Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

COVID-19 and the Liver: The Perils of Non–Peer-Reviewed Science in Times of a Pandemic

Dear Editors:

Since December 2019, the severe acute respiratory syndrome novel coronavirus-2 (SARS-CoV-2) (and the coronavirus disease-19 [COVID-19]) has caused a pandemic of proportions not seen before in modern times. As mortality associated with the virus advances at a pace without precedent, so does the research and sharing of important information between the scientific and clinical communities worldwide. I read with great interest the article by Gu et al[1] about COVID-19 and gastrointestinal manifestations. In the article, the authors report a detailed discussion about the role of angiotensin-converting enzyme-2 receptor and its presence in cholangiocytes, but not in hepatocytes as so to explain the pathophysiology of hepatic involvement by SARS-CoV-2.[1] The authors hypothesize on the importance of the angiotensin-converting enzyme-2 receptor referencing a manuscript that involves single cell RNA sequencing performed on liver cells. The study was performed in healthy subjects only (despite a title that seems to depict otherwise) and, more important, the study was not peer reviewed, but rather directly published.[2]

A number of opinions and original contributions, all in highly respected journals, have made reference to that single study to scientifically support this hypothesis.[1,3-5] This use is concerning, because it suggests a willingness of authors to bypass stringently reviewed data in their rush to share scientific knowledge. In the case of clinical manuscripts, it is possible that the average reader will understand the quality of a study by looking at a range of familiar parameters. However, when such studies involve data related to single cell RNA sequencing, particularly in hepatocytes, which have been shown to be particularly difficult to isolate and sequence, the reader is blind to the details of the study and directly susceptible to the conclusions of the authors. As we all—scientists and health care providers alike—participate selflessly in a race to mitigate the SARS-CoV2 pandemic and its implications to human health, we should become more efficient in navigating the current scientific standards, that is, be more willing to and expedite in reviewing manuscripts, but resist the temptation to bypass these standards, because doing so will further contribute to misinformation and misguide.

JOSE D. DEBES
Department of Medicine
University of Minnesota *and* Minneapolis, Minnesota *and*
Department of Gastroenterology and Hepatology
Hennepin Healthcare
Minneapolis, Minnesota

References

1. Gu J, et al. Gastroenterology 2020;158:1518–1519.
2. Chai X, et al. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. BioRxiv 2020.
3. Xu L, et al. Liver Int 2020;40:998–1004.
4. Zhang C, et al. Lancet Gastroenterol Hepatol 2020; 5:428–430.
5. Wu J, et al. Clin Infect Dis 2020;71:706–712.

Conflicts of interest
The author discloses no conflicts.

Most current article

https://doi.org/10.1053/j.gastro.2020.04.007

COVID-19 and *ACE2* in the Liver and Gastrointestinal Tract: Putative Biological Explanations of Sexual Dimorphism

Dear Editors:

The presence of severe acute respiratory disease coronavirus-2 (SARS-CoV-2) gastrointestinal infection has recently been reported by 2 independent groups from China.[1,2] Also, liver injury, in part presumably explained by viral infection of liver cells, may be present in about 60% of infected patients.[3] Therefore, patients with chronic liver disease may be vulnerable to the serious clinical consequences of coronavirus disease-9 (COVID-19). Likewise, emerging clinical data suggest that males with comorbidities, including obesity, are more likely to present severe disease.[4,5] Although the biological mechanisms behind this observation are unclear, it has been speculated that sex-based immunologic and/or hormonal differences may account in part for that.

There is evidence highlighting angiotensin-converting enzyme 2 (ACE2) as one of the host receptors for cell entry of members of the SARS-CoV group, including SARS-CoV-2.[6] Structural analysis showed several binding motifs between the SARS-CoV spike protein receptor-binding domain and human ACE2.[6] Beside its role in catalyzing the cleavage of angiotensin I into angiotensin 1–9, and angiotensin II into the vasodilator angiotensin 1–7, ACE2 is involved in cellular pathways associated with other viral entry into host cells.

Gene expression levels of *ACE2* differ across the human body. The highest expression levels are in the small intestine and terminal ileum, and *ACE2* expression levels in the liver and lung are much lower than that of the gastrointestinal tract. One remarkable aspect of the *ACE2* is that the gene maps on the nonpseudoautosomal, that is, the X-specific region of the chromosome X (Xp22.2). It is largely known that, to balance the dosage effect of X-linked genes, 1 of the 2 X chromosomes is randomly inactivated in females during development; this process is called X inactivation. Nevertheless, although most genes are silenced, about 15% of X-linked human genes escape from inactivation.[7] More

important, X escape is not uniform across different tissues. In fact, it was shown that approximately 10% of gene escape occurs selectively in specific tissues.[7] These molecular aspects are of medical importance because they could explain sex differences in the natural course of human diseases, including COVID-19.

