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REVIEW ARTICLE

Organoid Studies in COVID-19 Research

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The current COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has completely changed human life for more than two years. Upon the emergence of this new lethal virus, multiple approaches were utilized to gain basic knowledge about its biology. Moreover, modern technologies, such as the organoid model system and next-generation sequencing, enabled us to rapidly establish strategies to tackle the disease, including vaccines and therapeutics. The recently developed organoid technology reflects human physiology more closely than other model systems. Coupled with its rapidness, high efficiency, and outstanding reliability, it has provided an opportunity to develop new drugs and understand the impact of the viral pathogen on the host. Recent findings using organoids have successfully revealed the cellular tropism of the virus in different organs and identified potential drug candidates that impact the disease. This review will summarize current achievements made with organoids in the fight against COVID-19.

Keywords: COVID-19, SARS-CoV-2, Organoid

Introduction

Global pandemics, such as bubonic plague and Spanish flu, have challenged human life and economies multiple times across history (1). In 2019, another threat caused by SARS-CoV-2, which causes COVID-19, emerged as a new global pandemic from China (2). COVID-19 is the third lethal disease caused by coronaviruses that has emerged in many countries, after outbreaks of severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome virus (MERS-CoV) (3, 4). As of September 2021, more than 373 million cases have been diagnosed, with 5.6 million confirmed deaths from COVID-19 in total (5). According to a recent report, the number of deaths caused by COVID-19 in the US already exceeds that caused by the Spanish flu (6). COVID-19 has significantly impacted both the global economy and human life over the past two years. Advances in modern science have made fast and efficient diagnostic tools available in response to the outbreak, along with vaccines against the virus developed to prevent infection and severe symptoms (7). However, although Remdesivir treatment is approved by the FDA, other therapeutics to treat the disease remain under development (8). Recently, two pharmaceutical companies have announced clinical trials of antivirals against SARS-CoV-2 named Molnupiravir (Merck) (9), which almost halves the risk of severe COVID-19, and Paxlovid (Pfizer) (10), which reduces hospitalizations by 89%. However, the U.S. Food and Drug

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Administration has only recently approved these antivirals to quell new variant fears. Although an effective and safe oral antiviral could be a game-changer during the current pandemic, the emergence of diverse variants will necessitate the continued development of further antiviral drugs.

SARS-CoV-2 is a member of the beta coronavirus sub-family with positive-sense RNA as its genomic material (11). Its pathogenicity is similar to that of SARS-CoV, which belongs to the same family and contains a similar spike protein and cellular protease (12). The entry mechanism of SARS-CoV-2 relies on the presence of the host cell receptor angiotensin-converting enzyme 2 (ACE2), which interacts with its spike protein (13). Upon virus entry into the host cell, the spike protein is cleaved by transmembrane protease serine 2 (TMPRSS2) (14-16), which induces fusion of the virus with the host cell. SARS-CoV-2 has various animal reservoirs including bats, dogs, cats, and non-human primates. Although bats are considered the natural host of SARS-CoV-2, recent studies have identified more susceptible animal species, as well as possible animal-to-human transmission from minks (2, 17).

Developing advanced biological platforms that can successfully mimic *in vivo* conditions in order to study host-pathogen communication *in vitro* has been a top priority in modern biomedical science. Conventional 2D cell lines have long been the most widely utilized platform for infection studies because of their benefits including ease of handling, relatively fast result monitoring, and cost-effectiveness. However, they have several limitations, such as lack of cellular heterogeneity and limited pathogen infectivity caused by inaccurate representation of the natural host conditions. Animal models including mice and primates can provide cellular heterogeneity and similar physiological conditions, resulting in similar infection efficiency and corresponding disease phenotypes as those observed in humans. However, animal models are typically expensive to maintain, difficult to control and take longer to yield results than conventional 2D cell lines. More importantly, not all human pathogens can be studied in animal models because of differences in infectivity and disease susceptibility.

