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Histopathological features of SARS-CoV-2 infection and relationships with organoid technology

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Abstract

Coronavirus disease 2019 (COVID-19) following infection by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has caused a global pandemic that is still having serious effects worldwide. This virus, which targets the lungs in particular, can also damage other tissues. Angiotensin converting enzyme 2 (ACE-2) plays a key role in viral entry into host cells. The presence of ACE-2 in various tissues may permit viral infection. Studies of COVID-19 often make use of postmortem tissues. Although this information provides various useful results, it is also necessary to conduct *in vitro* studies to understand optimal treatment approaches. Because the virus may show species-specific differences, *in vitro* technologies using human cells are particularly important. Organoid technologies, three-dimensional structures that can be obtained from human cells, are playing increasingly important roles in studies of SARS-CoV-2. This technology offers a significant advantage in terms of mimicking *in vivo* tissue structures and testing antiviral compounds. In this mini-review, we summarize studies of SARS-CoV-2 using both histopathological and organoid technology approaches.

Keywords

Severe acute respiratory syndrome coronavirus-2, coronavirus disease 2019, histopathology, organoid technology, tissue, organ

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Introduction

In December 2019, a novel coronavirus was isolated from the bronchoalveolar fluid of patients with idiopathic pneumonia in Wuhan, China.[1] Although the first deaths following infection by the novel

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coronavirus occurred in China, similar cases in other countries quickly followed.[2] Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has spread worldwide.[3] On 11 March 2020, the World Health Organization announced that COVID-19 was a pandemic and that all countries should prepare appropriate emergency responses.[4]

COVID-19 can result in mild lung congestion, alveolar exudation, or acute respiratory distress syndrome.[5] In addition to the lung, the kidney,[6] liver,[7] gastrointestinal system,[8] and central nervous system[9] can be affected by the virus. Angiotensin-converting enzyme 2 (ACE-2) plays a key role in SARS-CoV-2 entry into host cells and related damage.[10–12] In addition to the lungs, ACE-2 is expressed in the oral mucosa, gastrointestinal tract, vasculature, kidney, brain, and heart.[11,13–15] During SARS-CoV-2 infection, ACE-2-expressing organs can be directly affected, resulting in multiple organ failure or death.[10]

The effects of COVID-19 on tissues have mostly been assessed by studying postmortem tissues.[16] Although this information is useful, *in vitro* studies are also required to fully understand viral pathology. Animal models may not recapitulate human infection because the virus shows species-specific differences; this fact makes such studies arduous and time-consuming. Hence, animal-free models should be used to understand the pathological mechanisms of the virus.[17] Understanding viral pathogenesis may lead to better treatment approaches.[18] Studies of human cells are therefore very important.

Organoids are three-dimensional (3D) structures formed from induced pluripotent stem cells (iPSCs) or multipotent adult tissue stem cells.[19] Structurally, organoids contain organ-specific cells and functionally mimic these tissues.[20] Organoids, which can also be created from human cells, can reveal how viruses affect cells. For example, viruses that cause gastroenteritis, such as noroviruses, have been tested using intestinal organoids generated from human iPSCs. These studies showed that noroviruses infect absorptive cells.[21] A link between microcephaly and Zika virus infection was hypothesized in 2015.[22] Studies using human brain organoids showed that the Zika virus infects and kills neural precursor cells and causes microcephaly by restricting cortical development.[23]

Organoid technologies may offer an opportunity to further our understanding of the pathologic mechanisms of SARS-CoV-2 in tissues. The goal of this mini-review is to summarize the histopathological effects of SARS-CoV-2 in tissues as well as studies using organoid technology (Table 1). A thorough literature search (PubMed, preprint servers, and Google Scholar) was performed using the terms SARS-CoV-2 and histology/histopathology, COVID-19 and histology/histopathology, SARS-CoV-2 and organoid technology/organoids, and COVID-19 and organoid technology/organoids. This summary will be useful for researchers to establish links between organoid technology, which permits study of the effects of SARS-CoV-2 on tissues *in vitro*, and tissue histopathology.

