**Name of Journal:** *World Journal of Gastrointestinal Oncology*

**Manuscript NO:** 61679

**Manuscript Type:** EDITORIAL

**Angiotensin-converting enzyme 2 connects COVID-19 with cancer and cancer immunotherapy**

Wang XS. ACE2, COVID-19, and cancer

Xiao-Sheng Wang

**Xiao-Sheng Wang,** School of Basic Medicine and Clinical Pharmacy, China Pharmaceutical University, Nanjing 211198, Jiangsu Province, China

**Author contributions:** Wang XS conceived of and wrote the manuscript.

**Corresponding author: Xiao-Sheng Wang, PhD, Associate Professor,** School of Basic Medicine and Clinical Pharmacy, China Pharmaceutical University, No. 639 Longmian Avenue, Nanjing 211198, Jiangsu Province, China. xiaosheng.wang@cpu.edu.cn

**Received:** December 16, 2020

**Revised:** January 18, 2021

**Accepted:** February 4, 2021

**Published online:** March 15, 2021

**Abstract**

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in more than two million deaths. Underlying diseases, including cancer, are high-risk factors for severe COVID-19 outcomes. Angiotensin-converting enzyme 2 (ACE2), as a SARS-CoV-2 host cell receptor, plays a crucial role in SARS-CoV-2 invading human cells. ACE2 also has significant associations with cancer. Recent studies showed that ACE2 was inversely correlated with the activities of multiple oncogenic pathways and tumor progression phenotypes, and was positively correlated with antitumor immune response and survival prognosis in diverse cancers, suggesting a potential protective role of ACE2 in cancer progression. Positive expression of ACE2 is also correlated with programmed death-ligand 1 (PD-L1) in cancer. The positive associations of ACE2 expression with antitumor immune signatures and PD-L1 expression indicate that ACE2 expression is a positive predictor for the response to immune checkpoint inhibitors (ICIs). This was evidenced in multiple cancer cohorts treated with ICIs. Thus, ACE2 may build potential connections between COVID-19 and cancer and cancer immunotherapy. The potential connections suggest that ACE2 inhibitors may not be a good option for treating COVID-19 patients with cancer, particularly in cancer patients who are receiving immunotherapy. Furthermore, the relationships between ACE2, COVID-19, and cancer are worth confirming by more experimental and clinical data, considering that many cancer patients are at high risk for COVID-19.

**Key Words:** Angiotensin-converting enzyme 2; COVID-19; Cancer progression; Antitumor immune responses; Cancer immunotherapy

**©The** **Author(s) 2021.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Citation:** Wang XS. Angiotensin-converting enzyme 2 connects COVID-19 with cancer and cancer immunotherapy. *World J Gastrointest Oncol* 2021; 13(3): 157-160

URL: https://www.wjgnet.com/1948-5204/full/v13/i3/157.htm

DOI: https://dx.doi.org/10.4251/wjgo.v13.i3.157

**Core Tip:** Angiotensin-converting enzyme 2 (ACE2) is a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) host cell receptor and plays a crucial role in SARS-CoV-2 invading human cells to cause coronavirus disease 2019 (COVID-19). ACE2 also plays a role in preventing tumor progression and promoting cancer immunotherapy response. Thus, the use of ACE2 inhibitors to prevent and treat COVID-19 should be carried out cautiously in cancer patients.

**INTRODUCTION**

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused more than 113 million cases of coronavirus disease 2019 (COVID-19) and 2.5 million deaths as of February 25, 2021[1]. More seriously, a second waveof the COVID-19 pandemic has emerged and is expected to be more infectious and more deadly. Abundant evidence[2] has shown that many underlying diseases, including cancer, are risk factors for severe COVID-19 outcomes. Thus, specific measures to protect people with underlying diseases from SARS-CoV-2 infection or the development of severe COVID-19 are crucial for reducing COVID-19 deaths. Similar to cancer, COVID-19 may affect various human organs or tissues, including the lungs, kidneys, liver, brain, colon, stomach, and skin, in light of the fact that the SARS-CoV-2 host cell receptor angiotensin-converting enzyme 2 (ACE2) is expressed in a wide range of human tissues[3]. In fact, the essential role of ACE2 in SARS-CoV-2 invasion into human tissues is well recognized[4].

**ASSOCIATION BETWEEN ACE2 AND CANCER**

ACE2 also plays an important role in cancer. For example, Dai *et al*[5] showed that increased ACE2 expression was associated with a better survival prognosis in liver cancer. ACE2 exerts antitumor effects by inhibiting tumor angiogenesis[6]. Several recent studies explored the associations of ACE2 with antitumor immunity and immunotherapy response[7-9]. Yang *et al*[7] showed that the elevated expression of *ACE2* was correlated with increased antitumor immune response in uterine corpus endometrial and renal papillary cell cancers. Bao *et al*[8] revealed strong associations between *ACE2* expression and immune gene signatures in cancer. Our recent study[9] systematically explored the associations of *ACE2* expression with antitumor immune signatures, tumor progression phenotypes, oncogenic signatures, and clinical features in 13 cancer cohorts. We found that the expression levels of *ACE2* were inversely correlated with the levels of tumor proliferation, stemness, and epithelial-mesenchymal transition in diverse cancers. Moreover, *ACE2* expression levels were inversely correlated with the activities of multiple oncogenic pathways in cancer, including the cell cycle, vascular endothelial growth factor, transforming growth factor-β, Wnt, and Notch signaling. In contrast, the expression levels of *ACE2* correlated positively with diverse antitumor immune signatures in cancer, including antigen processing and presentation, T cell and B cell receptor signaling, nucleotide-binding and oligomerization domain-like receptor signaling, chemokine signaling, cytokine-cytokine receptor interaction, natural killer cell-mediated cytotoxicity, and Jak-STAT signaling. As a result, increased *ACE2* expression was associated with a favorable survival prognosis in multiple cancer cohorts, including renal clear cell carcinoma, renal papillary cell carcinoma, lung adenocarcinoma, and ovarian carcinoma[9]. Interestingly, the expression levels of *ACE2* were significantly lower in advanced than in non-advanced tumors in renal clear cell carcinoma. Overall, these data suggest a potential protective role of ACE2 in cancer development. Interestingly, positive expression of *ACE2* was significantly correlated with the gene encoding programmed death-ligand 1 (PD-L1)in cancer. As both the inflamed immune microenvironment and high PD-L1 expression are positively associated with the response to immune checkpoint inhibitors (ICIs), *ACE2* upregulation may indicate an increased immunotherapy response in cancer. Indeed, in four cancer cohorts involving three cancer types (melanoma, renal clear cell carcinoma, and bladder cancer), the cancers with higher *ACE2* expression levels (> median) showed a higher rate of response to ICIs than the cancers with lower *ACE2* expression levels (< median).

