CONCISE TRANSLATIONAL REVIEW

Cystic Fibrosis Transmembrane Conductance Regulator: Roles in Chronic Obstructive Pulmonary Disease

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Abstract

Chronic obstructive pulmonary disease (COPD) manifests with a variety of clinical presentations, reflecting its complex pathology. Currently, care focuses on symptom amelioration and prevention of complications and thus is generally tailored to disease severity rather than targeting specific pathophysiologic mechanisms. Chronic inflammation and mucus hypersecretion are key features of COPD. Epithelial ion channel dysfunction may be important, as it results in airway dehydration and defective host defense, contributing to chronic airway inflammation. Recent evidence suggests considerable similarities between COPD and cystic fibrosis (CF), a disease in which chloride ion channel dysfunction has been extensively studied (in particular CFTR [CF transmembrane conductance regulator]). Understanding commonalities between CF and COPD, and the role of CFTR in CF, may help in designing strategies targeting ion channel dysfunction and lead to new treatments with potential to alter the natural history of disease progression. Here, we review the roles of airway mucus and CFTR in normal lung function, the previously underestimated contribution of mucus stasis to the development of COPD, and the evidence for targeting CFTR to counteract mucus accumulation.

Keywords: COPD; CFTR; calcium-activated chloride channel; mucus stasis; chronic bronchitis

Chronic obstructive pulmonary disease (COPD) is the third most common cause of death worldwide, with an estimated 3.23 million deaths in 2019 (1). COPD largely results from a chronic inflammatory response to environmental irritants, for example, noxious particles or gases, and is characterized by progressive lung function decline and airflow limitation (2). It is clinically and pathophysiologically distinct from other obstructive lung diseases such as asthma, bronchiectasis, and cystic fibrosis (CF) but shares common features, notably mucus hypersecretion and accumulation, precipitating chronic infection, whether overt or subclinical (3).

It is generally agreed that the airflow obstruction characteristic of COPD results from a combination of chronic bronchitis (inflammation of the bronchi and bronchioles, with mucus hypersecretion and impaired clearance), emphysema (destruction of the alveoli and airway collapse), and loss and narrowing of the small airway (4) (Figure 1). It is becoming clear that mucus is associated with luminal occlusion (mucus plugging) and airflow limitation. Mucus hypersecretion is a driver of the accelerated decline in FEV_1, which is characteristic of COPD, leading to a poor quality of life, increased exacerbations, and increased risk for death (5–8). Normal mucus viscoelasticity is maintained by a balance of water, solutes, and ions achieved through the coordinated action of ion channels, and the loss of this balance may

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play an important role in COPD pathophysiology by augmenting mucus stasis (9, 10). Dysfunction of ion channels, in particular CFTR (CF transmembrane conductance regulator), plays several roles in COPD and may be a major contributing factor in inducing mucoobstructive lung disease (11, 12).

Currently, pharmacotherapies for COPD focus primarily on symptom treatment and exacerbation reduction (2, 13). Treatments regulating mucus accumulation are a particular unmet need, with largely nonpharmacological recommendations such as physical exercise, smoking cessation, and pulmonary rehabilitation being the only recourse, given that first-generation mucolytics were not sufficiently bioactive to meaningfully alter outcomes (14).

The aim of this review is to synthesize the evidence and explore a revised position on the importance of mucus and ion channels as research and treatment targets in COPD. We propose ion channels as an example of a potentially tractable approach to treating mucus-related COPD pathology with particular focus on CFTR and the CFTR dysfunction and mucus hypersecretion endotype, as knowledge of this channel in other disease areas provides a detailed view of its role in mucus accumulation.

COPD Heterogeneity and Etiology

For many years the symptoms of chronic bronchitis were believed to predict patients who would develop airflow obstruction. This position changed radically after the publication of an 8-year study of British postal workers, which found no association between chronic bronchitis and loss of lung function (15). This led many clinicians to discount the importance of chronic bronchitis, although they failed to consider the fact that COPD can vary greatly among individuals, resulting in a complex array of clinical phenotypes, including chronic bronchitis and emphysema (4, 16). Clinical features of these phenotypes overlap with specific symptoms presenting with different severity, creating a continuum as opposed to distinct disease states. COPD is often preceded by chronic bronchitis, but spirometrically defined airflow limitation may or may not develop in a given individual (17). Importantly, symptomatic chronic bronchitis can vary over time and does not necessarily relate to the presence of mucus hypersecretion affecting the small airways.

For individuals with spirometrically defined COPD, the presence of chronic bronchitis can alter the prognosis and presentation of the disease. Several studies have shown that COPD with chronic bronchitis is associated with worse symptoms, higher risk for exacerbation, and greater airway wall thickening (18–20). Thus, patients with COPD and chronic bronchitis were more than twice as likely to have severe airflow limitation and almost half as likely to have only mild airway obstruction as those without chronic bronchitis (20).

Several factors can contribute to the development of chronic bronchitis and COPD, and mucus accumulation symptoms are often the first signs of COPD development (21). Tobacco smoking is by far the most important causal risk factor and a major contributor to mucus accumulation and stasis (22, 23). Estimated incidence of chronic bronchitis in current smokers varies from 12.2% to 42% depending on the country, although it can occur in ∼4–22% of never-smokers (24, 25).