SARS-CoV-2 structure and cell entry

Electron microscopy images showed that SARS-CoV-2 has a diameter of 60 to 140 nm and is usually spherical in shape. The diameter of the spike (S) protein on the viral surface, which gives virions their crown appearance, is 9 to 12 nm.[1]

ACE-2 plays a key role in viral entry into host cells.[24] Transmembrane serine protease 2 (TMPRSS2) activates the SARS-CoV-2 S protein and facilitates viral attachment to the cell surface (Figure 1).[25] TMPRSS2

Table 1. Histopathological features of SARS-CoV-2 and their relationships with organoid technology.

Organ	Histopathologic features	Organoid technology
Lung	• Hyperplasia of type II alveolar cells[39] • Dense inflammation[39] • Hyaline membrane development[39] • Dense fibrin formation around vessels[39] • Widespread lung injury[40] • Multi-core giant alveolar cells[40] • Microthrombi in the capillaries[41]	✓ Interferons, cytokines, and chemokines ↑[51] ✓ Genes associated with cell death ↑[51] ✓ Surfactant release ↓[51] ✓ Intracellular viral genome reproduction, cytotoxicity, pycnotic cells, moderate type I interferon signaling ↑[52] ✓ Type 2 alveolar cells infected but pulmonary neuroendocrine cells and lung mesenchymal cells not infected[53] ✤ Imatinib and mycophenolic acid[54] and low dose interferon[51] can inhibit SARS-CoV-2 infection
Kidney and Endothelium	• Proximal and distal tubules, endothelial cells, and podocytes damaged[56] • Fibrin thrombi in glomerular structures[56]	✓ SARS-CoV-2 can replicate in capillary and kidney organoids[58] ✤ Human recombinant soluble ACE-2 can inhibit viral infection[58]
Liver	• Apoptosis increased[61] • Liver cell damage[61]	✓ Cell death of cholangiocytes[63] ✓ NASH liver organoids are permissive to SARS-CoV-2[64]
Gut	• SARS-CoV-2 particles in the absorptive cells of the intestine[40]	✓ Dividing and absorptive cells infected by SARS-CoV-2[69] ✓ Changes in interferon regulatory gene expression[69] ✓ Enteroendocrine cells and absorptive cells infected by the virus[70] ✓ Paneth cells can be infected by SARS-CoV-2[67] ✤ Remdesivir and EK1, but not famotidine, inhibited SARS-CoV-2 infection[67]
Nervous System	• Reactive microglia in the olfactory bulb and medulla oblongata[31] • Viral RNA detected in the brain[72]	✓ SARS-CoV-2 infects neurons in the cortical areas of the brain[75] ✓ Increase in cell death and transcription of inflammation-related genes in choroid plexus organoids[76] ✓ Apolipoprotein- and ACE-2-expressing cells in the choroid plexus are infected by SARS-CoV-2[77] ✓ Neural progenitor cells are infected by SARS-CoV-2[79] ✤ Remdesivir reduced SARS-CoV-2 infection of neurons and astrocytes[78]

SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; ACE-2, angiotensin converting enzyme 2; NASH, non-alcoholic steatohepatitis.

