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Acquired CFTR Dysfunction in Chronic Bronchitis and Other Diseases of Mucus Clearance

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Summary

Chronic obstructive pulmonary disease (COPD) is a major public health problem accounting for more than 100,000 deaths and 750,000 hospitalizations each year in the United States alone. Though bronchodilators, inhaled steroids and other anti-inflammatory drugs can improve symptoms and reduce the risk of exacerbations, no therapies alter the natural history of the disease. This is the result of a number of factors including our poor understanding of the pathobiologic processes that drive specific COPD phenotypes, which has hindered drug development. Chronic bronchitis is perhaps the most clinically troublesome phenotype as most patients with COPD complain of cough and sputum production, and yet there are no effective treatments to target the mucus hypersecretion, accumulation and poor clearance that lead to these symptoms. Though it is well known that the absence of cystic fibrosis (CF) transmembrane receptor (CFTR) is the cause of CF, the prototypical disease of impaired mucociliary clearance, emerging data strongly suggest cigarette smoke and its components can lead to acquired CFTR

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Competing interest statement

G.M.S. has served on CF-related advisory boards for Bayer and Gilead. He has served as site PI for contracted CF clinical trials sponsored by Nivalis Therapeutics.

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dysfunction. Findings *in vitro*, in animal models, as well smokers with and without COPD also exhibit acquired CFTR dysfunction, which is associated with chronic bronchitis. This abnormality is not only present in the airways but is also present in extrapulmonary organs, suggesting CFTR dysfunction may contribute to smoking related lung disease as well as commonly associated comorbidities in which CFTR has a role. The development of potent CFTR modulators for the treatment of CF has made these findings clinically relevant as they may also have a role in treating COPD and other diseases of mucus clearance.

Introduction

New therapies are needed for the treatment of COPD, which accounts for over $40 billion in annual healthcare costs,[1] and recently surpassed stroke as the 3rd leading cause of death in the U.S.[2] Though smoking cessation is essential to slow the progression of disease, no current pharmaceuticals alter the natural history of the disease or improve mucus retention that is characteristic of COPD, persists even in ex-smokers, and is independently associated with FEV_1 decline and death.[3–5] The chronic bronchitis phenotype of the disease is particularly problematic, since over 60% of COPD patients exhibit chronic mucus hypersecretion, which is independently associated with rate of lung function decline and death, and is without effective treatment.[3–5] Published data from multiple laboratories strongly indicate that exposure to cigarette smoke inhibits cystic fibrosis (CF) transmembrane conductance regulator (CFTR), the causative protein in CF,[6–10] leading to delayed mucociliary transport (MCT) and mucus stasis.[6] Recent *in vivo* studies in mice[11] and humans[6,11,12] further demonstrate the presence of acquired CFTR dysfunction in COPD patients and that the defect can persist in both the lung and periphery despite smoking cessation and is associated with chronic bronchitis severity. Similar pathways may also be involved in other diseases where neutrophilic inflammation and mucus stasis is present, such as status asthmaticus. The development of efficacious modulators of CFTR anion transport has raised the exciting possibility that pharmacologic enhancement of CFTR activity may confer clinical benefit to this population, even in the absence of congenital CFTR mutations.[6,12,13] The concept that CFTR abnormalities may contribute to diseases beyond CF has captured the interest of prominent editorials,[14–16] and has the potential to elucidate a novel mechanism that could also apply to other diseases of mucus clearance, such as asthma and acute bronchitis. In this review, we will examine the latest data suggesting acquired CFTR dysfunction can occur in smoking related lung diseases and other related disorders of mucus clearance, and review the latest evidence suggesting this may be a therapeutic target.

