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Cystic Fibrosis Research News

Title:

The Proteostatic Network Chaperome is Downregulated in F508del Homozygote Cystic Fibrosis

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What was your research question?

Chronic protein misfolding is harmful to basic or normal cellular function. The most common cystic fibrosis (CF) mutation, F508del results in a misfolded CFTR protein. We asked whether the genes that cells need to correct protein folding (known as the “chaperome”) were present in cells from people with the F508del mutation at the same levels compared to cells from a group of healthy volunteers.

Why is this important?

While the new CFTR modulator drugs are highly effective, they are not curative and additional means of treating CF are needed. This could include using drugs to optimize chaperome expression and help the misfolded CFTR protein.

What did you do?

We collected cells from the nasal lining of people with CF and healthy volunteers. We isolated RNA (the instructions for cells to make proteins) from these cells and measured the levels of the different RNAs. Sophisticated analysis tools were used to compared between the two groups and identify the differences in individual RNAs, as well as what this might mean for the biological function of the cells. We initially studied a small “pilot” group, before moving onto a larger “validation” group to confirm the results of the pilot group.

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What did you find?

People with CF have several hundred RNAs expressed at different levels compared to healthy volunteers. These RNAs included those that control immune system and ciliary function (brush-like structures on the airway cells important in moving mucous and preventing infection). We found that chaperone RNAs and RNA for the *CFTR* protein were decreased in people with CF. We also found preliminary evidence for an ionocyte, a newly found cell that expresses high levels of CFTR.

What does this mean and reasons for caution?

We conclude that people living with CF may have decreased expression of chaperone RNAs and *CFTR* RNA, both of which could contribute to CFTR dysfunction and therefore worsen the clinical manifestations of CF. Drugs that could improve the production of chaperome and CFTR RNAs could possibly be used to work in combination with CFTR modulators.

What's next?

We would like to assess RNA expression differences within CF individuals to help us understand their different clinical course. We would also like to use a new technology called single-cell-RNA sequencing which will allow us to identify differences in gene expression at the level of individual cells, as this would tell us which types of cells are most affected.

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