EDITORIAL

Mucus hypersecretion in COPD: should we only rely on symptoms?

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In the present issue of the *European Respiratory Review*, Cervert and Brusasco [1] propose that “the view that chronic mucus hypersecretion plays a secondary role in the pathogenesis of COPD should be abandoned and instead, mucolytic agents should be considered as a treatment option” [1]. In the same series, Balsamo et al. [2] provide an overview of currently available mucoactive drugs, and Decramer and Janssens [3] examine the evidence for proposing long-term treatment with so-called “mucolytics” (e.g. N-acetylcysteine and carbocysteine) in patients with chronic obstructive pulmonary disease (COPD).

Mucus hypersecretion has long been limited to chronic cough and sputum production. Thus, epidemiological studies that have focused on the potential impact of chronic cough and sputum production in COPD called it chronic mucus hypersecretion [4, 5]. In this editorial, we examine the evidence suggesting that mucus hypersecretion is a major feature in all COPD patients, including those without cough and sputum production. We suggest that mucus hypersecretion should be a therapeutic target in all COPD subjects (i.e. subjects with and without chronic cough and sputum production) and discuss some aspects of the development of drugs targeting mucus hypersecretion in COPD.

Chronic cough and sputum production and COPD are associated with smoking exposure, but chronic cough and sputum production are present only in a subset of subjects with COPD [6, 7]. Although these symptoms were initially believed to be irrelevant to the natural history of COPD [4], Vestbo et al. [5] reported that chronic cough and sputum production were associated with disease progression (i.e. forced expiratory volume in 1 s (FEV1) decline) in subjects with COPD. Investigators further reported that chronic cough and sputum production were associated with premature death in subjects with COPD [7–9] and were closely associated with the occurrence of COPD exacerbations, including those requiring hospitalisations [10]. These studies revealed that chronic cough and sputum production, which are probably related to airway mucus hypersecretion, are not innocent bystanders in patients with COPD, but should be regarded as important clinical manifestations associated with major outcomes [11].

An important question needs to be addressed: should mucus hypersecretion in COPD airways be identified only based on symptoms of chronic cough and sputum production? Pathological studies have suggested that these symptoms were mostly associated with changes in large (proximal) airways [12, 13], where mucus-producing cells (epithelial goblet cells and mucus glands) are increased [14, 15]. Mucus accumulation was also identified in the epithelium and lumen of small conducting airways, and the extent of mucous exudates within airway lumens was closely associated with the severity of airflow limitation in a large group of subjects with COPD [16]. Furthermore, severity of luminal obstruction by mucous exudates was independently associated with mortality at 3 yrs in 101 COPD subjects undergoing lung volume reduction surgery [17]. In the latter study chronic cough and sputum production failed to associate with occlusion of the small airways by mucous exudates [17]. Another study also suggested that mucus hypersecretion in peripheral airways was independent of the presence of cough and sputum production [18]. These findings are perhaps not surprising because cough receptors are absent in peripheral airways, leading to the suggestion that mucus accumulation in small airways may occur in the absence of chronic cough and sputum production [19]. We conclude that mucus hypersecretion occurs in all COPD subjects, increases with airflow limitation and is not always associated with chronic cough and sputum production.

Currently available drugs have limited or no impact on hypersecretion in COPD. So-called mucoactives (e.g. N-acetylcysteine and carbocysteine) have shown some efficacy in reducing exacerbations in long-term randomised controlled trials, especially in COPD patients not receiving inhaled corticosteroids [3]. As discussed in this issue of the *European Respiratory Review* by Decramer and Janssens [3], there is no evidence that the effects of these drugs are mediated through effect on mucus hypersecretion. Inhaled and oral steroids may also have no or limited effect on mucus production in airways [17, 20], and mucus obstruction in small airways was present in patients treated with long-acting bronchodilators [16, 17]. The development of new drugs for targeting mucus hypersecretion in COPD patients will probably require: 1) a precise understanding of the pathophysiology of mucus accumulation...
in the airways of COPD patients; and 2) the definition of appropriate outcomes for testing these drugs in clinical trials. These issues are discussed in the following paragraphs.

Airway mucus is a complex mixture of watery secretions (water, ions and soluble mediators), inflammatory cells and secreted mucins. Mucus accumulation in the airway lumens can be the result of increased mucin production and secretion [19], decreased mucociliary clearance [21] and/or reduced mucin degradation within the airways [22]. Dissecting these mechanisms has been the focus of many studies within the past 15 yrs [23]. These studies have already identified potential molecular targets. For example, epidermal growth factor receptor (EGFR) is a convergent pathway of many stimuli (including cigarette smoke) leading to mucus overproduction in human airways [19], and therapies targeting complex cascades of events leading to EGFR activation and mucin production have been proposed in the treatment of COPD [19, 24]. Identification of important steps necessary for mucin secretion (e.g. myristoylated alanine-rich C kinase substrate, MARCKS) suggests the possibility of inhibiting mucin release within the airways [25]. As our understanding of the mechanisms of mucus accumulation in the airways increases, there is little doubt that many more targets will be identified.

The overall concept that excessive mucus accumulation in airways is detrimental and that reduction in mucus hypersecretion is beneficial in COPD patients will need to be tested in clinical trials. Before testing new drugs targeting mucus hypersecretion in large phase III trials assessing their safety and efficacy on usual outcomes (e.g. FEV₁, exacerbations, health-related quality of life, mortality), these drugs will first have to be tested for their ability to reduce mucus hypersecretion in human airways in vivo. Assessing mucus production and secretion in human airways is not an easy task. Technical aspects of measuring mucin concentrations in airway secretions (induced sputum or bronchoalveolar fluid) have not yet been standardised. A recent study used quantitative morphometric analysis of bronchial biopsies to evaluate mucin content in epithelium and mucin gene expression using qPCR in bronchial brushings [24]. Importantly, these pathological studies are limited to large airways, whereas small airways are not easily assessed. In the future, progress in imaging techniques may allow noninvasive assessment of mucous exudates obstructing small airways, but this is not achievable using current computed tomography scans. Thus, improvement in our ability to measure mucus hypersecretion in human airways in vivo will be an important step for designing future clinical studies.

In conclusion, current COPD therapies have limited effects in modifying the natural history of the disease. Mucus hypersecretion occurs in all COPD subjects and increases with airflow limitation. Pathological and physiological studies suggest that chronic cough and sputum production is a manifestation of mucus hypersecretion in proximal airways, but that mucus hypersecretion in small airways is not necessarily associated with symptoms. These major findings suggest that therapies targeting mucus hypersecretion in COPD could be beneficial regardless of the presence of chronic cough and sputum production. Proof of this concept will require carefully designed clinical trials evaluating the impact of novel therapies on mucus hypersecretion and COPD-relevant outcomes.

**STATEMENT OF INTEREST**

None declared.

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