The population of patients with COPD is heterogeneous: some people produce more mucus than others (either as an intrinsic characteristic or in response to smoking), and some have productive sputum, which gives a clinical indication of chronic bronchitis (18). However, although some patients do not report chronic bronchitis or productive sputum, they may still experience excessive mucus production, mucus plugging, and obstruction of the small airways (18).

An analysis from the SPIROMICS (Subpopulations and Intermediate Outcomes in COPD Study) research group examining 2,000 participants demonstrated the emergence of chronic bronchitis in patients who do not meet the diagnostic criteria for COPD but experience characteristic COPD exacerbations even in the absence of airflow obstruction (17). Further analyses from a subgroup of this patient cohort showed that increased mucin concentrations were associated with higher Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage and exacerbations, and even among individuals without obstruction, chronic bronchitis symptoms were associated with increased mucin concentrations (10). An additional SPIROMICS analysis demonstrated that in 400 current and former smokers, including 299 with COPD, only 33% of those with high mucus plug scores had mucus symptoms (mucus plug was defined as complete occlusion of a bronchus); both emphysema and high mucus plug scores were independently associated with reduced lung function (26).

Mucus accumulation and chronic bronchitis phenotype follow a relapsing–remitting pattern throughout life, increasingly developing during middle age (21). This may be driven by changing environmental or behavioral factors such as changing smoking habits, intrinsic or genetic factors such as an increased sensitivity to cigarette smoke during middle age as a result of physiologic changes, or effects of underlying susceptibility to cigarette smoke starting to manifest after prolonged exposure (21). Periods of infection and recovery also contribute to this pattern; mucus is secreted following acute infection and remains increased for some time after recovery.

Normal Function of Mucus Secretion at the Respiratory Epithelium

Mucus is essential for normal airway health, with its primary purpose being to protect against inhaled particles and pathogens by trapping them in viscous gel, which is then expectorated. Protection from pathogens is facilitated by host defense proteins, inflammatory or immune cells, and other antibacterial compounds (27, 28). A semiaqueous film known as the airway surface liquid (ASL) coats the apical surface of the respiratory epithelium. It comprises two layers: on the surface, a viscous mucus layer containing mucins (large, heavily glycosylated proteins that form the gel structure of the mucus layer) secreted by goblet cells forms the interface with the airway lumen. Beneath this is a layer of gel-like liquid (periciliary liquid [PCL]) that bathes the cilia, its lower viscosity allowing them to move freely and beat to propel foreign particles out of the airways (27). The PCL also contains large, membrane-spanning mucins and mucopolysaccharides that are tethered to the cell membranes on the airway surface. These provide a mesh-like structure within the PCL that maintains separation from the mucus layer that lies on

