Breath taking: lung physiology explained

Authors: Eline Geervliet, Suzie Grigorjan, Susan Roelofs

Function of the Lungs

The lungs are vital organs responsible for gas exchange, ensuring that oxygen is delivered to the bloodstream while expelling carbon dioxide from the body. This exchange occurs in the alveoli, tiny air sacs with thin walls that allow efficient diffusion of gases. The lungs also play a crucial role in immune defense, by inhibiting passage of pathogens from inhaled air, and support homeostasis by e.g. controlling the pH and CO_2 levels [1].

History of lung research

Over the past decades and even centuries, in vitro lung research has greatly developed. Early in vitro studies relied on simple 2D cell cultures, where lung epithelial cells were grown on flat surfaces. While these models provided fundamental insights, they lacked the structural complexity of lung tissue. Great progress has been made by the introduction of Transwell cultures, enabling air-liquid interface (ALI) cultures, that better mimicked the in vivo lung barrier function. After introduction of static ALI-cultures, in vitro research further innovated by using primary cells, creating organoids and designing lung-on-a-chip models. These innovations have provided even more physiologically relevant models, integrating mechanical forces, multiple cell types, and microfluidic flow to replicate in vivo lung conditions [2], [3].

Barrier function and dysfunction

The integrity of the lung barrier is critical for pulmonary health. If the barrier is compromised, harmful substances can infiltrate the lungs, leading to several diseases. This is a vicious circle; an impaired lung barrier can lead to disease, and diseases can further impair the lung barrier. Common diseases are:

- Infectious diseases such as bronchitis, pneumonia, tuberculosis, influenza and COVID-19 [4], [5].
- Chronic lung diseases such as chronic obstructive pulmonary disease (COPD), asthma and pulmonary fibrosis [6].
- Acute lung diseases such as acute respiratory distress syndrome (ARDS) and hydrostatic edema [7].

Barrier function of in vitro models of the lung

Impaired lung barrier functionality and lung disease go hand in hand. In order to better understand disease progression and treatment, in vitro models should allow barrier assessment. As discussed above, current models, in contrast to flat 2D models, focus on this barrier function by incorporating two sides of the cell layer: liquid-liquid interface or ALI. Techniques such as transepithelial electrical resistance (TEER) measurements and permeability assays help evaluate barrier integrity/function in these models. These measurements provide valuable data on how drugs, toxins, or disease conditions affect lung barrier function. Improved in vitro models with precise barrier function assessments enhance our ability to predict respiratory drug efficacy and toxicity, reducing the reliance on animal testing [8].

Conclusion

Understanding lung function and its barrier integrity is crucial for advancing respiratory research and developing effective treatments. The evolution of in vitro lung models, from simple 2D cultures to complex lung-on-a-chip systems, has significantly improved our ability to study lung diseases and test potential therapies. By focusing on barrier function, researchers can better predict drug efficacy and disease mechanisms, ultimately reducing the need for animal testing. As technology continues to evolve, refining these models will be key to bridging the gap between laboratory research and clinical applications.

Join the conversation

What do you think are the biggest challenges in accurately replicating lung function in vitro?

References

[1] I. Gopallawa, R. Dehinwal, V. Bhatia, V. Gujar, and N. Chirmule, "A four-part guide to lung immunology: Invasion, inflammation, immunity, and intervention," *Front Immunol*, vol. 14, p. 1119564, 2023, doi: 10.3389/FIMMU.2023.1119564.

[2] A. J. Miller and J. R. Spence, "In Vitro Models to Study Human Lung Development, Disease and Homeostasis," *Physiology*, vol. 32, no. 3, p. 246, May 2017, doi: 10.1152/PHYSIOL.00041.2016.

[3] E. Kolanko, A. Cargnoni, A. Papait, A. R. Silini, P. Czekaj, and O. Parolini, "The evolution of in vitro models of lung fibrosis: promising prospects for drug discovery," *European Respiratory Review*, vol. 33, no. 171, p. 230127, Jan. 2024, doi: 10.1183/16000617.0127-2023.

[4] C. Wang *et al.*, "COVID-19 and influenza infections mediate distinct pulmonary cellular and transcriptomic changes," *Communications Biology 2023 6:1*, vol. 6, no. 1, pp. 1–14, Dec. 2023, doi: 10.1038/s42003-023-05626-z.

[5] W. E. Khalbuss, R. Laucirica, and L. Pantanowitz, "Pulmonary Infections," *Cytopathology of Infectious Diseases*, vol. 17, p. 121, 2011, doi: 10.1007/978-1-4614-0242-8_6.

[6] F. M. Carlier, C. de Fays, and C. Pilette, "Epithelial Barrier Dysfunction in Chronic Respiratory Diseases," *Front Physiol*, vol. 12, p. 691227, Jun. 2021, doi: 10.3389/FPHYS.2021.691227/PDF.

[7] T. Gluecker *et al.*, "Clinical and radiologic features of pulmonary edema," *Radiographics*, vol. 19, no. 6, pp. 1507–1531, 1999, doi: 10.1148/radiographics.19.6.g99no211507.

[8] A. Doryab and O. Schmid, "Towards a gold standard functional readout to characterize In Vitro lung barriers," *European Journal of Pharmaceutical Sciences*, vol. 179, p. 106305, Dec. 2022, doi: 10.1016/J.EJPS.2022.106305.