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Induced Pluripotent Stem Cells (iPSCs) Derived 3D Human Lung Organoids from Different Ethnicities to Understand the SARS-CoV2 Severity/Infectivity Percentage

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Introduction

The SARS-CoV2 pandemic has indeed shrugged the entire world, changing the lifestyle and social interaction of people to a bare minimum. Despite the stringent measures, the pandemic continues to take many lives globally in most countries. However, the interesting fact is the difference in the mortality rates based on ethnicities. Hence, a better understanding of the Severity/Infectivity percentage of the SARS-CoV2 infections is the need of the hour since the severe infections affect the lower respiratory tract and often lead to death. So, we propose a better in-vitro understanding of the disease using a 3D lung organoid model derived from ethnicity-based induced pluripotent stem cells and the lung progenitor cells, namely the bronchial transient epithelial cells that are attacked more by the SARS-CoV2. So, it is important to understand why there is a difference in the death rates in populations of varying ethnicities across the world. Accordingly, we propose an in-vitro strategy to understand the difference in the death rates in varying ethnicities due to COVID-19 infections.

Human Lung Organoids Derived from iPSCs of Varying Ethnicities for Understanding the Severity/Infectivity Percentage of SARS-CoV2

Till date, the most commonly used in-vitro systems for understanding the behavior and drug responses of various severe acute respiratory distress syndrome (SARS) coronaviruses relied on 2D cultured cell lines. Such cell lines are Vero and Vero6+ from the African green monkey, HEK-293 derived from human fetal kidney, HEPG2, and Huh7-both hepatocellular carcinoma cell lines and the lung carcinoma A549 cell line [1]. However, due to non-lung origin of most of the cell lines, except for the A549 cell line, and two of these from monkey origin, our quest for understanding the Severity/Infectivity percentage of SARS-CoV2 using such model systems may not be the most appropriate. Secondly, the A549 cell line, being from the lung carcinoma origin, also may not be able to mimic a normal lung that is infected by SARS-CoV2. Most important, due to the difference in the Severity/Infectivity percentage of the current COVID-19 pandemic across various ethnic populations, we propose the use of 3D human lung organoid (HLO) model systems derived from iPSC of different ethnicities. In our opinion, such 3D-HLO models will be the best mimics of normal human lung tissue. Animal models cannot be regarded as the best alternative for such studies owing to our question regarding the Severity/Infectivity percentage in human populations.

Human pluripotent stem cells (hPSCs) can be differentiated into the endodermal lung tissue under 2D conditions. In vitro differentiation steps follow the in-vivo lung organogenesis by the modulation of various cell signaling pathways using various cytokines. 3D human lung organoids, as counterparts of human fetal lung tissue, have also been developed from iPSC sequentially by first obtaining spheroids from the ventral-anterior foregut, that upon expansion has resulted in the formation of 3D human lung organoids (HLO) [2]. Such 3D HLO is primarily a combination of multiple cell types and compartments that resembles a fetal lung. Again, due to SARS-CoV2 infections, the mortality rates amongst children were reportedly low; hence, a 3D HLO resembling fetal lung tissue, may not be of much significance. Therefore, a 3D mimic of the human adult lung would be required. Three-D HLO models of adult airways have been developed by the

