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How to optimize respiratory models for SARS-CoV-2 research

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Reviewer 1

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*Only major points from review and responses included.

Reviewer 1

Although the 3D respiratory models established in the authors' laboratory have been discussed in some detail, reference to the wider literature in this area is lacking. The review can be greatly improved by also referring to alveolar lung organoids, airway organoids, bronchial organoids that have been developed to study SARS-CoV-2 pathophysiology.

Authors

In the revised version, we added citations to the organoid-introduction section. The citations added address the different use of organoids and highlight the different organoid types in research. The citations added are listed as followed:

1) Clevers H. Modeling Development and Disease with Organoids. Cell. 2016;165(7):1586-97.
2) Li X, Ootani A, Kuo C. An Air-Liquid Interface Culture System for 3D Organoid Culture of Diverse Primary Gastrointestinal Tissues. Methods Mol Biol. 2016;1422:33-40.
3) Salahudeen AA, Choi SS, Rustagi A, Zhu J, van Unen V, de la OS, et al. Progenitor identification and SARS-CoV-2 infection in human distal lung organoids. Nature. 2020;588(7839):670-5.
4) Takahashi T. Organoids for Drug Discovery and Personalized Medicine. Annu Rev Pharmacol Toxicol. 2019;59:447-62.

Reviewer 1

The authors refer to organoids being used for high throughput testing of novel drugs and vaccines (P3), it is not clear what work has been done with these models. For this to be a comprehensive review, adding more detail, and references to papers looking at high throughput testing or inhibitor screening in respiratory organoids or other 3D respiratory culture systems is required, e.g.

Han et al. (https://pubmed.ncbi.nlm.nih.gov/33116299/);
Samuel et al. (https://pubmed.ncbi.nlm.nih.gov/33232663/);
Huang et al. (https://pubmed.ncbi.nlm.nih.gov/32979316/);
Duan et al. (https://pubmed.ncbi.nlm.nih.gov/34731648/).

Authors

Thank you for the comment. In the last section of page 3 we tried to highlight the background of organoids in different research topics by adding following references:

1) Salahudeen AA, Choi SS, Rustagi A, Zhu J, van Unen V, de la OS, et al. Progenitor identification and SARS-CoV-2 infection in human distal lung organoids. Nature. 2020;588(7839):670-5
2) Han Y, Duan X, Yang L, Nilsson-Payant BE, Wang P, Duan F, et al. Identification of SARS-CoV-2 inhibitors using lung and colonic organoids. Nature. 2021;589(7841):270-5.
3) Rijsbergen LC, Lamers MM, Comvalius AD, Koutstaal RW, Schipper D, Duprex WP, et al. Human Respiratory Syncytial Virus Subgroup A and B Infections in Nasal, Bronchial, Small-Airway, and Organoid-Derived Respiratory Cultures. mSphere. 2021;6(3).

Reviewer 1

Similarly with ALI cultures, it is not clear how others have used ALI cultures to study SARS-CoV-2 infections/antiviral screening.

Points 2 and 3 will need to be incorporated as part of Section 2.3 where the authors summarise the use of their models to study SARS-CoV-2

Authors

We included additional references at the end of the summary on page 6. The literature should show how other working groups used ALI cultures to study SARS-CoV-2 infection / antiviral screening and is listed as followed:

1) Djidrovski I, Georgiou M, Hughes GL, Patterson EI, Casas-Sanchez A, Pennington SH, et al. SARS-CoV-2 infects an upper airway model derived from induced pluripotent stem cells. Stem Cells. 2021;39(10):1310-21.
2) Raghavan S, Kenchappa DB, Leo MD. SARS-CoV-2 Spike Protein Induces Degradation of Junctional Proteins That Maintain Endothelial Barrier Integrity. Front Cardiovasc Med. 2021;8:687783.

Reviewer 1

More references in particular sections in the introduction should be added e.g. introduction to lung organoids (P2) introduction to ALI cultures (P4)

Authors

To round out our article, we added additional references
-to the introduction of lung organoids on page 3

1) Takahashi T. Organoids for Drug Discovery and Personalized Medicine. Annu Rev Pharmacol Toxicol. 2019;59:447-62.
2) Bergdorf K, Phifer C, Bharti V, Westover D, Bauer J, Vilgelm A, et al. High-throughput drug screening of fine-needle aspiration-derived cancer organoids. STAR Protoc. 2020;1(3):100212.
3) Bershteyn M, Nowakowski TJ, Pollen AA, Di Lullo E, Nene A, Wynshaw-Boris A, et al. Human iPSC-Derived Cerebral Organoids Model Cellular Features of Lissencephaly and Reveal Prolonged Mitosis of Outer Radial Glia. Cell Stem Cell. 2017;20(4):435-49 e4.
4) Drost J, Clevers H. Organoids in cancer research. Nat Rev Cancer. 2018;18(7):407-18.
5) Skardal A, Shupe T, Atala A. Organoid-on-a-chip and body-on-a-chip systems for drug screening and disease modeling. Drug Discov Today. 2016;21(9):1399-411.

-to the introduction of ALI cultures on page 4:

1) Bovard D, Sandoz A, Luettich K, Frentzel S, Iskandar A, Marescotti D, et al. A lung/liver-on-a-chip platform for acute and chronic toxicity studies. Lab Chip. 2018;18(24):3814-29.
2) Ghosh B, Park B, Bhowmik D, Nishida K, Lauver M, Putcha N, et al. Strong correlation between air-liquid interface cultures and in vivo transcriptomics of nasal brush biopsy. Am J Physiol Lung Cell Mol Physiol. 2020;318(5):L1056-L62.
3) Pharo EA, Williams SM, Boyd V, Sundaramoorthy V, Durr PA, Baker ML. Host-Pathogen Responses to Pandemic Influenza H1N1pdm09 in a Human Respiratory Airway Model. Viruses. 2020;12(6).