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An iPSC and organoid model for SARS-CoV-2 infection: from individual variation to drug discovery

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Abstract of the showcase

It is known that there are large individual differences in the symptoms of coronavirus disease 2019 (COVID-19). Differences in genetic background are considered to be one of the causes of these individual differences in the symptoms of COVID-19. Because human pluripotent stem cells (hPSCs) can be established from various individuals, it is thus expected to be a model that could reproduce the individual differences in COVID-19-related symptoms. In this study, highly efficient infection, replication, and progeny virus production were confirmed in hPSCs overexpressing angiotensin-converting enzyme 2 (ACE2). We also confirmed that the evaluation of antiviral drugs, such as entry inhibitors and replication inhibitors, can be performed. Furthermore, we found that the virus infection efficiency of male PSCs was higher than that of female PSCs. These results suggest that hPSCs are an excellent model for COVID-19 studies. Recently, to examine SARS-CoV-2 infection and replication in the airway, we also use human airway organoids. We are also conducting drug screening using these human airway organoids. In this seminar, we will introduce the latest findings and challenges of COVID-19 research utilizing hPSCs and organoids.

Important and difficult points

Since the first reported case of COVID-19 in December 2019, the pandemic has continued to spread. Unfortunately, an effective treatment for COVID-19 has not yet been developed. To develop such therapeutic drugs, an accurate model for drug discovery that can reproduce human physiological conditions is necessary. Vero cells are commonly used for SARS-CoV-2 replication, but we wanted to establish an accurate model which could better reproduce the human physiological condition. To achieve this, we utilized human organoid models and human induced pluripotent stem (iPS) cells. Unfortunately, we found that the viral infection efficiency on undifferentiated iPS cells is quite low. So, we needed to overcome this obstacle in order to proceed to research further.

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New research and technology

We demonstrated that human iPS cells expressing the SARS-CoV-2 receptor ACE2, with piggyBac system (ACE2-iPS cells), can be efficiently infected with SARS-CoV-2. Further data illustrated how the SARS-CoV-2 life cycle can be reproduced in the ACE2-iPS cells, how COVID-19 candidate drugs can be evaluated using ACE2-iPS cells, and how ACE2-iPS cells can reproduce individual differences in SARS-CoV-2 infection. Using this platform, we evaluated some antiviral drugs with ACE2-iPS cells. The results suggest that our model would be useful a resource for COVID-19 pharmaceutical research.

Reasons for using StemFit medium and experience of use

Since we used eight ACE2-iPS cell lines in this study, we used a very large volume of StemFit® medium and iMatrix™ ECM. Although a large volume of cells is required for COVID-19 drug evaluation, iPS cells cultured with StemFit® and iMatrix™ have a high replication capacity, which enables the easy preparation of sufficient cell numbers and the eventual cryopreservation as required using STEM-CELLBANKER®. In addition, single-cell cloning can be easily obtained by using StemFit® and iMatrix™. Given this, I believe this culture system is also suitable for genome editing experiments.

Future prospects, issues, etc.

We demonstrated that SARS-CoV-2 infection efficiency and the viral responses were different among the iPS cell lines. We are now working to address the mechanism underlying the observed individual differences. Furthermore, we are now attempting to combine organoid models with vascular and immune systems using organ-on-a-chip technology, to reproduce the cytokine storm.

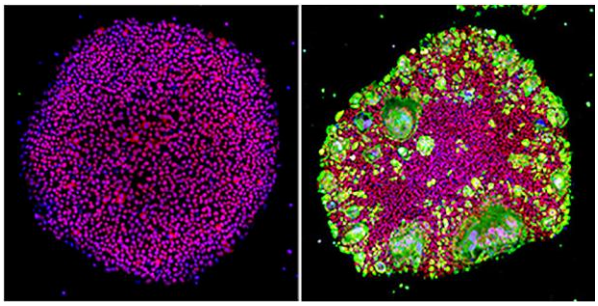

Fig.1 Control (left) and SARS-CoV-2 infected (right) ACE2-iPS cells. Cells stained red for pluripotency marker and green for SARS-Cov-2 NP using Rabbit Polyclonal Anti-SARS-CoV-2 Antibody. Images courtesy of Kazuo Takayama.

For further information, please contact us.
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The video of the lecture is available at the following link.
https://www.amsbio.com/news/an-ipsc-model-for-covid-19/