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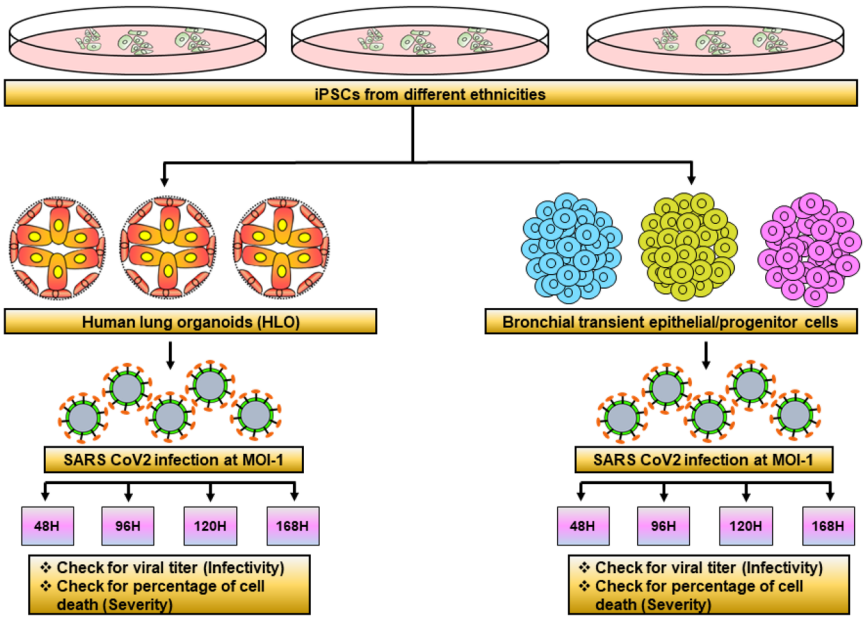

Fig. 1 Proposed in-vitro 3D human lung organoids (HLOs) and 3D Bronchial Transient Epithelial/Progenitor cells (BTECs) differentiated from iPSCs of varying ethnicities for understanding the SARS-CoV2 Severity/Infectivity percentage: 3D HLOs and 3D BTECs can be infected with multiplicity of infection (MOI) of 1 of SARS-CoV2 and assessed for the Severity/Infectivity percentage at different time points of progression of the infection

incorporation of certain biomaterials, namely, poly (lactide-co-glycolide) (PLG) scaffolds or polycaprolactone (PCL) during the differentiation process [3]. Hence, the current protocol by Dye et al. (2020) for obtaining 3D HLO resembling adult airways can be considered to be most appropriate [3].

For the source of ethnicity-specific iPSCs, one needs to first check the database for the choice of iPSC lines. Indeed, the large iPSC repositories have done and have been doing tremendous work for cryopreserving a big collection of iPSC lines from various ethnicities such as Chinese, Indians, Caucasians, Japanese, Africans, and Malaysians, etc. The European bank of induced pluripotent stem cells (EBiPSC-(https://ebisc.org/) has a stock of 894 cell lines till date and was opened to the public in 2016 [4]. This repository receives cell lines from various depositors and subjects them to quality check before storage and distribution. The details such as ethnicity, age, and disease specificities of all the available with the EBiPSCs are registered with the human Pluripotent Stem Cell Registry (hPSCreg) (https://hpscreg.eu/. Similarly, the New York stem cell foundation (NYSCF) (https://nyscf.org/research-institute/repository-stem-cell-search/) also has a collection of iPSCs from varying ethnicities.

A schematic representation for understanding the Severity/Infectivity percentage of SARS-CoV2 from varying ethnicities have been summarized in Figure 1. As an example of understanding the Severity/Infectivity percentage of SARS-CoV2, in Caucasians/Italian, the hiPSC line CSSi001-A can be taken (https://hpscreg.eu/cell-line/CSSi001-A) for deriving 3D HLO. The starting material of this cell line was the dermal fibroblast of a healthy Italian male being a carrier of a disease named Joubert syndrome. The 3D lung organoids differentiated from this cell line are expected to yield normal lung tissue since Joubert syndrome is associated with the developmental defects in the brain. Moreover, the tissue donor for this cell line had been a healthy carrier of the disease. Recently, a lung progenitor cell type, namely bronchial transient epithelial cells (BTEC), reportedly are attacked more by the SARS-CoV2 [5], as compared to other cell types. Hence, the iPSC from varying ethnicities can be differentiated into 3D- BTEC-spheroids for a possibly better readout of the experiments (Figure-1). Finally, for the in-vitro assessments of Severity/Infectivity percentage of SARS-CoV2 various parameters such as viral dose and time can be optimized for mild, moderate, and severe infections followed by the quantification for viral proteins (Figure-1).

Taken together, considering speculation for a second-bigger wave of SARS-CoV2 pandemic, drug screening for ethnicity-based 3D in-vitro models can give some hope.

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