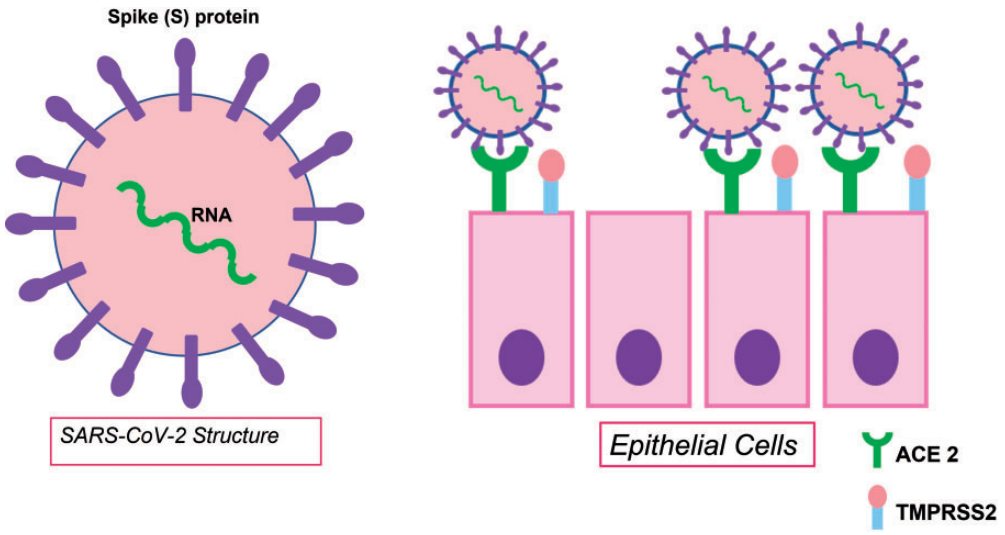

Figure 1. Structure of SARS-CoV-2 and its entry into the cell. The virus contains spike proteins that give it its distinctive crown appearance. ACE-2 plays a key role in viral entry into host cells. TMPRSS2 facilitates attachment of the virus to the cell surface.
SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; ACE-2, angiotensin converting enzyme 2; TMPRSS2, transmembrane serine protease 2.

cleaves both ACE-2 and the S protein leading to membrane fusion and cellular uptake of the virus.[10] Following endocytosis the virus releases its ribonucleic acid (RNA) into the cell and uses the host cell machinery to reproduce itself and create more virions.[26]

Because ACE-2 is critical for entry and is expressed in various organs, SARS-CoV-2 can cause serious systemic disease.[27–30] The wide range of COVID-19 symptoms, including fever, dry cough, fatigue, diarrhea, myalgia,[27] headache, and loss of smell and taste,[31] suggest that SARS-CoV-2 can affect multiple organs.

ACE-2 is a member of the renin–angiotensin–aldosterone system (RAAS) that plays important roles in maintaining blood pressure and electrolyte balance.[13] RAAS regulation begins with the release of angiotensinogen from the liver into the plasma. Renin then cleaves angiotensinogen into angiotensin I; this product is inactive and ACE is required to convert angiotensin I into its active form. ACE is expressed in the kidneys, lungs, heart, and intestine.[32] When SARS-CoV-2 binds to ACE-2, it is internalized by the cell. Downregulation of ACE-2 causes disruption of the RAAS and aggregation of angiotensin II. This can damage cells and tissues.[33]

When SARS-CoV-2 reaches the alveolar sac, the virus infects type 2 pneumocytes. These cells are responsible for tissue regeneration and surfactant production. When they are damaged, surface tension increases and dyspnea can develop. Furthermore, the alveolar immunological balance is disrupted and systemic inflammatory responses cause extensive cytokine production and a cytokine storm.[34–36] Excess cytokine production extensive tissue damage through systemic inflammatory responses. Large-scale activation of procoagulant factors favors microthrombus production in various tissues/organs, causing multiple organ failure.[37]

Research on lung tissue

The pathophysiological features of COVID-19 are acute pneumonia processes with wide radiological opacity, alveolar damage, microvascular thrombosis, and inflammatory infiltrates in the lungs.[38]

Examination of lung tissue extracted from four postmortem samples showed evidence of necrosis through hyaline membrane development, hyperplasia of type 2 pneumocytes, dense inflammation in the tissue, and dense fibrin structure formation around the vessel and cells.[39]

In another study, widespread lung injury and multi-core giant alveolar cells in the lung were observed. Using transmission electron microscopy, virions were observed in lung pneumocytes.[40]

Examination of postmortem lung tissues revealed development of microthrombi in the lung capillaries. Capillary networks were also disrupted, and intussusceptive pillar localizations of the virus were observed on the vessel wall by scanning electron microscopy. Moreover, the viral particles were detected in endothelial cell membranes. SARS-CoV-2 was compared with influenza virus in terms of angiogenesis using RNA analysis. While infection by these two viruses upregulated some common genes, distinct and separate genes were also upregulated. Following SARS-CoV-2 infection, severe damage to the endothelium, widespread vascular thrombosis, and neovascular networks developed in the lungs.[41]

Although histopathological results from postmortem lung tissues showed that widespread damage occurred in the lung, the mechanisms through which SARS-CoV-2 damages lung tissue are only partially understood. For this reason, laboratory investigations, especially using cell culture systems, are critical. Studies using organoid systems (3D miniature organs in culture media) are gaining importance in this regard.

