European Cystic Fibrosis Society

Journal of Cystic Fibrosis
The Official Journal of the European Cystic Fibrosis Society

Cystic Fibrosis Research News

Title:

Detection of CFTR Function and Modulation in Primary Human Nasal Cell Spheroids

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What was your research question?

We asked if cells from a person's nose could be used to create a laboratory model of their disease. Our long-term goal is to use this model to help doctors tailor treatments for each individual with cystic fibrosis (CF), and to increase the number of people that benefit from new medicines.

Why is this important?

New "modulator" medicines are changing the way we treat CF. These drugs improve the function of the mutant protein responsible for CF, which is called CFTR. While more than 2000 mutations have been found in CFTR, these medicines are only available to people with common mutations, where clinical trials are possible (approximately 50% of people with CF). For people with rare mutations, clinical trials aren't practical due to small numbers. Using a personalized model system could bypass this problem and help decide if an individual might benefit from these medicines, or tailor the ideal combination of drugs in a precise fashion.

What did you do?

We collected nasal cells from healthy volunteers and people with CF by a simple, well tolerated method. These cells were grown in the laboratory into 3-dimensional structures we have called "spheroids." Spheroids are a ball of respiratory cells with a center filled with fluid and mucus – like microscopic water balloons. We evaluated the structure of these spheroids, and then used drugs that turn on CFTR function to see how the spheroids respond. We compared these responses to clinical information and disease severity over CF patients with different mutations.

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What did you find?

When tested, spheroid size changes based on the amount of CFTR activity; the better the function, the more the spheroids grow after stimulation. This means spheroids from healthy controls (the study participants that act as comparators to the people with CF) swell significantly when stimulated, while spheroids from people with CF swell less, or may even shrink. CF disease severity correlated with spheroid growth across several CFTR mutations. The lack of swelling seen in spheroids from people with CF with a common mutation, F508del, can be improved by adding modulator drugs known to improve that mutant protein's function, meaning this model can demonstrate "rescue" of mutant CFTR.

What does this mean and reasons for caution?

Nasal cell spheroids are able to measure a person's CFTR function and show a response to drug-induced changes in that function. This suggests that these models may be useful as a drug testing ground for individuals, expanding medicine access to new people and optimizing combinations of drugs for people that are already using them. In order to do this, though, we must confirm that the spheroid results will consistently match an individual's clinical results – in short, prove that this model really can predict an individual's benefit from modulator drugs.

What's next?

We are testing spheroids from people with rare CFTR mutations, and then using an individualized clinical trial (called "N-of-1" testing) to determine if they benefit from modulator drugs. This will let us directly compare laboratory spheroid testing with real-world results, and understand the predictive value of this model.

Original manuscript citation in PubMed

https://www.ncbi.nlm.nih.gov/pubmed/?term=Detection+of+CFTR+Function+and+Modulation+in+Primary+Human+Nasal+Cell+Spheroids

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