Clinical Evidence of a CFTR Connection

Disease states associated with CFTR Dysfunction

An improved understanding of the role of CFTR in the maintenance of normal epithelial function has revealed that reduced CFTR activity plays a causative role in a number of diseases in addition to CF. For example, CFTR mutations that confer mild abnormalities are present in ~30% of individuals with recurrent idiopathic pancreatitis,[17,18] and similar associations have been established in congenital bilateral absence of the vas deferens,[19] allergic bronchopulmonary aspergillosis,[20] chronic sinusitis,[21] and idiopathic

bronchiectasis.[22,23] The genetic basis of these diseases illustrates that mild CFTR dysfunction can contribute to substantial pathology.[24] With the recent discovery and clinical validation of potent modulators of CFTR ion channel activity, there is considerable scientific interest from academic and commercial laboratories to examine the effects of CFTR stimulation for diseases in which CFTR plays pathogenic role, including COPD.[6–10,25]

Pathologic resemblance of CF and chronic bronchitis

Like CF, the defining feature of COPD is airflow limitation, although it is recognized that the disease exhibits heterogeneous pathologic features in the lung.[26–30] Of the two classically defined COPD phenotypes, emphysema and chronic bronchitis,[28,31] the latter exhibits pathologic features similar to CF, including mucin hyperexpression, mucus accumulation, and goblet cell hyperplasia, and affects nearly two-thirds of COPD patients.[27,31–33] A relatively high incidence of bronchiectasis has also been reported in COPD.[34] These abnormalities lead to impaired airway clearance, chronic bacterial colonization and persistent neutrophilic inflammation similar to CF lung disease.[26,29,32,35–39] Though these changes are usually less pronounced in patients with COPD, mucus obstruction is observed in the airways and is accompanied by delayed mucus clearance as judged by impaired tracheal mucus velocity and delayed elimination of inhaled radionuclear particles.[40–42] Furthermore, mucus obstruction also occurs in the small airways of COPD patients and is associated with excess morbidity and mortality.[3,5,43] Based on the pronounced CFTR suppression caused by tobacco smoke exposure,[6–10] neutrophilic inflammation,[44,45] and hypoxia,[46] and also supported by several other laboratories,[6–8,10,12,13,45–48] there is now a large body of evidence strongly indicating that CFTR dysfunction may contribute to COPD pathogenesis, particularly among individuals with chronic bronchitis. A robust association between smoking and decreased CFTR was observed in four independent studies each of which evaluated distinct CFTR readouts (e.g., nasal potential difference (NPD),[6] lower airway potential difference (LAPD),[12] sweat chloride,[47,49] and sweat rate[49,50]); all were associated with chronic bronchitis and/or cough severity, implicating the clinical significance of these findings.

Clinical Sub-Phenotyping in COPD

COPD patients have historically been grouped into two categories: individuals exhibiting emphysema (characterized by alveolar destruction and abnormally increased lung compliance), and those with chronic bronchitis (defined by chronic mucus production and characterized by goblet cell hyperplasia and mucus hypersecretion).[51] More recent data have established additional characteristics that contribute to patient phenotypes. These include the propensity to develop frequent exacerbations, cachexia, and airway hyperresponsiveness, among others.[51–54] Moreover, new technology enabling quantification of emphysema and airways disease by CT have emerged, enabling improved sub-phenotyping.[55] The need for a more targeted approach that identifies specific COPD subpopulations with discrete clinical or molecular characteristics has been emphasized at recent meetings of the ATS, and is currently being examined by observational studies intended to define specific COPD sub-phenotypes.[56] If successful, this may improve patient selection for targeted therapies, including the use of ion transport agonists that affect some, but not all, individuals with COPD (see below).

Experimental Data Demonstrating Acquired CFTR Dysfunction from Smoking

Cigarette Smoke Blockade of CFTR Function

Data generated *in vitro* have indicated that cigarette smoke exposure results in CFTR dysfunction. This finding is longstanding, beginning when Welsh reported that cigarette smoke decreases Cl^- secretion across canine airway epithelium with minimal effect on sodium absorption.[57] This complemented *in vitro* studies in normal epithelial monolayers by Kreindler et al., who showed that cigarette smoke or cigarette smoke extract (CSE) reduced CFTR mRNA levels, protein expression, and ion channel function in airway epithelial cells grown in culture, a finding that led to ion transport discovery programs led by Novartis.[7,8,10] Dr. Tarran's group confirmed these findings, and demonstrated that cigarette smoke decreased ASL depth by partial internalization of CFTR.[9] CSE effects on CFTR were not limited to airways alone; similar effects were also observed in T84 cells, an intestinal epithelial cell line, and sinonasal epithelia.[7,58]

