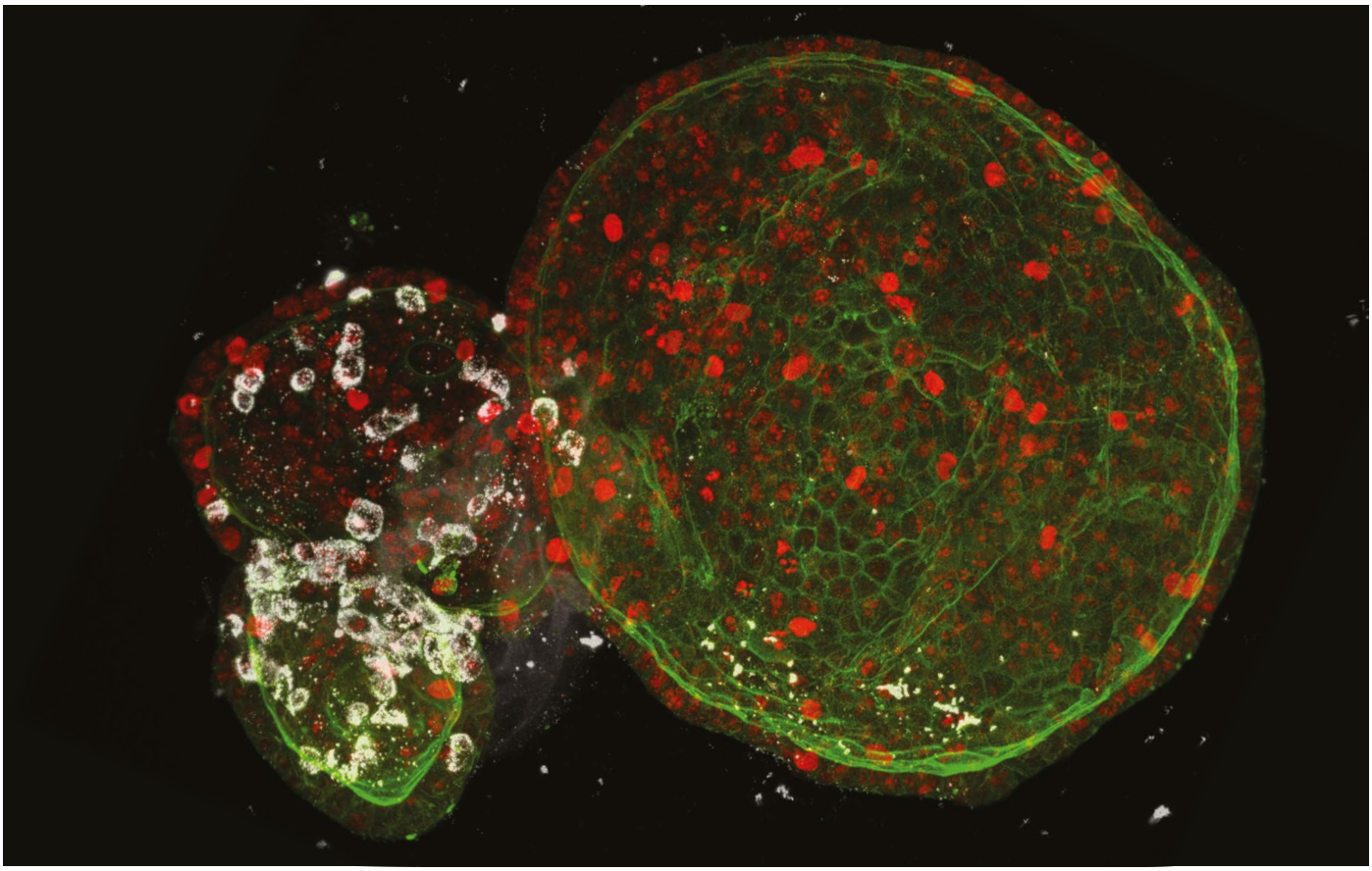
News in focus



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Human intestinal organoids infected with SARS-CoV-2 (white).

MINI ORGANS REVEAL HOW THE CORONAVIRUS RAVAGES THE BODY

The virus can damage lung, liver and kidney tissue grown in the lab, which might explain some severe COVID-19 complications in people.

By Smriti Mallapaty

Researchers are growing miniature organs in the laboratory to study how the new coronavirus ravages the body. Studies in these organoids are revealing the virus's versatility at invading organs, from the lungs to the liver, kidneys and gut. Researchers are also testing drugs in these mini tissues to see whether they might be candidates for treating people.

Physicians know from hospitalised patients and autopsies that SARS-CoV-2 can have a devastating effect on organs. But it's unclear whether some of this damage is directly caused by the virus or by complications of the infection. Multiple groups are using organoid studies to show where in the body the virus travels, which cells it infects and what damage it does. "The beauty of organoids is that they resemble the true morphology of tissues," says Thomas Efferth, a cell biologist at Johannes Gutenberg University of Mainz, Germany.

Virologists typically study viruses using cell lines or animal cells cultured in a dish[1]. But these don't model SARS-CoV-2 infection well, say researchers. Organoids better demonstrate what SARS-CoV-2 does to human tissue, says Núria Montserrat, a stem-cell biologist at the Institute for Bioengineering of Catalonia in Barcelona, Spain. They can be grown to include multiple cell types, and they take the shape of the original organ in weeks, she says. They are also less expensive than animal models, and avoid the ethical concerns they pose.

But studies of SARS-CoV-2 in organoids have limitations because they do not reflect the crosstalk between organs that happens in the body. This means that findings will still need to be validated in animal models and clinical studies, says Bart Haagmans, a virologist at Erasmus MC in Rotterdam, the Netherlands.