The organoid technology thus represents a significant advance for infection biology. Organoids are self-organizing 3D cultures that present an alternative to conventional platforms, while retaining the benefits of both conventional 2D cell lines and *in vivo* animal models. They are generated from stem cells that give rise to the specific cell types of the tissue origin. The first adult stem cell (AdSC) -derived organoid model was reported in 2009 using mouse Lgr5-positive small intestine stem cells (18). After this initial innovation, various organoids from different organs and stem cells have been generated from humans and other animals, including bats (19-21). Typically, two types of stem cells, pluripotent stem cells and adult stem cells, have been actively used to generate organoids. Organoid technology is now utilized in different research fields, including disease modelling, host-pathogen interaction, and patient-derived organoid biobanks (19). With the emergence of COVID-19, various organoid systems have been used as a fast, efficient, and accurate system to study the biology of the SARS-CoV-2, candidate drug efficiency, and cellular tropism. This review summarizes the achievements of organoid-based COVID-19 research over the past 2 years (Fig. 1).

COVID-19 and Pluripotent Stem Cell-Derived Organoids (PSC-Derived Organoids)

Lung organoids

Viral transmission of SARS-CoV-2 is considered to be mediated primarily by respiratory droplets (2) and respiratory system failure is a typical symptom of COVID-19, induced by the production of cytokines that lead to a cytokine storm in the lungs (11). The lung is a highly branched organ that exchanges gases at the alveoli. It comprises various cell types including epithelial, vascular, stromal, and immune cells (22). Since conventional lung cell lines do not reflect *in vivo* lung conditions appropriately, lung organoids have become a valuable tool to study SARS-CoV-2.

There are multiple reports on COVID-19 research in human PSC-derived lung organoids that cover various topics: cell tropism, host cell responses, genetic variation influencing virus susceptibility, novel drug candidates, and impact of the environment (23-28). Studies by Pei et al. (24) and Tiwari et al. (26) have demonstrated that SARS-CoV-2 can infect human PSC-derived lung organoids and that they are susceptible to SARS-CoV-2 infection and replication because they highly express ACE2 and TMPRSS2, which are both critical for viral entry. Interestingly, Pei et al. (24) observed no viral infection in AT1 cells, even though they are present in lung organoids, indicating that not all cells expressing ACE2 or TMPRSS2 are susceptible to SARS-CoV-2 infection. In contrast, another report by Han's research group (27) noted that ACE2 expression is primarily limited to the AT2-like cell population of lung organoids, and SARS-CoV-2 infection can be detected in a broad area of the lung organoid. These differences may be due to the different culture conditions