Organoids, self-organizing 3D structures, can histologically recapitulate *in vivo* tissues.[42–45] Research in basic biology, infectious diseases, and drug discovery can be accelerated this technology (Figure 2).[46]

iPSCs or multipotent adult tissue stem cells can be used in organoid technology.[19] In studies using iPSCs, the cells are first allowed to develop into embryoid bodies and then media are prepared that mimic the developmental signals of the selected organ *in vivo*. In studies using adult stem cells, fully specialized stem cells are isolated from tissues. While some tissues, such as the mouse gut, can produce a complete organoid using a single cocktail of growth factors, other tissues such as the brain require expansion in growth factor-containing medium to allow the proliferation of adult stem cells and iPSCs required for organoid formation.[20]

Although organoids imitate human tissues, the organoid microenvironment can sometimes be insufficient. Co-culture systems using organoids have not been fully established. Organoids seem to mimic structures from a single part of the body, but there is no inter-organ communication.[46] However, recent studies have aimed to overcome this problem. When anterior and posterior intestinal spheroids were formed and two spheroids were cultured in the same location, inter-organ connectivity was achieved and hepato-biliary-pancreatic organoids could be obtained.[47]

That human cells show different characteristics compared with animal cells is important for the development of antiviral therapeutics. For example, single-cell RNA sequencing of mouse, monkey, and human cells expressing ACE-2 and TMPRSS2, which are key targets for SARS-CoV-2 entry, showed that goblet cells in the nasal mucosa, type 2 pneumocytes in the lung, and absorptive cells in the intestine may

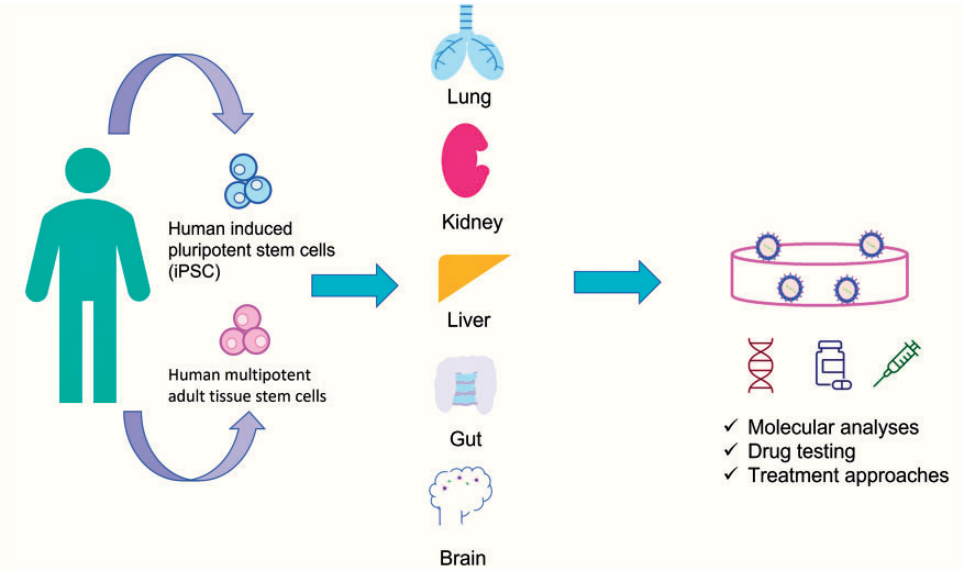

Figure 2. Applications of organoid technology in studies of SARS-CoV-2. Induced pluripotent stem cells or multipotent adult tissue stem cells can be used in organoid technology. Organoids are 3D structures that imitate human tissues. These 3D mini-organs can be infected with SARS-CoV-2. Molecular analyses, drug testing, and discovery of novel therapeutic approaches can be accomplished using organoid technology. SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; 3D, three-dimensional.

be targets of SARS-CoV-2. Furthermore, ACE-2 expression may be associated with expression of interferon regulatory genes only in human cells but not in mice.[48]

Organoid technology has advantages over two-dimensional (2D) culture technologies; these cannot faithfully mimic the *in vivo* environment in the absence of cell–cell and cell–extracellular matrix interaction.[49] Moreover, expression of ACE-2, the SARS-CoV-2 entry receptor, is twice as high in organoids compared with 2D cell cultures.[50] These data demonstrate the capacity of organoids to provide biologically relevant results in studies of SARS-CoV-2.

