Molecular Mechanism of Pancreatic Bicarbonate Secretion

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Thanks to recent progress in understanding the basolateral membranes of polarized epithelial cells mediates the transepithelial HCO₃⁻ transport, which involves HCO₃⁻ absorption in the resting state and HCO₃⁻ secretion in the stimulated state. The overall process of HCO₃⁻ secretion can be divided into two steps. First, HCO₃⁻ in the blood enters the ductal epithelial cells across the basolateral membrane either by simple diffusion in the forms of CO₂ and H₂O or by the action of an Na⁺-coupled transporter, a Na⁺-HCO₃⁻ cotransporter (NBC) identified as pNBC1. Subsequently, the cells secrete HCO₃⁻ to the luminal space using at least two HCO₃⁻ exit mechanisms at the luminal membrane. One of the critical transporters needed for all forms of HCO₃⁻ secretion across the luminal membrane is the cystic fibrosis transmembrane conductance regulator (CFTR). In the resting state the pancreatic duct, and probably other HCO₃⁻ secretory epithelia, absorb HCO₃⁻. Interestingly, CFTR also control this mechanism. In this review, we discuss recent progress in understanding epithelial HCO₃⁻ transport, in particular the nature of the luminal transporters and their regulation by CFTR.

Key Words: Pancreas, Bicarbonate, CFTR, Transporter

INTRODUCTION

Pancreatic duct secretes bicarbonate-rich fluid, which is important in maintaining the patency of ductal tree, as well as intestinal digestive function. Pancreatic HCO₃⁻ protects the duodenal epithelia by neutralizing gastric acid and aids in maintaining an optimal pH for the function of digestive enzymes (Argent & Case, 1994). Accumulating evidence suggests that secretion of the HCO₃⁻-rich fluid is also important in protecting the intrapancreatic ductal tree. Transepithelial Cl⁻ and HCO₃⁻ transport are the principal driving force for fluid secretion by ductal cells and reduced HCO₃⁻ concentration results in acidification of the luminal environment. The rheologic properties of mucins are affected by mucin concentration and the pH of the solvent. In general, mucin precipitation and viscosity progressively increase as the pH and volume of the secreted fluid decrease. Indeed, the most prominent change in the composition of the pancreatic juice of obstructive ductal diseases, such as cystic fibrosis (CF) or chronic pancreatitis, is a reduction in HCO₃⁻ concentration of the secreted fluid (Choi et al., 2001).

Recent technical advances, such as the use of microperfused ducts, molecular identification of transporters and the availability of genetically modified mice, permitted close examination of the basic cellular processes responsible for the formation and secretion of a HCO₃⁻-rich fluid by epithelial cells such as those of the pancreatic duct. In this review, after a brief introduction of current concepts on the basic molecular mechanisms of pancreatic bicarbonate secretion, we will focus on recent progress made in understanding the luminal HCO₃⁻ transport mechanisms, with an emphasis on the role of cystic fibrosis transmembrane conductance regulator (CFTR) in this processes and their pathophysiological implications.

The overall HCO₃⁻ secretory process

The coordinated action of various transporters in the luminal and basolateral membranes of polarized epithelial cells mediates transepithelial HCO₃⁻ transport. The overall HCO₃⁻ secretory process can be divided into two steps (Fig. 1). The first step encompasses the entry of blood c into pancreatic duct cells across the basolateral membrane. Early studies suggested that most of the bicarbonate is generated in the duct by carbonic anhydrase (CA). As depicted in Fig. 1, CA hydrates the diffused CO₂ to form the volatile carbonic acid, which dissociates to H⁺ and HCO₃⁻. To secrete HCO₃⁻ to the lumen, H⁺ generated in the cytosol must be disposed off by transport back to the blood. There is good molecular and functional evidence that

ABBREVIATIONS: CFTR, cystic fibrosis transmembrane conductance regulator; AE, Cl⁻/HCO₃⁻ exchanger; NHE, Na⁺-H⁺ exchanger; NBC, Na⁺, HCO₃⁻ cotransporter; CA, carbonic anhydrase.
an electrogenic H⁺-ATPase pump and a Na⁺/H⁺ exchanger (NHE) are expressed in basolateral membrane. However, their role in bicarbonate secretion is fully agreed upon. Several studies reported that inhibitors of the H⁺-ATPase and NHE reduced pancreatic HCO₃⁻ secretion, while others reported no effects of these compounds. Indeed, a recent computer modeling suggested that H⁺-ATPase and basolateral NHE are responsible for only 4% and 15% of H⁺ back leak (or HCO₃⁻ influx) during agonist-stimulated secretion, respectively (Sohma et al., 2000).

