A liver drug reduces SARS-CoV-2 entry into cells

A widely used drug called UDCA reduces SARS-CoV-2 infection in human organoid structures, animals and human organs maintained outside the body. Individuals using UDCA for liver conditions are less likely to develop severe COVID-19 than are people who did not use it. UDCA treatment could help to protect people with suppressed immune systems and offer protectionagainst vaccine-resistant variants.

This is a summary of:
Brevini, T. *et al*. FXR inhibition may protect from SARS-CoV-2 infection by reducing ACE2. *Nature* https://doi.org/10.1038/s41586-022-05594-0 (2022).

Cite this as:
Nature https://doi.org/10.1038/d41586-022-04149-7 (2022).

The problem

Vaccines changed the course of the COVID-19 pandemic by training people's immune systems to recognize and clear the SARS-CoV-2 virus. However, they are not always effective in individuals with weak immune systems, or against some viral variants[1]. Moreover, despite international efforts, not everyone has access to vaccination, owing to its cost and disparities in vaccine availability. A huge challenge in managing COVID-19 in this post-vaccine era is preventing SARS-CoV-2 infection in high-risk unvaccinated groups[2]. Using drugs that are widely accessible could provide a solution.

The solution

To help individuals with weak immunity, such drugs against SARS-CoV-2 should not require a well-functioning immune system. And to prevent the virus from being able to escape treatment by mutating, they should not act on the virus. To meet these requirements, we targeted a receptor protein called angiotensin-converting enzyme 2 (ACE2) that is found on the membrane of human cells and constitutes the main 'doorway' that SARS-CoV-2 uses to enter and infect cells[3]. To study ACE2's function and how it affects viral infection, we used human cells to create organoids — 3D tissue structures grown *in vitro* to resemble and model different organs — in the laboratory[4].

Through the organoid experiments, we discovered that blocking a bile-acid-sensing protein called farnesoid X receptor (FXR) — which is found in large amounts in the liver, but is also present in other parts of the body — reduces the amount of ACE2 on the surface of cells. We treated our organoids with a drug called ursodeoxycholic acid (UDCA), which blocks FXR[5] and is used to treat some liver diseases. UDCA reduced ACE2 levels and SARS-CoV-2 infection of cells in organoid models of the human lung, gut and liver.

To confirm these findings in living animals, we treated hamsters with UDCA and showed that the drug prevented SARS-CoV-2 infection. To test whether these findings could be translated to humans, we tested UDCA in a pair of donated human lungs that were not suitable for transplantation. The lungs were ventilated and perfused with a blood-like fluid to keep them functioning, and then treated with either UDCA dissolved in a saline solution or just the saline solution, before infection with SARS-CoV-2 (Fig. 1a). UDCA treatment reduced SARS-CoV-2 infection of samples from the lungs (Fig. 1b). In eight healthy volunteers who received UDCA, ACE2 levels in nasal cells — the main entry points for the virus into the body — were reduced, in theory increasing people's resistance to infection.

Given that UDCA is widely used in the clinic, we interrogated existing data to compare COVID-19 outcomes of people who were taking UDCA for liver conditions with those of people who were not. Individuals taking UDCA were less likely to have severe COVID-19 than were those who did not receive the drug.

The implications

UDCA is widely used, accessible, cost effective, off-patent and easy to manufacture and store — overcoming cost and distribution barriers. It does not target the immune system or the virus itself and could therefore be both effective in people with weak immune systems and protect against viral resistance. It could also be effective in future coronavirus pandemics, because ACE2 is a doorway for many such viruses.

This is one of the first studies to provide a proof of concept for drug testing in donated human organs. This approach could reduce the need for animal experiments and increase the predictive power of preclinical drug testing.

Our results suggest that UDCA could have an important role in the management of COVID-19. However, this study is not a clinical trial, and our findings must be validated and confirmed in large groups of individuals who are studied over time. Importantly, where possible, we propose that UDCA should be used together with vaccination, rather than replacing it. The obvious next step is to conduct large, randomized and controlled trials to assess its effectiveness in the clinic.

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EXPERT OPINION

"This manuscript presents large sets of experimental data as well as some translational data from retrospective registries, indicating that pharmacological inhibition of the farnesoid X receptor (FXR) could reduce ACE2 expression, thereby reducing SARS-CoV-2 infection in the lung, liver and gastrointestinal tract, which could be a novel approach to prevent or treat COVID-19."