One of the key insights from organoids is what SARS-CoV-2 does to cells in the respiratory system. Kazuo Takayama, a stem-cell biologist at Kyoto University, Japan, and his colleagues have developed bronchial organoids with four distinct cell types, made from frozen cells from the outer bronchial layer, or epithelium. When they infected the organoids with SARS-CoV-2, they found that the virus mainly targets stem cells that replenish epithelial basal cells, but did not easily enter protective, secretory 'club cells'[2]. The team, which posted its work on bioRxiv, now plans to study whether the virus can spread from basal to other cells.

Respiratory failure

From the upper airways, the virus can enter the lungs and cause respiratory failure, a severe complication of COVID-19. Using mini lungs in a dish, Shuibing Chen, a stem-cell biologist at Weill Cornell Medicine in New York City, has shown that some cells die after being infected, and that the virus induces the production of proteins known as chemokines and cytokines[3], which can trigger a massive immune response. Many people with severe COVID-19 experience this 'cytokine storm', which can be deadly.

But Chen, who also posted her results on bioRxiv, says that why lung cells are dying in patients remains a mystery — whether it's because of damage caused by the virus, self-induced destruction, or through being gobbled up by immune cells. Chen's approach to creating organoids was different from Takayama's: instead of adult cells, she used pluripotent stem cells that can develop into any cell type. Organoids grown in this way can include more cell types, but the final result is less mature and so might not represent adult tissue, says Chen.

From the lungs, SARS-CoV-2 can spread to other organs, but researchers weren't sure how exactly the virus travels until Montserrat and her colleagues published a study in *Cell* in May[4]. In experiments in organoids, also made from pluripotent stem cells, they showed that SARS-CoV-2 can infect the endothelium — the cells lining the blood vessels — which then allows viral particles to leak out into the blood and circulate around the body. Damaged blood vessels in people with COVID-19 also support this hypothesis, says Josef Penninger, a genetic engineer at the University of British Columbia in Vancouver, Canada, and co-lead author of the study[5].

Studies in organoids suggest that once in the blood, the virus can infect several organs including the kidney, say Penninger and Montserrat. Although it infected kidney organoids and some cells died, the researchers are not sure whether this is the direct cause of the kidney dysfunction observed in some people.

Another study in liver organoids found that the virus can infect and kill cholangiocytes — cells that contribute to bile production. Many researchers thought that liver damage seen in COVID-19 was caused by an overactive immune response or drug side effects, says Bing Zhao, a cell biologist at Fudan University in Shanghai, China, who published his results in *Protein & Cell*[6]. His work "suggests that the virus can directly attack the liver tissue, which can cause liver damage", says Zhao.

The virus can also destroy cells that control blood sugar in pancreatic organoids — which adds to mounting evidence that the virus can trigger diabetes in some people (see page 16).

Although such findings are illuminating, using organoids to study the virus–host interaction is in its infancy, says Haagmans, who has studied the virus in gut organoids. "It is too early to say how relevant they are," he says. More complex organoid systems are needed to better understand how the virus interacts with the body's immune system to cause damage, say researchers.

"We are fairly confident now that the virus that causes COVID-19 can infect tissue outside the lung and significantly contribute to disease," says Penninger. But more severe outcomes, such as kidney and heart damage, are probably due to viral infection and an excessive immune response, he says.

Scientists are also studying whether organoids can be used to assess potential COVID-19 therapies, some of which have already been rushed through to clinical trials without extensive testing in cell and animal models. "Due to the time sensitivity, many clinical trials were designed based on previous knowledge of other coronaviruses and launched without careful evaluation in model systems," says Chen. "As a result, many of them have failed."

Chen screened some 1,200 drugs approved by the US Food and Drug Administration for other illnesses, and found that the cancer medication imatinib suppressed SARS-CoV-2 in lung organoids[3]. Several human clinical trials of the drug in treating COVID-19 are under way.

Other groups are also testing existing drugs in organoids, with some success against coronavirus[2,7]. "We will only know at the end of this process what the predictive value of these systems is for testing drug efficacy," says Haagmans. "This is a long-term process."

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EVIDENCE SUGGESTS THE CORONAVIRUS MIGHT TRIGGER DIABETES

Mounting clues from tissue studies and individuals show the virus can damage insulin-producing cells.

By Smriti Mallapaty

In mid-April, Finn Gnadt, an 18-year-old student from Kiel, Germany, learnt that he had been infected with the SARS-CoV-2 coronavirus despite feeling well. Gnadt's parents had fallen ill after a river cruise in Austria, so his family was tested for virus antibodies, which are produced in response to infection.

Gnadt thought he had endured the infection unscathed, but days later, he started to feel worn out and exceedingly thirsty. In early May, he was diagnosed with type 1 diabetes, and his physician, Tim Hollstein at the University Hospital Schleswig-Holstein in Kiel, suggested that the sudden onset might be linked to the viral infection.

In most people with type 1 diabetes, the body's immune cells start destroying β-cells — which are responsible for producing the hormone insulin — in the pancreas, often suddenly. Hollstein suspected that the virus had destroyed Gnadt's β-cells, because his blood didn't contain the types of immune cell that typically cause the damage.

Diabetes is already known to be a key risk factor for developing severe COVID-19 (ref. 1) and people with the condition are more likely to die from the infection[2]. "Diabetes is dynamite if you get COVID-19," says Paul Zimmet, who studies the metabolic disease at Monash University in Melbourne, Australia.

Now Zimmet is among a growing number of researchers who think that diabetes doesn't just make people more vulnerable to the coronavirus, but that the virus might also trigger diabetes in some[3]. "Diabetes itself is