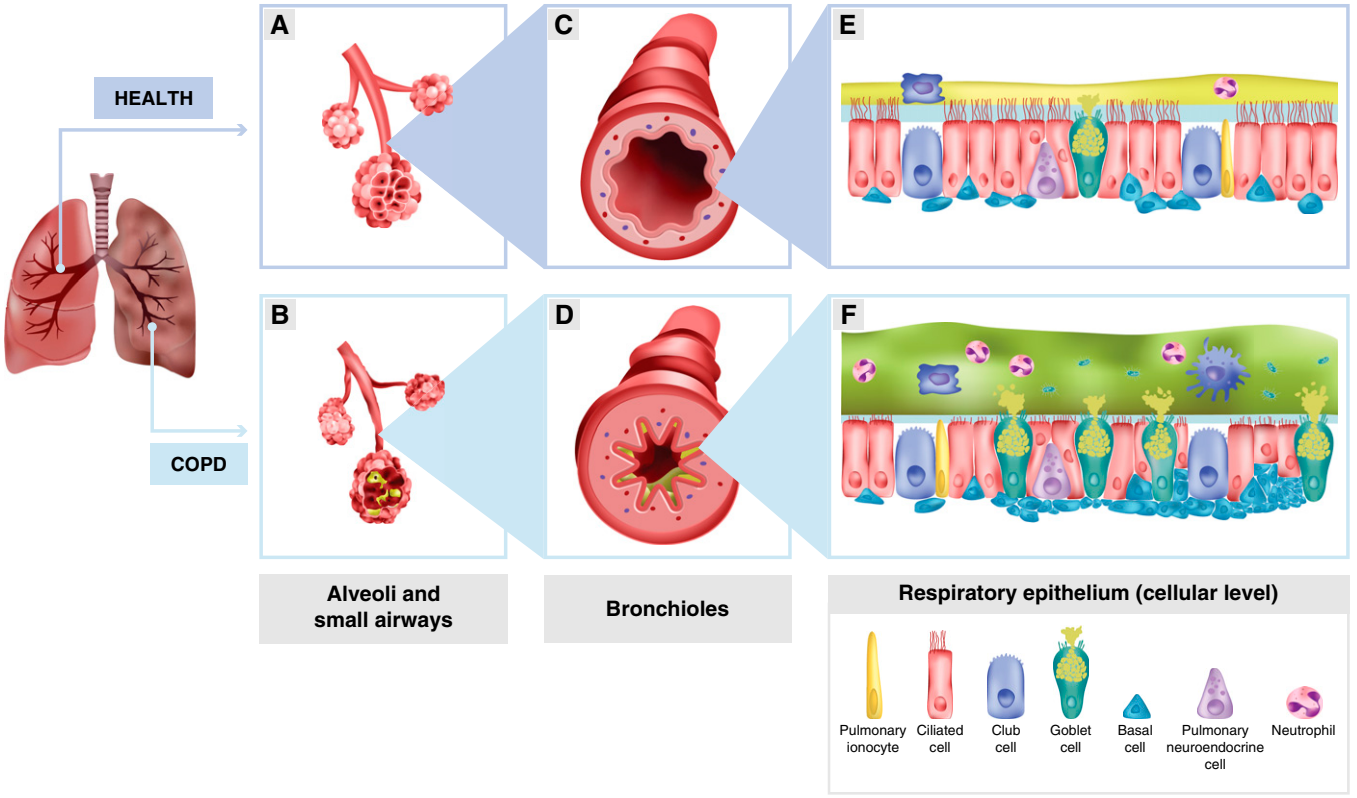

Figure 1. Pathological features of chronic obstructive pulmonary disease (COPD). An illustration of COPD pathology showing three levels of magnification. (*A* and *B*) Healthy alveoli, small airways, and alveolar sacs (*A*) differ from those in COPD (*B*). Predominant COPD pathological features include excessive mucus production, airway remodeling, and obstruction. (*C* and *D*) Healthy bronchioles (*C*) are clear and unobstructed, whereas in COPD or chronic bronchitis (*D*), a combination of airway wall thickening and excess mucus contributes to airway occlusion and "mucus plugging." (*E* and *F*) At the cellular level, compared with normal epithelium (*E*), the respiratory epithelium in COPD (*F*) has reduced airway surface liquid, thickened mucus layer, and epithelial remodeling, including goblet cell and basal cell hyperplasia and increased inflammatory immune response. Illustrations are not to scale.

top. Under normal conditions, the PCL is deep enough to just cover the cilia, enabling them to contact the mucus layer with their tips and move it along the respiratory tract as they beat (29). Thus, maintaining the composition and separation of the two layers is essential in healthy mucus clearance (29).

Mucus Composition

Healthy mucus is composed largely of secreted water (90–95%) (30). It contains sugars, proteins, lipids, and minerals, as well as mucins, which can generally be divided into two broad categories: membrane bound (tethered) and secreted (31). Tethered mucins not only contribute to maintaining the separation between the layers of the ASL (29) but also function as pathogen receptors and signal transduction mediators (32) and may have roles in maintaining the osmotic pressure of the PCL (29). Secreted mucins that form the mucus layer above the PCL are much larger than tethered mucins and form oligomeric complexes, creating a tangled, network-like formation that gives mucus its viscoelastic properties.

Mucins, ions, and water are secreted by goblet cells, serous cells, mucous glands, and ionocytes (enriched with membrane-bound ion channels) (27, 33, 34). Ion channels, including CFTR, ENaC (epithelial sodium channel), and others, maintain the required ion balance, serous cells secrete aqueous fluid devoid of mucus, and goblet cells control the secretion of mucins, together maintaining the correct pH, viscosity, and hydration of the mucus layers (9, 27). The regulated production of mucus requires coordinated ion and fluid secretion to allow its normal postsecretory maturation; in CF, this process is impaired in the absence of CFTR-mediated ion secretion (9).

Ion Movement at the Airway Surface

Various membrane-bound solute, water, and ion channels and transporters are located on the apical (airway surface) or on the basal epithelial cell membranes. Sodium (ENaC), chloride (CFTR, calcium-activated chloride channels, and chloride bicarbonate exchangers), and potassium ion channels are of particular importance in the homeostatic maintenance of airway mucosa (9).

CFTR, the best characterized of the airway ion channels, is a cAMP-activated Cl^- transporter that has a key function in maintaining and regulating airway surface hydration, mucus viscosity, and pH. Upon stimulation, CFTR actively transports Cl^- and HCO_3^- ions out of the cell, into the ASL on the apical cell surface. This active transport is coupled to the movement of Na^+ ions into the cells via ENaC. The movement of negatively charged ions out of the cell increases extracellular osmolarity, drawing water to the surface, while influx of Na^+ ions into the cell maintains intracellular osmolarity and drives water reabsorption into the cell to regulate the depth of the PCL

(27). These processes work in tandem to maintain the depth, composition, and pH of the ASL for optimal mucus transport fluid (35). The distribution of the cells and channels that drive secretion and absorption of water is not homogenous across the epithelium; the epithelial layer is organized into pleats and folds, which are specialized in secretion and absorption, respectively (36), allowing both processes to take place simultaneously (36).

