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Short Communication

The Use of 3D Models to Test Potential Anti-SARS-CoV-2 Drugs and Infection Mechanisms

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ABSTRACT

After more than a year of the pandemic caused by SARS-CoV-2, the development of vaccines reduced the impacts of COVID-19. However, the disease continues to affect millions of people worldwide, and the development of antivirals and effective treatments remains a challenge. We recently reviewed the strategies of the tissue engineering field in providing three-dimensional (3D) cell culture models suitable to study antiviral candidates to treat COVID-19, such as spheroids, organoids, and the use of 3D bioprinting technology. These models represent an advance over conventional monolayer cultures by providing more complex structures that better resemble native tissue, improving the prediction of results. Bioengineered organs could potentially contribute to our understanding of the infection mechanisms and help the research community to overcome the challenges of developing effective treatments against COVID-19.

Keywords: COVID-19; SARS-CoV-2; 3D culture; Bioprinting; Organoids

DESCRIPTION

As the COVID-19 outbreak continues to affect millions of people worldwide, developing strategies for effective treatment is still in need. Cell culture is a fundamental tool for drug discovery and drug repurposing studies, and until recently, bidimensional (2D) cultures were the most used model. The recent advances in tridimensional (3D) culture, such as organoids and 3D bioprinting, provide better reproduction of the native cellular microenvironment, cytoarchitecture, extracellular matrix composition, and mechanical properties [1].

We recently reviewed some strategies in the tissue engineering field, such as organ-on-a-chip and 3D biofabricated tissue-like structures, and how they can mimic the organs mainly affected by COVID-19 (Figure1) [2]. It is well accepted that SARS-CoV-2 infection leads to a systemic disease that can vary in severity and outcomes, from asymptomatic to death, and there are no means to predict how a given individual will react to the disease. Additionally, several sequelae were already reported, including pulmonary, cardiovascular, and neurological disorders [3].

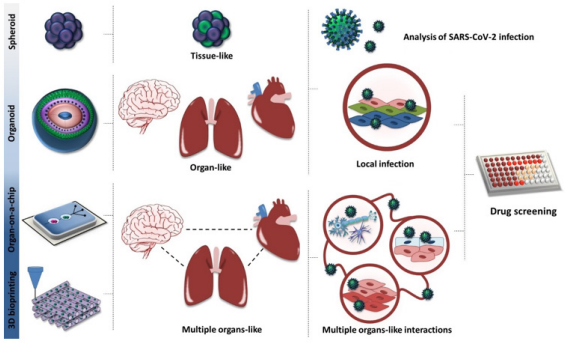

Figure 1: Schematic illustration of tissue engineering strategies to produce 3D *in vitro* models for studying SARS-CoV-2 infection of different organs and tissues, host-virus interaction, replication kinetics and drug screening.

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Even 3D structures that are less complex than bioprinted tissues, such as spheroids and organoids, are beneficial for studies of infection mechanisms and drug toxicity. The effects of the Zika virus on developmental neurogenesis were studied using neurospheres and brain organoids [4], cytopathic effects of SARS-CoV were demonstrated using lung and brain spheres [5], and SARS-CoV-2 neurotropism was shown in a 3D BrainSphere model produced from human induced pluripotent stem cells (hiPSC) [6].

Scaffold-based 3D models and organ-on-a-chip can significantly contribute to understanding SARS-CoV-2 infection mechanisms and test drugs identified through in silico screening. More than 350 published papers so far describe in silico approaches to identify new drugs or repurpose drugs already known for other uses. A few examples of candidates are RNA polymerase inhibitors [7], SARS-CoV-2 main protease inhibitors [8], and inhibitors of spike protein binding to ACE2 [9].

As an example, bioengineered 3D human ventricular cardiac tissue produced with cardiomyocytes derived from hiPSC were used to demonstrate the effects of the antimalarial hydroxychloroquine and azithromycin. The authors present data consistent with the reported clinical risks of hydroxychloroquine and azithromycin on ventricular arrhythmias and the development of heart failure [10]. These data suggest that bioengineered human cardiac tissue is an important platform to screen for anti-COVID-19 drug safety.

More than one-third of COVID-19 patients show neurological manifestations, and the presence of SARS-CoV-2 in the central nervous system has been shown in post-mortem assessment of victims of COVID-19 [11]. The route for neural cell infection is still debatable, and brain organoids have been used to understand the underlying mechanisms. For example, using hiPSC-derived brain organoids representing specific brain regions, Jacob and colleagues described that neurons and astrocytes are infected at low rates, whereas the epithelial cells in the choroid plexus are much more susceptible to SARS-CoV-2 infection [12-15].

CONCLUSION

There are many possibilities to use bioengineered tissues to understand SARS-CoV-2 multi-organ infection pattern, and the combination of 3D bioprinting, organoids, spheroids, and organ-on-a-chip technologies may give us a chance to move quicker towards understanding the devastating results of COVID-19 while pursuing effective treatments with no or low side effects.

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