More direct results obtained by microperfusion of the rat pancreatic duct (Zhao et al., 1994), and later confirmed in the guinea pig pancreatic duct as well (Ishiguro et al., 1998), indicate that most of HCO₃⁻ transport across basolateral membrane during active HCO₃⁻ secretion is achieved by a Na⁺-coupled HCO₃⁻ transporter, which mediates a Na⁺→HCO₃⁻ cotransport (NBC). Basolateral application of the NBC inhibitor, DIDS, inhibits 50% of HCO₃⁻ secretion, while inhibitor of NHE inhibits only 18% of the secretion. Subsequently the pancreatic isoform of the electrogenic family of NBCs, pNBC, was cloned and localized in the basolateral membrane of pancreatic (Abuladze et al., 1998) and salivary gland acinar and duct cells (Luo et al., 2001). In the computer model, pNBC can mediate as much as 80% of HCO₃⁻ influx during active HCO₃⁻ secretion (Sohma et al., 2000). The stoichiometry of pNBC was estimated as 1 Na⁺→2 HCO₃⁻. Since it is electrogenic, depolarization induced by cAMP-dependent activation of CFTR (see below) facilitates HCO₃⁻ influx through pNBC.

In the luminal membrane, CFTR and Cl⁻/HCO₃⁻ exchange activity (AE: anion exchange) are likely the main transporters mediating the luminal exit of HCO₃⁻. Increase in intracellular cAMP by secretin and VIP (vasoactive intestinal polypeptide), is the major signal for stimulation of pancreatic HCO₃⁻ secretion. Activation of CFTR Cl⁻ channel by the increase in cellular cAMP and a concurrent AE activity are responsible for the cAMP-induced HCO₃⁻ secretion. Under optimal conditions and HCO₃⁻-dependent inhibition of AE activity, this model can explain fluid secretion containing up to 70–120 mM. However, in some species, such as human and guinea pig, pancreatic HCO₃⁻ concentration reaches 140 mM. Therefore, it is conceivable that other electrogenic luminal HCO₃⁻ exit mechanism, such as HCO₃⁻ channel, are expressed and participate in HCO₃⁻ efflux across the luminal membrane. Indeed, it was shown that cAMP increases an electrogenic HCO₃⁻ permeability in the luminal membrane of guinea pig pancreas, albeit the molecular identity of which is unknown (Ishiguro et al., 1998).

Also unknown with certainty are the nature of the luminal AE. However, recently, we reported that the activity of luminal AE is dependent on the expression and activation of CFTR (Lee et al., 1999a; 1999b). Considering the fact that disruption of CFTR causes obstructive ductal diseases such as cystic fibrosis (CF) or chronic pancreatitis, this finding may have implications to the pathophysiological mechanism for such diseases. The original observation of luminal NHE activity in the luminal membrane of the duct (Zhao et al., 1994) appeared problematic. A priori, this activity appeared to be counter-productive to the main function of the duct. However, subsequent work confirmed these observations and extended them to show that in addition to HCO₃⁻ secretory mechanisms, the pancreatic duct and other HCO₃⁻ secretory cells express HCO₃⁻ absorbing mechanisms such as NBC3 (Lee et al., 2000) and the electroneutral NBCs (Luo et al., 2001). Interestingly, the HCO₃⁻ secreting AE activity and the HCO₃⁻ absorbing NBC3 are closely associated with CFTR to coordinate the entire HCO₃⁻ transport in the luminal membrane (Ahn et al., 2001). Below, we will discuss these findings and their potential pathophysiological consequences.

**Activation of Cl⁻/HCO₃⁻ exchange by CFTR**

Pancreatic HCO₃⁻ secretion is impaired in patients with cystic fibrosis or chronic pancreatitis due to mutations in the CFTR gene. Since the major mechanism of HCO₃⁻ secretion in CFTR-expressing cells is mediated by the action of a Cl⁻/HCO₃⁻ exchanger (AE), the possible regulation of AE activity by CFTR was examined.

