ALI *in vitro* cultures for airway epithelium research

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The respiratory epithelium

Epithelial cells border most tissues, establishing a selective barrier that regulates the exchange of solutes, ions and nutrients between different compartments. The respiratory epithelium is the lining of the airway tract, it facilitates gas exchange, moistens, and protects from pathogens and debris [1]. The respiratory tract epithelium represents an attractive and non-invasive route for drug-delivery as it is accessible through the mouth or nose. In addition, it contains 100 m^2 of highly vascularized surface and a low amount of drug metabolizing enzymes, enhancing bioavailability [2]. The respiratory epithelium is ciliated, polarized and pseudostratified. The following cell types form the respiratory epithelium: secretory club cells, ciliated cells, basal progenitor cells and rare cell types (tuft cells, solitary neuroendocrine cells, pulmonary ionocytes and goblet cells).

Airway ALI cultures

In vitro ALI cultures are pivotal and widely used to simulate the respiratory tract. In lung ALI cultures, airway epithelial cells are grown on permeable membranes at the air-liquid interface (**Figure 1**). Under these conditions cells differentiate, polarize and form a pseudostratified epithelium, closely resembling *in vivo* conditions [3,4].

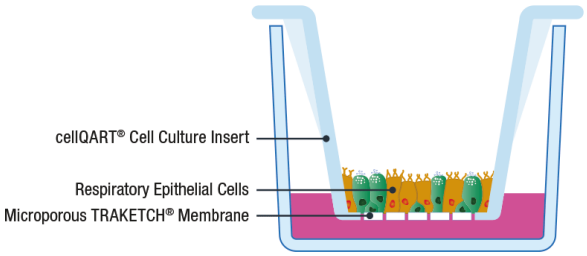

Figure 1. *Schematic representation of an airway ALI culture on cell culture inserts.*

The general procedure to set up an ALI culture starts with the seeding of epithelial cells on the porous support of a cell culture insert, such as SABEU's cellQART®. The typically used inserts/membranes have a pore size of 0.4 um. The high porosity-translucent membrane is ideal for fast barrier formation, whereas the low porosity-clear membrane has superior optical properties in phase contrast microscopy.

Following cell propagation, the medium from the apical compartment is discarded. By doing this, the apical side is exposed to the air while the basal side is supplied with nutrients through the lower compartment. By providing an *in vivo*-like environment, it is possible to create a physiological relevant *in vitro* model (**Figure 2**).

Airway ALI cultures have many applications, for example they can be used to test aerosolized drugs, measure the health effect of certain air pollutants, perform research on the health effects of tobacco, conduct studies on both normal and disease states and study respiratory viral infections such as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), among others.

Conclusion

The *in vitro* study of the respiratory system is of cardinal importance to increase our knowledge on the basic mechanisms in normal and altered states. This will accelerate the development of potent and targeted therapeutic approaches.

It is important to mention that ALI cultures have many other uses such as *in vitro* skin models, organoids and biofilm assays.

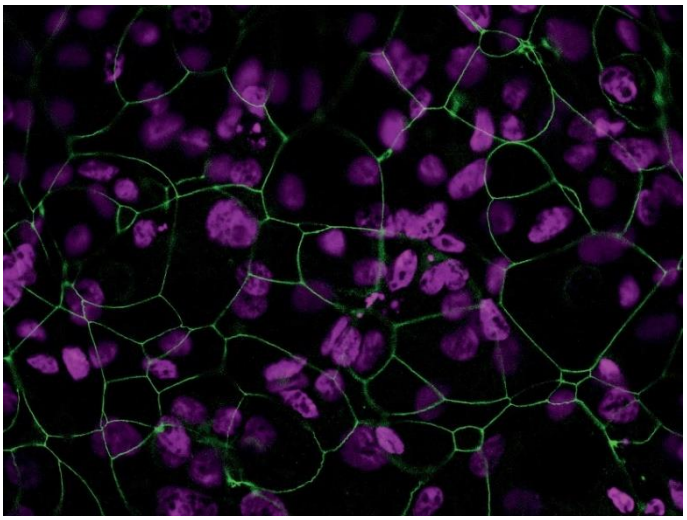

Figure 2. *Tight junctions on airway ALI cultures on cellQART® inserts by InSCREENeX [5].*

Whereas animal models to study lung physiology have provided invaluable information, there is a growing demand for physiologically relevant human *in vitro* models. For this purpose, the precise *in vitro* modelling of the airway epithelium is crucial. Air-Liquid-Interface cultures offer an exceptional option to model and study the respiratory tract. Airway cells cultivated in this way predict more accurately the normal biology and physiology than cells in submerged culture, where they fail to display the essential mucociliary phenotype. ALI models offer the possibility to use human cells, eliminating cross species variability, and their scalability increases reproducibility and statistical power. Their regulatory acceptance is a current challenge, as animal testing has been the gold standard. Nevertheless, legislation changes have been a driving force towards the use of non-animal models.

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