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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.

## References

1. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell.* (2020) 181: 271–80. doi: 10. 1016/j. cell. 2020. 02. 052

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/32142651) | [CrossRef Full Text](https://doi.org/10.1016/j.cell.2020.02.052) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=M.+Hoffmann&author=H.+Kleine-Weber&author=S.+Schroeder&author=N.+Krüger&author=T.+Herrler&author=S.+Erichsen+&publication_year=2020&title=SARS-CoV-2+cell+entry+depends+on+ACE2+and+TMPRSS2+and+is+blocked+by+a+clinically+proven+protease+inhibitor&journal=Cell.&volume=181&pages=271-80)

2. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. *Science.* (2020) 367: 1444–8. doi: 10. 1126/science. abb2762

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/32132184) | [CrossRef Full Text](https://doi.org/10.1126/science.abb2762) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=R.+Yan&author=Y.+Zhang&author=Y.+Li&author=L.+Xia&author=Y.+Guo&author=Q.+Zhou+&publication_year=2020&title=Structural+basis+for+the+recognition+of+SARS-CoV-2+by+full-length+human+ACE2&journal=Science.&volume=367&pages=1444-8)

3. Zhou P, Yang X, Wang X, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature.* (2020) 579: 270–3. doi: 10. 1038/s41586-020-2012-7

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/32015507) | [CrossRef Full Text](https://doi.org/10.1038/s41586-020-2012-7) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=P.+Zhou&author=X.+Yang&author=X.+Wang&author=B.+Hu&author=L.+Zhang&author=W.+Zhang+&publication_year=2020&title=A+pneumonia+outbreak+associated+with+a+new+coronavirus+of+probable+bat+origin&journal=Nature.&volume=579&pages=270-3)

4. Cheng H, Wang Y, Wang G. Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19. *J Med Microbiol.* (2020) 2020: 1–5. doi: 10. 1002/jmv. 25785

[CrossRef Full Text](https://doi.org/10.1002/jmv.25785) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=H.+Cheng&author=Y.+Wang&author=G.+Wang+&publication_year=2020&title=Organ-protective+effect+of+angiotensin-converting+enzyme+2+and+its+effect+on+the+prognosis+of+COVID-19&journal=J+Med+Microbiol.&volume=2020&pages=1-5)

5. Sama I, Ravera A, Santema B, Goor H, Maaten J, Cleland J, et al. Circulating plasma concentrations of angiotensin-converting enzyme 2 in men and women with heart failure and effects of renin-angiotensin-aldosterone inhibitors. *Eur Heart J.* (2020) 41: 1810–7. doi: 10. 1093/eurheart/ehaa373

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/32388565) | [CrossRef Full Text](https://doi.org/10.1093/eurheart/ehaa373) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=I.+Sama&author=A.+Ravera&author=B.+Santema&author=H.+Goor&author=J.+Maaten&author=J.+Cleland+&publication_year=2020&title=Circulating+plasma+concentrations+of+angiotensin-converting+enzyme+2+in+men+and+women+with+heart+failure+and+effects+of+renin-angiotensin-aldosterone+inhibitors&journal=Eur+Heart+J.&volume=41&pages=1810-7)

6. Wang Z, Li H, Jiang Z, Zhou T. Relationship between angiotensin-converting enzyme insertion/deletion gene polymorphism and prostate cancer susceptibility. *J Can Res Ther.* (2018) 14: 375–80. doi: 10. 4103/0973-1482. 171366

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/29970692) | [CrossRef Full Text](https://doi.org/10.4103/0973-1482.171366) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=Z.+Wang&author=H.+Li&author=Z.+Jiang&author=T.+Zhou+&publication_year=2018&title=Relationship+between+angiotensin-converting+enzyme+insertion%2Fdeletion+gene+polymorphism+and+prostate+cancer+susceptibility&journal=J+Can+Res+Ther.&volume=14&pages=375-80)

7. Shang J, Wan Y, Luo C, Ye G, Geng Q, Auerbach A, et al. Cell entry mechanisms of SARS-CoV-2. *Proc Natl Acad Sci USA.* (2020) 117: 11727–34. doi: 10. 1073/pnas. 2003138117