A recent systematic survey of the landscape of human X-linked genes inactivation using RNA sequencing-based approaches showed that *ACE2* presents remarkable differences in male–female expression levels.[8] Tukiainen et al[8] suggested that tissue differences in X escape can directly translate into tissue-specific sex biases in gene expression.[8] Specifically, the study showed not only that *ACE2* is among the 82 X-escaping genes, but also highlighted that there might be differences in the liver and lung *ACE2* expression levels between males and females.[8] Paradoxically, escape of *ACE2* from X inactivation resulted in low levels of expression in the liver, lung, and visceral adipose tissue of women.[8] Conversely, *ACE2* expression levels in colon transverse and subcutaneous adipose tissue were significantly higher in females than males.[8]

Collectively, these novel observations may have important clinical implications for patients with COVID-19. First, differences between men and women in liver *ACE2* expression levels may help to explain potential clinical differences in the course of COVID-19 in patients with underlying chronic liver disease. Second, differences between men and women in *ACE2* expression levels in gastrointestinal tissues due to escaping from X inactivation, including the colon, could result in different transmission patterns, including fecal–oral transmission. Third, sex-linked differential expression levels in adipose tissue and/or visceral fat might also shed light into potential differences in the odds of presenting severe complications and in-hospital death associated with comorbidities, including severe obesity.

CARLOS J. PIROLA
University of Buenos Aires
School of Medicine
Institute of Medical Research A Lanari *and*
NationalScientific and Technical Research Council (CONICET)
University of Buenos Aires
Institute of Medical Research (IDIM)
Department of Molecular Genetics and Biology of Complex Diseases
Ciudad Autónoma de Buenos Aires, Argentina

SILVIA SOOKOIAN
University of Buenos Aires
School of Medicine
Institute of Medical Research A Lanari *and*
NationalScientific and Technical Research Council (CONICET)
University of Buenos Aires
Institute of Medical Research (IDIM)
Department of Clinical and Molecular Hepatology
Ciudad Autónoma de Buenos Aires, Argentina

References

1. Gu J, et al. Gastroenterology 2020;158:1518–1519.
2. Xiao F, et al. Gastroenterology 2020;158:1831–1833.
3. Zhang C, et al. Lancet Gastroenterol Hepatol 2020;5:428–430.
4. Chen N, et al. Lancet 2020;395:507–513.
5. Huang C, et al. Lancet 2020;395:497–506.
6. Lu R, et al. Lancet 2020;395:565–574.
7. Prothero KE, et al. Chromosome Res 2009;17:637–648.
8. Tukiainen T, et al. Nature 2017;550:244–248.

SS and CJP should be considered joint senior authors.

Funding
This study was partially supported by grants PICT 2014-1816, PICT 2015-0551, and PICT 2016-0135 (Agencia Nacional de Promoción Científica y Tecnológica, FONCyT), CONICET Proyectos Unidades Ejecutoras 2017, PUE 0055.

Conflicts of interest
The author discloses no conflicts.

Most current article

https://doi.org/10.1053/j.gastro.2020.04.050

Fecal–Oral Transmission of SARS-COV-2: Practical Implications

Dear Editors:

We read with great interest the study by Xiao et al[1] on evidence for gastrointestinal infection of coronavirus disease-19 (COVID-19). Testing for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) RNA in stool specimens of 73 hospitalized patients resulted in virus detection in 53.4% of patients, both with and without gastrointestinal manifestations (ie, diarrhea, nausea, vomiting, gastrointestinal bleeding). In addition, COVID-19 nucleic acid was positive in feces of 23.3% of patients in which respiratory samples had already turned negative. Stool positivity after respiratory sample switched negative had already been reported by Tang et al.[2] As the authors stated, these findings support a possible role of fecal–oral transmission and suggest the need of enhanced control measures, especially during the convalescence period of infected patients.

However, the reported data have also other potential consequences that deserve further investigations. First, stool sampling could be a complementary, noninvasive test for initial diagnosis. Currently, real-time reverse transcriptase polymerase chain reaction test for COVID-19 nucleic acid in nasopharyngeal swabs is the recommended modality for etiological diagnosis.[3] However, false-negative results are documented and can be responsible of misdiagnoses or missed isolation of sources of infection.[4,5] Even if the study by Xiao et al[1] evaluated only patients with positive throat swabs, stool sampling could be effective for detecting viral load even in patients with negative nasopharyngeal swabs. Large-scale studies would be useful to determine accuracy of this noninvasive test.