COPD Pathophysiology and Mucus Accumulation

Consequences of Ion Transport Disruption

In both CF and chronic bronchitis, the delicate balance of mucus and water is shifted toward an excess of mucus because of airway surface dehydration resulting from ion channel dysfunction and reduced anion secretion through CFTR, goblet cell hyperplasia, and enhanced mucin production (37). Airway mucin concentration is higher in current and former smokers with COPD (10), although some evidence suggests that gene expression of particular mucins may decrease upon smoking cessation, suggesting that this effect may be at least partially reversible (38). Loss or shortening of cilia may also contribute to the collapse of the ASL and the impaired ability to remove foreign particles and pathogens from the surface (29). Elevated mucin concentrations can further contribute to PCL depletion through osmotic force as water is drawn from the PCL to the mucus layer, augmenting mucus stasis (29), particularly in chronic bronchitis (39). Mucus accumulation also leads to chronic bacterial colonization and neutrophilic inflammation (11, 12). In turn, this chronic inflammatory state results in goblet cell hyperplasia and excess mucus production (18), feeding a cycle of mucus accumulation, infection, and inflammation. Chronic inflammation is also associated with dysregulation of ion channel expression and function of the airway epithelium (40), leading to reduced mucus hydration, a crucial covariate of mucus viscoelasticity and transportability, as manifest by reduced ASL and PCL depth.

Deficient CFTR may also reduce pH of the airway surface because of reduced HCO_3^- secretion, affecting antibacterial host defense, as prominently demonstrated in the CF airway (41–44). ASL pH has an integral role in maintaining the host defense mechanism (30) and regulates expression of ENaC and CFTR (45). Antimicrobial peptides present in the ASL kill bacteria more effectively at normal physiologic pH than at lower pH (43, 44). Secreted HCO_3^- ions also have an intrinsic bacteriostatic effect, inhibiting colonization and biofilm formation (46), so impaired CFTR activity would also compromise this defense mechanism. Although changes to the microbiome because of reduced CFTR function in COPD have not specifically been investigated at the time of this publication, it is likely that changes to channel function will affect the bacterial community composition on the airway epithelia. Individuals with CF show an altered microbiome compared with healthy individuals, and there is some preliminary evidence that CFTR potentiators may restore the microenvironment to more closely resemble a healthy state and reduce populations of harmful pathogens, as summarized in a recent review (47). Changes to the microbiome have also been described in smokers with COPD compared with "healthy" smokers or nonsmokers. In patients with moderate and severe COPD, bacterial community diversity was lower than in patients with mild COPD or the other groups (48). As CFTR function is also impaired in "healthy" smokers (49), these differences in airway microbiome are likely to be multifactorial in cause, of which CFTR dysfunction is one of several mechanisms. Long-term antibiotic therapy can be effectively used as a prophylactic measure to reduce exacerbations in COPD (50). Azithromycin likely induces multiple changes within the lung, including alterations in the microbiome, reduction in inflammatory mediators, and inhibition of mucus hypersecretion, and possibly interacts with CFTR (51–53). Further human studies investigating the effect of antibiotics and the associated microbiome changes on CFTR function and mucus hypersecretion would be of value.

Consequences of Mucus Accumulation

The lung is constantly exposed to foreign particles and pathogens. Under normal circumstances, these are trapped in airway mucus to be eliminated by the cilia and expectorated. When mucociliary clearance is impaired, pathogens and foreign particles are not eliminated effectively, increasing the risk for infection and chronic inflammation (40). Chronic inflammation impairs cilia activity and ciliogenesis, closing the vicious circle (54). Lowered airway pH and reduced HCO_3^- also inhibit ciliary beating (55) and increase mucus viscosity in CF (30), and likely in COPD (56), leading to reduced mucociliary clearance and further contributing to the heightened risk for infection (57).

Mucus accumulation is considered a potential key contributor to irreversible disease progression as part of a complex set of pathological processes. These include epithelial metaplasia because of sustained inflammation, obstructed airflow, thickening of the small airways, and increased risk for infection and exacerbation (58, 59). Recent animal studies have shown that reduced CFTR activity also contributes to airway loss (60), and a study of more than 14,000 participants demonstrated a 3.5-fold increased risk for mortality from pulmonary infection in patients reporting mucus symptoms compared with those without (61). In the large airways, submucosal gland hypertrophy has also been observed (62).

Severity of airway obstruction is directly linked to mucus plugging. Mucus plugs in the lower large airways can lead to local hypoxia, necrosis, and airway loss (26), as well as dysregulated host defense response against pathogens (37), which can in turn contribute further to ion channel dysfunction (63, 64). Mucus hypersecretion also leads to small airway inflammation, remodeling, and thickening of airway walls and ultimately earlier death (7, 18). The longer the duration of mucus accumulation, the greater the decline in lung function (21, 65), which may contribute to emphysema phenotype with small airway loss. The SPIROMICS investigative group has also demonstrated that increased MUC5AC concentration in induced sputum, as opposed to MUC5B, is associated with small airway disease on computed tomography, exacerbation burden, and FEV_1 decline (66).

