CEO Clinical and Experimental Otorhinolaryngology Vol. 15, No. 3: 201-202, August 2022
https://doi.org/10.21053/ceo.2022.00997
pISSN 1976-8710 eISSN 2005-0720

Editorial

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-

• Received July 14, 2022
Accepted July 19, 2022

• Corresponding author: **Sung Won Kim**
Department of Otolaryngology-Head and Neck Surgery, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea,
222 Banpo-daero, Seocho-gu, Seoul 06591, Korea
Tel: +82-2-2258-6216, Fax: +82-2-535-1354
E-mail: kswent@catholic.ac.kr

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.

ACKNOWLEDGMENTS

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Ministry of Science & ICT (2019M3A9H2032424, 2019M3E5D5064110). This work was also supported by the Alchemist Project (20012378, Development of Meta Soft Organ Module Manufacturing Technology without Immunity Rejection and Module Assembly Robot System) funded by the Ministry of Trade, Industry & Energy (MOTIE, Korea). The sponsors had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

ORCID

Do Hyun Kim https://orcid.org/0000-0002-9248-5572
Sung Won Kim https://orcid.org/0000-0002-8981-2536

AUTHOR CONTRIBUTIONS

Conceptualization: all authors. Writing–original draft: DHK. Writing–review & editing: all authors.

REFERENCES

1. Hogan BL, Barkauskas CE, Chapman HA, Epstein JA, Jain R, Hsia CC, et al. Repair and regeneration of the respiratory system: complexity, plasticity, and mechanisms of lung stem cell function. Cell Stem Cell. 2014 Aug;15(2):123-38.
2. Huang SX, Green MD, de Carvalho AT, Mumau M, Chen YW, D'Souza SL, et al. The in vitro generation of lung and airway progenitor cells from human pluripotent stem cells. Nat Protoc. 2015 Mar;10(3):413-25.
3. Hynds RE, Butler CR, Janes SM, Giangreco A. Expansion of human airway basal stem cells and their differentiation as 3D tracheospheres. Methods Mol Biol. 2019;1576:43-53.
4. Kotton DN, Morrisey EE. Lung regeneration: mechanisms, applications and emerging stem cell populations. Nat Med. 2014 Aug;20(8):822-32.
5. Hui KP, Ching RH, Chan SK, Nicholls JM, Sachs N, Clevers H, et al. Tropism, replication competence, and innate immune responses of influenza virus: an analysis of human airway organoids and ex-vivo bronchus cultures. Lancet Respir Med. 2018 Nov;6(11):846-54.
6. Sachs N, Papaspyropoulos A, Zomer-van Ommen DD, Heo I, Bottinger L, Jonkers J, et al. Long-term expanding human airway organoids for disease modeling. EMBO J. 2019 Feb;38(4):e100300.
7. Tan Q, Choi KM, Sicard D, Tschumperlin DJ. Human airway organoid engineering as a step toward lung regeneration and disease modeling. Biomaterials. 2017 Jan;113:118-32.
8. Zhou J, Li C, Sachs N, Chiu MC, Wong BH, Chu H, et al. Differentiated human airway organoids to assess infectivity of emerging influenza virus. Proc Natl Acad Sci U S A. 2018 Jun;115(26):6822-7.
9. Hild M, Jaffe AB. Production of 3-D Airway organoids from primary human airway basal cells and their use in high-throughput screening. Curr Protoc Stem Cell Biol. 2016 May;37:IE.9.1-IE.9.15.