Airway Epithelial Progenitors and the Natural History of Chronic Obstructive Pulmonary Disease

The natural history of chronic obstructive pulmonary disease (COPD), the major smoking-induced lung disorder, comprises several decades of accelerated decline in FEV₁, a hallmark of airway obstruction (1). Airway remodeling, a major histologic correlate of airway obstruction in COPD (2, 3), has been observed already at early stages of disease and even in healthy smokers with COPD-like symptoms and a minor decline in FEV₁ (4–6). Thus, an early time-point might exist in the developmental trajectory of COPD when homeostatic regenerative mechanisms responsible for the maintenance of airway structure become ineffective and/or instead produce tissue remodeling phenotypes, a morphologic basis for airflow limitation.

The airway epithelium is essentially reliant on such a homeostatic mechanism because it is continuously exposed to environmental stressors, including cigarette smoke. Basal progenitors (BPs) residing in the basal epithelial layer among basal cells (BCs) generate all cellular elements of the airway epithelium: BCs, via self-renewal, and ciliated, mucus-producing and nonmucous secretory cells via differentiation. In response to smoking, BPs produce remodeling patterns, including squamous metaplasia, hyperplasia of BCs and mucus-producing cells, and loss of ciliated and nonmucous secretory cells (7). Reduced function of airway BPs has been observed in smokers with COPD (8). Whether this occurs earlier in the natural history of COPD has remained an open question.

In this issue of the *Journal*, Ghosh and colleagues (pp. 885–896) address this question by evaluating the regenerative potential of BPs in airway biopsy samples obtained from current and former smokers with and without COPD (9). First, they determined the BP count by quantifying the number of clones produced after coculturing the heterogeneous mixture of cells from each biopsy sample with feeder fibroblasts. Ghosh and colleagues show how this classic assay, which was previously employed to address basic aspects of BP biology (10), can be used as a preclinical test to quantify active progenitors in patient-derived samples. Using this method, they found that the BP count was ~60% lower in COPD samples than in non-COPD airways, accompanied by a dramatic reduction of BP self-renewal, as assessed by serial passaging of original clones.

Whereas a uniform decrease in airway BP counts was determined in COPD samples, subjects without COPD were heterogeneous, and those with low, COPD-like BP counts had reduced lung function measurements (e.g., FEV₁ and FEV₁/FVC) compared with individuals with normal BP counts. Thus, these subjects might be at risk for COPD. Longitudinal evaluation of symptoms and lung function would be required to determine whether subjects with reduced airway BP counts will develop COPD. If so, this parameter might be a biomarker of “pre-COPD.”

One particularly intriguing question from the perspective of COPD development is whether decreased BP counts in smokers “at risk for COPD” precedes and/or contributes to airway remodeling. Although Ghosh and colleagues did not address this question, they assessed the capacity of BPs from subjects with and without COPD to regenerate differentiated airway epithelium *in vitro* in an air–liquid interface model. It was previously noticed that BPs from COPD airways generate abnormal differentiation phenotypes (8, 11). Ghosh and colleagues extend this concept by showing that airway BPs from COPD airways produce an epithelium with BC and mucous cell hyperplasia, and a reduced number of ciliated cells—histologic patterns that contribute to airway remodeling in COPD. By contrast, BPs from subjects without COPD were capable of normal differentiation.

These findings suggest that alterations in airway BPs occur during COPD development in a stepwise manner with unique contributions to early and late phases of disease pathogenesis (Figure 1). The initial decline in airway BP potential, expressed as reduced BP counts in susceptible healthy subjects, might be relevant to the loss of airways observed in early COPD (6, 12). Loss of BPs can be compensated for by activation of the remaining BPs (13). Later, BPs may become exhausted and incapable of regenerating properly differentiated epithelium, and produce remodeling phenotypes that mediate airway obstruction, demarcating the transition to symptomatic, spirometrically detectable disease. A longitudinal analysis of airway BP potential in “at-risk” subjects, coupled with an evaluation of histologic and clinical parameters, is required to determine whether this scenario is correct.

One mechanism underlying stable changes in airway BP function in COPD could involve epigenetic reprogramming of these cells, as proposed earlier (8). In healthy smokers, alterations in BPs are likely less stable and rather depend on the tissue microenvironment. For example, epidermal growth factor receptor ligands induced in the airway epithelium of smokers skew BPs to produce COPD-relevant epithelial remodeling patterns (14). One of these patterns, reprogramming of small airway epithelium to a proximal airway-like phenotype, was found in healthy smokers, who also displayed a lower FEV₁/FVC ratio compared with those with a preserved airway pattern (15).