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/32376634) | [CrossRef Full Text](https://doi.org/10.1073/pnas.2003138117) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=J.+Shang&author=Y.+Wan&author=C.+Luo&author=G.+Ye&author=Q.+Geng&author=A.+Auerbach+&publication_year=2020&title=Cell+entry+mechanisms+of+SARS-CoV-2&journal=Proc+Natl+Acad+Sci+USA.&volume=117&pages=11727-34)

8. Danilov SM, Kadrev AV, Kurilova OV, Tikhomirova VE, Kryukova OV, Mamedov VN, et al. Tissue ACE phenotyping in prostate cancer. *Oncotarget.* (2019) 10: 6349–61. doi: 10. 18632/oncotarget. 27276

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/31695843) | [CrossRef Full Text](https://doi.org/10.18632/oncotarget.27276) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=SM.+Danilov&author=AV.+Kadrev&author=OV.+Kurilova&author=VE.+Tikhomirova&author=OV.+Kryukova&author=VN.+Mamedov+&publication_year=2019&title=Tissue+ACE+phenotyping+in+prostate+cancer&journal=Oncotarget.&volume=10&pages=6349-61)

9. Yasumatsu R, Nakashima T, Masuda M, Ito A, Kuratomi Y, Nakagawa T, et al. Effects of the angiotensin-I-converting enzyme inhibitor perindopril on tumor growth and angiogenesis in head and neck squamous cell carcinoma cells. *J Cancer Res Clin Oncol* . (2004) 130: 567–73. doi: 10. 1007/s00432-004-0582-7

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/15449186) | [CrossRef Full Text](https://doi.org/10.1007/s00432-004-0582-7) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=R.+Yasumatsu&author=T.+Nakashima&author=M.+Masuda&author=A.+Ito&author=Y.+Kuratomi&author=T.+Nakagawa+&publication_year=2004&title=Effects+of+the+angiotensin-I-converting+enzyme+inhibitor+perindopril+on+tumor+growth+and+angiogenesis+in+head+and+neck+squamous+cell+carcinoma+cells&journal=J+Cancer+Res+Clin+Oncol&volume=130&pages=567-73)

10. Li D, Jin M, Bao P, Zhao W, Zhang S. Clinical characteristics and results of semen tests among men with coronavirus disease 2019. *JAMA Netw Open.* (2020) 3: e208292. doi: 10. 1001/jamanetworkopen. 2020. 8292

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/32379329) | [CrossRef Full Text](https://doi.org/10.1001/jamanetworkopen.2020.8292) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=D.+Li&author=M.+Jin&author=P.+Bao&author=W.+Zhao&author=S.+Zhang+&publication_year=2020&title=Clinical+characteristics+and+results+of+semen+tests+among+men+with+coronavirus+disease+2019&journal=JAMA+Netw+Open.&volume=3&pages=e208292)

11. Couture F, D'Anjou F, Desjardins R, Boudreau F, Day R. Role of proprotein convertases in prostate cancer progression. *Neoplasia.* (2012) 14: 1032–42. doi: 10. 1593/neo. 121368

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/23226097) | [CrossRef Full Text](https://doi.org/10.1593/neo.121368) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=F.+Couture&author=F.+D'Anjou&author=R.+Desjardins&author=F.+Boudreau&author=R.+Day+&publication_year=2012&title=Role+of+proprotein+convertases+in+prostate+cancer+progression&journal=Neoplasia.&volume=14&pages=1032-42)

12. Song H, Seddighzadeh B, Cooperberg MR, Huang FW. Expression of ACE2, the SARS-CoV-2 receptor, and TMPRSS2 in prostate epithelial cells. *Eur Urol.* (2020) 78: 296–8. doi: 10. 1016/j. eururo. 2020. 04. 065

