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Organoids Technology: A Pathway to the Permanent Treatment of Pulmonary Diseases

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Organoids are a miniature, simplified version of a human organ that are produced in three dimensions in the laboratory and show the true anatomical array. These organelles originate from one or more cells - embryonic stem cells or induced multipotent stem cells - that can organize themselves in three-dimensional culture media. The use of stem cells due to the unlimited capacity of tissue division and regeneration is a great promise as a therapeutic tool. These three-dimensional models of human tissue can be used to test drugs before they are tested on humans. Lung organoids are one of the different types of organoids that, like other organoids, can be formed through a process of self-organizing stem cells or specific parts of an organ. These organoids can also be utilized as a useful tool for screening drugs and vaccines for infections such as the novel SARS-COV-2 infection. The aim of this study was to investigate the potential of lung organoids in the treatment of pulmonary diseases.

Keywords: Lung organoids, Pulmonary diseases, SARS-CoV-2

Dear editor

Various pulmonary vascular diseases can lead to lung disorders and impaired physiological lung function. Today, the most important causes of pulmonary disorders in the world are viruses such as the influenza virus and various viruses of the coronavirus family (such as SARS-CoV-2) which cause severe inflammation, extensive damage, and cell death of the lung epithelium (1,2). After infection, the damaged epithelium cannot resist infection by other pathogens, which in turn may lead to more severe damage and prolongation of the disease. However, some lifestyle habits such as smoking also reduce epithelial integrity and prevent epithelial regeneration, which can be observed in Chronic Obstructive Pulmonary Disease (COPD) and lung cancer (3,4). Diseases such as asthma lead to changes in the structure and function of the airway epithelium that can have a negative effect on human health (5,6). In addition, Idiopathic Pulmonary Fibrosis (IPF) is a serious disease characterized by abnormal lung epithelial cells and it is exacerbated by a lack of alveolar repair (7). The prognosis of most patients with IPF is very poor and the average survival is 3-5 years after diagnosis (8). These pulmonary diseases related to different affected areas of the lung epithelium impair lung function and affect patients' quality of life. Evaluation of the response to lung epithelial injury can increase our insight into the pulmonary disease and help us to treat them. Lung organoids are useful tools for these researches. "Lung organoids" are one of the various types of organoids that, like other organoids, can be formed through a self-organizing process of stem cells or specific parts of an organ (9,10). The process of culturing lung organoids *in vitro* is quite different from traditional cell culture. Lung organoids can mimic lung growth, as well as three-dimensional (3D) organizational structures (such as alveoli, airways, endothelium, and lung buds) and lung function *in vitro* (11). In the last two decades, lung organoid technology has developed rapidly. Lung organoids are useful tools for expanding the understanding of lung damage by identifying stem cells / epithelial components associated with the epithelial recovery and demonstrating related factors that can manipulate signaling pathways to improve or prevent epithelial regeneration. Such information allows a deeper understanding of the pathological processes and drug purposes of lung disease. However, there are many limitations to the proper implementation of this path. First, due to the novelty of this topic, training and standardization of the exact implementation of this technology are required. By changing the culture conditions, different organoids can be formed from one cell (12). Depending on the purpose of the research, this strategy allows the extraction of organoids, but at the same time, it may also affect the reproducibility of organoids, resulting in disrupted research. In these circumstances, using a stable ECM may be the solution to this problem. The branching airway is an important structure for achieving air conduction in the lungs. Lung organoids are often spherical and fail to fully mimic the morphology of lung cells. This issue may require increased nutritional support or optimized compounds for organoids in culture systems and long culture times. Bioengineering technology, such as biological 3D printing technology, can combine with organoid morphogenesis to produce fully structured organoids in a short period (13). In addition, the intermittent passage between multiple signaling pathways in epithelial repair requires further confirmation. This is a complex relationship that involves different types of cells in addition to the epithelium. At present, the relationship between these types of cells using lung organoids is not well understood. The addition of immune cells or vascular endothelial cells regularly during pulmonary organoid production and culture can be used; both to produce environments for epithelial repair *in vitro* and to better observe the relationship between cells and ECM during epithelial regeneration. SARS-CoV-2 infection is spreading worldwide, and organoids play an important role in studying the new virus. Researchers have combined lung organoids and other organoids to mimic the SARS-CoV-2 post-infection status in patients. Pulmonary organoids and other organoids can be utilized to detect pathological processes in organs after SARS-CoV-2 infection, to screen for selected drugs, and to develop and evaluate vaccines for their safety and efficacy (14,15). As a result, we believe that a combination of lung organoids and different technologies can enable a more accurate understanding of lung epithelial repair and preventive treatment of lung disease.

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