Clinical Applications of Human Nasal Organoids

Do Hyun Kim · Sung Won Kim
Department of Otolaryngology-Head and Neck Surgery, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

Increases in fine dust concentrations due to industrialization and the emergence of respiratory diseases such as coronavirus disease 2019 (COVID-19) pose serious threats to human life. Organoids have recently received attention as tools to study embryogenesis, as well as for their potential applications as disease models and transplantable mini-organs. Advances in the field of stem cells and genetically engineered cells have enabled great progress in methods for generating mature respiratory organoids. Therefore, research is continuing on the developmental mechanisms of the upper and lower airways, disease modeling, and drug screening in the respiratory field [1-4]. There have also been studies of organoid transplantation, but transplant models in which the lumen is in direct contact with air are difficult to generate, and clinical trials of transplants developed using embryonic or induced pluripotent cells are currently limited. Thus, recent research has focused on the use of nasal organoids for disease modeling and high-throughput drug screening [3,5-8]. Consequently, several viral and bacterial infection models, patient-derived lung cancer models, and genetic disease models have been generated using nasal organoids.

Despite these promising advances, several challenges must be addressed before human nasal organoids can serve as non-clinical trial models. For example, fully differentiating human pluripotent stem cells into specialized airway cell types is difficult and requires multiple validations. To overcome these obstacles, researchers are exploring ways to promote organoid maturation, such as by using immunodeficient mouse kidney capsules [7]. Another limitation of organoid models is the lack of reproducibility of results, which is necessary to establish organoids as reliable disease models. To improve upon this issue, research on standardization of the organoid production process and the development of a systematic high-throughput mass screening tool is being conducted [9]. In addition, the culture medium used to induce organoids usually contains complex supplements such as bovine extracts or mouse sarcoma derivatives, which can be a major obstacle to organoid transplantation. To overcome this, processes using xenogeneic-free or chemically defined media are being developed.

Organoids are often defined as “mini-organs.” However, it is difficult to produce large complex structures in realistic organ sizes. The most important factor in size limitation is that when organoids reach a certain size threshold, internal cells often undergo necrosis due to restrictions in nutrient and oxygen exchange. To overcome this, various bio-engineering scaffolds are being developed. In addition, for intestinal and respiratory organoids, apical structures of the epithelium are formed in the direction of the luminal side of the globular organoids as they are generated. The response detected by the epithelium may differ from the response to the basement membrane. Techniques such as microinjection, cell shear using a Pasteur pipette, two-dimensional re-digested organoid culture, and apical-outward structure development using bioengineered niches have been developed to overcome these physiological differences.

Finally, disease modeling and drug screening using organoids are currently limited to rare respiratory diseases with a relatively simple genetic basis (such as cystic fibrosis), and tumor models using tissues acquired from patients. However, these models are difficult to apply to patients with complex etiologies such as asthma and chronic obstructive pulmonary disease, which are frequently encountered in clinical practice. Efforts are being made to create organoid cancer models that are well-integrated within the vasculature to reflect the in vivo system more accurately, and co-culture methods to reproduce the immune re-
sponse are also being studied. As efforts to resolve the limitations of these respiratory organoids continue, useful organoid models can be expected to replace in vivo and in vitro experiments in the future.

**CONFLICT OF INTEREST**

No potential conflict of interest relevant to this article was reported.

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**ORCID**

Do Hyun Kim  https://orcid.org/0000-0002-9248-5572

Sung Won Kim  https://orcid.org/0000-0002-8981-2536

**AUTHOR CONTRIBUTIONS**

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