CFTR Dysfunction

CFTR is best known for its role in CF, in which genetic mutations cause its dysfunction, leading to impaired Cl^-

transport, airway dehydration, and disrupted host defense, resulting in severely impaired mucociliary clearance and airway obstruction (11). A mounting body of evidence suggests that acquired CFTR dysfunction is an important driver of COPD pathophysiology (11, 12, 67). CFTR dysfunction is associated with chronic bronchitis and computed tomography–determined bronchiectasis in several independent COPD cohorts (68), suggesting a potential target endotype that links to mucus hypersecretion (12). Two recent studies have shown links between CFTR mutations and chronic bronchitis (69, 70). Decrements in CFTR function have been observed in the upper airway, lower airway, colonic epithelium, and sweat duct, suggesting the pervasive nature of the defect in the individuals affected (12). Beyond epidemiological associations, *in vitro* and animal studies have confirmed the causal role of cigarette smoking (71–73). CFTR activity is reduced in smokers with COPD and more heterogeneously in smokers who have not developed COPD (49, 74). Although the reduction is variable across individuals, a study using sweat ion measurements as a functional measure of systemic CFTR activity showed a mean ~40% decrease in CFTR activity in smokers and former smokers with COPD and a mean ~25% decrease in "healthy" smokers compared with healthy control subjects (49). The same study demonstrated a 65% decrease in CFTR activity in smokers compared with nonsmokers using intestinal current measurements (49, 74). Overall, a substantive minority of individuals with COPD exhibit a degree of CFTR dysfunction that would be expected to diminish normal organ function.

Mechanisms of Reduced CFTR Function in COPD

There are several mechanisms by which CFTR activity is reduced or impaired in COPD. Both CFTR intrinsic functionality and expression at the cell surfaces of the airway lumen can be affected, contributing to reduced CFTR activity (Figure 2).

Decreased CFTR protein and mRNA expression. Recent evidence from *in vitro* and *in vivo* animal studies, as well as in primary human cell cultures, has shown that cigarette smoke exposure reduces CFTR mRNA expression (71, 75). Smokers with or without COPD have reduced CFTR activity in the nasal passage as measured by potential difference in the nasal cavity, which correlates with symptoms of bronchitis (71, 74, 75). Total CFTR protein and mRNA were decreased in lung samples from patients with GOLD stage 4 COPD compared with those with GOLD stage 0, and the decrement in CFTR correlated with the presence of heavy metals from cigarette smoke in the sample. *In vitro* data from the study revealed that cigarette smoke decreased CFTR expression by about 40–50% in primary human bronchial epithelial cells and that this effect

