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Airway models in a pandemic: Suitability of models in modeling SARS-CoV-2

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In a global pandemic involving respiratory pathogens such as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), intensified scientific research is required to delineate pathways involved in infectivity, transmissibility, and pathogenicity of the causative pathogen. SARS-CoV-2, the causative agent of Coronavirus Disease 2019 (COVID-19), is highly contagious and significantly threatens public health. This single-stranded positive RNA virus consisting of approximately 30 kb genome size virus is from the same *Sarbercovirus* subgenus as SARS-CoV [1]. While most people who are infected exhibit only mild–moderate respiratory symptoms including cough and dysgeusia, some may develop acute respiratory distress syndrome. Postmortem lungs of COVID-19 patients showed severe pulmonary damage and abundant inflammatory infiltrates [2]. Given the urgent need to study the pathogenesis of this disease and to test the efficacy of potential therapeutics, several in vitro and in vivo models have been developed. Herein, the use and limitations of two-dimensional (2D) and animal models in COVID-19 research are discussed, followed by a review on the use of lung organoids in advancing our knowledge on COVID-19 pathogenesis.

Two-dimensional models: Their usability in SARS-CoV-2 research and limitations

Two-dimensional cell lines display a wide range of usability and are readily available in a pandemic for identifying potential pathways of infection and tissue tropism of human pathogens. SARS-CoV-2 cultured in Vero-E6 cells (monkey kidney cells) showed high sequence homology and morphology similarity compared to viruses inoculated in human airway epithelial cells [3,4]. In addition, Vero-E6 cells enable higher level of SARS-CoV-2 amplification and infectivity compared to several human cell lines including A549, Calu-3, HUH7.9, HEK-293, and U251, suggesting its usefulness in generating viral stocks for translational research [5,6]. HEK-293 cells (human embryonic kidney cells) enabled the identification of S1 and S2 subunits of the SARS-CoV-2 transmembrane spike glycoprotein as the ligands that bind host receptors [7]. Using Vero-E6 cells, these subunits were also shown to be involved in viral fusion to host cell membrane to establish infection [8]. Consequently, these cell lines have been used to evaluate drugs and vaccines response [9]. In vitro cell models also enabled the identification of host factors that are involved in SARS-CoV-2 infection. Using parental BHK-21 cells (hamster-derived), the importance of angiotensin-converting enzyme 2 (ACE2) receptor in mediating infection has been discovered [7,10]. Using human HeLa cells, several proteases including transmembrane protease serine 2 and lysosomal protease cathepsin were identified as essential determinants of viral infectivity [7,10]. In addition, genome-wide CRISPR screens in various cell lines have identified functional pathways that are involved in

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