In the first set of experiments, we studied regulation of AE activity by CFTR in a heterologous expression system (Lee et al., 1999a). We used stably transfected NIH 3T3 cells that express high levels of the CFTR protein. Mock-transfected cells of the same parental line were used as controls. A standard protocol of removal and addition of Cl⁻ to the incubation medium buffered with HCO₃⁻ was used to follow Cl⁻/HCO₃⁻ exchange activity. Fig. 2 illustrates the basic observation in which CFTR expressing cells exhibited a forskolin stimulated AE activity. Removal of Cl⁻ from the incubation medium of mock-transfected cells resulted in a slow and modest increase in pH, which was completely reversed on addition of Cl⁻ to the medium. Stimulation of control cells with 5 μM forskolin had no effect on basal level of pH, or the pH changes observed upon removal and re-addition of Cl⁻. Stimulation of CFTR expressing 3T3 cells with forskolin caused a time-dependent intracellular acidification that was complete after 3 min of incubation at 37°C. The nature of this acidification is not known. However, it was clearly dependent on the expression of CFTR and was markedly reduced or abolished by depo-
larizing the cells with high bath K⁺, suggesting that it might reflect conductive HCO₃⁻ transport by CFTR. Most notably, removal of Cl⁻ from the incubation medium of forskolin-stimulated, CFTR expressing cells caused a rapid and a large increase in pHᵢ that was reversed upon re-addition of Cl⁻ to the medium. After forskolin stimulation, the rate of pHᵢ change due to the changes in transcellular Cl⁻ gradient in CFTR expressing cells was 8 fold faster than that of the same cells before forskolin stimu-

Fig. 2. CFTR activates Cl⁻/HCO₃⁻ exchange activity in NIH 3T3 cells stably expressing CFTR. Cl⁻/HCO₃⁻ exchange activity was estimated from the ratio of changes in pHᵢ. Note that stimulation of CFTR with forskolin was needed to activate AE activity (adopted with permission from Lee et al., 1999a).

![Digital image of Figure 2 showing Cl⁻/HCO₃⁻ exchange activity in NIH 3T3 cells transfected with CFTR.](image-url)

![Digital image of Figure 3 showing changes in AE activity with forskolin stimulation and DIDS treatment.](image-url)

Fig. 3. CFTR stimulates the luminal but not the basolateral AE activity in the perfused pancreatic ducts. The main pancreatic ducts of WT (a, b) and ΔF/ΔF (c) mice were used to evaluate Cl⁻/HCO₃⁻ exchange activity. Note that stimulation of CFTR activated luminal Cl⁻/HCO₃⁻ exchange activity only in ducts from WT mice (adopted with permission from Lee et al., 1999b).
nings led to the conclusion that CFTR activates Cl⁻/HCO₃⁻
exchange activity in HCO₃⁻ secretory epithelia.

The importance of the CFTR-stimulated, Cl⁻-dependent
HCO₃⁻ transport to the function of secretory epithelia and
CF was revealed by comparing effects of mutations in CFTR
associated with CF on Cl⁻ channel activity and HCO₃⁻
transport. CFTR is a cAMP-regulated Cl⁻ channel and
most CF-causing mutations in CFTR inhibit Cl⁻ channel
activity. However, identification of several CF-causing mu-
tants with substantial or normal Cl⁻ channel activity
indicates that other CFTR-dependent processes contribute
to manifestation of the disease. Therefore, it was of interest
to examine Cl⁻-coupled HCO₃⁻ transport by CF-associated
CFTR mutants that retain substantial or normal Cl⁻
channel activity. In general, all mutations in CFTR inhib-
ited Cl⁻-dependent HCO₃⁻ transport more than Cl⁻ channel
activity, supporting the notion that CFTR mediate two
separate activities. Furthermore, although the correlation
was not perfect, the trend found was that mutations in
CFTR reported to cause CF with severe clinical presenta-
tions did not support HCO₃⁻ transport and those with
mild clinical presentations showed reduced HCO₃⁻ trans-
port (Choi et al., 2001). Fig. 4 shows the correlation be-
 tween the reported pancreatic status of the patients and the HCO₃⁻ /
Cl⁻ transport ratio. When the ratio measured with CFTR
is taken as 1, mutants that cause a severe form of CF show
an HCO₃⁻ /Cl⁻ transport ratio of less than 0.1. By compari-
son, most mutations that cause a mild form of CF showed
an HCO₃⁻ /Cl⁻ transport ratio between 0.31–0.46. Conse-
quently, the CFTR-dependent HCO₃⁻ /Cl⁻ transport ratio
appears to correlate reasonably well with the reported pan-
creatic status of CF patients. It is important to note that
altered HCO₃⁻ transport show particular correlation with
pancreatic function since the pancreas secret copious
amount of HCO₃⁻ (Argent & Case, 1994). The same may
not hold for other tissues, for example the sweat gland,
since fluid secreted by the sweat gland contains less HCO₃⁻
than the systemic HCO₃⁻ concentration. The aberrant HCO₃⁻
transport by the CF-causing mutations examined indicates
that HCO₃⁻ transport by CFTR-expressing epithia is
critical for normal tissue physiology and that impaired
HCO₃⁻ transport is sufficient to derange the pancreatic
function even in the presence of Cl⁻ channel activity.