To better understand these effects in the context of COPD, our laboratory defined the magnitude and dose dependence using well-differentiated primary epithelial cells derived from non-CF (CFTR wild type) donors. Incubation of CSE on the apical surface of primary airway epithelial cell monolayers resulted in dose-dependent reductions in CFTR mediated Cl^- transport;[6] we also confirmed this with various whole cigarette smoke (WCS) exposure intensities.[48] Our group confirmed CFTR inhibition *in vivo* using a murine model by demonstrating that WCS exposure causes a decrement in CFTR activity as determined by nasal potential difference (NPD), short circuit current of excised trachea, and intestinal current measurements.[47]

Our current understanding of the effects of cigarette smoke, and its interaction with CFTR, continues to expand.[6,7,59] Single channel conductance studies demonstrated the deleterious effect of CSE on CFTR open channel probability (Po).[60] CSE exposure also reduced mature, fully-glycosylated (the post ER glycoform) CFTR C-band by Western blot, and was accompanied by reductions in CFTR mRNA expression by Real-Time RT-PCR.[6] These findings are concordant with results seen in Calu-3 pulmonary glandular monolayers with high-level wild type CFTR expression.[6] Rasmussen et. al., reported that cigarette smoke removes CFTR from the plasma membrane by increased cytoplasmic Ca^{2+}, depositing these channels into aggresome-like perinuclear compartments other than the lysosome.[61] Further linking cytoplasmic Ca^{2+} as a pathway relevant to CFTR homeostasis, Maouche et. al., showed that chronic nicotine reduces α7 nicotinic acetylcholine receptor (nAChR) expression, affecting Ca^{2+} entry and cAMP-dependent CFTR activation.[62] Combined with the effects of tobacco smoke on other ion channels including basolateral K^+ conductance,[10] and results from others investigating whole cigarette smoke (WCS),[10] CSE,[7,8] and cigarette smoke *in vivo*,[7] the data establish very specific and clinically meaningful reductions in CFTR dependent ion transport due to cigarette smoke exposure. The levels of reduced CFTR activity caused by smoke exposure are similar to the severity of CFTR reductions observed *in vivo* among individuals with non-classic CF,[63] a phenotype that frequently presents with adult onset chronic bronchitis or bronchiectasis.[24] Interestingly, these findings

can persist even in culture, suggesting the potential for epigenetic influences to maintain these abnormalities.

Given the deleterious effects of cigarette smoke on CFTR-dependent anion conductance, we also examined the impact of smoke exposure on mucus expression and transport *in vitro*, pathways severely affected in COPD. CSE generated a pronounced increase in mucus expression measured by *in vitro* staining,[6] which was also observed in human smokers.[64] To establish whether the potent effects of CSE also result in downstream alterations of mucus propulsion, we monitored transport of fluorescent particles placed on the apical surface of primary human airway epithelial cells (HBE) following exposure to CSE. Mucus transport was severely reduced by CSE at 24 hours. Of note, a large proportion of particles following CSE exposure were completely static due to entrapment in thick mucus (75% with CSE vs. 11% with control, $P<0.05$), a finding consistent with mucus expression studies and prior observations of enhanced mucus secretion due to CSE exposure.[8] Combined with the observation that tobacco smoke reduces cilia beat frequency (CBF) and ciliogenesis,[58,65,66] we hypothesize that reduced CFTR-mediated anion secretion, together with stimulated mucin expression, results in a mucus to fluid secretion imbalance, thus severely inhibiting mucus transport.

