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Cystic Fibrosis Research News

Title:

Creation and characterization of an airway epithelial cell line for stable expression of CFTR variants

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What was your research question?

Cells taken from living organisms and grown in a laboratory offer a quick and easy way to study biological processes. We wanted to use cells (a cell line) taken from the lung of a person with cystic fibrosis and modify them for the study of mutations in the gene that causes cystic fibrosis.

Why is this important?

There have been over 2000 mutations discovered in the gene that causes cystic fibrosis (CFTR). A large majority of these mutations have not yet been studied because they are so rare. These rare mutations need to be analyzed in a laboratory to determine what effect they have on the CFTR protein, as well as what drugs are effective to treat different mutations. The easiest way to study many different CFTR mutations is to use a model based on using these cells. Several cell models are currently available, but they are not helpful for these experiments as some are from animals and some have too many different mutations.

What did you do?

We placed a target site into the DNA of a cell line that was created using the cells from the lung of a person with cystic fibrosis. The newly created cell line was named CF8Flp. The target site allows for the insertion of any single gene into the DNA of the CF8Flp cells. Therefore, a

mutated form of CFTR can be inserted into the cells to observe what happens to the resulting CFTR protein. Additionally, we can test whether adding a drug will affect that mutated protein.

What did you find?

A mutant form of CFTR carrying the well-studied G551D mutation was successfully placed into the target site of the CF8Flp cell line. When treated with ivacaftor, the first drug that treats the underlying cause of CF, the inserted G551D-CFTR mutation had increased response similar to what has been previously shown in cells from patients. We then looked at all of the expressed genes within the CF8Flp cells and compared them to other cell types. In CF8Flp cells, genes that are related to CFTR are expressed at levels similar to what is observed in cells taken directly from the lung.

What does this mean and reasons for caution?

The G551D-CFTR results show us that the CF8Flp cells can be used to study CFTR mutations and their response to drugs. Additionally, the similar expression levels of CFTR related genes (number of copies created within the cell at a particular time) between the CF8Flp line and cells from the lung is encouraging. The similar gene expression profiles suggest that the CF8Flp cells will provide an accurate genetic model similar to what is observed in the lungs in which to study CFTR. However, there are a few technical limitations that still need to be overcome while using the CF8Flp cells, including varying expression levels of CFTR between some cells.

What's next?

Results obtained from studying additional CFTR mutations in the CF8flp cells will be compared to the clinical data from patients who have the same mutations. These comparisons will allow us to assess how well the CF8Flp cells work as a model for studying CFTR mutations.

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