Researchers have developed 3D alveolar structures, called alveolospheres, that are rich in type 2 pneumocytes. To better understand the histopathological effects of SARS-CoV-2 infection, alveolospheres were infected with the virus. Following infection, expression of interferons, cytokines, and chemokines as well as genes associated with cell death were activated, while surfactant release decreased.[51] This result may indicate direct damage to pneumocyte function following SARS-CoV-2 infection. Low-dose interferon administration prior to infection inhibits SARS-CoV-2 replication in these 3D structures.[51]

In another study, researchers produced 3D organoids containing basal, club, ciliated, and goblet cells derived from commercially available cryopreserved human bronchial epithelial cells. ACE-2 and TMPRSS2 were expressed in these organoids. Following infection of these organoids with SARS-CoV-2, intracellular viral genome reproduction, cytotoxicity, pycnotic cells, and type 1 interferon signals were increased. Application of camostat, an inhibitor of TMPRSS2, reduced the viral copy number in the organoids. These

data revealed that organoids can be important tools for drug development. The data also suggested that SARS-CoV-2 can replicate in basal cells: expression of the viral S protein was observed in keratin 5-expressing cells but not in club cell protein 10-expressing cells.[52]

In a different study, multipotent human distal tip cells from fetal lungs were expanded and an air-liquid interface was used to differentiate cells. When lung organoids were infected with SARS-CoV-2, type 2 pneumocytes were primarily infected, while pulmonary neuroendocrine and lung mesenchymal cells were not infected.[53]

In another study, lung organoids were produced using human iPSCs. Following infection of the organoids with SARS-CoV-2, transcriptomic analyses revealed that cytokines were released, chemokine signaling occurred, and type 1 and 3 interferon release was induced; these effects were similar to those observed in COVID-19 patients. The Food and Drug Administration (FDA)-approved drugs imatinib and mycophenolic acid were tested as inhibitors of SARS-CoV-2 entry In lung organoids. Pre- or postinfection treatment with these drugs reduced the levels of SARS-CoV-2 replication.[54]

Research on the kidneys and endothelium

Although the direct targets of SARS-CoV-2 are the respiratory and immune systems, patients with acute kidney damage have increasingly been observed through the course of the pandemic.[55] When postmortem kidney tissues were examined, the proximal tubules in particular were damaged with fibrin thrombi observed in glomerular structures. Electron microscopy studies revealed that the virus was present in the proximal and distal tubules, as well as in endothelial cells and podocytes.[56] Other studies showed contrary results. Some researchers claimed that the structures thought to be viruses in electron microscopy images were in fact clathrin-coated vesicles.[57]

Although it is not well understood how SARS-CoV-2 affects multiple organs, some researchers believe that the 80- to 100-nm diameter virus can travel through and infect blood vessels before it affects various tissues.[58] The expression of ACE-2 in vascular endothelial cells[59] and viral inclusion bodies in endothelial cells overlap with the localization of inflammatory cells and apoptotic bodies.[60] Thus, endothelial cells may represent an easy target for SARS-CoV-2. On the basis of these findings, researchers have created human blood vessel organoids from iPSCs. These capillary organoids, which have a lumen surrounded by endothelial and pericyte cells, mimic the human capillary structure quite well. Following infection of these organoids with SARS-CoV-2, an increase in viral RNA was observed from day 3 to day 6 postinfection, indicating active replication of SARS-CoV-2. Kidney organoids were also developed from human embryonic stem cells and viral RNA was detected 6 days after infection with SARS-CoV-2. When the supernatant of infected kidney and blood vessel organoids was added to Vero E6 cell cultures, infection of these cells indicated that organoids could successfully produce the virus. The authors also showed that infection of both blood vessel and kidney organoids was reduced in the presence of human recombinant soluble ACE-2.[58]

