The spike of SARS-CoV-2 promotes metabolic rewiring in hepatocytes

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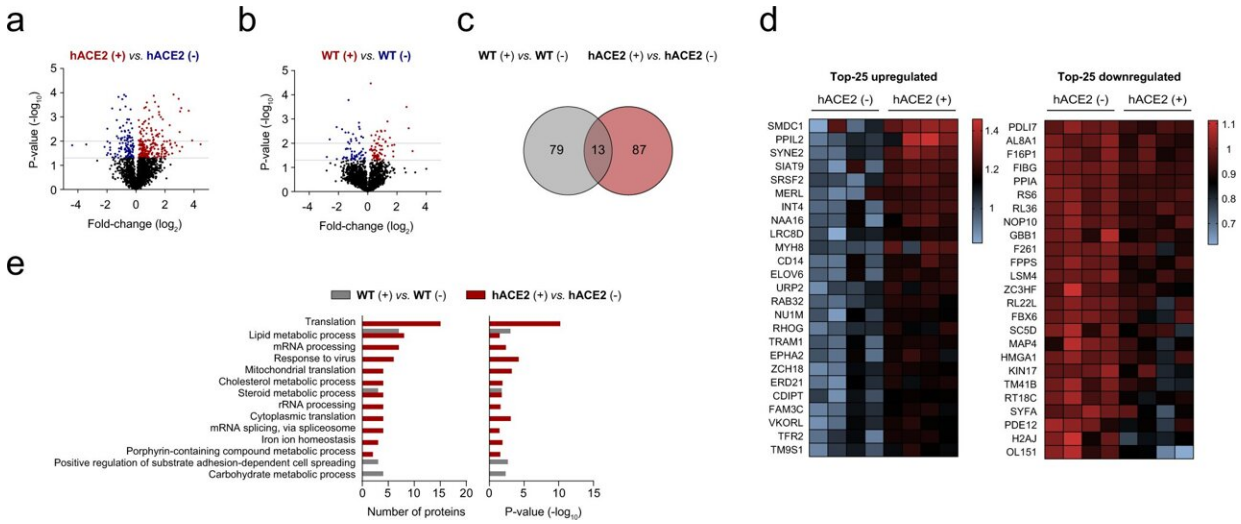

Proteomic analyses reveal changes in hACE2 mouse hepatocytes after infection with pseudotyped viral particles expressing the spike of SARS-CoV-2. a Volcano plot showing the 354 differentially expressed peptides between hACE2 mouse hepatocytes in the presence (+) or absence (−) of pseudotyped viral particles after 48 h. b Volcano plot showing the 132 differentially expressed peptides between WT mouse hepatocytes in the presence (+) or absence (−) of pseudotyped viral particles. For a detailed list of all peptides, including their fold-change and p values refer to the Supplementary Data 1. c Venn diagram showing common peptides between hACE2 (+ vs. −) and WT (+ vs. −) mouse hepatocyte comparisons. d Heatmap showing the top-25 up- or downregulated peptides between hACE2 mouse hepatocytes in the presence (+) or absence (−) of pseudotyped viral particles. e Gene ontology term enriched pathways representing the unique differentially expressed peptides in the WT (+ vs. −) or hACE2 (+ vs. −) mouse hepatocyte comparisons. The number of proteins

belonging to the identified dysregulated pathways (left) and their corresponding p values (right) are shown. Credit: *Communications Biology* (2022). DOI: 10.1038/s42003-022-03789-9

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes multi-organ damage, including liver dysfunction identified in more than 50% of COVID-19 patients. Liver damage in COVID-19 patients could be attributed to cytopathic effects induced by the interaction between the virus and liver cells, to an increased immune response or to drug toxicity associated with the treatment of these patients, according to research carried out at CIC bioGUNE.

Since the beginning of the pandemic, the impact of SARS-CoV-2 on the liver has been widely debated. "Clinical studies conducted in patients with COVID-19 described liver lesions, however, it was not clear whether the observed damage was a direct consequence of SARS-CoV-2 tropism to this organ or if, on the contrary, it was the result of the administration of the antibiotic/antiviral treatments used in these patients," says Maria Mercado-Gómez, first author of the publication. In this context, "other viruses targeting the upper respiratory tract, such as SARS-CoV and MERS-CoV, have shown tropism towards the liver, so we wonder if the new coronavirus could do so as well," explains Dr. Prieto-Fernández.

The groups of Dr. Martínez-Chantar and Dr. Asís Palazón at CIC bioGUNE, synergized their expertise in hepatic and immunological research to demonstrate that hepatocytes are susceptible to infection in different models, i.e., primary hepatocytes derived from humanized angiotensin-converting enzyme-2 (hACE2) mice and primary human hepatocytes. This study is also the result of collaboration with the laboratories of Dr. Jiménez-Barbero, Dr. Nogueiras, Dr. Vicent Prevot

and Dr. Félix Elortza, and results have been published in *Communications Biology*, on August 17, 2022.

"We used pseudotyped viral particles decorated with SARS-CoV-2 spike particles that induced the expression of ZsGreen in host cells upon infection, a fluorescent protein that allows quantification of infection by flow cytometry," explains Dr. Prieto-Fernandez.

After demonstrating the interaction between the spike of SARS-CoV-2 and hepatocytes, the researchers studied the metabolic impact of this interaction using a battery of experimental procedures, including metabolic flux experiments employing carbon-labeled glucose and proteomic analysis by liquid chromatography-tandem mass spectrometry. This multi-method approach led to the discovery that the SARS-CoV-2 spike promotes metabolic reprogramming in hepatocytes toward glycolysis, but also impaired mitochondrial activity, which partly explains the liver damage associated with COVID-19.

"Importantly, we found that primary human and hACE2 hepatocytes, in which steatosis and inflammation were induced by methionine and choline deprivation, are more vulnerable to infection, and these data support the predisposition of patients with metabolically associated fatty liver disease, MAFLD, to a more severe prognosis of COVID-19," said Dr. Malu Martinez-Chantar. In this context, metformin, a common therapeutic option for hyperglycemia in patients with type 2 diabetes that is known to partially attenuate fatty liver, reduces human and mouse hepatocyte infection.

In summary, the research provides evidence that hepatocytes are susceptible to SARS-CoV-2 pseudovirus infection and propose that metformin could be a therapeutic option to attenuate SARS-CoV-2 infection in patients with fatty liver.

More information: Maria Mercado-Gómez et al, The spike of SARS-CoV-2 promotes metabolic rewiring in hepatocytes, *Communications Biology* (2022). DOI: 10.1038/s42003-022-03789-9