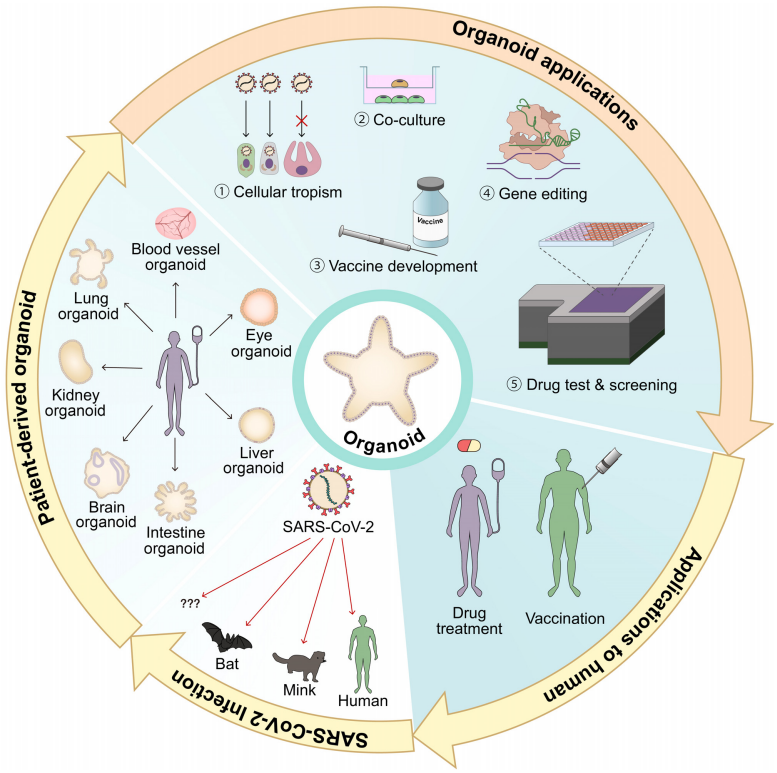

Fig. 1. Overview of organoids on COVID-19 research.

and differentiation methods used in these studies.

Host cell responses upon SARS-CoV-2 infection have also been investigated in organoids, such as virus-induced interferons, cytokines, and chemokines. Gene set enrichment analysis (GSEA) revealed that genes involved in rheumatoid arthritis, tumor-necrosis factor signaling, interleukin-17 signaling, and cytokine-cytokine receptor interactions are overrepresented in the genes upregulated following infection. Another interesting report by Kim and colleagues (25) has demonstrated increased SARS-CoV-2 infection susceptibility induced by diesel fine particulate matter (dPM2.5). The addition of dPM2.5 was found to upregulate ACE2 and TMPRSS2 expressions, leading to higher SARS-CoV-2 susceptibility, in addition to increasing the expression of genes associated with inflammation, fibrosis, and epithelial-to-mesenchymal transition. Lung organoid research has also shown that the single nucleotide polymorphism rs4702 influences viral infection, which was also observed in intestinal organoids (28). Finally, metabolic changes have been reported in response to SARS-CoV-2 infection. RNA-seq analysis has shown that genes involved in cellular metabolism are down-regulated after viral infection, whereas immune response genes are upregulated (24). As male patients exhibit higher prevalence and more severe complications (29) Samuel et al. (30) have used a human PSC-derived lung organoid model to investigate the potential reason behind the gender-dependent severity of COVID-19. They showed that androgen receptor signaling regulates ACE2 expression levels and that treatment with antiandrogenic drugs can reduce ACE2 expression, thereby decreasing viral infection.

Brain organoids

Numerous case reports have suggested that COVID-19 can present with neurological symptoms including temporal or complete loss of olfactory function (31, 32). These reports suggest that SARS-CoV-2 has neurotropic characteristics. Moreover, viral RNA has been detected in patient brain samples (33-36). Recent progress in SARS-CoV-2 research using human PSC-derived brain organoids has broadened our knowledge about neurotropism and related cellular responses.

Neural tropism is currently debated because individual reports have indicated different primary target cells for viral infection, with neurons suggested by several studies (37-41). In addition, astrocytes (41, 42), choroid plexus cells (43, 44), and pericyte-like cells (45) were shown to be susceptible to SARS-CoV-2 infection in different organoid models. Interestingly, in contrast to neurons and pericyte-like cells, the astrocytes in the study by Andrews et al. (42) did not exhibit high levels of ACE2 expression. Instead, this study identified alternative SARS-CoV-2 re-

ceptors on astrocytes, including DPP4 and CD147 (42). Different models also showed different host cell responses. The studies by Jacob and by Pellegrini and colleagues (43-45) described an upregulation of genes related to inflammatory signaling in a choroid plexus organoid model, while Song et al. (37) did not observe any evidence of type I interferon responses using 10× single-cell sequencing on brain organoids. In addition, Wang et al. (41) have identified another important risk factor for COVID-19: ApoE4, a known genetic risk factor for Alzheimer's disease, was found to be strongly correlated with SARS-CoV-2 infection and disease severity. Lastly, Poirier and colleagues (46) have confirmed that antiviral Dicer (aviD), an isoform of Dicer, which cleaves double-stranded viral RNA, participates in innate mammalian immunity protecting stem cells from SARS-CoV-2 infection in human brain organoids.

