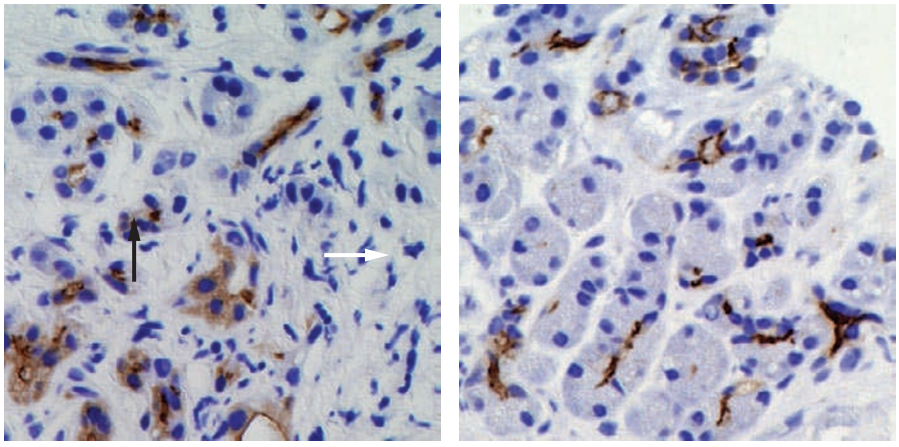
PANCREAS

Autoimmune pancreatitis—mislocalization of CFTR ion channel corrected by corticosteroids

New research explains how corticosteroids reduce inflammation and improve secretion of bicarbonate and digestive enzymes in patients with autoimmune pancreatitis—the steroids correct mislocalization of the cystic fibrosis transmembrane conductance regulator (CFTR) protein in pancreatic duct cells and aid regeneration of acinar cells in these patients.

"Corticosteroids have become established as a treatment of autoimmune pancreatitis. However, it [has] remained largely unsolved how steroids affect the pancreas, decrease tissue damage and improve pancreatic exocrine function," comments lead author Shigeru Ko, from the Nagoya University Graduate School of Medicine, Aichi, Japan.



CFTR (black arrow) is wrongly located in the cytoplasm of pancreatic duct cells in an untreated patient with autoimmune pancreatitis (left), but after corticosteroid therapy (right) CFTR (white arrow) is correctly localized to the apical membrane of duct cells in this patient. Courtesy of S. B. H. Ko.

> "...CFTR was mislocalized in ... other types of chronic pancreatitis..."

The CFTR anion channel has a central role in transport of chloride and bicarbonate ions across epithelial cell membranes. Mutations in the *CFTR* gene impair the function of the chloride channel and are associated with cystic fibrosis and congenital absence of the vas deferens. Existing data have shown that CFTR anion channels—expressed in the apical plasma membrane of pancreatic duct cells—regulate the secretion of ductal fluid and bicarbonate in the pancreas. Ko and colleagues wanted to elucidate "the precise molecular role of [the] CFTR chloride channel in pancreatic ductal dysfunction in chronic pancreatitis".

The investigators examined exocrine function (using the secretin-stimulated function test) and obtained biopsy samples from the pancreases of patients at the time of diagnosis of autoimmune pancreatitis and after the initial 3 months of corticosteroid therapy. They found that steroid treatment restored bicarbonate and digestive enzyme secretion, reduced inflammation (the number of $IgG4^+$ plasma cells decreased after corticosteroid therapy), and repaired tissue damage (including the partial regeneration of acinar cells) in patients with autoimmune pancreatitis.

Ko *et al.* observed that CFTR was incorrectly located in the cytoplasm of pancreatic duct cells in patients with autoimmune pancreatitis; corticosteroid therapy corrected this abnormal location and after 3 months of prednisolone, CFTR was rightly found in the apical plasma membrane of pancreatic duct cells. Intriguingly, the researchers also found that CFTR was mislocalized in patients with other types of chronic pancreatitis, including alcoholic, idiopathic and obstructive forms of the disease.

"These observations support the hypothesis that inflammation can cause the mislocalization of membrane proteins … [to] cause dysfunction in epithelia," concludes Ko who believes that further research into this improper cellular trafficking of membrane proteins in inflammatory conditions could lead to a cure for diseases like chronic pancreatitis and cystic fibrosis.

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Original article Ko, S. B. H. *et al.* Corticosteroids correct aberrant CFTR localization in the duct and regenerate acinar cells in autoimmune pancreatitis. *Gastroenterology* **138**, 1988–1996 (2010)