Acquired CFTR Dysfunction in COPD Patients

COPD patients exhibit reduced CFTR activity in the upper and lower airways

Cantin et. al., were the first to describe that healthy cigarette smokers (confirmed to be wild type CFTR homozygotes) exhibit decreased CFTR activity.[7] They documented a ~40% reduction in chloride transport *in vivo* by NPD (Figure 1A). Acute reductions in chloride transport by NPD were also observed in healthy smokers immediately after smoke insufflation of the nares.[9] Others have shown reduced MCC in the nose of smokers, and posited this may be due to acquired CFTR abnormalities. We established that individuals with smoking-related COPD exhibit reduced CFTR expression (mRNA levels) and activity (~50% decrement) measured by NPD.[6] The defect in chloride conductance in smokers with and without COPD was not attributable to changes in mucosal integrity and appeared specific to CFTR, as no significant difference in potential difference was observed following adenosine triphosphate (ATP) perfusion, which stimulates activity of Cl^- channels other than CFTR. Reduced CFTR activity measured by NPD was also predictive of the severity of bronchitis symptoms as determined by the Breathless Cough and Sputum Score, even when controlled for cigarette smoking, indicating a significant association with the chronic bronchitis phenotype. Furthermore, individuals with a history of COPD exacerbations during the past year exhibited 35% less CFTR function than those without a history of exacerbations, a result that points to important clinical consequences associated with acquired defects in CFTR activity.[6]

To confirm if these findings were also present in the lung, we conducted the first lower airway PD measurements performed under conscious sedation in COPD patients. Results demonstrated marked reductions in CFTR activity among affected subjects compared to controls (CFTR function ~50% of normal in COPD patients and smokers; Figure 1B).[12] Like NPD, CFTR decrements in LAPD were associated with chronic bronchitis as well as

dyspnea. These results indicate that clinically relevant CFTR dysfunction is present in the lung and detectable with *in vivo* markers of CFTR activity. In addition to cigarette smoking, increased levels of neutrophil elastase may also play a role, since neutroophil elastase can induce CFTR degradation and is found in high levels in the COPD airway.[44]

Sustained and Systemic CFTR Defects in COPD

Since COPD is known as a systemic disease with a number of non-pulmonary manifestations,[67,68] we studied patients using sweat chloride analysis (the hallmark diagnostic test for CF) in patients who did not harbor an asymptomatic CFTR mutation. Sweat chloride levels demonstrated that the sweat gland, a site sensitive to CFTR function and representative of peripheral CFTR activity, was affected by cigarette smoking and COPD. This included evidence of a sustained decrement after smoking cessation (Figure 1C).[47] In light of the established non-linear relationship between sweat chloride and CFTR activity,[63] the severity of CFTR dysfunction in the sweat duct was similar to that observed in the airway in individuals with CFTR related disorders and other clinical manifestations of CFTR deficiency (i.e., ~50% decrement, similar to the NPD studies; Figure 1D). As in other studies in COPD patients, CFTR dysfunction in the sweat gland was associated with chronic bronchitis (as measured by BCSS score), an effect that persisted even when smoking, COPD status, and BMI were included in a multivariate regression model.[47] Sweat chloride elevation ≥ 35 mEq/L also indicated disease severity, as it was associated with more severe airflow limitation (i.e., COPD GOLD Stage).[47] Confirmatory studies in human intestine were consistent with an acquired extra-pulmonary CFTR deficit in smokers (60% decrement in CFTR activity[47]). To corroborate these findings, β adrenergic sweat rate, an assay well suited to detect modest CFTR abnormalities,[69] was used to demonstrate reduced CFTR function in COPD (Figure 1E) and was associated with dyspnea severity.[49] In addition, sweat rate steadily improved in healthy smokers following smoking cessation, suggesting causality.[50] These results indicate that CFTR abnormalities in smoking related COPD can occur at sites remote from direct inhalation even in those who no longer smoke, and correlate with symptoms of bronchitis and COPD severity.[14,15] These data also suggest that CFTR dysfunction may be transmitted systemically, and point to a potential mechanism underlying the increased incidence of systemic disorders attributed to smoking that are also strongly associated with CFTR abnormality, including idiopathic pancreatitis,[70] diabetes mellitus,[71–73] and male infertility.[74]

