

Cystic Fibrosis Research News

Title:

Pancreatic duct organoid swelling is chloride-dependent

Lay Title:

A mini-pancreas model shows its activity is dependent on chloride

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What was your research question?

Pancreatic involvement is very common in people with cystic fibrosis (PwCF); mutations in the *CFTR* (cystic fibrosis transmembrane conductance regulator) gene cause protein to malfunction, or not be produced. As a result, the proper flow of salt (mainly chloride and bicarbonate) and fluid is impaired, leading to a build-up of thick secretions, blockage and damage to the pancreas. The question is whether a commonly used test to measure CFTR function is dependent on chloride and/or bicarbonate secretion in an organoid (mini pancreas) model.

Why is this important?

Forskolin-induced swelling (FIS) assay has been developed in laboratory models, such as organoids or mini-organ models to measure the CFTR function. The pancreas secretes chloride and large concentrations of bicarbonate to inhibit gastric acid and to keep digestive enzymes from premature activation within the pancreas. It is not known whether FIS assay reflects bicarbonate and/or chloride secretion in a mini pancreas model. This is important in order to measure CFTR function in pancreas and for potential drug development.



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What did you do?

We generated organoids from CF and healthy pig pancreatic ducts and confirmed their origin and purity using microscopy and PCR (polymerase chain reaction). We conducted FIS assay to measure organoid responsiveness to bicarbonate and/or chloride. We have done at least 3 independent experiments for each section and utilized 10-15 organoids from each pig donor.

What did you find?

Organoids from CF pig pancreas were small, lacked CFTR and did not swell in response to forskolin, as expected, confirming that the model was valid. In FIS assay utilizing forskolin, healthy pancreas organoids swelled only in response to chloride, not bicarbonate.

What does this mean and reasons for caution?

Healthy pancreatic organoids secreted chloride not bicarbonate in response to forskolin using this methodology. Thus, in this widely used assay to measure CFTR function (FIS assay), forskolin was a better indicator of CFTR function. Caution should be exercised in interpreting FIS assay results from PwCF and *CFTR* mutations impacting bicarbonate secretion as the test measures chloride, not bicarbonate secretion.

What's next?

The pancreatic organoid model would be useful in PwCF and *CFTR* mutations that can impact chloride secretion in the pancreas.

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