Research on the liver

Over the course of the COVID-19 pandemic, liver enzyme abnormalities have been observed in some patients.[61] When the effects of SARS-CoV-2 on the liver were examined, it was revealed that apoptosis was increased, virus-like structures were

observed in the liver, and signs of cell damage such as swelling of mitochondria were observed. Because SARS-CoV-2 targets tissues with abundant ACE-2 expression, it seemed unlikely that the virus would affect the liver, where low levels of ACE-2 are found. Thus, researchers theorized that the virus may change receptor arrangement after entering the cell.[62]

In a study of SARS-CoV-2 infection of liver organoids, it was observed that cholangiocytes undergo membrane fusion and form syncytia. SARS-CoV-2 was found to regulate various apoptotic factors and induce cell death of cholangiocytes. This suggested that SARS-CoV-2 may cause a decrease the expression of cell linkage regulatory genes that may lead to disruption of the bile duct epithelium. Researchers determined that expression of bile acid transporter genes, such as solute carrier family 10 member 2 and cystic fibrosis transmembrane conductance regulator, decreased following SARS-CoV-2 infection. These data suggested that liver damage in some patients with SARS-CoV-2 infection may result from damage to cholangiocytes and bile acid accumulation.[63]

In a recent study, organoids were produced from the liver cells of patients with nonalcoholic steatohepatitis (NASH). Organoids from NASH patients may be important in the development of drugs for treatment of this disease. The NASH liver organoids showed increased permissiveness to SARS-CoV-2 infection.[64]

In another study, organoids generated from human hepatocytes and cholangiocytes were found to be susceptible to SARS-CoV-2 infection. Chemokine responses following organoid infection recapitulated the features of those observed in patients with COVID-19. One of the most interesting results of this study was that pancreatic beta cells could be infected by SARS-CoV-2.[65] There are important clinical studies showing associations between SARS-CoV-2 infection of organoids and the hallmarks of diabetes.[66]

Research on the gut

Roughly half of patients with COVID-19 have gastrointestinal symptoms such as diarrhea or nausea.[67] Transmission electron microscopy showed SARS-CoV-2 virions in the absorptive cells of the intestine.[40] Replication of the virus also occurs in the rectum.[68]

ACE-2 is expressed in human small intestine organoids and these organoids can be infected with SARS-CoV-2. The virus infects dividing and absorptive cells in the intestine. RNA sequencing has revealed changes in interferon regulatory gene expression following infection of these cells.[69] The emphasis on changes in interferon regulatory gene expression in this study and in another[48] clearly indicated the importance of the research technologies used. In another study of intestinal organoids derived from human iPSCs, enteroendocrine cells were infected in addition to absorptive cells. Infection damaged absorption and transport of metabolites as well as hormone release. In the same study, various drug treatment approaches for SARS-CoV-2 infection were tested. Application of remdesivir, which was developed to prevent infection by Ebola virus, in intestinal organoids infected with SARS-CoV-2 resulted in decreased viral infection and replication.[70] Another study found that in addition to enterocytes, enteroendocrine and Paneth cells were infected by SARS-CoV-2. In organoids infected with SARS-CoV-2, infection and replication were inhibited by remdesivir and EK1, a peptidic pan-coronavirus fusion inhibitor, but not by a histamine-2 receptor antagonist called famotidine, which was thought to suppress expression of proteins required for viral replication.[67]

Research on the central nervous system

The symptoms of COVID-19 include headache as well as loss of smell and taste.[71] Schurink et al. (2020) postulated that microglia in the olfactory bulb and medulla oblongata were reactive following SARS-CoV-2 infection. The authors suggested that these symptoms might be caused by inflammation, as T lymphocyte staining was observed in these tissues.[31] In another study, SARS-CoV-2 RNA was detected in brain tissue samples[72] and was associated with hemorrhage and encephalopathy in postmortem brain magnetic resonance imaging (MRI). This finding suggested that SARS-CoV-2 can cause neuronal stress, inflammation, and central nervous system damage.[73]

Although neurological symptoms have been reported in patients with COVID-19,[74] it is not yet known whether SARS-CoV-2 directly damages neurons.

