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CFTR-beyond the airways: Recent findings on the role of the CFTR channel in the pancreas, the intestine and the kidneys ☆

Peter Hegyi [a,b,c,1], Ursula Seidler [d,1,*], Karl Kunzelmann [e,1]

[a] Institute for Translational Medicine, Medical School, University of Pécs, 7624 Pécs, Hungary
[b] Center for Translational Medicine and Institute of Pancreatic Diseases, Semmelweis University, 1085 Budapest, Hungary
[c] Translational Pancreatology Research Group, Interdisciplinary Centre of Excellence for Research Development and Innovation, University of Szeged, 6725 Szeged, Hungary
[d] Department of Gastroenterology, Hannover Medical School, 30625 Hannover, Germany
[e] Institute of Physiology, Regensburg University, 93040 Regensburg, Germany

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ABSTRACT

With increased longevity of patients suffering from cystic fibrosis, and widespread lung transplantation facilities, the sequelae of defective CFTR in other organs than the airways come to the fore. This minireview highlights recent scientific progress in the understanding of CFTR function in the pancreas, the intestine and the kidney, and explores potential therapeutic strategies to combat defective CFTR function in these organs.

1. Introduction

The organizers of the 2022 ECFS basic science conference scheduled a session in which important new aspects of the pathophysiological role of a dysfunctional CFTR channel and potential new treatment strategies in the pancreas, the intestine and the kidney were highlighted. These three presentations are briefly summarized in this minireview.

2. CFTR and pancreatitis

Pancreatic ductal cells play an extremely important role in the physiological function of the pancreas [1]. The pancreatic acinar cells produce more than 200 bioactive substances, including the pancreatic enzymes responsible for digestion such as trypsin, amylase or lipase [2]. It is important to note that these enzymes are produced by the acinar cells in an inactive form and are physiologically activated only in the small intestine. In order to maintain these enzymes in an inactive state within the pancreas, it is crucial that the trypsinogen produced by the acini remains in an inactive form. This is ensured by the pancreatic secretory trypsin inhibitor (SPINK1), which inhibits trypsinogen activation produced by acinar cells [3], and by the fluid and HCO_3^- secretion produced by pancreatic ductal cells [4]. The latter is important because the acinar cells also secrete protons, which creates an acidic medium for the enzymes which accelerates trypsinogen autoactivation at pH below 7 [4]. It is well documented that the SLC26A6 Cl^-/HCO_3^- ex-

Abbreviations: NHE3, Na^+/H^+ exchanger 3 isoform; DIOS, distal intestinal obstruction syndrome.

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* Corresponding author at: Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Carl Neuberg Straße 1, D 30625 Germany.
E-mail address: seidler.ursula@mh-hannover.de (U. Seidler).

[1] These three authors contributed equally.

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changers regulate CFTR activity, and that the well-coordinated interaction of these transporters and channels ensures the necessary HCO_3^- concentration in the lumen of the pancreatic duct [5].

Mutations in the SLC26A6 transporter were found not to be associated with the development or risk of chronic pancreatitis [6], but mutations in the CFTR channel clearly increase the risk of developing pancreatitis or exacerbate its progression in both animal and human studies [7,8].

Extensive research over the last 15 years has shown that toxic substances involved in the induction of pancreatitis, such as bile acids [9], tobacco [10], alcohol or fatty acids [11,12] inhibit both the SLC26A6 transporter as well as the CFTR Cl^- channel. In the latter case, not only is the activity of the channel inhibited, but the folding and translocation of the channel to the membrane is severely impaired [11]. The link between CFTR and pancreatitis is well proven by the fact, that the early phase of both acute and chronic pancreatitis can be characterized by a decrease of fluid and bicarbonate secretion, intraductal acidosis and elevation of mucoprotein levels. These physiological dysfunctions are identical to those seen in the presence of a mutated CFTR channel [13]. In summary, it was previously known that genetic mutations in CFTR with loss-of-function can induce pancreatitis or exacerbate existing inflammation, but the new research results clearly show that CFTR damage induced by toxic factors mimics the phenotype of genetic alteration [14]. This is important because CFTR inhibition by toxic factors is more common in everyday life.