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/32418620) | [CrossRef Full Text](https://doi.org/10.1016/j.eururo.2020.04.065) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=H.+Song&author=B.+Seddighzadeh&author=MR.+Cooperberg&author=FW.+Huang+&publication_year=2020&title=Expression+of+ACE2,+the+SARS-CoV-2+receptor,+and+TMPRSS2+in+prostate+epithelial+cells&journal=Eur+Urol.&volume=78&pages=296-8)

13. Mani RS, Amin MA, Li X, Kalyana-Sundaram S, Veeneman BA, Wang L, et al. Inflammation-induced oxidative stress mediates gene fusion formation in prostate cancer. *Cell Rep.* (2016) 17: 2620–31. doi: 10. 1016/j. celrep. 2016. 11. 019

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/27926866) | [CrossRef Full Text](https://doi.org/10.1016/j.celrep.2016.11.019) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=RS.+Mani&author=MA.+Amin&author=X.+Li&author=S.+Kalyana-Sundaram&author=BA.+Veeneman&author=L.+Wang+&publication_year=2016&title=Inflammation-induced+oxidative+stress+mediates+gene+fusion+formation+in+prostate+cancer&journal=Cell+Rep.&volume=17&pages=2620-31)

14. Zhou Y, Bolton EC, Jones JO. Androgens and androgen receptor signaling in prostate tumorigenesis. *J Mol Endocrinol.* (2015) 54: R15–29. doi: 10. 1530/JME-14-0203

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/25351819) | [CrossRef Full Text](https://doi.org/10.1530/JME-14-0203) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=Y.+Zhou&author=EC.+Bolton&author=JO.+Jones+&publication_year=2015&title=Androgens+and+androgen+receptor+signaling+in+prostate+tumorigenesis&journal=J+Mol+Endocrinol.&volume=54&pages=R15-29)

15. Matsuyama S, Nagata N, Shirato K, Kawase M, Takeda M, Taguchi F. Efficient activation of the severe acute respiratory syndrome coronavirus spike protein by the transmembrane protease TMPRSS2. *J Virol.* (2010) 84: 12658–64. doi: 10. 1128/JVI. 01542-10

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/20926566) | [CrossRef Full Text](https://doi.org/10.1128/JVI.01542-10) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=S.+Matsuyama&author=N.+Nagata&author=K.+Shirato&author=M.+Kawase&author=M.+Takeda&author=F.+Taguchi+&publication_year=2010&title=Efficient+activation+of+the+severe+acute+respiratory+syndrome+coronavirus+spike+protein+by+the+transmembrane+protease+TMPRSS2&journal=J+Virol.&volume=84&pages=12658-64)

16. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol.* (2020) 20: 1–12. doi: 10. 1038/s41577-020-0311-8

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/32346093) | [CrossRef Full Text](https://doi.org/10.1038/s41577-020-0311-8) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=MZ.+Tay&author=CM.+Poh&author=L.+Rénia&author=PA.+MacAry&author=LFP.+Ng+&publication_year=2020&title=The+trinity+of+COVID-19%3A+immunity,+inflammation+and+intervention&journal=Nat+Rev+Immunol.&volume=20&pages=1-12)

17. Hattori N, Ushijima T. Epigenetic impact of infection on carcinogenesis: mechanisms and applications. *Genome Med.* (2016) 8: 1–13. doi: 10. 1186/s13073-016-0267-2

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/26823082) | [CrossRef Full Text](https://doi.org/10.1186/s13073-016-0267-2) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=N.+Hattori&author=T.+Ushijima+&publication_year=2016&title=Epigenetic+impact+of+infection+on+carcinogenesis%3A+mechanisms+and+applications&journal=Genome+Med.&volume=8&pages=1-13)

18. Sfanos KS, de Marzo AM. Prostate cancer and inflammation: the evidence. *Histopathology.* (2012) 60: 199–215. doi: 10. 1111/j. 1365-2559. 2011. 04033. x

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/22212087) | [CrossRef Full Text](https://doi.org/10.1111/j.1365-2559.2011.04033.x) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=KS.+Sfanos&author=AM.+de+Marzo+&publication_year=2012&title=Prostate+cancer+and+inflammation%3A+the+evidence&journal=Histopathology.&volume=60&pages=199-215)