A search for the mechanism in the luminal membrane
that mediate the AE activity revealed that secretory
epithelia do not express members of the classical AE family
SLC4. On the other hand colonocytes (Silberg et al., 1995),
the renal proximal tubule (Knauf et al., 2001) and the
auditory epithelia (Everett et al., 1997) and β-intercalated
cells (Royaux et al., 2001) express members of the newly
discovered family of Cl⁻/HCO₃⁻ exchangers of SLC26.
Based on this finding it was logical to test the effect of
CFTR on the activity of these Cl⁻/HCO₃⁻ exchangers. Pre-
liminary work showed that CFTR markedly activate Cl⁻/
HCO₃⁻ exchange by all members of the SLC26 tested (Ko
et al., 2002). Confirmation of these findings and revealing
the mechanism by which CFTR activates the SLC26
exchangers will undoubtedly clarify the mechanism by
which CFTR regulate the electroneutral portion of HCO₃⁻
secretion of secretory epithelia.

![Fig. 4. The HCO₃⁻ /Cl⁻ transport ratio of CFTR mutants associated with CF. The HCO₃⁻ /Cl⁻
transport ratios were calculated from the rates of net Cl⁻ and HCO₃⁻ transport. The ratio
measured in WT CFTR was set to 1. The inset schematically illustrates the different cytoplasmic
domains of CFTR. CL1, Cytoplasmic Loop 1; CL2, Cytoplasmic Loop 2; NBD1, Nucleotide Binding
Domain 1; RD, Regulatory Domain; CL3, Cytoplasmic Loop 3; CL4, Cytoplasmic Loop 4; NBD2,
Nucleotide Binding Domain 2 (adopted from Choi et al., 2001 with permission from Nature
publishing group).]
Regulatory HCO₃⁻ absorption by luminal mechanisms

An interesting feature of HCO₃⁻ transport in HCO₃⁻-secreting epithelium is the existence of regulatory HCO₃⁻ absorptive pathways in the luminal membrane. Prominent among them is a Na⁺/H⁺ exchange activity. Na⁺/H⁺ exchange activity is mediated by members of the NHE family of Na⁺/H⁺ exchangers. To date, 7 Na⁺/H⁺ exchangers have been identified, which are mostly expressed in the plasma membrane, with several isoforms residing in intracellular organelles (Miyazaki et al. 2001). The best characterized NHEs are NHE1, NHE2, and NHE3. The housekeeping NHE1 is expressed virtually in all cells and is always in the basolateral membrane of epithelial cells. NHE2 and NHE3 are expressed in the luminal membrane of epithelial cells. In spite of its wide spread expression in the luminal membrane of epithelial cells, the role of NHE2 remain a mystery (Lee et al., 1998). Deletion of NHE2 had minimal a physiological phenotype (Schultheis et al., 1998). NHE3 is the exchanger mediating about 50% of Na⁺ and HCO₃⁻ absorption in the renal proximal tubule (Choi et al., 2000).