Gut organoids

COVID-19 patients also present with various gastrointestinal symptoms including diarrhea, nausea, vomiting, anorexia, and abdominal pain (29). Single-cell analyses have shown that ACE2 and TMPRSS2 expression can be detected in enterocytes from the ileum and colon (47), with the small intestine exhibiting the highest level of ACE2 expression in the human body. Therefore, both PSC-derived and AdSC-derived gut organoids have been widely used for SARS-CoV-2 studies.

Multiple studies have confirmed that human PSC-derived intestinal organoids also express ACE2 and TMPRSS2 and are susceptible to SARS-CoV-2 infection. Krüger and colleagues (48) have reported that ACE2 expression is broadly detected in all the different cell types found in human gut organoids, except in goblet cells, which do not express ACE2. Other studies have monitored responses to infection, such as interferon signaling. Mithal et al. (49) have demonstrated that human intestinal organoids can be infected by the virus, resulting in the stimulation of interferon-related genes, including BST2, OASL, MX1, IFITM1, and IRF7. Bozzo et al. (50) found that the viral spike protein is able to hijack interferon-induced transmembrane proteins (IFITM 1, 2 and 3) for more efficient infection, and interfering IFITMs can suppress viral infection in gut organoids.

Other organoids

Other types of PSC-derived organoids that have been employed in COVID-19 research, include kidney, retinal, blood vessel, and liver organoids.

In one of the first studies on COVID-19, Monteil et al. (51) demonstrated that SARS-CoV-2 can directly interact with blood vessel and kidney organoids, and that this interaction can be blocked by treatment with clinical-grade soluble human ACE2. A follow-up study by the same group also reported that the combination with remdesivir further improved the therapeutic activity of human soluble ACE2 against SARS-CoV-2 infection in human kidney organoids (52). Similarly, Wysocki and colleagues (53) used kidney organoids to show that a shorter ACE2 variant had improved neutralizing activity against the infection. A new potential drug candidate, MEDS433, also demonstrated its inhibitory activity on SARS-CoV-2 replication in kidney organoids (54).

A study of patient eye samples noticed that the virus can be detected in the ocular fluid; however, it could not determine whether the human retina can also be a target for viral infection and replication. Lai et al. (55) subsequently used PSC-derived human retinal organoids to show that they express both ACE2 and TMPRSS2 and are susceptible to SARS-CoV-2 infection and replication.

In addition, Yang et al. (56) have demonstrated that PSC-derived human liver organoids, as well as adult hepatocyte and cholangiocyte organoids, are also susceptible to SARS-CoV-2 infection. In response to the infection, they observed induction of chemokines in a pattern similar to that found in patient samples.

COVID-19 and Adult Stem Cell-Derived Organoids (AdSC-Derived Organoids)

Lung organoids

With respiratory system failure among the most common symptoms of COVID-19, many studies have employed adult stem cell-derived (AdSC-derived) lung organoids for COVID-19 research.

Cellular tropism of SARS-CoV-2 was the primary interest of these studies and different studies have identified different target cells, similar to the observations made in PSC-derived lung organoids. A report by Tindle et al. (57) suggested that the proximal airway is important for infection while the distal alveolar region controls host responses against infection. Another report from Suzuki et al. (58) showed that AdSC-derived lung organoids comprise basal, club, ciliated, and goblet cells, which express high levels of ACE2 and TMPRSS2, allowing infection with SARS-CoV-2. Hysenaj et al. (59) have identified mainly ciliated-like and goblet-like cells, marked by expression of TUBA and MUC5AC, respectively, to retain the highest tropism. However, the correlation of TUBA, MUC5AC, and ACE2 expression with infection rate was not investigated.

Instead, the authors identified a novel mediator, Tetraspanin 8 (TSPAN8), which exhibits a strong correlation with the rate of viral infection. In contrast, Salahudeen et al. (60) have suggested that club cells are the primary targets of SARS-CoV-2. The question of viral tropism in the lung thus requires further studies and validations.

