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NEWS
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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.

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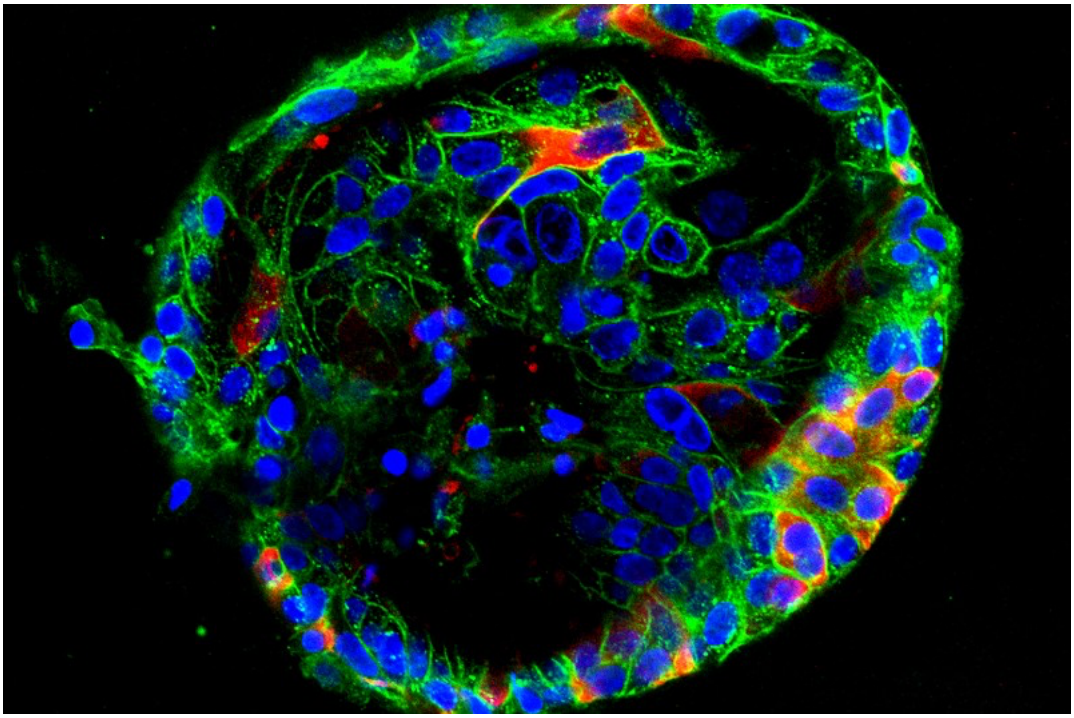


Organoids made from human liver ductal cells infected with SARS-CoV-2 (red).Credit: Bing Zhao

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 experimenting with drugs in these mini tissues to see whether such therapies might be candidates to treat 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 secondary 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 because they don't mimic what happens in the body, 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 take the shape of the original organ in weeks, says Montserrat. They're 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, which 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.

Breathed in

One of the key insights from organoids is what SARS-CoV-2 does to cells in the respiratory system, from the upper airway to the lungs.

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 his team infected the organoids with SARS-CoV-2, they found that the virus mainly targets stem cells that replenish cells in the epithelium known as 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 cells to other cells.

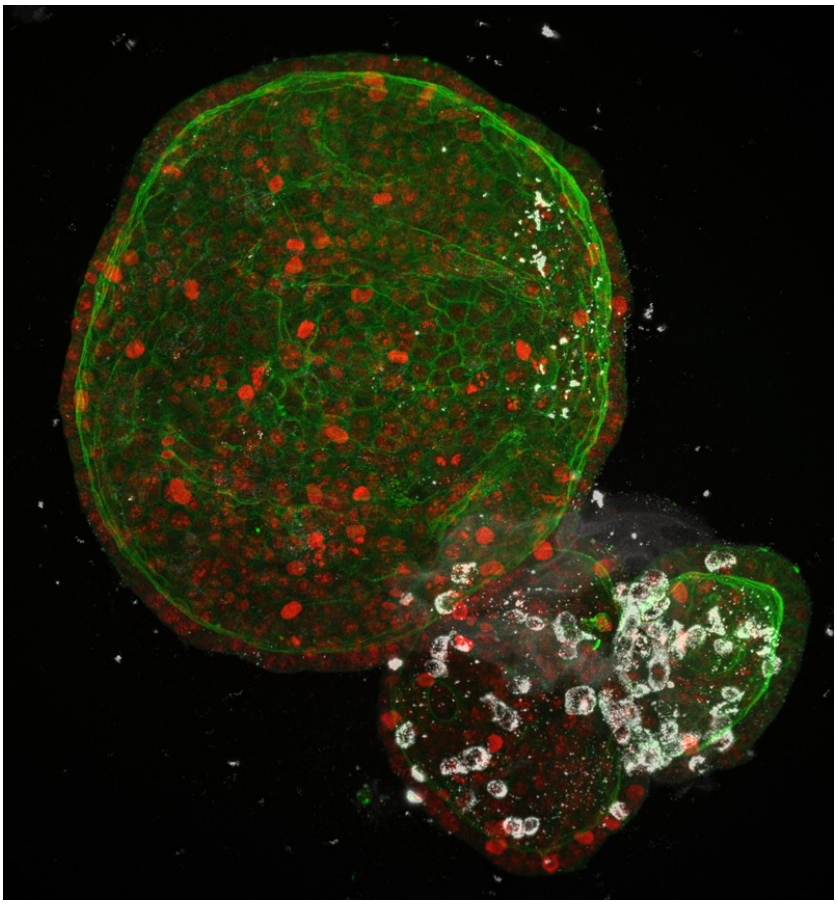
From the upper airways, the virus can enter the lungs and cause respiratory failure, a severe complication of COVID-19. Using mini lungs in a dish, Shuibing Chen, a stem-cell biologist at Weill Cornell Medicine in New York City, has shown that some cells die after being infected, and that the virus induces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

But Chen, who also posted her results on bioRxiv, says 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. "We know the cells die but we don't know how," says Chen, whose approach to creating organoids was different from Takayama's. Instead of creating them from adult cells, she used pluripotent stem cells that can develop into any cell type in the body. 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, who is now growing lung organoids with immune cells.

Blood rush

From the lungs, SARS-CoV-2 can spread to other organs, but researchers weren't sure how exactly the virus was travelling 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. Pathology

reports of 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].



Human intestinal organoids infected with SARS-CoV-2 (white). Credit: Joep Beumer/Clevers group/Hubrecht Institute

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

Another study in liver organoids found that the virus can infect and kill cells that contribute to bile production, known as cholangiocytes. Many researchers thought that the liver damage seen in people with 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 replicate in the cells that line the small and large intestines, known as enterocytes, according to a *Science* study that used gut organoids[7].

Although such findings are illuminating, using organoids to study the virus–host interaction is in its infancy, says Haagmans, who developed the 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 a combination of viral infection and an excessive immune response, he says.

Drug test bed

Scientists are also studying whether organoids can be used to model how drugs react in the body. The hope is that organoids can be used to test 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 organoids3. Several human clinical trials of the drug as a treatment for COVID-19 have since been launched.

Other groups are also testing existing drugs against the coronavirus in organoids, with some success2,8. "We will only know at the end of this process what the predictive value of these systems are for testing drug efficacy," says Haagmans. "This is a long-term process."

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