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

BERNARD CHANTAL/ALAMY

People with type 1 diabetes, a known COVID-19 risk factor, can't produce the hormone insulin.

a pandemic just like the COVID-19 pandemic. The two pandemics could be clashing," he says.

Their hunch is based on a handful of people such as Gnadt, who have spontaneously developed diabetes[4] after being infected with SARS-CoV-2, and on evidence from dozens more people with COVID-19 who have arrived in hospital with extremely high levels of blood sugar and ketones[5], which are produced from fatty deposits in the liver. When the body doesn't make enough insulin to break down sugar, it uses ketones as an alternative source of fuel.

Researchers cite other evidence, too. Various viruses, including the one that causes severe acute respiratory syndrome (SARS), have been linked with autoimmune conditions such as type 1 diabetes[6]. And many organs involved in controlling blood sugar are rich in a protein called ACE2, which SARS-CoV-2 uses to infect cells[7].

The latest clue comes from an experimental study in miniature lab-grown pancreases. Published last month[8], the work suggests that the virus might trigger diabetes by damaging the cells that control blood sugar.

But other researchers are cautious about such suggestions. "We need to keep an eye on diabetes rates in those with prior COVID-19, and determine if rates go up over and above expected levels," says Naveed Sattar, a metabolic-disease researcher at the University of Glasgow, UK.

To establish a link, researchers need more robust evidence, says Abd Tahrani, a clinician–scientist at the University of Birmingham, UK.

One initiative is now under way. Earlier this month, an international group of scientists, including Zimmet, established a global database[3] to collect information from people with COVID-19 and high blood-sugar levels who do not have a history of diabetes or problems controlling their blood sugar.

Cases are beginning to trickle in, says Stefan Bornstein, a physician at the Technical University of Dresden, Germany, who also helped to establish the registry. The researchers hope to use the cases to understand whether SARS-CoV-2 can induce type 1 diabetes or a new form of the disease. And they want to investigate whether the sudden-onset diabetes becomes permanent in people who've had COVID-19. They also want to know whether the virus can tip people who were already on their way to developing type 2 diabetes into a diabetic state.

The organoid study shows how SARS-CoV-2 could be damaging the pancreas[8]. Shuibing Chen, a stem-cell biologist at Weill Cornell Medicine in New York City, and her colleagues showed that the virus can infect the organoid's α- and β-cells, some of which then die. Whereas β-cells produce insulin to decrease blood-sugar levels, α-cells produce the hormone glucagon, which increases blood sugar. The virus can also induce the production of proteins known as chemokines and cytokines, which can trigger an immune response that might also kill the cells, according to the study, which was published in *Cell Stem Cell* on 19 June.

Chen says the experiments suggest that the virus can disrupt the function of key cells involved in diabetes – by directly killing them or by triggering an immune response that attacks them.

The virus also attacked pancreatic organoids that had been transplanted into mice, and cells in liver organoids. The liver is important for storing and releasing sugar into the blood stream when it senses insulin.

The organoid study adds strength to the argument that SARS-CoV-2 might cause or worsen diabetes, but the paper itself is not enough to prove the link, says Tahrani.

There could be more going on than some scientists suggest, says Shane Grey, an immunologist at the Garvan Institute of Medical Research in Sydney, Australia. The virus could trigger an extreme inflammatory state, which would impair the ability of the pancreas to sense glucose and release insulin, and dampen the ability of the liver and muscles to detect the hormone, he says. This could trigger diabetes.

Only long-term studies will reveal what's really going on, says Sattar.

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CRISPR EDITING WREAKS CHROMOSOMAL MAYHEM IN HUMAN EMBRYOS

Studies showing large DNA deletions and reshuffling heighten concerns about heritable genome editing.

By Heidi Ledford

A suite of experiments that use the gene-editing tool CRISPR–Cas9 to modify human embryos have revealed that the process can make large, unwanted changes to the genome at or near the target site.

The studies were published last month on the preprint server bioRxiv, and have not yet been peer-reviewed[1–3]. But taken together, they give scientists a good look at what some say is an underappreciated risk of CRISPR–Cas9 editing. Previous experiments have revealed that the tool can make 'off target' gene mutations far from the target site, but the nearby changes identified in the latest studies can be missed by standard assessment methods.

"The on-target effects are more important