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Cystic Fibrosis Research News

Title:

Significant functional differences in differentiated Conditionally Reprogrammed (CRC)- and Feeder-free Dual SMAD inhibited-expanded human nasal epithelial cells

Authors:

Nikhil T. Awatade[a,b,1], Sharon L. Wong[a,b,1], Elvis Pandzic[d], Iveta Slapetova[d], Alexander Capraro[a,b], Ling Zhong[e], Nihan Turgutoglua[a,b], Laura K. Fawcett[a,b,c], Renee M. Whan[d], Adam Jaffe[a,b,c] and Shafagh A. Waters*[a,b,c]

Affiliations:

[a] School of Women's and Children's Health, Faculty of Medicine, University of New South Wales, Sydney, NSW, Australia
[b] Molecular and Integrative Cystic Fibrosis Research Centre (miCF_RC), University of New South Wales and Sydney Children's Hospital, Sydney, NSW, Australia
[c] Department of Respiratory Medicine, Sydney Children's Hospital, Sydney, NSW, Australia
[d] Biomedical Imaging Facility, University of New South Wales, Sydney, NSW, Australia
[e] Bioanalytical Mass Spectrometry Facility, University of New South Wales, Sydney, NSW, Australia
[1] These authors contributed equally.

What was your research question?

Human nasal cells obtained by brushing the nose can be grown in the lab to create a personalised model of that individual's airway. We wanted to know what effect using different methods to grow these cells might have on the activity of the cystic fibrosis chloride channel (CFTR), the protein which is defective in cystic fibrosis (CF). We also wanted to if the response to modulator drugs such as Kalydeco or Orkambi, which directly enhance CFTR function, is altered as a result of using these different growth methods.

Why is this important?

These personalised airway models are used as an alternate in the lab to test CFTR activity with and without drugs that have the capacity to activate CFTR channel. Current experimental work suggests that these models have the capacity to predict a person's response to modulator/corrective drugs. For example, when a person's airway cell model in the lab responds favourably to a CFTR modulator that person's actual response to the drug is usually also favourable. With more labs creating and using these models across the globe,

standardisation of growth conditions is needed for any of the preclinical cell models to be routinely used in health care.

What did you do?

We enrolled 14 individuals (nine with CF and five non-CF controls). To minimise variables, the same clinician brushed the inside of the nose of each person. The brushed cells were divided equally. One half of the cells were grown in the lab with a growth medium commonly called CRC. The other half of the cells were grown with a very different growth medium (called SMADi). When a large number of cells were created using each technique we then created a lab-grown airway model for each person. Each individual's CRC and SMADi models were compared by measuring several cell markers that report on health and function of the airway, including the function of the CFTR channel.

What did you find?

We found that cell composition and structure of the airway models grown from the same individual with these two different methods is very similar. However, the activity of CFTR and its response to modulator drugs was very different. The CFTR channel activity in cells grown with the SMADi method was significantly reduced in comparison to the CRC method.

What does this mean and reasons for caution?

Our study highlights the importance of standardising the growth condition of cells used to measure the CFTR channel activity. Our results indicated that the results from cells grown using one method cannot be compared against results from cells grown using the other technique. It appears that the alteration of ion channel function when cells are grown in the lab environment occurs more easily than structural changes. We cannot ascertain which one of the two growth methods studied here correlates more with the clinical CFTR function, since none of the people with CF in this study were receiving CFTR modulator therapy. It is necessary to recognise the limitations of the lab grown airway models for CF. Culture conditions significantly influence CFTR activity. This could lead to false conclusions when data from various labs are compared against each other. With the current variety of techniques in use, it is important to compare like for like and report a patient's cell model's response to drugs against technique/lab specific references.

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What's next?

Moving forward, a standardised international protocol to grow patient airway epithelial cells is needed across CF labs to ensure consistency in laboratory data and ultimately, translation of clinical care to patients.

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cfresearchnews@gmail.com