3. CFTR-targeted therapy reduces pancreatic damage

Für et al. recently published a study demonstrating that the combined use of a CFTR corrector (VX-661) and potentiator (VX-770), drugs that prevent degradation and enable membrane expression and/or function of the mutated CFTR channel, reduces the severity of experimentally induced pancreatitis [15]. Our unpublished results also show that not only experimental but also alcohol-induced cell damage and pancreatitis are ameliorated by corrector/potentiator combination therapy. This was confirmed not only during pretreatment before alcohol administration but also during alcohol treatment. The latter has a very important clinical implication, as one of the most common causes of recurrence of acute pancreatitis is alcohol consumption, which first presents as recurrent acute pancreatitis and later transforms into chronic pancreatitis [16].

There are a growing number of case reports showing that pharmacological therapy can be effective not only in vitro or in animal models but also in human patients as well. Carrion et al. demonstrated in 6 patients with CF and recurrent acute pancreatitis that no patient developed recurrent pancreatitis during a 9-month-period ivacaftor therapy [17]. Kounis et al. demonstrated that ivacaftor therapy improved pancreatic damage in a 48-year-old patient with CF with pancreatic manifestations [18]. In this patient, restoration of CFTR channel function also had a feedback effect on acinar cells and a detectable increase in fecal elastase levels occurred. The patient required less pancreatic enzyme replacement therapy and did not develop a new episode of pancreatitis during the therapy. Johns et al. achieved no recurrence of acute pancreatitis episodes during a 19-month-period of ivacaftor therapy in a 24 year-old male patient with CF but no respiratory symptoms [19]. Ivacaftor therapy not only restored pancreas function in these cases, but also prevented recurrence, i.e. slowed or prevented the development of chronic pancreatitis. Whether CFTR damage caused by toxic factors (alcohol, smoking, fatty acids) can be repaired in patients or whether recurrent attacks can be prevented still remains to be proven.

4. Clinical features of the “CF gut”

Recent reviews focused on the gastrointestinal manifestations of cystic fibrosis, the so-called “CF gut”, which include luminal dehydration and acidosis, mucus-hyperviscosity, dysmotility, dysbiosis, abnormal bile acid homeostasis and inflammation, resulting in gastroesophageal reflux, malabsorption, constipation, intestinal obstruction, and colonic malignancy [20,21]. How exactly these various abnormalities are caused at the molecular level by the defective CFTR channel is still a matter of research and debate. Fig. 1 presents a schematic diagram of some of the secondary alterations that result from a defective intestinal CFTR channel. CFTR-null (no functional CFTR protein at all) animal models are all extremely sensitive to develop intestinal obstructions, while the pancreatic and pulmonary function of CFTR-null mice is hardly or not at all affected [22,23].

5. The search for alternative (non-CFTR) intestinal anion channels

This prompted researchers to start a search for alternative pathways for anion and fluid transport. A significant number of anion channel proteins are expressed in the murine wt and CFTR-null intestine [24]. Nevertheless, secretagogue-stimulated electrogenic anion secretion, whether elicited by cAMP, cGMP or Ca^{2+}-dependent agonists, cannot be elicited in the small and large intestine of mice with CFTR deletion [25,26]. In intestinal organoids from the small or large intestine of CFTR-null mice, or in organoids from patients withwith loss of function mutations in the *Cftr* gene, secretagogues fail to stimulate a “swelling” reaction [27]. Recent data suggest, however, that a full anion secretory response by the CFTR channel in the intestine or the airways requires the coexpression of TMEM16a (Ano1) chloride channels, possibly by optimizing intracellular signal transduction [28,29]. They may indicate (although it is not yet prven clinically) that loss of function mutations in TMEM16a may results in a CF phenotype in intestinal epithelia. In contrast to the situation in the intestine, alternative anion channels can be activated in the airways, the pancreatic, biliary and reproductive ductal system in the absence of CFTR expression [30–32].

6. Intestinal HCO_3^- transport pathways in the CF gut

A lack of HCO_3^- release into the intestine has first been described during measurements of pancreatic exocrine secretion and has already been implicated in the pathophysiology of meconium ileus and nutrient malabsorption (rev. in [33]). While agonist-induced intestinal alkaline output is strongly (but not exclusively) dependent on CFTR expression in the murine proximal small intestine and is mediated by direct HCO_3^- efflux via the CFTR channel as well as CFTR-dependent stimulation of Slc26a3/a6-mediated Cl^-/HCO_3^- exchange [34,35], this is not the case in the large intestine. While no agonist-stimulated short circuit current (Isc) response was elicited in chambered colonic mucosa in the absence of CFTR expression, a significant agonist-dependent increase in HCO_3^- output was observed [36]. Because the agonist-stimulated HCO_3^- output in the CFTR-null colonic mucosa was electroneutral, the transport mechanism(s) could not have been (an) alternative anion channel(s). Further investigation revealed that the likely mechanism of HCO_3^- output in CFTR-null intestine is an agonist-mediated inhibition of the NHE3 (Slc9a3) isoform of Na^+/H^+ exchangers in the brush border membrane, with preserved Cl^-/HCO_3^- exchange activity, likely by Slc26a3 (DRA), which is highly expressed in murine and human colonic mucosa. This concept was further validated by the finding that the deletion of Slc26a3 abrogated both the relatively high basal HCO_3^- output

