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iPSCs-Derived Platform: A Feasible Tool for Probing the Neurotropism of SARS-CoV-2

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ABSTRACT: Coronavirus Disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a severe public health problem with a high rate of morbidity and mortality. A mounting number of clinical investigations illustrate that COVID-19 patients suffer from neurologic conditions in addition to respiratory symptoms. In a recent article, Yuen and colleagues present the first experimental evidence of SARS-CoV-2 infection in the human central nervous system using induced pluripotent stem cells (iPSCs)-derived platform including human neural progenitor cells, neurospheres, and three-dimensional brain organoids (Yuen, K.Y., and Huang, J.D. et al. (2020) *Cell Res.* DOI: 10.1038/s41422-020-0390-x).

KEYWORDS: *SARS-CoV-2, iPSCs, human neural progenitor cell, neurosphere, organoid, brain infection*

Coronavirus Disease 2019 (COVID-19) evoked by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a global public health threat due to a high rate of morbidity and mortality worldwide. As of August 5, 2020, it is estimated that a total of 18,142,718 confirmed cases including 691,013 deaths have been announced. Initially, SARS-CoV-2 was considered to mainly attack the respiratory system. However, increasing cases exhibit neurological symptoms including disturbed consciousness, headache, seizures, ageusia, dysphagia, hyposmia, and cerebrovascular diseases in COVID-19 patients,[1,2] which suggests that the novel coronavirus likely invades the central nervous system (CNS). This evidence stems from recent work indicating that 36.4% (78/214) of SARS-CoV-2-infected patients had neurologic conditions and severely infected patients were especially more vulnerable to brain dysfunction than patients with mild infection.[1] Furthermore, the presence of the virus was found in neural and capillary endothelial cells in the postmortem brain tissues of a patient with COVID-19. These clinical data implicate the invasive potential of SARS-CoV-2 in the human brain. Detailed experimental evidence supporting that how the coronavirus ravages the brain is warranted.

Recently, Yuen and colleagues used induced pluripotent stem cells (iPSCs)-derived human neural progenitor cells (hNPCs), neurospheres, and three-dimensional (3D) brain organoids for evaluation of SARS-CoV-2 infection in the brain.[3] Unlike previous investigations, Yuen et al. provided the first experimental evidence showing that SARS-CoV-2 could replicate in hNPCs and neurospheres and also the novel virus could productively infect cortical neurons and NPCs in 3D brain organoids (Figure 1).[3] In hNPCs, the expression of angiotensin-converting enzyme 2 (ACE2), the entry receptor of SARS-CoV-2 and critical coronavirus entry-associated proteases including TMPRSS2, cathepsin L and furin were analyzed.[3] The experimental data showed that these indices were readily detected. After infection with SARS-CoV-2 or SARS-CoV, virus replication was found for SARS-CoV-2 and it caused substantial cytotoxicity of hNPCs, which indicates that hNPCs are attacked by SARS-CoV-2. To further verify the neuroinvasive potential of this virus, iPSCs-derived neurospheres were cultivated for SARS-CoV-2 infection as this model represents early human neurogenesis.[3] Results from this study revealed that increased copy number of viral RNA-dependent RNA polymerase (RdRp), viral antigen nucleocapsid protein, and extensive viral particles in vacuoles were detected in SARS-CoV-2-infected neurospheres. These data hint that neurospheres were vulnerable to SARS-CoV-2 infection and built up an environment for productive viral replication. Brain organoids could also be employed in this work to evaluate whether SARS-CoV-2 infected the human brain. Generally, organoids can be generated by two sorts of stem cells, namely, iPSCs and organ-restricted adult stem cells (also known as tissue stem cells).[4] Both approaches have potent expansion potential of normal stem cells in culture. Brain organoids model can recapitulate neuro-developmental process and model neurological diseases.[5] Yuen and colleagues further validated SARS-CoV-2 infection in the human brain through an organoids model generated by iPSCs. Consistent with the results obtained in hNPCs and neurospheres, presentation of viral antigen and elevation of RdRp gene copy number were detected in infected brain organoids.[3] Additionally, after collecting supernatant samples from brain organoids challenged with SARS-CoV-2, plague assays showed increased infectious virus titer, which further supports that SARS-CoV-2 directly productively infects brain organoids with