It is noteworthy to mention that Ghosh and colleagues analyzed large airway samples from subjects who participated in clinical studies of airway premalignancy. Thus, not all of their findings may be directly related to pathologic changes in COPD, which occur in the small airways independently of carcinogenesis. BPs in the large and small airways have distinct molecular and functional properties (10). Despite these limitations, the observation made by Ghosh and colleagues that reduced BP counts in the large airway samples are associated with changes in spirometric parameters that define airflow limitation in COPD supports its relevance to COPD pathogenesis. Although the mechanistic basis for this association is unknown, widespread smoking-induced molecular changes across

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Figure 1. Conceptual model of airway basal progenitor cells (BPs) in the natural history of chronic obstructive pulmonary disease (COPD). Airway BPs play a critical role in airway homeostasis owing to their ability to maintain the airway epithelium via self-renewal and differentiation into ciliated, mucus-producing, and nonmucous secretory cells. Alterations in BP function may occur in susceptible individuals at different stages of COPD development and contribute to various aspects of disease pathogenesis. As demonstrated by Ghosh and colleagues (9), the initial decline in BP counts occurs in subjects with a minimal decline in lung function, as measured by FEV₁ and FEV₁/FVC, indicative of an early, pre-diagnostic stage of COPD (disease initiation, pre-COPD). At this stage, BPs retain their differentiation capacity, suggesting that transitional remodeling phenotypes observed in “at-risk” individuals could be driven by microenvironmental (e.g., smoking-related) rather than BP-intrinsic changes. Loss of BP regenerative potential may be related to loss of airway structural integrity observed at early stages of COPD (6). As also shown by Ghosh and colleagues (9), in individuals with established COPD, loss of functional BPs is accompanied by stable changes in their differentiation capacity relevant to generation of airway remodeling phenotypes. These stable, tissue microenvironment-independent alterations in BP regenerative function could be driven by epigenetic changes and may contribute to chronic airway obstruction, the hallmark of COPD.

the airway tree, known as the “field of injury” (16), might lead to a similar type of alterations in BPs in different airway regions. If this is the case, altered BP potential in large airway samples could serve as a surrogate marker of the pathologic process in small airways.

To summarize, the study of Ghosh and colleagues provides evidence linking the altered biology of airway BPs to the natural history of COPD. Further studies will determine whether dysregulation of these cells is a biomarker of pre- or early COPD and contributes to progressive airflow limitation in this disease. If so, therapeutic targeting of mechanisms that mediate alterations in BPs might represent a novel strategy to prevent COPD development before it is clinically manifested. ■

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Is Cisatracurium the Neuromuscular Blocking Agent of Choice in Acute Respiratory Distress Syndrome?

Neuromuscular blockade in acute respiratory distress syndrome (ARDS) is a topic of great clinical and research interest. After two small randomized trials showed neuromuscular blockade with cisatracurium improved oxygenation (1) and decreased inflammation (2) in ARDS, the 2010 publication of the multicenter French trial ACURASYS (ARDS et Curarisation Systematique) caught the attention of many (3). ACURASYS tested cisatracurium for 48 hours in 340 patients with ARDS and found improved adjusted 90-day survival without evidence of increased muscle weakness. Since then, a U.S. observational study of 3,518 mechanically ventilated patients with sepsis and respiratory infection also found evidence of survival benefit from neuromuscular blockade (4), and a multicenter U.S. randomized trial of cisatracurium and ARDS is underway (5). However, none of these studies addresses whether benefit is from cisatracurium *per se*, or neuromuscular blockade in general. Compared with other neuromuscular blocking agents, cisatracurium has several attractive properties, including elimination independent of renal and hepatic function, no active metabolites, and a short half-life. Cisatracurium also appears to have direct anti-inflammatory properties, independent of the effect of neuromuscular blockade on ventilator dyssynchrony (6). However, cisatracurium is more expensive than other neuromuscular blocking agents, and similar to many drugs, has experienced shortages. Thus, choice of neuromuscular blocking agent is an important question, as cisatracurium may not be widely available in all hospitals, whether because of national drug shortages, local availability, or financial concerns.

In this issue of the *Journal*, Sottile and colleagues (pp. 897–904) sought to answer this question (7). Using the same nationally representative dataset as Steingrub and colleagues (4), they performed an observational study of 3,812 U.S. mechanically ventilated patients with an administrative code diagnosis of ARDS or an ARDS risk factor, and who received

neuromuscular blockade. In this data set, vecuronium was the second most highly used neuromuscular blocking agent behind cisatracurium, and the authors focused their analysis on comparing these two agents. To mimic the duration of neuromuscular blockade and enrollment criteria used in ACURASYS, they examined patients who received at least 2 days of blockade within 2 days of hospital admission. To control for differences in patients who received cisatracurium versus patients who received vecuronium, they performed propensity matching to balance both patient and hospital factors. Their primary finding was that compared with vecuronium, treatment with cisatracurium was associated with no difference in mortality or likelihood to be discharged home, but was associated with one fewer ventilator and ICU day.

This analysis was a well-conducted, large, observational study of a question unlikely to be tested in a randomized trial or tested in a larger data set in the near future. The propensity score was appropriately designed and performed well. Findings were robust to multiple methodologies and sensitivity analyses, and biologically plausible. The authors acknowledge that their work cannot prove causality, indication bias may still exist, and administrative code use can result in misclassification bias, as well as their lack of ability to adjust for severity scores, laboratory results, or radiologic findings because of data unavailability. We would also add that if mortality and discharge home are unchanged, one fewer ventilator or ICU day is not a particularly patient-centered outcome, although if generalizable, there would be a modest healthcare system benefit in terms of resource consumption and ICU throughput. An evaluation of muscular strength is also lacking, as neuromuscular blocking agents exert different muscular effects (8), which could partly explain the observed difference in duration of mechanical ventilation.

In conclusion, this study provides further evidence that cisatracurium may be the neuromuscular blocking agent of choice in ARDS. However, as the observed effect is modest and not