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**SARS-CoV-2 virus and liver expression of host receptors: Putative mechanisms of liver involvement in COVID-19**

**Short running title:** COVID-19 and liver

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To the Editor,

Zhang et al. showed that COVID-19 affected patients’ present liver biochemistry abnormalities, including elevation of aminotransferases, gamma-glutamyl transferase, and alkaline phosphatase. Hence, several possible clinical scenarios in the setting of liver diseases have been postulated. First, patients with chronic liver disease may be more vulnerable to the severe clinical consequences of COVID-19, including oxygen desaturation and hypoxemia due to severe pneumonia or the cytokine storm. Second, liver biochemistry abnormalities are the consequence of drug toxicity.

There is a third potential but poorly explored clinical scenario, which is the possibility that the novel 2019 coronavirus, also known as SARS-CoV-2, may directly or indirectly cause liver injury. In fact, SARS-CoV2 viral load in the stool, which has been detected in about 48% of patients even in stool collected after respiratory samples tested negative, is likely to be associated with portal venous viremia.

We assessed the gene expression levels of SARS-CoV2-interacting host receptors in the liver tissue and their distribution across cell types according to single-cell transcriptomic experiments retrieved from the Single Cell Portal. We focused on angiotensin-converting enzyme 2 (ACE2), transmembrane serine protease 2 (TMPRSS2), and paired basic amino acid cleaving enzyme (FURIN) gene expression levels. Our analysis shows that the three human host receptors are expressed in the liver tissue; however, expression levels extensively vary across cell types. ACE2 presents the highest expression levels in cholangiocytes, followed by hepatocytes (Figure 1C). TMPRSS2 is expressed in cholangiocytes, hepatocytes, periportal liver sinusoidal endothelial cells, erytroid cells, and in a much lesser extent in non-inflammatory macrophages and alpha-beta T cells (Figure 1D). FURIN shows expression levels across all cell types, from hepatocytes to all populations of liver resident cells (Figure 1E).

Together, these findings support the possibility that SARS-CoV-2 may cause direct liver injury by viral cytopathic effect (directly by lysis and/or by inducing necrotic/apoptotic effect/s). Furthermore, the expression pattern in cell clusters associated with numerous active immune pathways, for example, inflammatory macrophages, natural killer cells, plasma cells, mature B cells, and cells of the liver endothelial microenvironment, opens the possibility of SARS-CoV-2-immune-mediated liver damage.

Not surprisingly, reports from the past 2003-SARS (severe acute respiratory syndrome) epidemic showed not only liver impairment in up to 60% of the patients but also confirmed the presence of
SARS-coronavirus by RT-PCR in liver biopsies presenting mild to moderate lobular inflammation and apoptosis 4.

In conclusion, to understand the pathogenesis of SARS-CoV-2–related liver disease, additional research must be guaranteed, including the search for evidence of viral replication in hepatocytes and liver histology characterization.

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REFERENCES


Figure 1

Liver gene expression profiling across cell types of host receptors implicated in SARS-CoV-2 infection

Profiling of gene expression was retrieved from the Single Cell Portal available at https://singlecell.broadinstitute.org/single_cell. The analysis was focused on the adult liver dataset from the Human Cell Atlas March 2020 Release, a collection of 23 human single-cell datasets. The human liver cellular landscape analysis by single cell RNA-seq is based on the study of MacParland et al. 5. Human liver tissue was obtained from livers procured from deceased donors deemed acceptable for liver transplantation.

A. Annotation of liver whole transcriptome involved 15 clusters, including hepatocytes, alpha-beta T cells, central liver sinusoidal endothelial cells, cholangiocytes, erythroid cells, gamma-delta T cells, hepatic stellate cells, inflammatory macrophage, mature B cells, natural killer cells, non-inflammatory macrophages, periportal liver sinusoidal endothelial cells, plasma cells, portal liver sinusoidal endothelial cells, and unannotated cells (A).

B. To illustrate the pattern and magnitude of differential gene expression levels at different cells in the liver, we assessed the pattern of gene expression of albumin (ALB)- the most abundant protein in human blood that is highly expressed in the liver.

C-E. Exploration of ACE2, TMPRSS, and FURIN expression in the liver.