A breathing lung-on-chip model of alveolar inflammation illustrating human drug response

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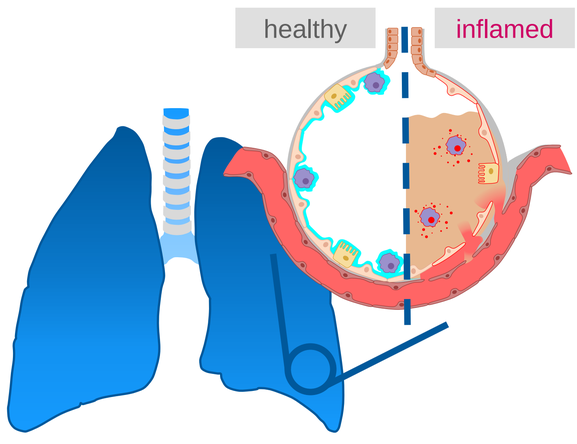
Introduction

The deep lung is characterized by a very large surface area (~140 m²), a high vascularization and a very thin epithelial barrier separating the blood stream from the inhaled air, including possible toxins and pathogens. This makes the deep lung a primary starting point for inflammatory and infectious diseases, but also for inhaled pharmaceutical agents.
In this study, we established an inflamed alveolus model on a breathing lung-on-chip to mimic (patho-) physiological processes and predict human anti-inflammatory drug response.

To reconstitute the air-blood-barrier in the lung-on-chip "AX12"[a], we used the human alveolar epithelial cell line Arlo[b]. To enhance the physiological relevance of the model, the importance of certain parameters was investigated, including the presence of alveolar macrophage surrogates as the main immune system component during early acute lung inflammation, the application of stretching of the epithelial cells to emulate the breathing motion in the alveoli, and the nebulization of anti-inflammatory treatment.

Methods

***in vivo:* alveolus**

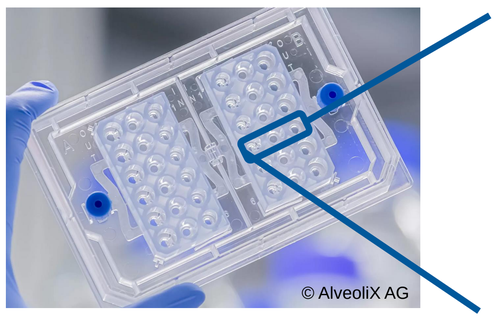


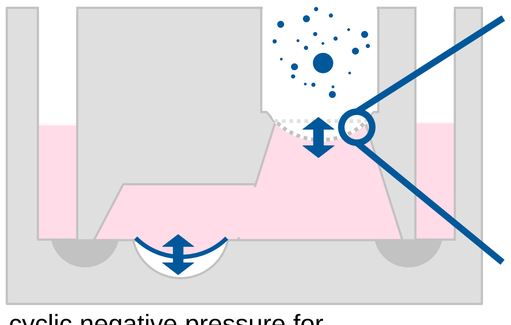
Inflammation of the deep lung

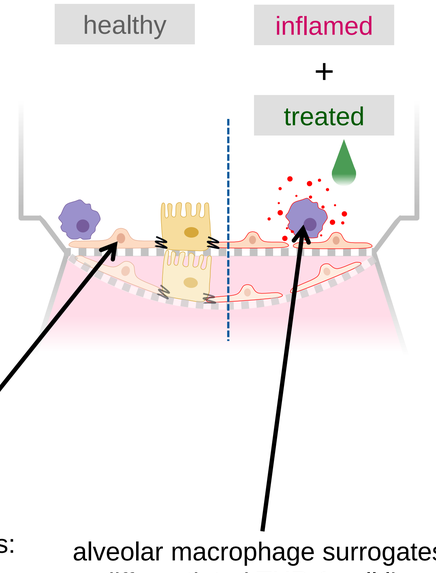
Acute inflammation is characterised - amongst others - by increased cytokine release and decreased barrier functionality.

transfer

***in vitro:* breathing lung-on-chip AX12**







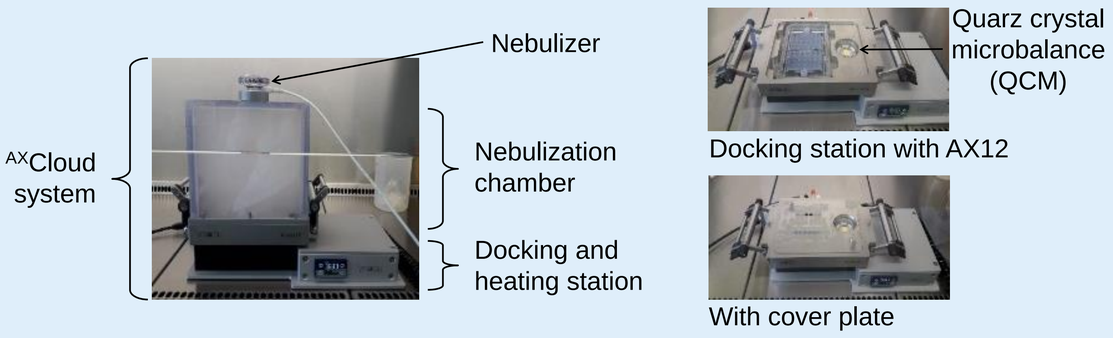
Goal

Develop an alveolus model on chip that illustrates human anti-inflammatory drug response and might later be used for potential drug candidates

