Acquired Cystic Fibrosis Transmembrane Conductance Regulator Dysfunction in Chronic Bronchitis and Other Diseases of Mucus Clearance

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KEYWORDS

• Chronic obstructive pulmonary disease • Cystic fibrosis transmembrane conductance regulator
• Chronic bronchitis • Mucociliary clearance

KEY POINTS

- There is a considerable overlap in the clinical phenotypic features of patients with cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD) (chronic bronchitis phenotype), 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 CF transmembrane conductance regulator (CFTR) dysfunction through a variety of molecular pathways, including reduced CFTR messenger RNA expression, diminished protein levels through accelerated degradation, and altered channel gating.
- Cigarette smokers and patients with COPD 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.

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INTRODUCTION

New therapies are needed for the treatment of chronic obstructive pulmonary disease (COPD), which accounts for more than $30 billion in annual health care costs,[1] and recently surpassed stroke as the third leading cause of death in the United States.[2] Although smoking cessation is essential to slow the progression of disease, no current pharmaceuticals alter the natural history of the disease or improve the mucus retention that is characteristic of COPD, persists even in ex-smokers, and is independently associated with forced expiratory volume in 1 second FEV1 decline and death.[3–5] The chronic bronchitis phenotype of the disease is particularly problematic, because, more than 60% of patients with COPD show 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 and mucus stasis.[6] Recent in vivo studies in mice[11] and humans[6,11,12] further show the presence of acquired CFTR dysfunction in patients with COPD and that the defect can persist in both the lung and periphery despite smoking cessation, and also that it is associated with chronic bronchitis severity. Similar pathways may also be involved in other diseases in which neutrophilic inflammation and mucus stasis are present, such as status asthmaticus. The development of efficacious modulators of CFTR anion transport has created the 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. This article examines the latest data suggesting that acquired CFTR dysfunction can occur in smoking-related lung diseases and other related disorders of mucus clearance, and reviews the latest evidence suggesting that this may be a therapeutic target.

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 several 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 shows that mild CFTR dysfunction can contribute to substantial disorder.[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 a pathogenic role, including COPD.[6–10,25]

Pathologic Resemblance of Cystic Fibrosis and Chronic Bronchitis

Like CF, the defining feature of COPD is airflow limitation, although it is recognized that the disease shows heterogeneous pathologic features in the lung.[26–30] Of the 2 classically defined COPD phenotypes, emphysema and chronic bronchitis,[28,31] the latter shows pathologic features similar to CF, including mucin hyperexpression, mucus accumulation, and goblet cell hyperplasia, and affects nearly two-thirds of patients with COPD.[27,31–33] A 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] Although 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 patients with COPD 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 activity was observed in 4 independent studies, each of which evaluated distinct CFTR readouts (eg, nasal potential difference [NPD],[6] lower airway potential difference,[12] sweat chloride,[47,49] and sweat rate[49]); all were associated with chronic bronchitis and/or cough