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Title:

The exogenous human recombinant ACE2 has therapeutic potential against covid-19

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ACE2 plays a crucial role to opposes the deleterious actions of Ang II in the RAAS

In the renin angiotensin-aldosterone system (RAAS), angiotensinogen is the first contributing protein factor to be released by liver into the blood stream. Then, it is truncated by a lung protease, renin, to angiotensin I (Ang I) which subsequently cleaved by angiotensin converting enzyme (ACE) to generate Ang II. This protein (Ang II) performs its functions mainly through its two receptors (AT_1R and AT_2R), distributing in different organs. While binding of Ang II to AT_1R results in hypertension, vasoconstriction and vascular growth, sympathetic activation, aldosterone release, and renal sodium resorption, its binding to AT_2R leads to vasodilation, inhibition of cell growth, apoptosis and natriuresis [1].

As a part of RAAS, ACE2 is a single-pass type I membrane protein which shows highest expression level in the lungs, heart, endothelium and kidney [2]. This membrane enzyme plays an important role to opposes many deleterious effects of Ang II on the AT_1R, including hypertension, vasoconstriction, oxidative stress, inflammation, endothelial dysfunction, endothelial cell, and vascular smooth muscle cell migration, growth, proliferation, and thrombosis [3]. In fact, ACE2 degrades Ang II, resulting in formation of a vasodilator peptide, angiotensin 1–7 (Ang 1–7), which upon binding to its membrane receptor (Mas), lowers blood pressure and exerts important protective functions in the cardiovascular system and kidney. Previous study also indicated that the extracellular domain of ACE2 can be cleaved from the transmembrane domain by another enzyme known as sheddase, and the resulting soluble protein is released into the blood stream and ultimately excreted into urine.

Both down regulation and upregulation of ACE2 may increase the risk of development of severe and fatal COVID-19.

The main entry of some coronaviruses, including the virus that causes COVID-19 (SARS-CoV-2) into cells is initiated by binding of their spike envelope glycoprotein (S) to a ACE2 receptor. The interaction of the spike protein of the coronavirus with ACE2 is to reduce the level of cell membrane ACE2 by internalization and degradation [5]. Since ACE2 has an important protective role by increasing the production of the vasodilator peptide Ang 1–7, its reduction level may contribute to the severity of coronavirus infections, leading to lung damages. On the other

hand, the medical conditions that upregulate ACE2 expression may affect the severity of coronavirus infection by increasing viral loading capacity of tissues such as lung [6]. The previous study indicated that the islet ACE2 expression can be increased in early and decreased in the late stages of type 2 diabetes [7]. Moreover, decreased glomerular expression of ACE2 has been described in rodent models of diabetes and in human kidney biopsies from patients with diabetic nephropathy. The ACE inhibitors and angiotensin receptor blockers (ARBs) that are used to treat high blood pressure have been shown in rodent studies to enhance ACE2 expression [8]. Also, the diabetic and hypertensive patients who treated with the ACE inhibitors and ARBs show a substantial increase in ACE2 expression. Moreover, the expression of ACE2 can also be increased by thiazolidinediones and ibuprofen and in those patients with cardiovascular diseases and smoker individuals [9, 10]. Thus, the increased expression of ACE2 would facilitate infection with COVID-19.

Recombinant human ACE2 (rhACE2) has a dual beneficial effects

The recombinant human ACE2 (rhACE2) has been found to be safe, with no negative hemodynamic effects in healthy volunteers and with a half-life of about 10 hours in human being. Since, the major product of ACE2 (Ang 1–7), has a range of anti-inflammatory, antioxidant and vasodilation effects, the soluble rhACE2 has important therapeutic potentials [11]. Several studies suggest that rhACE2 may be a promising drug for the patients with diabetes and lung injury [12]. In murine models, treatment with catalytically active rACE2 protein improved the symptoms of acute lung injury in wild-type mice as well as in ACE2 knockout mice [13]. In diabetic patients, the replenishment of ACE2 with rhACE2 in a mouse model attenuated diabetic kidney injury as well as lead to a significant reduction in blood pressure. Additionally, overexpression of human ACE2 enhanced disease severity in a mouse model of SARS-CoV infection, demonstrating that viral entry into cells is a critical step. This concept is currently being tested in a pilot study in patients with COVID-19. Thus, for SARS-CoV pathogenesis, ACE2 is not only the entry receptor of the virus but also protects from lung injury. Delivering excessive soluble form of ACE2 may competitively bind with SARS-CoV-2 not only to neutralize the virus but also rescue cellular ACE2 activity which negatively regulates the RAAS to protect the lung from injury. Indeed, enhanced ACE activity and decreased ACE2 availability contribute to lung injury during acid- and ventilator-induced lung injury. Thus, treatment with a soluble form of ACE2 itself may exert dual functions, slowing the viral entry into cells and hences viral spread and protect the lung from injury [14].