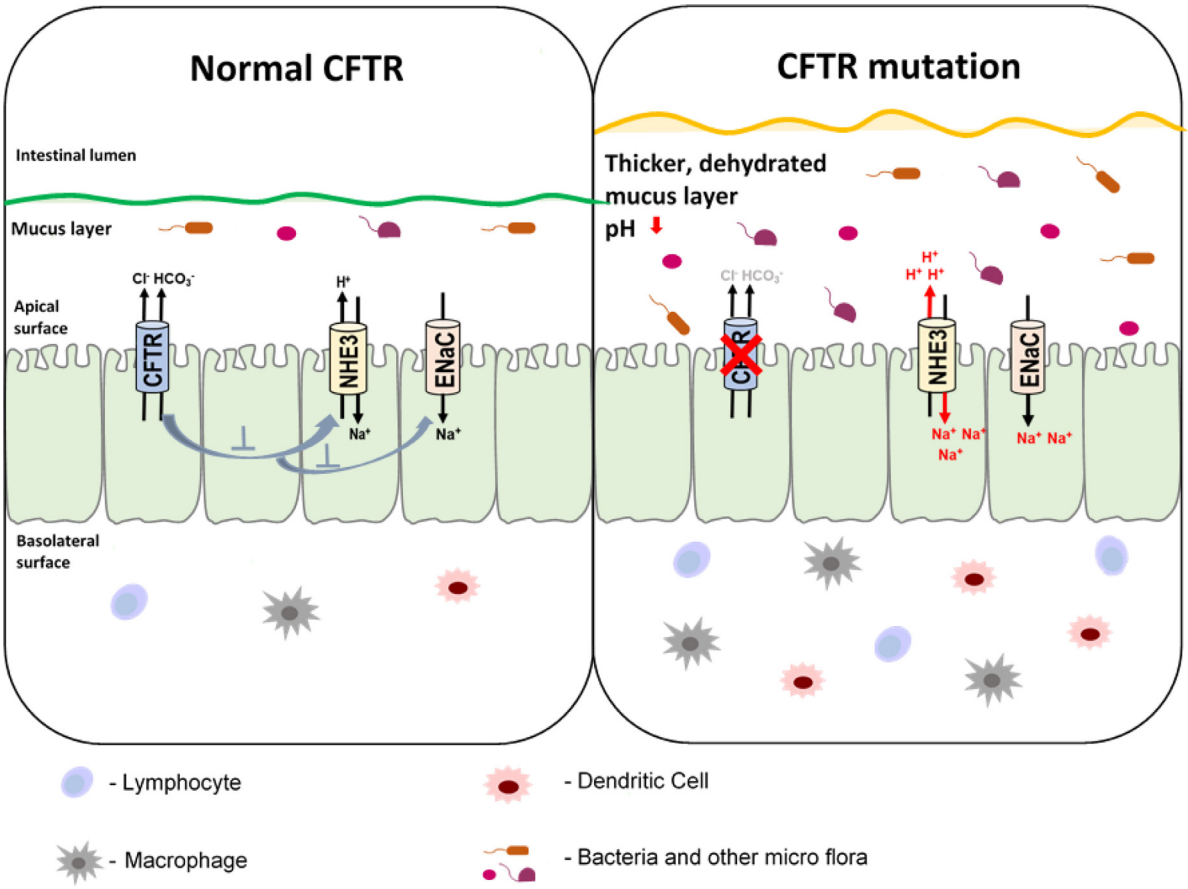

Fig. 1. The "CF gut": A functional CFTR channel results in a decrease in cellular pH (pH_i) and volume, depolarizes the apical membrane, and increases luminal fluidity and alkalinity. These events curb the activity of the salt absorptive transporters NHE3 and ENaC. A defective CFTR channel results in a dehydrated, acidic and viscous ("sticky") mucus layer, which dilates the cryptal openings and harbours a dysbiotic microbiome. A proinflammmatory phenotype, epithelial hyperproliferation, intestinal obstructive episodes and an increased rate of intestinal malignancies are among the clinical sequelaue of the CF gut.

as well as the agonist-induced increase in HCO_3^- output in the colon [37,38].

