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EC NEUROLOGY
Short Communication

Modelling Neurological Symptoms of COVID-19 with Cerebral Organoids

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Received: March 22, 2021; **Published:** April 09, 2021

As noted in a multitude of sources, understanding the effects of infection with SARS-CoV-2 is a rapidly developing field. Although pulmonary symptoms present most noticeably upon infection, concern is growing regarding the peripheral sequelae that arise in other organ systems, including the brain. The lasting neurological effects of COVID-19 are potentially worrying and understanding the causes and effects of these sequelae are of exceptional importance for healthcare professionals aiming to manage COVID-19.

The need for developing a common vocabulary for discussing neurological effects of COVID-19 has already been recognized. Noted neurological symptoms include "headache, myalgia, dizziness, and anosmia, along with encephalitis, encephalopathy, necrotizing hemorrhagic encephalopathy, stroke, epileptic seizures, rhabdomyolysis and Guillain-Barre syndrome" [1]. It has been hypothesized that primary infection of central nervous system (CNS) tissue may work synergistically with complications of pulmonary symptoms, such as systemic hypoxia and pathological inflammation, to induce the neurological symptoms observed in certain cases of COVID-19 [1].

However, many questions remain unanswered including: How does the virus spread to the brain? Why are only certain individuals affected while others are not? How do these symptoms develop? And, lastly, what are the long term effects of SARS-CoV-2 infection in the brain? Because researchers do not have access to live human tissue to examine the effects of the virus, investigating these questions is a challenge.

A particularly intriguing tool that has been recently developed are three-dimensional neuronal cultures, termed as cerebral organoids, cortical organoids, or spheroids. Organoids are generated from induced pluripotent stem cells (iPSCs). iPSCs are generated from donor adult fibroblasts, via the introduction of four defined factors that confer a pluripotent stem cell-state on differentiated cells [2]. These iPSCs are then cultured in media prompting differentiation into neural progenitor cells (NPCs), which finally differentiate into cortical neurons. Finally, one of a few methods may be used to coax two-dimensional neuronal cultures into three-dimensional formations. Lancaster., *et al*. [3] leveraged the self-organizing capacity of pluripotent stem cells to generate cortical organoids without having to use patterning factors. Arlotta [4] and Pasca [5] also describe their own systems, with their own slightly varied generation methods.

Regardless of the systems used, organoid systems invariably exhibit a number of advantages. Firstly, the three-dimensional structures better model the structural characteristics of fully functional organs. Given the inaccessibility of functional, primary human brain tissues, this is a critical advantage over *in vitro* cellular monolayer cultures. Lancaster demonstrated that RNA interference tools can be used in cortical spheroids to model microcephaly [2]. Secondly, the enhanced complexity of spheroids over cellular monolayers enables greater study of interactions between more than one organ systems. Some evidence shows that cerebral interactions with the cardiovascular system are critical to mediating the aetiology of neurological symptoms that arise due to COVID-19 [6]. Lastly, their derivation from patient

donor human fibroblasts via induced pluripotency preserves the genetic background of patient donors. For instance, in a recent study Kathuria., *et al*. demonstrated that cortical organoids developed from patient-derived iPSCs preserved the genetic dysregulation found in patients experiencing bipolar disorder [7]. This quality of cultured organoids allows researchers to show how different host genomic backgrounds influence the course of SARS-CoV-2 infection in a tissue-specific model. Existing research, showing the SARS-CoV-2 virus's interaction with various host receptor proteins, highlights the importance of considering host genomic variability [8]. Therefore, potentially leading us to answer the question why certain individuals are susceptible to the neurological symptoms.

In the brain, it has been found that brain infection by SARS-CoV-2 involves modulation of the following genes and proteins: Spike, EK1, TMPRSS2; ACE2 low in neurons; neurons activate TLR3/7, OAS2, "complement system," and apoptotic genes [9]. Given research showing neuronal differences in response to SARS-CoV-2 infection with different genetic backgrounds, the manipulation of cortical organoid models is a promising research avenue that will provide insight into new molecular pathways involved in COVID-19, aiding in the identification of potential drug targets.

Some studies have begun utilizing organoid models to study COVID-19's symptoms. Shasi., *et al*. [9] utilized iPSC-derived lung organoids (LORGs) and cerebral organoids (CORGs) to identify various protein expression changes involved in the process of SARS-CoV-2 infection in pulmonary and nervous tissue. Their report identified high ACE2 and TMPRSS2 expression in LORGs, CORGs, NPCs, astrocytes, and neurons as positively correlating with susceptibility to SARS-CoV-2 infection. Additionally, neuronal cells expressed greater levels of toll-like receptors 3 and 7 (TLR3/7) and OAS2 as a result of SARS-CoV-2 infection [9]. Further research studies using similar techniques can provide more definite answers on how the pathophysiology of SARS-CoV-2 infects the brain.

Organoid models of CNS tissue present exciting tools for faithfully modelling SARS-CoV-2 infection. The minimally-invasive process of generating cerebral organoids from adult, patient-derived fibroblasts provides significantly better access to brain tissue systems than traditional methods of obtaining primary neural tissue. As *in vitro* cultured systems, organoids possess the same easy access and manipulability that render tissue culturing such an indispensable technique in molecular biology, but notably, the addition of three-dimensional structure generation increases researchers' abilities to study complex interactions that emerge from physiological structures. The suggested interplay between circulatory and nervous systems in giving rise to the neuro-pathophysiologies of COVID-19's nervous system sequelae may be studied if cerebral organoid systems are made to integrate cardiovascular tissues to mimic *in vivo* brain perfusion and oxygenation conditions. As various organoid generation methods exist, a plurality of studies executed with a variety of methods will benefit the scientific community. By uncovering the nuances of COVID-19 presentations in the brain, scientists and healthcare workers will develop valuable insights into how to treat cases of SARS-CoV-2 infection on an informed and holistic basis.

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Volume 13 Issue 5 May 2021