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A Commentary on   
SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor

*by Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., et al. (2020). Cell 181, 271–280. doi:* [*10. 1016/j. cell. 2020. 02. 052*](https://doi.org/10.1016/j.cell.2020.02.052)

In December 2019, a novel pneumonia condition termed coronavirus disease 2019 (COVID-19) was reported in Wuhan, China ( [1](#B1) ). The global burden of COVID-19 is increasing exponentially and as of 2nd July 2020, there were over 10, 834, 240 confirmed cases in about 213 countries and territories, with more than 519, 590 fatalities ( [https://www. worldometers. info/coronavirus/](https://www.worldometers.info/coronavirus/) ). Currently, there are no specific antivirals or vaccines approved against COVID-19.

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a new member of coronaviruses, a group of enveloped, positive-sense, single-stranded RNA viruses ( [2](#B2) ). SARS-CoV-2 likely originated from *Rhinolophus affinis* bat species, based on 96. 2% nucleotide sequence identity to the bat coronavirus, BatCoV RaTG13 ( [3](#B3) ). The virus causes more severe disease in males than in females. Furthermore, COVID-19 is more severe in older persons than the youth ( [4](#B4) ). It is largely unclear why there is differential severity in age and sex. However, the severity of COVID-19 in males could be related to their higher ACE2 profiles ( [5](#B5) ).

Here, leveraging the recent finding by Hoffmann et al. ( [1](#B1) ) that ACE2 and TMPRSS2 are critical for SARS-CoV-2 cell entry, we discuss the potential link between the SARS-CoV-2 receptors and the prostate gland and whether SARS-CoV-2 is a potential oncogenic virus for prostate cancer.

## SARS-CoV-2 Entry Into Human Cells

Entry of coronaviruses into target cells is facilitated by the spike (S) protein. Entry is dependent on binding of the surface unit, S1, of the S protein to a cellular receptor, which enhances viral attachment to the surface of target cells. Entry also requires priming of S protein by cellular proteases. The priming involves S protein cleavage at the S1/S2 and the S2' site to allow viral and cellular membrane fusion, a process driven by the S2 subunit. SARS-CoV-2 engages angiotensin-converting enzyme 2 (ACE2) as the entry receptor and serine protease TMPRSS2 for the S protein priming ( [1](#B1) ). The primary physiological role of ACE2 is the maturation of angiotensin, a peptide hormone that regulates vasoconstriction and blood pressure ( [2](#B2) ). ACE2 is a type I membrane protein expressed in the heart, lungs, kidneys, testes and intestine ( [2](#B2) , [4](#B4) ). Reduced expression of ACE2 is linked with many chronic conditions ( [2](#B2) ). Other conditions that are exacerbated by high ACE activity, such as prostate cancer ( [6](#B6) ), are potentially affected by SARS-CoV-2 infection, which reduces ACE2 since reduced ACE2 implies upregulated ACE activity ( [4](#B4) ).

On the other hand, TMPRSS2 plays a major role in SARS-CoV-2 cell entry and is coincidentally dysregulated in prostate cancer. Additionally, TMPRSS2 is highly expressed in prostate epithelial cells in an androgen-dependent manner. Taken together, the findings that SARS-CoV-2 utilizes ACE2 and TMPRSS2 presupposes that SARS-CoV-2 could be an oncogenic virus for prostate cancer. For cells lacking or with reduced TMPRSS2 expression, Furin preactivation promotes SARS-CoV-2 entry into target cells ( [7](#B7) ). Subsequently, we discuss why SARS-CoV-2 could be linked with prostate carcinogenesis.

## Interplay Between SARS-CoV-2 Cell Entry Molecules and Prostate Biology

The role of renin-angiotensin system (RAS) and ACE in the pathology of carcinomas is well-established. ACE generates an effector peptide of the RAS system, angiotensin II (Ang II) via degradation of the vasodilator kinins ( [8](#B8) ). The prostate independently synthesizes ACE. The angiotensin II type 1 receptor is the predominant Ang II prostatic receptor. Inhibition of ACE activity has been shown to suppress tumor growth and angiogenesis *in vitro* and *in vivo* in animal models ( [9](#B9) ). Considering that ACE2 antagonizes the effects of ACE, it is probable that downregulation of ACE2 expression as in SARS-CoV-2 infection ( [4](#B4) ), which implies elevated ACE activity, may potentiate prostate carcinogenesis. This view is fortified by recent observation of SARS-CoV 2 in the semen of COVID-19 patients ( [10](#B10) ). The observation suggests that the virus could infect the prostate gland via SARS-CoV-2 entry molecules (ACE2 and TMPRSS2 or Furin), which are expressed by the prostate cells ( [11](#B11) , [12](#B12) ).

