Using organ-on-a-chip technology to elucidate the liver pathophysiology of COVID-19 patients

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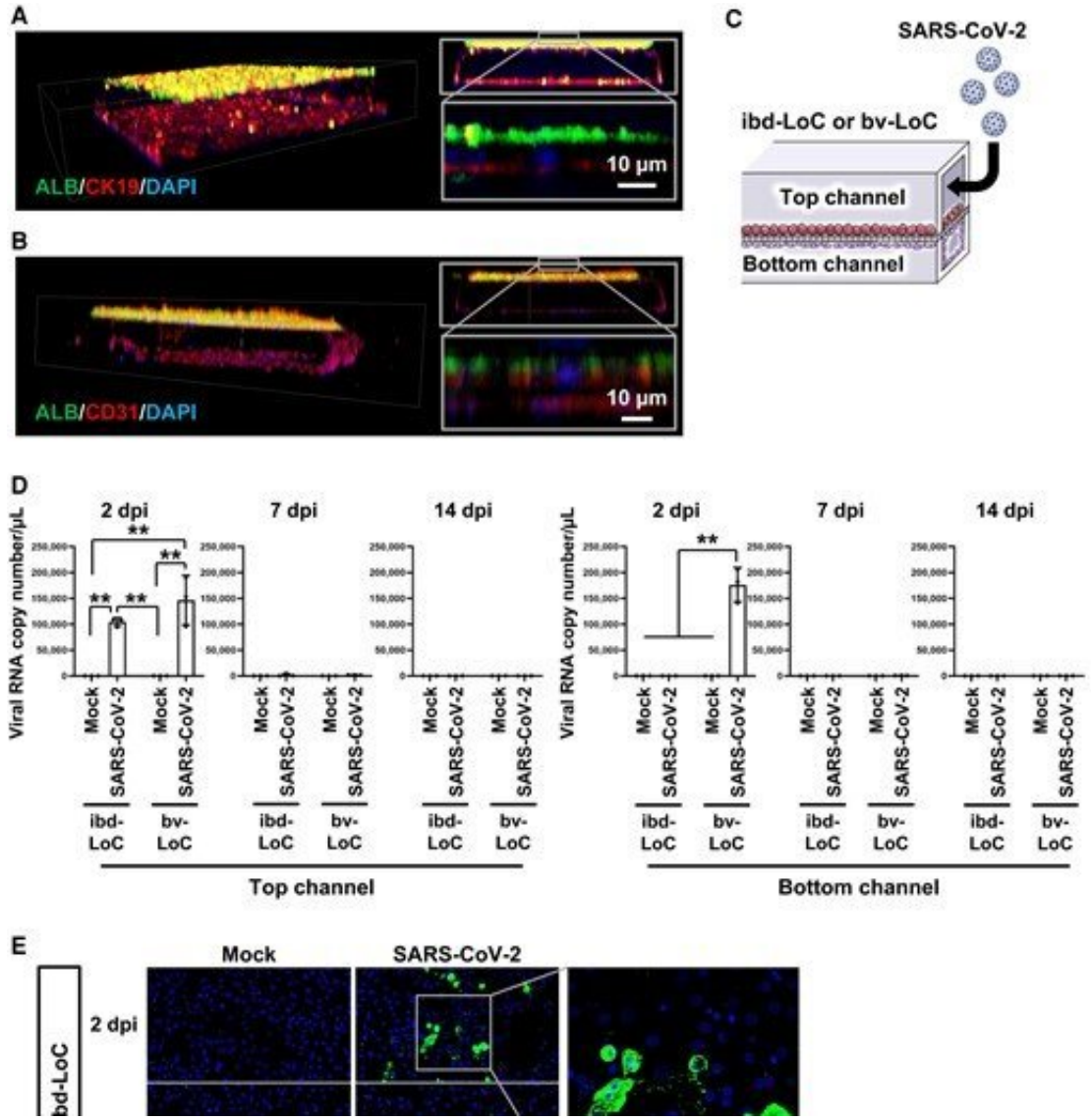

Generation of ibd- and bv-LoCs. (A, B) 3D images of the ibd- and bv-LoCs.

Immunostaining analysis of ALB and CK19 in the ibd-LoC (A) and of ALB and CD31 in the bv-LoC (B) were performed. Nuclei were counterstained with DAPI. (C) Schematic overview of the SARS-CoV-2 infection experiment using ibd- and bv-LoCs. SARS-CoV-2 (0.1 MOI) was injected into the top channel. (D) At 2, 7, and 14 dpi, the viral RNA copy number in the cell culture supernatant was measured by quantitative real time-PCR (qPCR). Two-way ANOVA followed by Tukey's post hoc test (**P PNAS Nexus (2023). DOI: 10.1093/pnasnexus/pgad029

SARS-CoV-2 infects and causes damage to multiple organs in COVID-19 patients. In particular, liver damage has been associated with COVID-19 severity. However, an understanding of the liver pathophysiology of these patients remains largely incomplete.

To investigate this pathophysiology, the group developed liver models that mimic the liver around blood vessels or bile ducts using organ-on-a-chip technology. Human hepatocytes and cholangiocytes (bile duct epithelial cells) were cultured in the top and bottom channels of microfluidic devices, respectively, to create the liver-on-a-chip with intrahepatic bile duct (ibd-LoC). Similarly, human hepatocytes and vascular endothelial cells were cultured in adjacent channels of microfluidic devices to produce the liver-on-a-chip with a blood vessel (bv-LoC).

The researchers infected these LoCs with SARS-CoV-2 to model the liver pathophysiology of COVID-19 patients and detected the virus in both ibd-LoCs and bv-LoCs two days following infection. Interestingly, despite observing viral clearance after two weeks, increased hepatotoxicity and lipid droplet accumulation continued in the infected bv-LoCs, but not in the infected ibd-LoCs.

These findings suggest that the vascularized parts of the liver are more

vulnerable to damage by SARS-CoV-2 infection, and such damage is responsible for the liver dysfunctions experienced by COVID-19 patients.

In addition, the team screened for therapeutic drugs that can treat these liver abnormalities and found the combined treatment of remdesivir and baricitinib to significantly reduce the hepatotoxicity and lipid droplet accumulation observed in the infected bv-LoCs, suggesting that these two drugs could be effective to treat liver injuries caused by SARS-CoV-2 infection.

Organ-on-a-chip technologies, such as the ones described in this study, will help to broaden the understanding of organ dysfunctions in COVID-19 patients and accelerate the development of therapeutic agents to treat this catastrophic disease.

The results of this research were published online in *PNAS Nexus* on March 7, 2023.

More information: Sayaka Deguchi et al, Elucidation of the liver pathophysiology of COVID-19 patients using liver-on-a-chips, *PNAS Nexus* (2023). DOI: 10.1093/pnasnexus/pgad029

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