**CONCLUSION**

Emerging evidence suggests potential associations between COVID-19 and cancer and cancer immunotherapy through ACE2 (Figure 1). In light of the important roles of ACE2 in preventing tumor progression and promoting cancer immunotherapy response, ACE2 inhibitors may not be a good option for treating COVID-19 patients with cancer, particularly in cancer patients who are receiving immunotherapy. The protective role of ACE2 in cancer progression and the function of ACE2 in promoting cancer immunotherapy response need to be further confirmed by more experimental and clinical data.

**ACKNOWLEDGEMENTS**

I appreciate Mr. Feng QS from China Pharmaceutical University for editing the manuscript.

**REFERENCES**

1 **Johns Hopkins University**. COVID-19 Dashboard by the Center for System Science and Engineering (CSSE) at Johns Hopkins University (JHU) [Internet]. 2020. Available from: https://coronavirus.jhu.edu/map.html

2 **Li M**, Zhang Z, Cao W, Liu Y, Du B, Chen C, Liu Q, Uddin MN, Jiang S, Chen C, Zhang Y, Wang X. Identifying novel factors associated with COVID-19 transmission and fatality using the machine learning approach. *Sci Total Environ* 2020; **764**: 142810 [PMID: 33097268 DOI: 10.1016/j.scitotenv.2020.142810]

3 **Li MY**, Li L, Zhang Y, Wang XS. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. *Infect Dis Poverty* 2020; **9**: 45 [PMID: 32345362 DOI: 10.1186/s40249-020-00662-x]

4 **Hoffmann M**, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* 2020; **181**: 271-280.e8 [PMID: 32142651 DOI: 10.1016/j.cell.2020.02.052]

5 **Dai YJ**, Hu F, Li H, Huang HY, Wang DW, Liang Y. A profiling analysis on the receptor ACE2 expression reveals the potential risk of different type of cancers vulnerable to SARS-CoV-2 infection. *Ann Transl Med* 2020; **8**: 481 [PMID: 32395525 DOI: 10.21037/atm.2020.03.61]

6 **Zhang Q**, Lu S, Li T, Yu L, Zhang Y, Zeng H, Qian X, Bi J, Lin Y. ACE2 inhibits breast cancer angiogenesis *via* suppressing the VEGFa/VEGFR2/ERK pathway. *J Exp Clin Cancer Res* 2019; **38**: 173 [PMID: 31023337 DOI: 10.1186/s13046-019-1156-5]

7 **Yang J**, Li H, Hu S, Zhou Y. ACE2 correlated with immune infiltration serves as a prognostic biomarker in endometrial carcinoma and renal papillary cell carcinoma: implication for COVID-19. *Aging (Albany NY)* 2020; **12**: 6518-6535 [PMID: 32339157 DOI: 10.18632/aging.103100]

8 **Bao R**, Hernandez K, Huang L, Luke JJ. *ACE2* and *TMPRSS2* expression by clinical, HLA, immune, and microbial correlates across 34 human cancers and matched normal tissues: implications for SARS-CoV-2 COVID-19. *J Immunother Cancer* 2020; **8** [PMID: 32675312 DOI: 10.1136/jitc-2020-001020]

9 **Zhang Z**, Li L, Li M, Wang X. The SARS-CoV-2 host cell receptor ACE2 correlates positively with immunotherapy response and is a potential protective factor for cancer progression. *Comput Struct Biotechnol J* 2020; **18**: 2438-2444 [PMID: 32905022 DOI: 10.1016/j.csbj.2020.08.024]

**Footnotes**

**Conflict-of-interest statement:** No potential conflicts of interest.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Peer-review started:** December 16, 2020

**First decision:** January 11, 2021

**Article in press:** February 4, 2021

**Specialty type:** Oncology

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Mostaf-Hedeab G **S-Editor:** Fan JR **L-Editor:** Webster JR **P-Editor:** Li JH

**Figure Legends**



**Figure 1 An illustration of the relationships between angiotensin-converting enzyme 2, coronavirus disease 2019, and cancer.** ACE2: Angiotensin-converting enzyme 2; COVID-19: Coronavirus disease 2019; EMT: Epithelial-mesenchymal transition; PD-L1: Programmed death-ligand 1; TGF-β: Transforming growth factor-β; VEGF: Vascular endothelial growth factor.



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** bpgoffice@wjgnet.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2021 Baishideng Publishing Group Inc. All rights reserved.**