Journal Pre-proof

COVID-19 and *ACE2* in the liver and gastrointestinal tract: Putative biological explanations of sexual dimorphism

Carlos J. Pirola, Silvia Sookoian

PII: S0016-5085(20)30569-2
DOI: https://doi.org/10.1053/j.gastro.2020.04.050
Reference: YGAST 63409

To appear in: *Gastroenterology*
Accepted Date: 7 April 2020

Please cite this article as: Pirola CJ, Sookoian S, COVID-19 and *ACE2* in the liver and gastrointestinal tract: Putative biological explanations of sexual dimorphism, *Gastroenterology* (2020), doi: https://doi.org/10.1053/j.gastro.2020.04.050.

COVID-19 and *ACE2* in the liver and gastrointestinal tract: Putative biological explanations of sexual dimorphism

Carlos J Pirola [1,2*] , Silvia Sookoian [1,3*],

[1] University of Buenos Aires, School of Medicine, Institute of Medical Research A Lanari, Ciudad Autónoma de Buenos Aires, Argentina.

[2] National Scientific 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.

[3] National Scientific 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.

[*] Co-corresponding authorship

Correspondence: Co-Corresponding Authors

Carlos J. Pirola, PhD and Silvia Sookoian, MD, PhD

Instituto de Investigaciones Médicas, IDIM-CONICET

Combatientes de Malvinas 3150, CABA-1427, Argentina

E-mail: pirola.carlos@conicet.gov.ar and ssookoian@intramed.net

Phone: 54-11-52873905

SS and CJP should be considered joint senior authors

Acknowledgment: 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.

The presence of SARS-CoV-2 gastrointestinal infection has recently been reported by two 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 the infected patients [3]. Therefore, patients with chronic liver disease may be vulnerable to the serious clinical consequences of COVID-19 infection. Likewise, emerging clinical data suggest that males with comorbidities, including obesity, are more likely to present severe disease [4, 5]. While the biological mechanisms behind this observation are unclear, it has been speculated that sex-based immunological 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]. Besides 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 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 non-pseudoautosomal, that is, the X-specific, region of the chromosome X (Xp22.2). It is largely known that in order to balance the dosage effect of X-linked genes, one of the two X chromosomes is randomly inactivated in females during development; this process is called X inactivation. Nevertheless, while most genes are silenced, about 15% of X-linked human genes escape from inactivation [7]. More importantly, X-escape is not uniform across different tissues. In fact, it was shown that ~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. 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 COVID-19 infected patients. First, differences between men and women in liver *ACE2* expression levels may help to explain potential clinical differences in the course of COVID-19 infection 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 colon, could result in different transmission patterns, including fecal-oral transmission. Third, gender-linked diferential 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.

Declaration of interests: None

References

1. Gu J, Han B, Wang J. COVID-19: Gastrointestinal manifestations and potential fecal-oral transmission. Gastroenterology 2020. doi: 10.1053/j.gastro.2020.02.054

2. Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for gastrointestinal infection of SARS-CoV-2. Gastroenterology 2020. doi: 10.1053/j.gastro.2020.02.055

3. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol 2020. doi: 10.1016/S2468-1253(20)30057-1.

4. **Chen N, Zhou M, Dong X**, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507-513.

5. **Huang C, Wang Y, Li X**, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.

6. **Lu R, Zhao X, Li J**, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020;395:565-574.

7. Prothero KE, Stahl JM, Carrel L. Dosage compensation and gene expression on the mammalian X chromosome: one plus one does not always equal two. Chromosome Res 2009;17:637-648.

8. Tukiainen T, Villani AC, Yen A, et al. Landscape of X chromosome inactivation across human tissues. Nature 2017;550:244-248.

Author names in bold designate shared co-first authorship