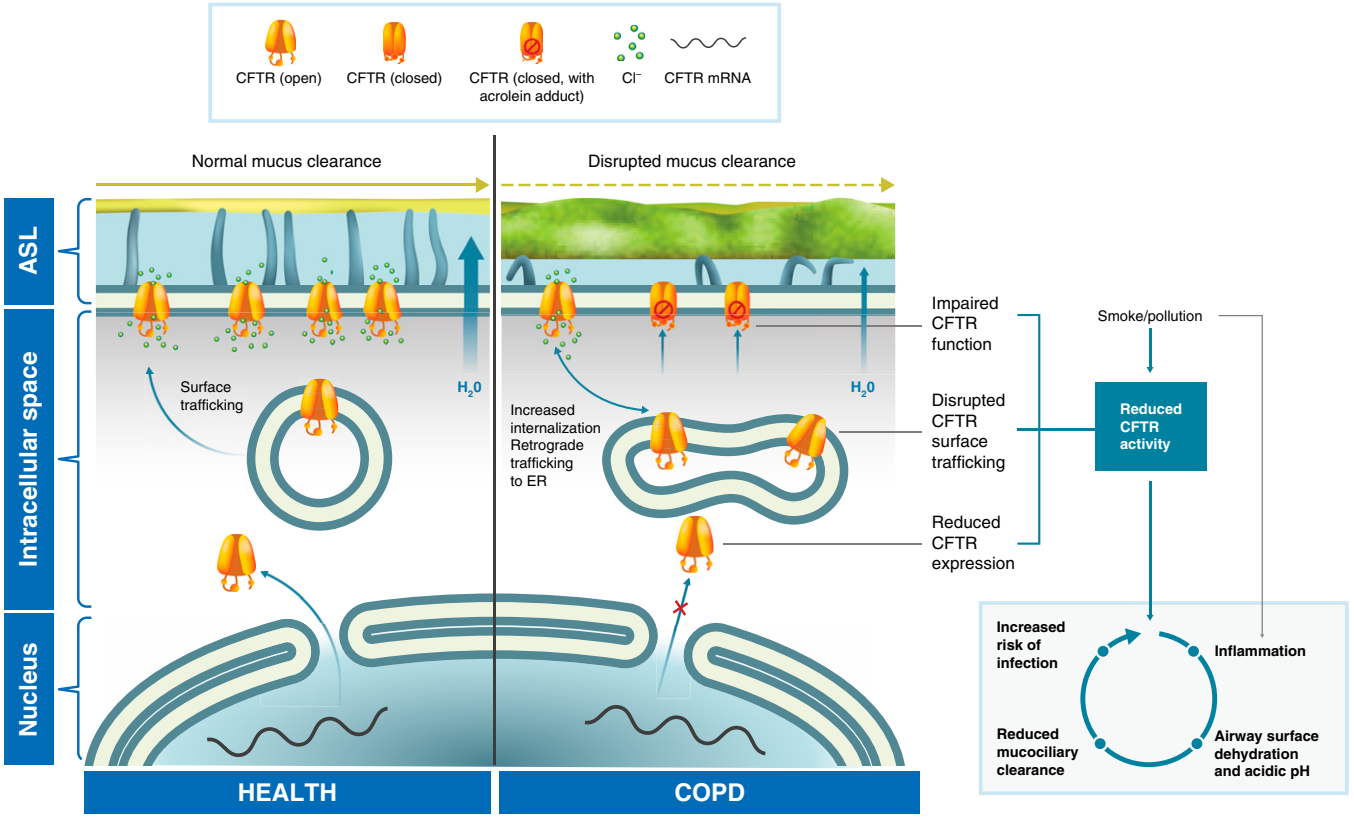

Figure 2. The CFTR (cystic fibrosis transmembrane conductance regulator) cycle of destruction. The impact of smoke and/or pollution on CFTR function includes disrupted CFTR surface trafficking, reduced surface expression of CFTR, and reduced expression of CFTR mRNA and protein. As downstream consequences of reduced CFTR function, impaired transport of chloride ion and water across the epithelial cell membrane contributes to the mucus accumulation phenotype (damaged cilia, viscous mucus, and disrupted mucociliary clearance) and leads to increased risk for infection and inflammation, along with surface dehydration and acidification. Sodium- and calcium-activated chloride channels also play a role, but for the sake of simplicity they are not included in this schematic. ASL = airway surface liquid; COPD = chronic obstructive pulmonary disease; ER = endoplasmic reticulum.

was dependent on the presence of heavy metals (76). The study also showed that cigarette exposure of primary human cells decreased CFTR protein to a greater extent than it did mRNA, suggesting that protein degradation or depletion may play a greater contributing role in inducing CFTR functional deficits than diminished transcription (76), particularly given that goblet cell hyperplasia may partially compensate for reduced CFTR transcripts, as CFTR exhibits greater expression in secretory as opposed to ciliated cells. Furthermore, *in vitro* work in human cell lines and *in vivo* animal experiments demonstrated that several airway hypoxia models (submerging, hypoxia-mimetic agents, ambient oxygen restriction) decreased CFTR mRNA and protein expression. As mucus plugging can induce a hypoxic state in the airways of patients with COPD or chronic bronchitis, it is likely that this also contributes to decreased CFTR expression and function in these patients, further feeding into the cycle of mucus overproduction and airway dehydration (64).

Cigarette smoke and air pollution stimulate a cholinergic reflex resulting in increased activation of CFTR through cAMP, initially conferring activation of protective mucus and fluid secretion; this protective effect wanes with prolonged exposure as CFTR expression is reduced (77).

CFTR degradation by protease activity. Increased neutrophil elastase activity is a component of the inflammatory response seen in chronic bronchitis, and *in vitro* and *in vivo* studies have demonstrated the ability of neutrophil elastase to degrade CFTR. Neutrophil activity can result from infection or mucus accumulation independent of infection (40, 78, 79). For example, elevated cytokine activity and hypoxia, both features of COPD pathology, can modulate neutrophil function by "priming," whereby neutrophils are more readily activated to deliver their protease cargo, increasing the potential for tissue destruction and CFTR protein degradation (80, 81).

Reduced CFTR cell surface expression. An *in vitro* study on primary human respiratory epithelial cells showed that chronic cigarette smoke exposure diminished CFTR surface expression (82) because of changes to intracellular trafficking. Further *in vitro* and *in vivo* studies have demonstrated that cigarette smoke exposure can lead to increased internalization of CFTR (71), Ca^{2+} release–induced inhibition (73), and dephosphorylation-related retrograde trafficking to the endoplasmic reticulum (83). Several studies correlate reduced CFTR function resulting from cigarette smoke exposure to reduced CFTR cell surface expression. An ∼25% reduction in total and surface CFTR protein in primary human bronchial epithelial cells was reported after 24-hour (but not 20-min) exposure to cigarette smoke extract, corroborating previous results showing a reduction in CFTR activity and loss of surface expression after prolonged exposure (75, 84). However, although surface expression changes took place over a longer period, an immediate decrease in CFTR activity was also observed. Alterations in open-channel probability were found to be the cause of reduced activity on an acute time scale (82).

Direct modifications to the CFTR channel. Raju and colleagues showed that short-term effects were likely attributable to direct covalent modifications to the channels themselves by acrolein, a highly reactive component of cigarette smoke (82). Other studies have shown that cigarette smoke exerts direct effects on the CFTR protein that alter channel function and reduce channel open probability, resulting in increased mucus viscosity and reducing mucociliary clearance (42, 72). Acrolein forms adducts with nucleophilic side chains of cysteine, lysine, and histidine residues and with the free amino terminus of proteins (85), as well as DNA (86). These adducts can lead to reduced CFTR channel open probability (12, 49) and extend CFTR defects beyond the lung, inducing systemic CFTR dysfunction (i.e., not limited to organs in contact with cigarette smoke) in smokers and people with COPD. The cysteine residues in the nucleotide binding domains of CFTR that regulate the open probability and conductance of CFTR channels are particularly susceptible to the formation of toxic acrolein adducts (49, 87). These adducts are postulated to explain longer lasting CFTR deficits, present in smokers even upon smoking cessation (49).