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FIGURE

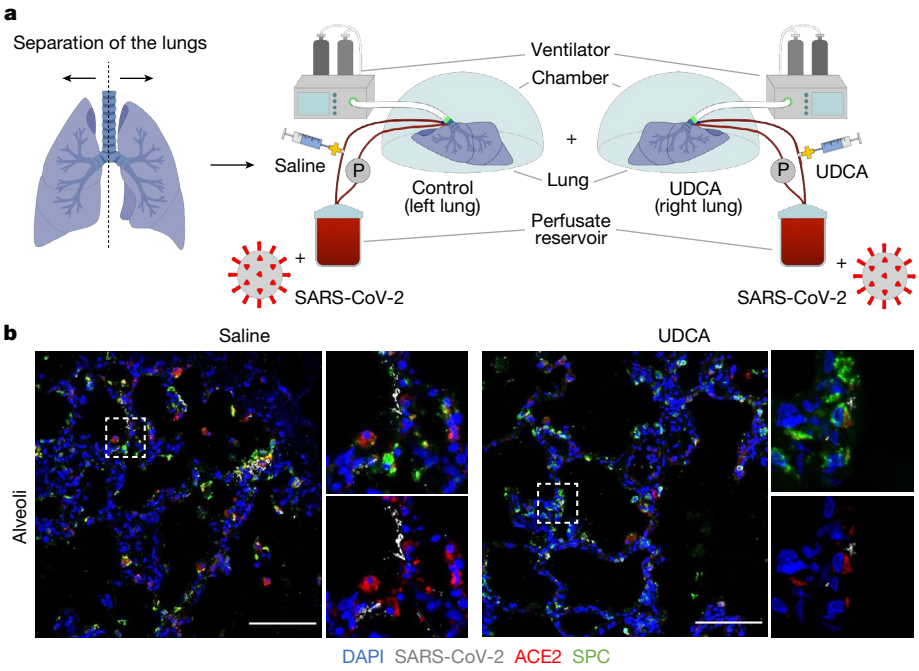

Figure 1 | The drug UDCA reduces SARS-CoV-2 infection in human lungs maintained outside the body. The widely used drug UDCA reduces the levels of a receptor protein called ACE2, which SARS-CoV-2 uses to enter cells. **a**, A pair of human lungs was maintained outside the body using a pump (P) to perfuse a body-temperature blood-like fluid, and a ventilator. One lung received UDCA dissolved in saline, whereas the other received only saline, as a control. Both lungs were exposed to SARS-CoV-2 six hours after treatment. **b**, Immunofluorescence images of alveoli (air sacs) showing that the level of ACE2 (red) and evidence of SARS-CoV-2 infection (viral particles in white) were reduced in the UDCA-treated lung compared with in the control. DAPI (blue) shows the cell nuclei; SPC (green) indicates surfactant protein C, a marker of alveoli. Dashed outlines highlight the location of the insets. Scale bars, 100 µm.

BEHIND THE PAPER

Our research started early in the COVID-19 pandemic, with the serendipitous finding that blocking FXR in bile-duct cells reduces ACE2 expression. When ACE2 was identified as the SARS-CoV-2 receptor[3], everything 'clicked'. We reasoned that, if UDCA reduced the expression of the entry point for the virus into cells, it could prevent SARS-CoV-2 infection. Proving this during the pandemic was challenging, with disruptions at every step, from reagent shortages and institute lockdowns to losing access to animal facilities, human tissue and volunteers for clinical studies. Nevertheless, as we shared our findings, colleagues far and wide came to our help. On-site scientists for the company Abcam hand-delivered antibodies; the Blood and Transplant branch of the United Kingdom's National Health Service fast-tracked one of the first pairs of human lungs that was available for research during the pandemic; and our physician colleagues volunteered to receive UDCA. This has been our most collaborative and most enjoyable work so far.

F.S.

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FROM THE EDITOR

Brevini *et al.* identify the receptor FXR as a regulator of ACE2 protein expression. They show that blocking FXR in organoids made from human cells, and in hamsters, can reduce infection with SARS-CoV-2. Data from retrospective studies suggest that people with a liver disease who took the drug UDCA, which inhibits FXR, had less severe COVID-19 than did those infected with SARS-CoV-2 who did not receive the therapy.

Editorial team, *Nature*