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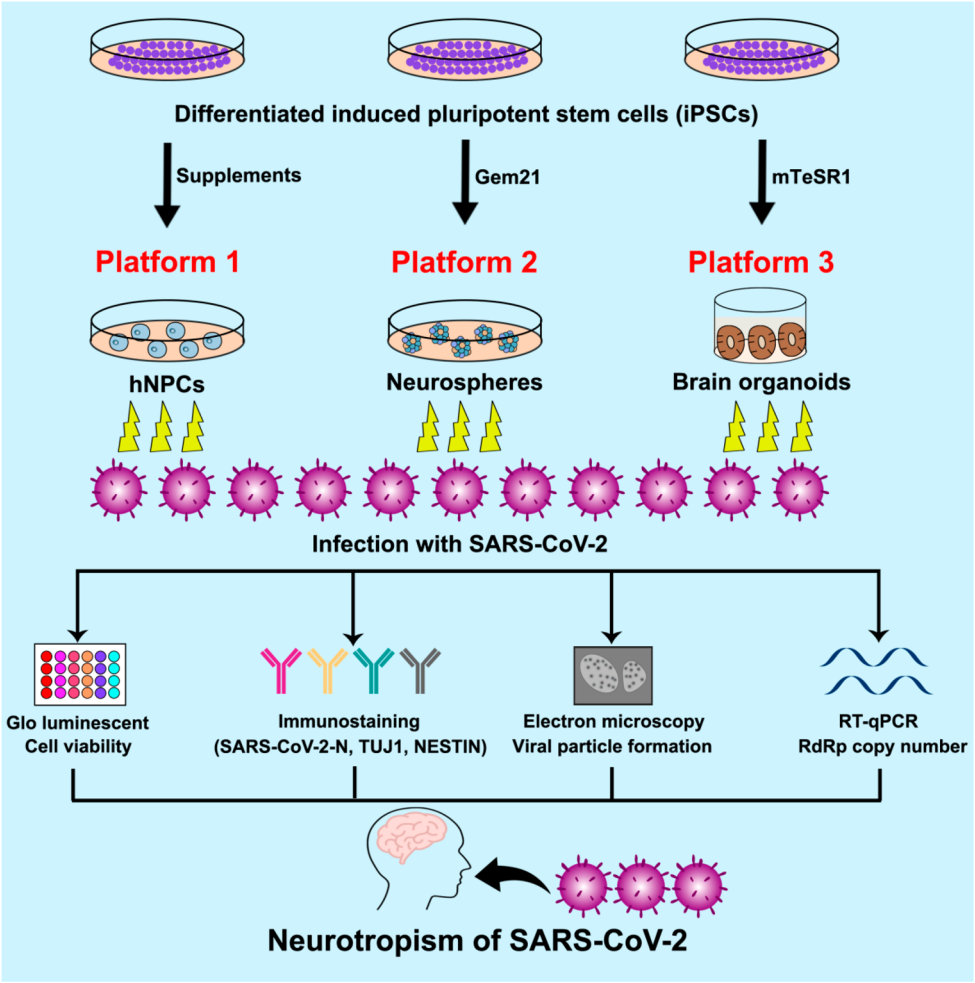

Figure 1. Presentation of the first experimental evidence showing SARS-CoV-2 infection in the hIPSC-derived platform including human neural progenitor cells, neurospheres, and brain organoids by Yuen et al.[3]

the release of viral particles. Intriguingly, detection of colocalizations between SARS-CoV-2 nucleocapsid protein and neuronal marker TUJ1 or NPC marker NESTIN suggests that there is a direct infection of this virus on cortical neurons and NPCs in 3D brain organoids. Taken together, these findings provide solid experimental data to corroborate the neuroinvasive property of SARS-CoV-2 using multiple models.

While the data obtained from Yuen and colleagues is able to present the experimental evidence supporting the fact that SARS-CoV-2 attacks the human brain, there are several future steps that can be considered to enable further testing of the hypothesis regarding brain infection by this virus. First, the observed effects involving SARS-CoV-2-induced brain infection are short-term. However, in clinical practices, neurological symptoms are often persistent in COVID-19 patients. Therefore, it is essential to closely monitor the long-term consequence of SARS-CoV-2 infection in the CNS in order to advance the knowledge of durative effects of this virus on the brain. Second, three models, which are employed for the evaluation of the infection of SARS-CoV-2 on the CNS, do not possess the complete brain structure, especially lacking the integrity of blood-brain barrier (BBB). It may be difficult to explain how this virus gains entry into the brain. Our previous publications have summarized that the virus enters the brain via three possible pathways, namely, the olfactory nerves in the nasal cavity, interaction with ACE2, and a cytokine storm-induced BBB disruption.[6] Figuring out the route by which SARS-CoV-2 attacks the human brain is beneficial for the development of specific therapeutic approach to improving neurological disturbance induced by the virus. To our knowledge, future investigations involving two aspects as we mentioned above are required for the good management of COVID-19 patients with neurological symptoms.

In summary, the data provided by Yuen and colleagues offer useful experimental evidence supporting that SARS-CoV-2 can infect the human brain using an iPSCs-derived platform including hNPCs, neurospheres, and 3D human organoids. The results that hNPCs are infected by SARS-CoV-2 are emerging, as Zika virus, which associates with neurological disorders and congenital malformation,[7,8] has also been shown to target hNPCs. It implicates that therapeutic strategies targeting Zika virus may be useful for SARS-CoV-infected brain dysfunction. With respect to human brain organoids employed by Yuen and colleagues, a previous study also unambiguously proved the neurotrophic property of SARS-CoV-2 in the brain,[9] which once again highlights the advantages of brain organoids in the evaluation of CNS infection by the virus. In any way, an iPSCs-derived platform including hNPCs, neurospheres, and brain organoids is a feasible tool for probing the neurotrophic potential of SARS-CoV-2.

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Author Contributions

X.-Y.M. and W.-L.J. conceived and designed the paper. X.-Y.M. wrote the paper. W.-L.J .and X.-Y.M. revised the paper. All the authors read and approved with submission and publication of the paper.

Notes

The authors declare no competing financial interest.

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