7. CFTR-dependent and independent improvement of gut fluidity and alkalinity in the CF gut

Recent clinical investigations suggest that CFTR-targeted therapy is able to improve small intestinal alkalinity [39] as well as improve gut health [40], but this issue is controversial [41]. In addition, this extremely expensive therapy is not available to all patients with CF, and not all CFTR mutations are amenable to rescue. Early work demonstrated that the additional embryonic deletion of NHE3 increased survival in CFTR-null pups, which usually die from intestinal obstructions during the weaning period [42]. The application of FDA-approved drugs that inhibit NHE3 (and stimulate CFTR, if present) to luminally perfused intestinal segments of anesthetized CFTR-null mice was indeed able to reduce fluid absorption and increase alkaline output in perfused segments of the small the large intestine, with the specific NHE3 inhibitor tenapanor being the best candidate for further study [43]. Fig. 2 presents a schematic diagram that explains the molecular mechanism how tenapanor application results in a CFTR-independent increase in luminal fluidity and alkalinity. An experimental trial in CFTR-null mice demonstrated that oral application of tenapanor, an intestinal selective NHE3 inhibitor, prevented intestinal obstructions, accelerated gastrointestinal transit time and improved gut health during the treatment course [44]. The data suggest that NHE3 inhibitors may soon offer safe and affordable adjunctive therapy in patients with CF to alleviate constipation and prevent recurrent distal intestinal obstructive syndrome (DIOS).

8. Physiology and pathology of CFTR in the kidney

Cystic fibrosis transmembrane conductance regulator (CFTR) is broadly expressed in most types of epithelial cells. Expression was also detected in proximal tubular epithelial cells of the kidney. Thus, a renal Cl^- secretory function of CFTR was hypothesized, despite the fact that renal tubules reabsorb but do not secrete NaCl [45,46]. Renal epithelial Cl^- secretion was based on experiments with cultured renal epithelial cells, which remarkably change their transport properties during cell culture, typically switching transport from reabsorption to secretion. Global renal parameters and electrolyte handling appeared normal in patients with CF, who do not present an obvious renal pathology. However, studies from the 1970s provided some evidence for enhanced renal Na^+ absorption, [47], while Bretscher and co-workers found an abnormal response of renal handling of sodium and bicarbonate upon application of the gastrointestinal hormone secretin [48].

Expression of CFTR in the proximal tubule was implicated in the regulation of protein reabsorption by receptor-mediated endocytosis. Dysfunctional CFTR was proposed to lead to reduced acidification of endosomes, thereby leading to low molecular weight proteinuria. Thus, endolysosomal acidification is not only based on CLC-5 chloride transporters [49,50], but is also supported by CFTR and by the Ca^{2+} activated Cl^- channel TMEM16A. Notably,

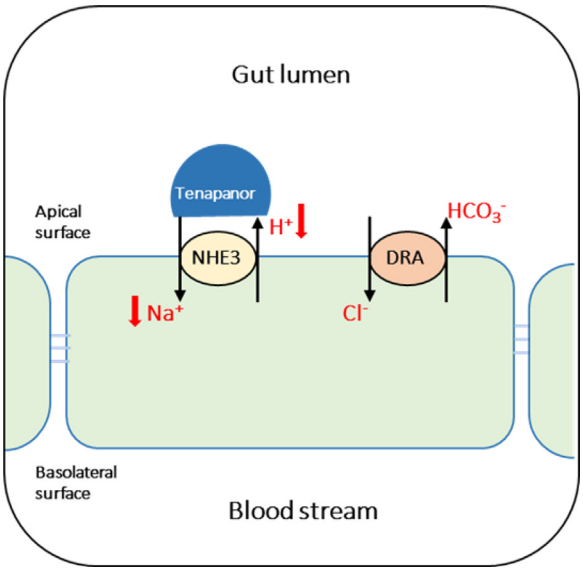

Fig. 2. The increase in intestinal luminal fluid content and alkaline output by tenapanor is explained by the inhibition of the apical Na^+/H^+ exchanger NHE3 (Slc9a3), resulting in decreased Na^+ and water absorption and decreased proton extrusion. The activity of the Cl^-/HCO_3^- exchanger DRA (Slc26a3) is functionally not tightly coupled to NHE3, and will continue to export base (albeit at a reduced rate).