Interfering with the interaction interface of ACE2 and viral spike protein

Blocking the surface ACE2 receptor by using anti-ACE2 antibody or peptides is yet another important strategy to be considered against SARS-CoV-2. The interaction sites between ACE2 and SARS-CoV have been identified at the atomic level. Thus, one could target this interaction site with antibodies or small molecules. The residue 394 (glutamine) in the SARS-CoV-2 receptor-binding domain (RBD), can be recognized by the critical lysine 31 on the human ACE2 receptor [14]. Additionally, initial spike protein priming by transmembrane protease serine 2 (TMPRSS2) is essential for entry and viral spread of SARS-CoV-2 through interaction with the ACE2 receptor. The serine protease inhibitor camostat mesylate which has been approved in Japan to treat unrelated diseases, can block TMPRSS2 activity [15]. This medicine is an interesting candidate to fight against covid-19.

References

[1] Kaschina E, Unger T (2018) Prehypertension and the Renin-Angiotensin-Aldosterone System. Prehypertension and Cardiometabolic Syndrome pp 307-318.

[2] Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H, Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004 Jun;203(2):631-7.

[3] Jasmina Varagic, Sarfaraz Ahmad, Sayaka Nagata, Carlos M. Ferrario (2014) ACE2: Angiotensin II/Angiotensin-(1-7) balance in cardiorenal injury. Curr Hypertens Rep. 2014 Mar; 16(3): 420.

[4] Lambert DW, Yarski M, Warner FJ, Thornhill P, Parkin ET, Smith AI, et al., Tumor necrosis factor-alpha convertase (ADAM17) mediates regulated ectodomain shedding of the severe-acute respiratory syndrome-coronavirus (SARS-CoV) receptor, angiotensin-converting enzyme-2 (ACE2). The Journal of Biological Chemistry, 2005, 280 (34): 30113–9.

[5] Chakraborti S, Prabakaran P, Xiao X, Dimitrov DS, The SARS Coronavirus S Glycoprotein Receptor Binding Domain: Fine Mapping and Functional Chara. Virol J. 2005, 2: 73.

[6] Clarke NE, Turner AJ, Angiotensin-Converting Enzyme 2: The First Decade. International Journal of Hypertension, 2012, 12:9-12.

[7] Batlle D, Soler MJ, Ye M, ACE2 and Diabetes: ACE of ACEs? Diabetes. 2010, 59 (12): 2994–2996.

[8] Patel AB, Verma V, COVID-19 and Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor BlockersWhat Is the Evidence?, JAMA. Published online March 24, 2020. doi:10.1001/jama.2020.4812.

[9] Fang L et al., Lancet Respir Med. 2020 Mar 11. doi: 10.1016/S2213-2600(20)30116-8.

[10] Brake JS, et al., Smoking Upregulates Angiotensin-Converting Enzyme-2 Receptor: A Potential Adhesion Site for Novel Coronavirus SARS-CoV-2 (Covid-19). J. Clin. Med. 2020, 9(3), 841.

[11] Zhang H, Baker A, Recombinant human ACE2: acing out angiotensin II in ARDS therapy, Crit Care. 2017; 21: 305.

[12] Oudit GY et al., Human Recombinant ACE2 Reduces the Progression of Diabetic Nephropathy, Diabetes 2010 Feb; 59(2): 529-538.

[13] Tikellis C, Thomas MC, Angiotensin-Converting Enzyme 2 (ACE2) Is a Key Modulator of the Renin Angiotensin System in Health and Disease. Int J Pept. 2012; 2012: 256294.

[14] Zhang H et al., Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target, Intensive Care Medicine (2020).

[15] Hoffmann M, et al., The novel coronavirus 2019 (COVID-19) uses the SARS-1 coronavirus

receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells. bioRxiv. https ://doi.org/10.1101/2020.01.31.929042.