Originally, a paradoxical NHE activity was identified in the luminal membrane of the pancreatic duct (Zhao et al., 1994). Subsequently this activity was identified as mediated by NHE3 and a novel Na⁺-dependent H⁺/OH⁻/HCO₃⁻ transporter in the pancreatic (Lee et al., 2000) and submandibular ducts (Luo et al., 2001). The H⁺ efflux/HCO₃⁻ influx mechanisms were characterized in pancreatic ducts from wild type (WT), NHE2⁻/⁻ and NHE3⁻/⁻ mice. RT-PCR analysis in combination with immunolocalization showed that the pancreatic duct expresses NHE1 in the basolateral membrane and NHE2 and NHE3 in the luminal membrane. Measurement of Na⁺-dependent H⁺ efflux in the microperfused duct demonstrated a basolateral activity inhibited by 1.5 μM of the AE1 inhibitor HOE 694, consistent with expression of NHE1, and a luminal activity inhibited by 50 μM HOE 694, consistent with expression of NHE2. However, disruption of the NHE2 gene had no effect on luminal transport. By contrast, disruption of the NHE3 gene reduced luminal Na⁺-dependent H⁺ efflux by about 45%. Notably, the remaining luminal Na⁺-dependent H⁺ efflux was not inhibited in ducts from NHE2⁻/⁻; NHE3⁻/⁻ double knockout mice (Choi et al., 2000; Lee et al., 2000). Therefore, nearly 55% of luminal H⁺ efflux in the pancreatic duct is mediated by a novel, HOE 694 (or amiloride)-sensitive, Na⁺-dependent mechanism. H⁺ transport by the two luminal mechanisms is inhibited by cAMP stimulation, albeit to a different extent.

A potential mediator of the novel Na⁺-dependent H⁺ efflux mechanism is one or a combination of splice variants of the electroneutral NBCs, NBCn1A-NBCn1D (Choi et al., 2000). PR-RT-PCR analysis and immunolocalization showed that the submandibular gland (Luo et al., 2001) and pancreatic (MGL and SM, unpublished observations) ducts express at least one NBCn1 splice variant in the luminal membrane. Furthermore, experiments in microperfused ducts revealed an activity with properties resembling those of NBCn1 was found in the luminal membrane of the duct. However, it remained to be determined whether any NBCn1 splice variant can account for this activity and whether regulation of the activity by elevation of cAMP (Luo et al., 2001) is mediated by CFTR.

Another aspect of the interaction between CFTR and the H⁺/OH⁻/HCO₃⁻ transporters is the possibility of reciprocal regulation of their activity. As will be discussed below, CFTR and the HCO₃⁻ transporters exist in the same HCO₃⁻-transporting complex. The complex is assembled with the aid of scaffolding proteins. The scaffolding proteins are not inert. They actually affect the activity of CFTR. Thus, modification of CFTR by binding to the two PDZ binding domains of EBPS0 (Raghuram et al., 2001) of PDZK (Wang et al., 2000) increase channel activity. This raises the possibility that interaction of CFTR and one of the HCO₃⁻

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Fig. 5. The role of luminal Na⁺-dependent H⁺ efflux mechanisms in pancreatic ductal HCO₃⁻ transport. A) The resting pancreatic duct maintains a transepithelial voltage of -5 mV, lumen negative and has a leaky tight junction. Hence, Na⁺ flows from the interstitium to the luminal space. The luminal Na⁺-dependent H⁺ efflux mechanisms absorb the Na⁺ in exchange for H⁺ (or in coupling with HCO₃⁻ influx). H⁺ efflux is equivalent to HCO₃⁻ re-absorption. HCO₃⁻ can originate in luminal Cl⁻/HCO₃⁻ exchange activity of the resting duct (apical mode), or present in the fluid secreted by acinar cells. B) Upon feeding, the gastrointestinal hormone secretin is released from neuroendocrine intestinal cells and stimulates pancreatic secretion by increasing intracellular cAMP in duct cells. The luminal Na⁺-dependent H⁺ efflux mechanisms are down regulated to reduce Na⁺/HCO₃⁻ re-absorption (adapted from Lee et al., 2000 with permission).
transporters will disrupt/minimize multimerization of CFTR to reduce channel activity. This possibility was examined recently. As expected, the expression of rat NHE3 significantly decreased PKA-dependent activation of CFTR without altering CFTR expression and the decrease in activity was prevented by mutation of either of the two NHE3 PKA targets (Bagorda et al, 2002). Based on the findings summarized above, it is possible to propose that multiple Na⁺-dependent H⁺ efflux mechanisms in the luminal membrane of the pancreatic and submandibular gland ducts and likely other epithelia absorb Na⁺ and HCO₃⁻ to produce a HCO₃⁻-poor and Cl⁻-rich fluid during basal secretion. Inhibition of the transporters during active pancreatic or salivary secretion aids in producing the HCO₃⁻-rich and Cl⁻-poor fluid.