Mediators of CFTR Dysfunction in cigarette smoke

The systemic nature of CFTR dysfunction in COPD patients suggests the presence of toxic agents derived from tobacco that affect CFTR in extra-pulmonary tissues. Initial testing suggested that nicotine and cotinine did not impact CFTR function in vitro.[47] Acrolein is a highly reactive component of cigarette smoke known to cause deleterious effects by reacting with biological nucleophiles in proteins and DNA and forming adducts within the lungs.[75–78] Free acrolein levels in the serum of smokers with and without COPD determined by mass spectroscopy were elevated as compared to controls.[47] Serum proteins exhibited acrolein modifications in smokers, evidence that acrolein could induce post-translational modifications. Acrolein exposure caused acute and dose-dependent reductions in CFTR

function *in vitro* and *in vivo*.[47] In addition, single channel studies demonstrated acrolein dramatically reduced the open probability of CFTR, akin to cigarette smoke.[47] These data provide evidence that acrolein is an important contributor to CFTR dysfunction caused by smoking and may systemically transmit these defects beyond respiratory tissues. The rapid effect of acrolein on CFTR channel gating suggests direct modification of nucleophilic amino acid residues on CFTR protein that are critical for channel opening may be occurring.

Cigarette smoking is also associated with chronic accumulation of cadmium and arsenic.[79] Cadmium has been shown to reduce CFTR expression via a miRNA dependent pathway, reducing channel function. Moreover, cadmium levels in lung were correlated with COPD disease severity independent of the duration of cigarette smoking.[80,81] Arsenic, another highly toxic contaminant, is elevated in smokers and reduced CFTR surface expression by enhancing its ubiquitination.[82] Interestingly, environmental arsenic exposure even in the absence of smoking in Bangladesh workers revealed significant reductions in CFTR function as detected by sweat chloride analysis and measures of pulmonary function.[83] Thus, cigarette smoke can affect CFTR expression and function via more than one mechanism, in addition to indirect effects such as oxidative stress, unfolded protein response, and ER stress that can adversely impact CFTR homeostasis.[28,84,85]

Second Hand Smoking

Exposure to second hand smoke (SHS) is associated with a number of respiratory diseases, including COPD.[86] Exposure to SHS causes delayed mucociliary clearance in never smokers, and may contribute to chronic bronchitis.[87,88] Savitsky et. al., demonstrated that exposure to SHS, like mainstream smoke, significantly suppressed CFTR ion transport *in vitro*, which may explain delayed MCC.[10] Interestingly, circulatory acrolein is highly enriched in SHS and may be present in even greater amounts than mainstream smoke, suggesting causality. Ni et. al., have shown that SHS significantly reduces phagocytic clearance of pathogenic bacteria by affecting CFTR function in macrophages, extending potential manifestations beyond the airway.[89] The detrimental effects of SHS warrant further investigation into the mechanistic basis and physiologic significance underlying airway epithelial dysfunction in passive smokers, including its potential to contribute to COPD and respiratory infections, such as acute bronchitis or otitis media in the young.[90,91]

Acquired CFTR dysfunction and asthma

Asthma is an episodic airways disease[92] characterized by airway recruitment of eosinophils and CD4+ lymphocytes[92] that secrete an array of T_H2 cytokines with varying phenotypes.[93,94] Most predominant among these are IL-13, IL-4, and IL-5,[95] which have individually been targeted to treat severe asthma.[92] Persistence of this inflammatory process drives epithelial surface and glandular mucus metaplasia that characterizes the airways remodeling present in asthmatics.[96,97] The resultant mucus is pathologically distinct from normal subjects, particularly during status asthmaticus.[98] The abnormal mucus in asthmatics shares properties of CF mucus including increased mucin density, high plasma protein concentration, and distinctly high protease levels (e.g., neutrophil elastase).[97,98] Notably

many of these features are present in patients with clinically severe asthma at the onset of neutrophil-associated inflammation.[99]