Other related mechanisms impairing CFTR channel function include redox-related injury as a result of inflammation (74) and acute or chronic infection (viral or bacterial), which can release factors that alter CFTR function and expression, as in the case of *Pseudomonas aeruginosa* (78, 88). Given several mechanisms contribute to CFTR dysfunction, and on different time scales, further research is warranted to discern their relative importance.

Roles of Other Ion Channels in the Mucus Hypersecretion and Accumulation Phenotype

Although CFTR is the best characterized of the channels involved in normal regulation of ASL, dysfunction of other ion channels is also implicated in COPD pathology and mucus hypersecretion phenotype. Reduced CFTR function has been reported to cause disproportionate ENaC activity and hyperabsorption of Na^+, further contributing to airway dehydration, although this has not been seen in all studies (9). Chronic neutrophilic inflammation leads to an increase in neutrophil elastase, which causes aberrant, excessive activation of ENaC and contributes to the ionic imbalance and dehydration of the airway mucosa (89). Exposure to reactive oxygen species may also reduce ENaC activity, which has been shown to impair the ionic balance in ASL (90). Nevertheless, data on ENaC activity in COPD are less conclusive than those on CFTR activity, which, together with several unsuccessful clinical trials of ENaC inhibitors in CF, necessitates more research to understand the therapeutic role of ENaC in COPD.

Basolateral and apical (surface) large-conductance, calcium-activated, and voltage-gated K^+ channels regulate mucus composition by creating ion gradients that enable CFTR to function (91). Voltage-gated K^+ channels are also important in mucus and ASL homeostasis and mucociliary clearance (91). They respond to decreases in the volume of ASL, and cigarette smoke–induced decrease in their (in addition to CFTR) activity reduced ASL depth, whereas increased activity was associated with restored ASL depth (91). Calcium-activated chloride channels such as TMEM16A also have the potential to circumvent CFTR-mediated chloride secretion (92).

TRP (transient receptor potential) channels have also been implicated in COPD pathogenesis. In a mouse asthma model, TRPA1 antagonists reduce mucus amounts and leukocyte infiltration (93), and cold-induced increase in TRPM8 expression resulted in mucus hypersecretion in normal, nondiseased airway epithelial cells (94).