An advantage of using AdSC-derived human lung organoids is that they can reveal varying sensitivities of the different SARS-CoV-2 variants to host immune responses, with the delta variant exhibiting 6–8-fold lower sensitivity (61). Moreover, Mykytyn and colleagues (62) have used this model to identify novel characteristics of SARS-CoV-2, including the multi-basic cleavage site (MBCS), which distinguish the virus from SARS-CoV. The presence of the MBCS on SARS-CoV-2 enables the virus to penetrate host cells with greater ease and speed. AdSC-derived human lung organoids have also been used to broadly monitor host cell responses to SARS-CoV-2 infection (57, 58, 63-67). The most common response was the induction of genes related to interferon-responsive signaling. Recent findings also suggest that perturbed metabolism, autophagy, and immune response are among the top listed common features induced by virus-mediated gene expression changes.

Gut organoids

Detection of SARS-CoV-2 infection in human AdSC-derived gut organoids by Clevers' group was one of the earliest reports to explain why COVID-19 patients often struggle with the above-mentioned gastrointestinal symptoms (68). This report highlights the speed and efficiency with which organoids are able to recapitulate viral infection events *in vitro*. The study observed high levels of ACE2 expression on enterocytes, making the gut organoids susceptible to SARS-CoV-2 infection. Subsequently, Zang et al. (69) demonstrated that TMPRSS2 and TMPRSS4 also have the potential to induce SARS-CoV-2 infection in intestinal organoids. Interestingly, the host responses to SARS-CoV-2 in gut organoids reported by Stanifer and colleagues revealed only an induction of type III interferon as a host response (70), while others also reported a type I interferon response (68, 71).

Other organoids

COVID-19 patients with severe symptoms are more likely to exhibit liver failure than patients with mild symptoms (72). While one reason could be the hepatotoxicity induced by drug treatments, Zhao and colleagues (73) have described that SARS-CoV-2 infection itself can cause misregulation of tight junctions and tight junction-related gene expression in cholangiocytes. They have suggested that this malfunction directly stems from the toxicity induced by viral infection of ACE2 and TMPRSS2-positive target cells.

Another rare type of organoid employed in COVID-19 research is the tonsil organoid model, representing a lymphoid organ. Using this new type of organoid, Wagar et al. (74) could successfully recapitulate the function of the original organ, such as antibody production and maturation. Moreover, they showed that tonsil organoids can be used to validate vaccine efficacy.

Applications of organoid in COVID-19 drug development

Conventional high-throughput drug screening based on 2D cell lines is cost-efficient, fast, and able to cater to high chemical complexity, with hundreds of thousands of chemical candidates. Numerous drug screenings have utilized this platform to identify novel therapeutic candidates. However, the limitations of 2D cell lines, such as non-physiological conditions and lack of cellular heterogeneity, call for a new high-throughput strategy for drug screening on organoids. Since their development, many studies have performed drug discovery tests on organoids for various reasons, from validating the effects of candidate drugs shortlisted from prior screening in 2D cell lines, to initial drug screening with a set of drugs including FDA-approved molecules, and drug responsiveness monitoring.

However, as organoid cultures are still expensive and more difficult to handle than a conventional 2D cell line model, currently the most widely accepted use of organoids in drug screening is to validate candidate molecules identified from conventional screening, e.g. examining their efficiency and monitoring their cytotoxicity. The current emergency caused by the pandemic demands the rapid development of efficient therapeutics against COVID-19. To this end, a preliminary screening on 2D cell lines with higher complexity, and validating the efficacy of selected candidates on organoids is considered a well-designed strategy. Multiple cell lines have been utilized for primary drug screening, including Vero E6, A549, and Calu-3. Saul et al. (75) have tested 4,413 compounds on the Vero E6 cell line to identify candidates that reduce lethality caused by SARS-CoV-2 infection, followed by a second round of screening to monitor dose-dependency. The authors identified an antiviral effect of Lapatinib and other inhibitors against the ErbB family. These were then validated in human AdSC-derived lung organoids, which exhibited suppressed viral replication upon Lapatinib treatment. Duarte

and colleagues (23) have reported another screening of FDA-approved drugs using a similar strategy. The authors started from available large-scale data sets and identified candidates that might potentially affect COVID-19, based on gene expression profiles. Consequently, they identified atorvastatin as a promising candidate for COVID-19 treatment, which was further validated using human PSC-derived lung organoids.

