. 4, p. 445, Apr. 2020.

23. S. Xia et al., "A pan-coronavirus fusion inhibitor targeting the HR1 domain of human coronavirus spike.," Sci. Adv., vol. 5, no. 4, p. eaav4580, 2019.

24. S. Xia et al., "Inhibition of SARS-CoV-2 (previously 2019-nCoV) infection by a highly potent pan-coronavirus fusion inhibitor targeting its spike protein that harbors a high capacity to mediate membrane fusion," Cell Res., vol. 30, no. 4, pp. 343–355, Apr. 2020.

25. N. Vankadari, "Arbidol: A potential antiviral drug for the treatment of SARS-CoV-2 by blocking trimerization of the spike glycoprotein," Int. J. Antimicrob. Agents, p. 105998, Apr. 2020.

26. I. Hamming et al., "Differential regulation of renal angiotensin-converting enzyme (ACE) and ACE2 during ACE inhibition and dietary sodium restriction in healthy rats," Exp. Physiol., vol. 93, no. 5, pp. 631–638, May 2008.

27. C. M. Ferrario et al., "Effect of Angiotensin-Converting Enzyme Inhibition and Angiotensin II Receptor Blockers on Cardiac Angiotensin-Converting Enzyme 2," Circulation, vol. 111, no. 20, pp. 2605–2610, May 2005.

28. L. Zhu et al., "Activation of angiotensin II type 2 receptor suppresses TNF-α-induced ICAM-1 via NF-κB: possible role of ACE2," Am. J. Physiol. Circ. Physiol., vol. 309, no. 5, pp. H827–H834, Sep. 2015.

29. F. Lovren et al., "Angiotensin converting enzyme-2 confers endothelial protection and attenuates atherosclerosis," Am. J. Physiol. Circ. Physiol., vol. 295, no. 4, pp. H1377–H1384, Oct. 2008.

30. F. Jiang et al., "Angiotensin-converting enzyme 2 and angiotensin 1–7: novel therapeutic targets," Nat. Rev. Cardiol., vol. 11, no. 7, pp. 413–426, Jul. 2014.

31. K. Tikoo et al., "Tissue specific up regulation of ACE2 in rabbit model of atherosclerosis by atorvastatin: Role of epigenetic histone modifications," Biochem. Pharmacol., vol. 93, no. 3, pp. 343–351, Feb. 2015.

32. Y. H. Shin et al., "The effect of fluvastatin on cardiac fibrosis and angiotensin-converting enzyme-2 expression in glucose-controlled diabetic rat hearts," Heart Vessels, vol. 32, no. 5, pp. 618–627, May 2017.

33. C. G. Benítez-Cardoza and J. L. Vique-Sánchez, "Potential inhibitors of the interaction between ACE2 and SARS-CoV-2 (RBD), to develop a drug," Life Sci., vol. 256, p. 117970, Sep. 2020.