In asthma, airway metaplasia and pathological alteration of mucus is associated with airway plugging[100] due to impaired mucus clearance.[101,102] In addition, epithelial abnormalities may cause inherent ciliary dysmotility in severe asthmatics.[103] These processes cause episodic mucus plugging during acute exacerbations that complicate severe asthma.[100] In its most severe and chronic form, asthma that is affected by bronchiectasis has particularly poor outcomes including increased infectious burden, exacerbation frequency, and poor treatment response, reminiscent of a mild form of CF.[104]

A large body of literature has examined the link between genetic abnormalities of the CFTR gene and the propensity for asthma.[105] Schroeder et. al., initially reported protection against bronchial asthma in patients heterozygous for Phe508del (also known as F508del), the most common CFTR mutation,[106] although a larger Danish study by Dahl et. al., refuted this finding[107] and noted an association with more severe airway obstruction in Phe508del heterozygotes.[107,108] This body of literature is inconclusive to determine if the general asthma patient population has CFTR dysfunction.[109,110] However, more recent evidence suggesting a link between neutrophilic bronchitis-type asthma and Phe508del-heterozygosity[105,111] suggests a need to further phenotype asthma patients to determine populations most at risk for CFTR dysfunction.

In addition to the role of CFTR, non-CFTR anion channels have been implicated in modifying the mucus properties in murine asthma models. SLC26A9 and TMEM16A knockout mice demonstrate impaired mucociliary clearance, enhanced mucin production, and airway remodeling in response to induction of allergic asthma.[112,113] These findings provide further support that the ion transport environment is key to initiating and perpetuating asthma.

Due to the central role of CFTR in airway diseases, recent studies evaluated whether asthmatic inflammation may induce altered CFTR function in the absence of genetic mutations. *In vitro* studies by Skowron-Zwarg et. al., demonstrated that IL-13 exposure caused reduced mature protein at the plasma membrane surface in human airway epithelial cells, at least when cells were exposed to IL-13 prior to differentiation at air-liquid interface.[114] In contrast, chronic IL-13 exposure in mature human airway monolayers enhanced CFTR and Ca^{2+}-dependent chloride conductance, and reduced ENaC activity.[115] Perhaps through a common signaling pathway, chronic IL-4 exposure had similar effects on CFTR and ENaC channels.[116] *In vivo* studies demonstrated CFTR activity in excised trachea of mice following intratracheal exposure of IL-13 was increased, complementing these more recent studies.[117] These findings were confirmed in a fungal exposure mouse-model.[117] While these models suggest increased, rather than reduced, CFTR currents with IL-13 and IL-4 exposures, these models have focused on pathways related primarily to allergic asthma. Whether these are relevant to severe, recalcitrant asthma, or during acute exacerbations, which tend to exhibit neutrophil-dominated inflammation and more closely resembles CF and chronic bronchitis, remains an open question.

Therapeutic approaches

Because CF and COPD share phenotypic and pathophysiologic mechanisms, therapies initially directed towards CF have potential as treatments for COPD and other airways diseases. While CF-specific mucolytic therapies for COPD have yielded marginal benefits,[118–120] as well as in non-CF bronchiectasis,[121] other mucolytic therapies show potential, including hypertonic saline.[122] To target the underlying common mechanism between chronic bronchitis, CF, and potentially specific phenotypes of asthma, an approach that addresses acquired CFTR dysfunction has been proposed, initially to study in patients with chronic bronchitis,[123] based on the concept that potentiation of wild type CFTR may be beneficial in this population.[6] In addition, this approach with a systemically-active agent may overcome limitations of aerosolized therapies that may exhibit poor drug delivery to obstructed airways. Similarly, therapies that inhibit ENaC to address airway dehydration are under development.[6,124]