Despite the cost, drug screening for COVID-19 treatments directly based on a lung organoid model represents an excellent strategy because the system accurately reflects *in vivo* conditions. Han and colleagues (27) have performed high-throughput screening of FDA-approved drugs on human PSC-derived lung organoids. The authors identified the three most efficient compounds to be imatinib, mycophenolic acid, and quinacrine dihydrochloride, from the first screening. The effects of these three drugs in preventing SARS-CoV-2 infection in host cells were also validated further.

Human organoids are considered to be among the best *in vitro* models to monitor drug responsiveness against COVID-19; therefore, numerous studies have employed organoids as a validation platform for known drug candidates. For example, soluble ACE2 treatment is considered a straightforward strategy to interfere with SARS-CoV and SARS-CoV-2 infection in humans. Starting from the study by Penninger's group, the efficacy of clinical-grade soluble ACE2 in treating COVID-19 patients has been demonstrated *in vitro* using blood vessel and kidney organoid systems (51). A follow-up study of ACE2 variants with prolonged neutralizing activity has been reported by Wysocki et al. (53). Moreover, Monteil et al. (52) showed that combined treatment of remdesivir along with soluble ACE2 is more effective in preventing viral entry and replication. In addition, Ebisudani and colleagues (63) have tested the effects of three selected antiviral drugs on lung organoids, identifying remdesivir as the one with the highest activity in preventing SARS-CoV-2 infection. Recent studies have discovered further inhibitors of SARS-CoV-2, including a spike protein inhibitor (EK1 peptide), TMPRSS2 inhibitors (camostat/nafamostat), and a human dihydroorotate dehydrogenase inhibitor (MEDS433) (26, 54).

Conclusions

The emergence of this pandemic, which can cause severe illness and death, has required urgent development of new vaccines and drugs. New advanced technologies such as mRNA vaccines, antibody engineering, and organoid models have allowed us to develop vaccines and antivirals against SARS-CoV-2 at an unprecedented pace. In particular, organoid models have already proven their value during the Zika virus epidemic, when studies involving brain organoids revealed a clear connection between microcephaly and Zika virus infection. During the COVID-19 pandemic, we have once again witnessed the utility of the human organoid system to study infectious diseases. It provides an ideal platform to investigate SARS-CoV-2 with proper cellular heterogeneity, viral susceptibility, and appropriate host cell responses. Evidently, human organoid systems have also been instrumental in screening and validating drug candidates.

However, despite all its advantages over conventional 2D cell line models, the human organoid system still has numerous limitations. Organoid cultures are more expensive, difficult to handle, and still lack many physiological aspects of *in vivo* models. In the aforementioned examples, it is evident that anti-viral responses and cellular tropism are often not consistent among different studies. This could be caused by the lack of standardized protocols among labs, which may influence the maturation status and cellular composition of the organoids. Finally, although organoids are comparatively cheaper than animal models, performing large-scale drug screening in organoids remains challenging.

Despite all these hurdles, organoid models are the best available choice for future biomedical studies and drug development. Organoids are currently under development or in clinical trials to identify drugs not only against SARS-CoV-2, but also to treat other diseases. The organoid system will continue to be useful in reducing and eventually replacing animal experiments. With the massive *in silico* prediction of drug candidates based on predicted target protein structures and protein-protein interactions, more and more drug candidates will need to be tested rapidly on an appropriate *in vitro* system that closely mimics human physiology. Therefore, we believe that the value of the human organoid system as a suitable preclinical model system will continue to increase in the future.

Potential Conflict of Interest

The authors have no conflicting financial interest.

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