



Cystic Fibrosis Research News

Title:

Molecular characterization of gene regulatory networks in primary human tracheal and bronchial epithelial cells.

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What was your research question?

The layer of cells lining the airway (epithelial cells) is of critical importance in the development and treatment of lung disease in CF. It contains many different cell types, which have subtly different properties depending on where they are located within in the airway. Our goal was to find molecular signatures of the genetic information, reflecting unique markers of gene activity, in cells from different regions of the lung.

Why is this important?

The cells lining the airways are the gold standard tool for researchers to investigate the biology and biochemistry of the airway and how CF impacts these processes. However, since their preparation depends on availability of lungs from an organ donor, they are an extremely valuable and limited resource. Instead research is often performed on long-term cultures of cells grown in the laboratory. However, these are not the same and may not respond properly to new therapies. It is important to know the molecular similarities and differences between primary cells in different parts of the lung and lung-derived long term cell lines.

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What did you do?

We used state-of-the-art methods to investigate the molecular signature of primary cells from human trachea (windpipe) and bronchi (the tubes that carry air to the right and left lung) and also lung- derived cell lines. DNA is normally tightly coiled in the cell within the master control region, the nucleus, but the coils relax and open when genes become active to produce proteins. Our experiments show which genes are accessible and active in the lung cells and which switches are used to turn them on and off. They also show the unique molecular features of each cell type, which predicts what proteins are made to maintain a healthy layer of cells lining the lung. Each cell type has a unique signature.

What did you find?

Our data reveal an airway cell signature that is different from cell types that line other organs in the body. It also diverges from the signature of commonly used cell lines derived from the airway, which are often used in lung research. The differences between tracheal and bronchial cells are clearly evident as are common switches that turn genes on and off. Of interest only minor variation is seen between bronchial cells from healthy or CF donors. These data will be valuable for other investigators who work on specific genes and key functions of the lung surface..

What does this mean and reasons for caution?

Many approaches to develop new therapies for human lung disease rely on assays in cells cultured in the laboratory. For example, screens for new drugs, gene therapy protocols and most recently gene editing methods rely on preclinical studies in human airway epithelial cells. The challenges of culturing and expanding primary cells, which are collected directly from live tissue, leads to the use of surrogate cultured cell models, but we show these are very different from the fresh cells. Similar analysis of primary cells from more donor lungs will build upon and reinforce our data set.

What's next?

Our data will be useful to guide researchers to the most robust cellular model systems in order to perform relevant assays while developing new therapies for human lung disease.

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