Cystic Fibrosis Research News

Title:
Lack of CFTR Alters the Ferret Pancreatic Ductal Epithelial Secretome and Cellular Proteome: Implications for Exocrine/Endocrine Signalling

Lay Title:
CF Pancreatic Duct Secretions Can Alter Islet Function

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What was your research question?
Different types of cells in the pancreas communicate through signals, like networked messages, that together are important to help the pancreas regulate food digestion and blood glucose levels. We bred ferrets with CF and looked at their ductal cells to see whether CFTR (cystic fibrosis transmembrane regulator – which is responsible for regulating the flow of salt and fluids in and out of cells) affects the signals ductal cells send to other types of pancreatic cells including insulin-producing islets.

Why is this important?
CF pancreatic insufficiency can lead to diabetes and worsen lung disease. It is not clear what leads to the abnormal function of cells that produce insulin and eventually cause diabetes, but it is generally believed that these cells function abnormally in people with CF because the pancreas is scarred and inflamed. We thought that a change in messaging between the pancreatic cells in CF may affect how the insulin producing cells work. We wanted to see if the pancreatic ductal cells sent altered signals (i.e., messages) when CFTR was not present. Blocking damaging messages from CF ducts or generating missing messages could be a useful treatment for improving how insulin producing cells function.

What did you do?

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Like people with CF, ferrets without normal CFTR develop pancreatic disease and diabetes. So, we worked out how to isolate pancreatic duct cells from both normal and CF ferrets. We grew these cells in the laboratory to mimic the function of cells in pancreatic ducts. This cell system simulates the secretions found in the inside of the pancreatic duct (apical secretions) and those secreted through the other membranes (basolateral secretions). We identified the secreted and cellular proteins and quantified them using mass spectrometry, to compare changes in messages from normal and CF ducts.

What did you find?

We found 35 proteins were abnormally secreted by CF duct cells. Likewise, 303 proteins found inside duct cells were significantly different in CF, including 85 proteins known to directly interact with CFTR. We found that the messages sent and received by CF ductal cells were very different from normal, suggesting that the pathways of communication with other cells in the pancreas could also be changed. For example, CF ductal cells in culture produced less of a protein called IGFBP7 and this mirrored the reduced IGFBP7 content in the intact CF ducts of the pancreas. Notably, when IGFBP7 pure protein was put onto isolated islets they were more sensitive to glucose and produced more insulin.

What does this mean and reasons for caution?

We have seen that CF pancreatic ductal cells behave differently compared to normal ducts. Our investigations suggest that CFTR directly affects how the ductal cells behave and how these cells communicate with other cell types in the pancreas. Some of these altered messages may be damaging to cells and could be targeted with treatment to restore function. While our study describes the signals sent between CF duct cells, we can only speculate on the mechanisms that cause these changes. Their role in the onset of diabetes in CF needs further study.

What's next?

More research is needed to understand the mechanisms that lead to changes in CF ductal cell composition and secretions. Determining whether altered messages from CF ductal cells contribute to development of CF-related diabetes will require studies in CF animal models. Such studies would need to manipulate each altered message using small molecules and test whether there is therapeutic protection from diabetes.

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