Conclusions

Airway obstruction due to mucus stasis is a consistent feature of many chronic airway diseases including CF, COPD and asthma. Their shared manifestations suggest similarities in underlying pathologic mechanisms may be present. However, heterogeneity between phenotypes remains a challenge in defining common mechanisms. Emerging data regarding the physiologic role of CFTR, even in the absence of congenital CFTR mutations, indicate acquired CFTR dysfunction may significantly contribute, particularly to phenotypes characterized by chronic bronchitis. Clear evidence *in vitro* indicate cigarette smoking induces acquired CFTR dysfunction by several distinct mechanisms, including reduced expression, aberrant internalization, and disordered gating; these processes contribute to a partial deficiency of CFTR function, and when accompanied by increased mucus expression, induce delayed mucociliary clearance. This evidence is supported by clinical evidence of CFTR functional decrements observed in smokers with and without COPD, and a consistent association with chronic bronchitis. Similar features may be present in neutrophilic asthma, although eosinophil-dominated asthma appears relatively protected from these maladaptive responses. Future work should focus on the therapeutic potential of these pathways to determine if CFTR activation, or alternatively blocking detrimental effects on ion transport, confers clinically meaningful benefits.

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Key Points

- There is considerable overlap in the clinical phenotypic features of patients with CF and COPD (chronic bronchitis), and to a lesser extent neutrophil-dominated asthma
- CF, chronic bronchitis, and asthma are all associated with impaired mucociliary clearance and mucus hypersecretion, leading to chronic airway disease
- Cigarette smoking, along with many other environmental exposures, results in acquired CFTR dysfunction through a variety of molecular pathways including reduced CFTR mRNA expression, diminished protein levels through accelerated degradation, and altered channel gating
- Cigarette smokers and COPD patients develop a clinical phenotype similar to mild CF that may be related to acquired CFTR dysfunction despite normal genetics; this is associated with the presence of chronic bronchitis.
- The role of CFTR dysfunction in asthma is unknown, but may be distinct across various allergic or inflammatory phenotypes

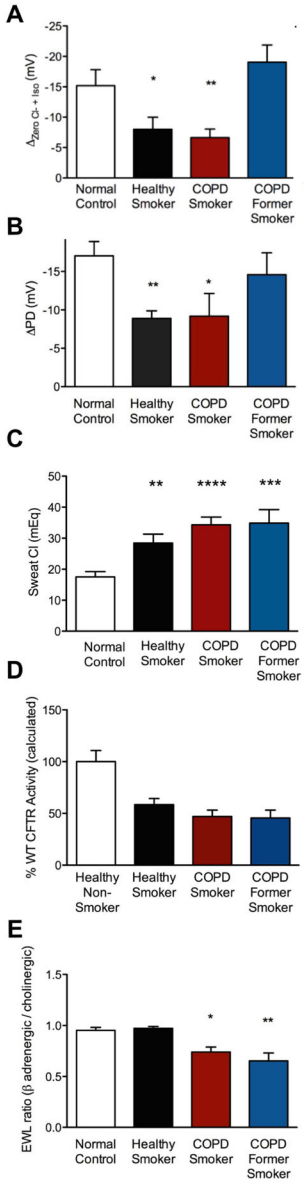

Figure 1. Acquired CFTR Dysfunction in smokers and COPD patients

A: Reduced CFTR activity in smokers with and without COPD as measured by nasal potential difference (change Cl^--free plus isoproterenol). See reference.[6] **B:** Reduced CFTR activity in smokers with and without COPD measured by lower airway potential difference (change Cl^--free plus isoproterenol). See reference.[12] **C:** Elevated sweat chloride, a measure of CFTR activity, in smokers and COPD patients. See reference.[47] **D:** Normalized CFTR activity estimated using sweat chloride values and *c*orrected for the non-linear relationship between sweat chloride and CFTR function. See reference.[47] **E:** Reduced CFTR-dependent, beta-adrenergic stimulated sweat secretion measured by evaporative water loss (EWL) in patients with COPD. See reference.[49] *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001.