When human 3D brain organoids were produced from iPSCs and infected with SARS-CoV-2, it was observed that SARS-CoV-2 infected neurons in the cortical areas of the brain. Examination of these organoids showed elevated Tau protein distribution, hyperphosphorylation, and neuronal death. Although SARS-CoV-2 can infect brain organoids, the virus did not efficiently replicate in this tissue, suggesting that active replication of SARS-CoV-2 may not occur in the central nervous system.[75] In another study, the effects of SARS-CoV-2 were evaluated on both single-layer neuron cell cultures and brain organoids (cerebral cortex, hippocampus, hypothalamus, and midbrain organoids). Infection of neurons and astrocytes was observed to be minimal, but infection was evident in the choroid plexus. Subsequently, the researchers developed choroid plexus organoids and found that SARS-CoV-2 infection of these tissues caused cell death and functional disorders associated with an increase in transcription of inflammation-related genes.[76]

In a different study using brain organoids, SARS-CoV-2 did not directly target neurons but could infect the choroid plexus. The authors concluded that cells that produced apolipoprotein and expressed ACE-2 in the choroid plexus were infected by SARS-CoV-2. This result also confirmed that lipid-producing adult choroid plexus cells were more sensitive to SARS-CoV-2 infection. The choroid plexus, an important barrier against the entry of pathogens, immune cells, and cytokines into the brain and cerebrospinal fluid, may be targeted by SARS-CoV-2 and thus infection may result in damage and leakage in this region.[77]

Another study found that expression of ApoE4, a strong risk factor for Alzheimer's disease, increased sensitivity to SARS-CoV-2 infection in brain organoids created from human iPSCs. ApoE4-expressing cells exhibited severe responses to infection. However, remdesivir reduced SARS-CoV-2 infection of neurons and astrocytes.[78]

When human brain organoids that faithfully mimicked ventricle structure were infected with SARS-CoV-2, the virus targeted neural progenitor cells. When the supernatants of infected brain organoids were examined, the SARS-CoV-2 genome copy number increased in a time-dependent manner, indicating that active viral progeny were released by infected brain organoids.[79]

Conclusions

Although SARS-CoV-2 generally affects the lungs and causes acute respiratory stress, the kidney, liver, and central nervous system can also be affected by the virus. Because ACE-2 is the entry receptor for SARS-CoV-2, ACE-2-expressing cells can be directly targeted by the virus. Information regarding the effects of

SARS-CoV-2 on tissues has primarily come from postmortem tissues. Widespread lung injury, intense inflammation, hyperplasia of type 2 pneumocytes, and hyaline membrane formation were observed in lung samples. Similar data on the impact of COVID-19 in tissues have been produced. However, it is not yet understood exactly how COVID-19 affects tissues. Because the virus can show species-specific features, animal experiments may not yield meaningful results. Organoids give faster results than animal experiments and can be derived from human cells. Using studies of organoids, cells that are targeted by the virus can be identified and agents that prevent viral infection and replication can be tested. Organoid studies revealed that the most affected cells in the lung are type 2 pneumocytes and that various FDA-approved substances can suppress entry and/or replication of SARS-CoV-2. Similar studies have been conducted using kidney and gut organoids. These data demonstrate the importance of organoid technology in developing novel treatment approaches.

The ability to accurately model disease and to use cells obtained from patients in organoid technology are important advantages. Organoids generated from the cells of NASH patients have been shown to be more permissive to SARS-CoV-2 infection than those generated from healthy individuals. Similarly, ApoE4-producing cells, which are risk factors for the development of Alzheimer's disease, are more sensitive to SARS-CoV-2 than other cells in brain organoids. These data indicate that individuals with certain comorbidities may be more susceptible to COVID-19.

Organoid technology has also been applied in pioneering studies of the impact of SARS-CoV-2 on cells. Neurological symptoms such as headache and loss of taste or smell occur in some patients with COVID-19. It is unclear from postmortem tissue studies whether SARS-CoV-2 directly targets neurons. Studies using brain organoids have shown that the virus targets the choroid plexus, where it triggers cell death and induces expression of inflammation-related genes. Recent studies have observed that like Zika virus, SARS-CoV-2 targets neuroprogenitor cells. This information will be useful for organoid studies examining the long-term effects of SARS-CoV-2.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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