TMPRSS2 protein, utilized by SARS-CoV-2 for S protein priming is highly expressed in normal prostate epithelial and prostate cancer cells. Moreover, TMPRSS2 is expressed in an androgen-dependent manner, particularly in the prostate ( [13](#B13) ). Additionally, the fact that signaling through the androgen receptor (AR) axis facilitates prostate cancer development ( [14](#B14) ), suggests a relationship between TMPRSS2 and prostate cancer. Studies have linked TMPRSS2 to prostate cancer via a chromosomal translocation resulting in the fusion of the TMPRSS2 promoter-enhancer with the Erythroblast Transformation Specific (ETS) transcription factors ETS-related gene ( *ERG* ) and ETS translocation variant 1 ( *ETV1* ) ( [13](#B13) ). This fusion recruits AR and TOP2B topoisomerase to chromosomal sites, where TOP2B instigates double-stranded breaks in DNA. Indeed, TMPRSS2-ERG fusion is associated with 40–70% of prostate cancer ( [13](#B13) ). SARS-CoV-2, cell entry is expected to reduce TMPRSS2, hence, lowering the TMPRSS2-ERG fusion. However, TMPRSS2 expression is increased in cells adjacent to SARS-CoV-2-infected cells ( [15](#B15) ). The increased TMPRSS2 expression could then promote TMPRSS2-ERG fusion events, hence predisposing male SARS-CoV-2-infected patients to prostate cancer. Alternatively, for cells lacking or with reduced TMPRSS2 expression, Furin preactivation promotes SARS-CoV-2 entry into target cells ( [7](#B7) ). Notably, the prostate gland and prostate cancer cells express Furin ( [11](#B11) ); thus, the virus may efficiently enter the prostate gland and/or prostate cancer cells using TMPRSS2 or Furin to initiate or enhance carcinogenesis.

## Is SARS-CoV-2 a Potential Oncogenic Virus for Prostate Cancer?

Is SARS-CoV-2 therefore an oncogenic virus? First, the expression of SARS-CoV-2 cell entry molecules in the prostate gland strongly suggests a SARS-CoV-2 prostate gland tropism. Secondly, SARS-CoV-2 infection is characterized by chronic inflammation ( [16](#B16) ). Chronic inflammation causes aberrant DNA methylation, which promotes cancer development ( [17](#B17) ). Inflammation is linked to about 60% of prostate cancer cases ( [18](#B18) ).

Changes in expression levels of TMPRSS2 have been previously associated with prostate cancer independently of SARS-CoV-2. Elevated expression of TMPRSS2 in the context of SARS-CoV-2 infections ( [15](#B15) ) implies that SARS-CoV-2 infection could increase chances of TMPRSS2 fusions, a phenomenon well-associated with prostate cancer development and progression ( [13](#B13) ). It is not precisely clear how SARS-CoV-2 may induce prostate cancer considering that it has not been shown to encode any known oncoprotein. However, given that SARS-CoV-2 can infect prostate cells, at least theoretically, it is probable that the virus can prompt prostate carcinogenesis via modulation of TMPRSS2 and/or exacerbating chronic inflammation in SARS-CoV-2 infected males ( [16](#B16) ). Taken together, it is plausible to hypothesize that SARS-CoV-2 could be an oncogenic virus for prostate cancer.

## Conclusions

SARS-CoV-2 and other coronaviruses are likely to remain in our midst for a long time. Although efforts are now geared toward the immediate preventive and treatment measures to avert fatalities, what we have presented above suggests that SARS-CoV-2 and similar coronaviruses could have long term effects such as involvement in cancer development. Specifically, we have highlighted a possible link between SARS-CoV-2 and prostate cancer based on the involvement of SARS-CoV-2 cell entry molecules on prostate biology. Nevertheless, detailed molecular and cell biology studies are warranted to prove our hypotheses.

## Author Contributions

AD and CO conceived and prepared the first draft of the manuscript. TS and LP critically reviewed the draft. All authors approved the final version of the manuscript.

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## Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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