TMEM16A knockout in mice also causes a lack of endosomal acidification and proteinuria [51].

Abnormal renal Na^+ handling observed in patients with CF [47,52] was confirmed later in mice, by showing enhanced fractional Na^+ absorption via the amiloride-sensitive epithelial sodium channel (ENaC) in F508del-CFTR mice under salt restriction [53]. This finding corresponded to earlier observations in cystic fibrosis airways, which demonstrated enhanced amiloride-sensitive Na^+ absorption in CF, possibly caused by defective regulation of ENaC through CFTR or imbalanced transport in secretory and reabsorptive directions [54]. Recent studies with improved antibodies show sparse expression of CFTR in the collecting duct of healthy kidneys, only in the apical membrane of so-called ß-intercalated cells. Because ENaC is expressed in principal cells, this excludes a direct regulation of ENaC by CFTR. Whether these mild transport abnormalities are related to the enhanced glomerular filtration observed in infants with CF, is currently not clear [55,56].

9. Reduced renal HCO_3^- secretion in cystic fibrosis

The early finding of Bretscher et al. indicating abnormal renal response to application of secretin [48] was confirmed in subsequent studies [57]. Renal HCO_3^- excretion was found to be reduced in people with CF [33,58]. A detailed analysis in mice with knockout of CFTR or knockout of the HCO_3^- transporter SLC26A4 (pendrin) demonstrated the underlying mechanisms: CFTR serves as a Cl^- recycling channel that drives urinary HCO_3^-excretion by SLC26A4 in ß-intercalated cells of the renal collecting duct [58,59]. In addition, HCO_3^- may be excreted into the urine directly through CFTR channels. Because CFTR is not functional in cystic fibrosis, HCO_3^- is not adequately excreted when plasma HCO_3^- or secretin levels increase. This leads to metabolic alkalosis, which is occasionally observed in patients with CF. Excitingly, Berg et al. developed a simple drinking test to assess the function of CFTR in vivo, which was used to detect efficacy of CFTR-correctors in patients with CF [58]. Because in ß-intercalated cells CFTR is coexpressed with the Ca^{2+} activated Cl^- channel TMEM16, which was shown to be required for CFTR to operate properly, one may speculate that volunteers currently treated in a phase one clinical trial with the TMEM16A-activator ETD002 may present enhanced urinary HCO_3^- excretion. As defective renal HCO_3^- excretion can lead to alkalosis in patients with CF [59,60], it may even lead to suppressed alveolar ventilation [61]. This could be a factor contributing to CF lung disease. In fact, Berg et al. convincingly demonstrated alkalosis-induced hypoventilation by loss of CFTR function in mice [62]. Thus, metabolic alkalosis may contribute to reduced lung function in CF, via a suppression of ventilatory drive.

10. CFTR and polycystic kidney disease

CFTR was also proposed to play a major role in autosomal polycystic kidney disease (ADPKD) [63]. In contrast, we recently identified TMEM16A as the essential Cl^- channel in ADPKD [64]. While CFTR was not required for cyst formation in mice, knockout or inhibition of TMEM16A almost abolished cysts growth in ADPKD in vivo [65]. Overall, loss of CFTR function in people with cystic fibrosis only slightly compromises renal function, but can lead to clinical symptoms depending on drug intake, nutritional status, or dehydration. However, a potential unrecognized life-long suppression of ventilation could contribute to CF lung disease and should be taken into consideration.

11. Compromised renal function in CF outside ion transport

Additional renal cellular dysregulations were found in CF kidneys. As mentioned above, patients with CF may develop a proteinuria, which is due to defective proximal tubular endocytosis [66]. Moreover, an analysis of urinary exosomal proteins suggested that CF kidneys adapt to the CFTR defect by upregulation of proteasome activity and impaired autophagy and endosomal targeting [67].

12. Summary

This minireview demonstrates that either genetic or functional damage to CFTR can cause serious disease outside the lungs. The review also points out novel treatment strategies. CFTR potentiators and/or modulators may be of therapeutic benefit in treating pancreatic diseases not only for genetic mutations but also for toxin-induced impairment. CF intestinal disease may be ameliorated not only by CFTR targeted therapy, but also by decreasing luminal fluid absorption and proton secretion via NHE3 inhibition. Renal CFTR dysfunction may result in metabolic alkalosis and reduced ventilatory drive. Alternative anion channel activation may enhance urinary HCO_3^- secretion.

Declaration of Competing Interest

Regarding the review: *CFTR-beyond the airways*, the authors confirm that they have nothing to disclose.

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