**HCO₃⁻ transport complexes**

As stated above, the pancreatic and submandibular gland ducts express CFTR-dependent HCO₃⁻ secretory and an NHE3-mediated HCO₃⁻ absorptive mechanism in the luminal membrane. Regulatory interaction between all transporters is possible, since CFTR and NHE3 interact with cellular scaffolding proteins such as EBP50 (NHERF1) and E3KARP (NHERF2). This possibility was tested directly by molecular, biochemical and functional approaches in heterogeneous expression systems and in the native pancreatic duct. When present in the same membrane, CFTR regulates NHE3 activity by both acute and chronic mechanisms. In the pancreatic duct, CFTR affected expression of NHE3 in the luminal membrane. Thus, luminal NHE3 was reduced by 53% in ducts of F508 mice. CFTR and NHE3 were co-immunoprecipitated from PS120 cells expressing both proteins and the pancreatic duct of wild type mice, but not from PS120 cells lacking CFTR or the pancreas of DF508 mice. The interaction between CFTR and NHE3 required the COOH-terminal PDZ binding motif of CFTR. Mutant CFTR constructs lacking the C-terminus were not co-immunoprecipitated with NHE3. Furthermore, when expressed in PS120 cells, wild type CFTR, but not CFTR mutants lacking the C-terminal PDZ binding motif, augmented cAMP-dependent inhibition of NHE3 activity by 31% (Fig. 6).

These findings provide initial evidence for the existence of a HCO₃⁻ transport regulatory complex with CFTR in its center. By analogy with assembly of the PSD-95 (Kim et al, 1995), it is likely that such a complex is assembled with the aid of several scaffolding proteins. Indeed, the complex contains at least two scaffolding proteins, an EBP50 like and at least one AKAP. All known AKAPs have multiple protein-protein interacting domain and function as scaffolding proteins (Michel & Scott, 2002). In the complex a coordinated regulation of HCO₃⁻ secretion is mediated by interaction of CFTR with several HCO₃⁻ transporters as was found for the CFTR-NHE3 protein complex. In this respect, it is of particular interest that many of the G protein-coupled receptors and transporters related to HCO₃⁻ secretion in secretory epithelial cells have a PDZ-binding motif on their C-terminus (Fig. 7). In addition, most of them are associated with cAMP-dependent processes. As noted above, not only CFTR regulates the activity of the HCO₃⁻ transporters, but also binding of the transporters can regulate the activity of CFTR. Therefore, precise understanding of protein interactions between members of the HCO₃⁻ transport complex in the future will contribute to elucidate the overall regulatory mechanism of epithelial HCO₃⁻ transport.

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**Fig. 6.** The PDZ binding motif in the C-terminus of CFTR is required for formation of CFTR-NHE3 complexes and regulation of NHE3 activity by CFTR. WT and mutant CFTR were expressed in cells stably expressing NHE3 to demonstrate that cAMP-dependent stimulation of CFTR inhibits NHE3 activity and the role of the PDZ binding motif in this function of CFTR (adopted from Ahn et al, 2001 with permission).
Concluding remarks

Acidic fluid secretion due to a defect in epithelial HCO₃⁻ transport could lead to precipitation of mucin and plugging of ductal system and facilitate bacterial infection via binding to the precipitated mucin. In the special case of the pancreas, acidic pH would lead to premature activation of digestive enzymes, destruction of the pancreas and pancreatic insufficiency. Thus, aberrant HCO₃⁻ transport can account for the diverse pathological states observed in the obstructive diseases of ductal system such as CF, bronchiectasis and chronic pancreatitis. Recent findings suggest that enhancing HCO₃⁻ transport by epithelial cells or increasing the HCO₃⁻ content on the apical surface of affected tissues might be considered as additional means of ameliorating the debilitating effects of these diseases.

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