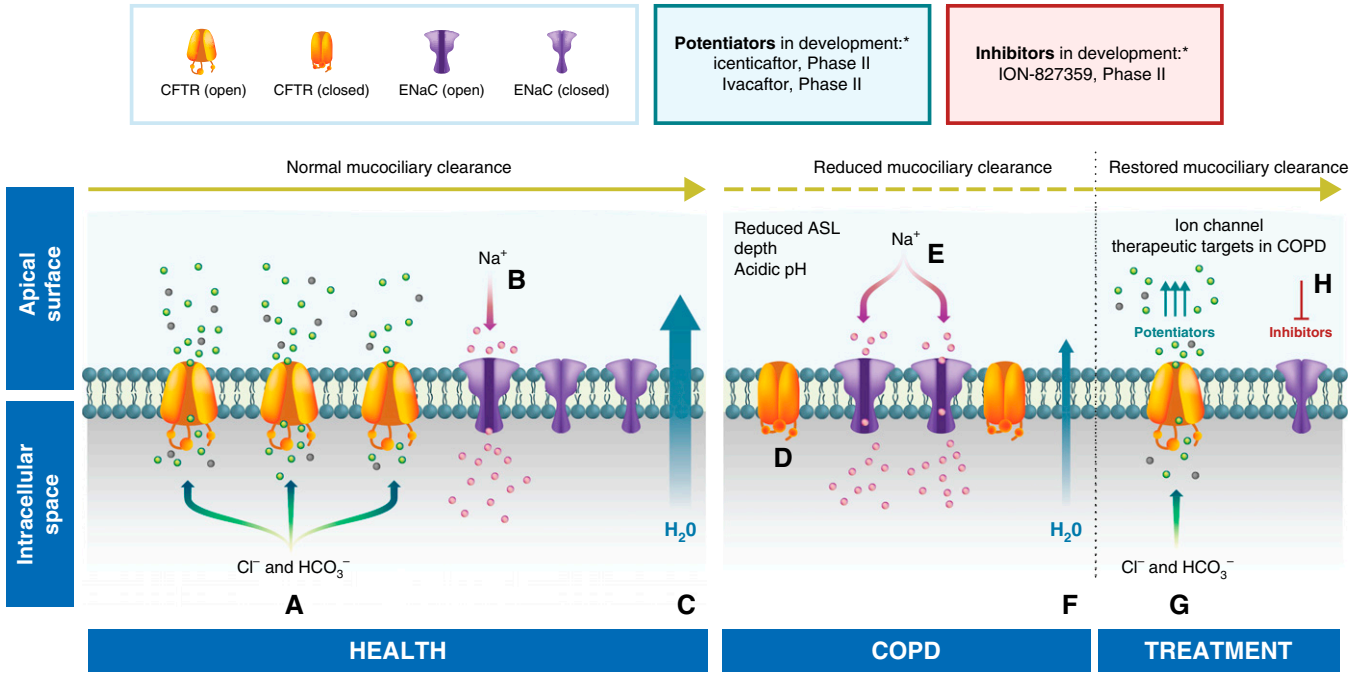

Figure 3. Potential therapeutic interventions for correction of ion channel dysfunction. Comparative optimal and suboptimal actions of ENaC (epithelial sodium channel) and CFTR (cystic fibrosis transmembrane conductance regulator) channel proteins. (*A*) In health, CFTR actively transports anions to the apical cell surface. (*B*) This is coupled to transport of positively charged Na^+ ions into the cell. (*C*) Increased osmotic pressure at the apical cell surface draws water from the intracellular compartment to the airway surface liquid (ASL). (*D*) In chronic obstructive pulmonary disease, CFTR function is impaired, and anion transport out of the cell is reduced. (*E*) Consequently, ENaC activity is increased, and Na^+ ion influx into the cell in increased. (*F*) This lowers the osmotic pressure at the cell surface compared with that in a healthy state and reduces efflux of water to the surface. (*G* and *H*) This pathological state may be rescued by modulating ion channel activity: CFTR potentiators can increase the efflux of anions into the ASL (*G*), while ENaC inhibitors can reduce the influx of cations into the cell (*H*). Either of these channel-modulating activities could potentially restore the ion balance required to maintain the ASL. *Only ion channel therapeutic targets with drugs in current clinical development are shown. COPD = chronic obstructive pulmonary disease.

Targeting Ion Channel–mediated Mechanisms of Mucus Accumulation in COPD

Currently, no treatments target the underlying mechanisms of mucus accumulation for patients with COPD, and there is a lack of clinical parameters that measure the severity of mucus hypersecretion to help define the target population (12, 78). Pharmacological measures currently used to improve mucus clearance include expectorants, mucolytics, and mucokinetics (95). Although mucolytics provide symptomatic relief, studies to date have reported inconclusive results or only marginal effects, suggesting that either mucolytic therapy alone is not sufficient to provide long-term benefit, or current agents lack sufficient bioactivity in patients (95).

Direct modulation of mucus properties via ion channel targeting could be a viable strategy in treating patients with COPD (Figure 3). This approach may be particularly well suited to patients with chronic bronchitis symptoms or individuals with documented mucus stasis or accumulation. Ion channels are a common target in other disease types but historically less so in respiratory disease. However, in recent years there has been increasing interest in these proteins as therapeutic targets in lung disease such as COPD (9). Studies in CF have shown that CFTR potentiators can reverse mucus obstruction in both large and small airways (96), leading to reduced airway obstruction and pronounced clinical benefit.

Currently, several interventional trials are investigating augmenting CFTR activity to combat mucus hypersecretion. Icenticaftor (NCT04072887) and ivacaftor (NCT03085485 and NCT04066751) are small-molecule channel potentiators of CFTR (97). Although some features of COPD are currently not reversible (98), smoke-induced changes to CFTR are at least partially reversible after smoking cessation (75, 82). Roflumilast, a phosphodiesterase-4 inhibitor that is currently approved for treatment of COPD, is effective in reducing exacerbations and bronchitic symptoms, specifically in patients with mucus hypersecretion. *In vivo*, *ex vivo*, and *in vitro* studies have shown that it may exert its effect mainly via CFTR potentiation; roflumilast was shown to potentiate CFTR channels in cell culture, human tracheal sections, and mice after acute administration and to reverse smoke-induced CFTR dysfunction after acute and chronic administration (84, 99).

Beyond CFTR, other ion channels may be candidate drug targets to deliver hydration to the airway, including inhibition of ENaC. Activation of alternative chloride channels to circumvent CFTR deficiency could be another approach and has been proposed as a treatment for individuals with CF (100).

Further potential targets to improve mucociliary transport include the cholinergic system, bearing in mind that targeted activation could be complex. Carbachol (which mimics the effect of acetylcholine) treatment has been found to increase ASL depth, frequency of ciliary beating, and

mucociliary transport. However, people with COPD often experience increased cholinergic activity; thus the mechanism may already be compensating for mucus stasis (78). Animal studies have shown that cholinergic stimulation with carbachol can abrogate the effects of cigarette smoke on airway surface dehydration (67). Despite potentially improving mucociliary transport, carbachol may also induce mucin synthesis and consequently lead to deleterious effects. Furthermore, antimuscarinic receptor antagonists are an established bronchodilator treatment in COPD, so it is not clear whether the opposite (cholinergic activation) would have therapeutic benefit in COPD, unless activation were targeted to the epithelial surface (101).

Conclusions

Mucus hypersecretion has been previously considered a secondary characteristic of COPD rather than an important primary disease feature. However, evidence from the past decade suggests a more prominent role in disease progression. Targeting mucus hypersecretion in COPD may be a promising option for future disease-modifying therapies, which could include modulating ion channel function. CFTR is the most extensively studied of these channels because of its central, established role in CF, and some clinical evidence suggests that CFTR potentiation may improve mucus hypersecretion in CF. Given the numerous similarities in disease pathophysiology and the common role for CFTR in the two conditions, CFTR may also be a viable disease-modifying treatment target for COPD. ■

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