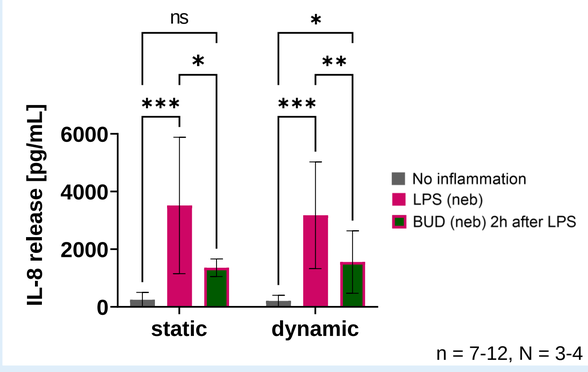
Results

Reduction of inflammatory signals

Nebulization setup



Reduction of chemokine release on chip after nebulized Budesonide treatment

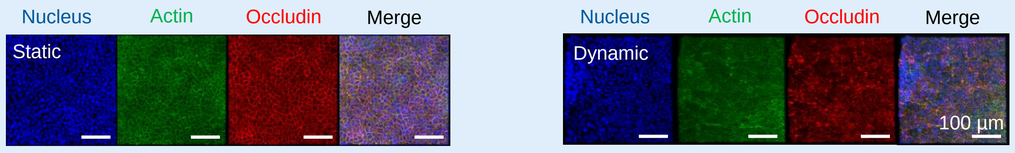


n = 7-12, N = 3-4

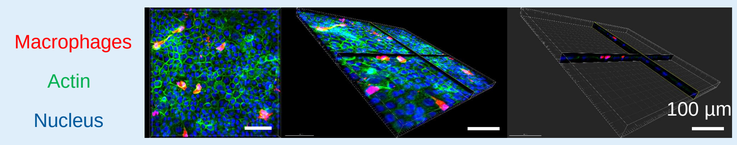
Results:
- Successfull modelling of inflamed alveolus on chip
  - ✓ With epithelial cells and macrophages
  - ✓ With breathing-like dynamics
  - ✓ With nebulization of anti-inflammatory treatment
- Balance between inflamed state and effective anti-inflammatory treatment

Protection of weakened barrier

Epithelial cells on chip

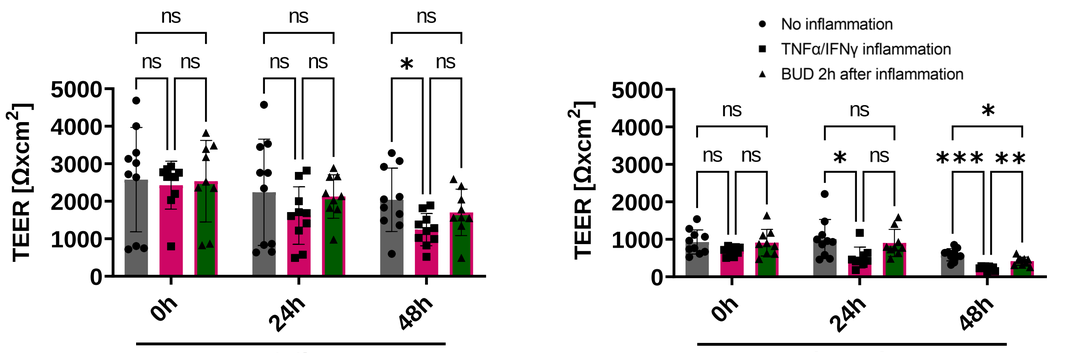


Co-culture of epithelial cells with macrophages



No barrier weakening or drug effect in static conditions

Barrier weakening and protective drug effect in dynamic conditions



n = 9-10 N = 3-5

Results:
- Strong barrier formation on chip in both static and dynamic conditions
- Barrier weakening after inflammation with TNFα/IFNγ is strongest in dynamic conditions
- Protective anti-inflammatory drug effect of Budesonide is only detectable in dynamic conditions

Conclusion and Outlook

Conclusion: Macrophages, breathing dynamics and air-liquid interface are key parameters when modelling alveoli and alveolar inflammation.

Outlook: This model is intended as complex and relevant model for inhaled anti-inflammatory drug efficacy testing.

References

a) Sengupta A., Roldan N. et al. (2022). A New Immortalized Human Alveolar Epithelial Cell Model to Study Lung Injury and Toxicity. Front Toxicol. doi: 10.3389/ftox.2022.840606.
b) Carius, P., Jungmann A. et al. (2023). A Monoclonal Human Alveolar Epithelial Cell Line ("Arlo"). Advanced Sience. doi: 10.1002/advs.202207301.

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