Lung inflammation affect the degree of airway closure, impacting relationships between supine TAC and upright residual volume/TLC in COPD (2) and asthma (5). Although it is possible for lung models to estimate the posture-dependent effect (15), many physiological tests can be performed in both the upright and supine positions. A practical challenge for future HRCT studies is to reduce radiation exposure, enabling dynamic CT images to investigate the intermittent nature of airway closure in asthma, or the expansion dynamics of the thinned airway walls in COPD (2) and thickened airway walls in asthma (5). On both the image and lung function sides, we owe it to patients with lung disease to make every possible effort to extract as much structural information from the images we have, and to make the lung models that can help us interpret the structure–function link as realistic as possible. This is where morphometric and ventilation data obtained from the same patients (5) can be very helpful.

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FSTL-1: A New Player in the Prevention of Emphysema

Emphysema is an incurable destructive lung disease that causes impairment in gas exchange, gas trapping, hyperinflation, and ultimately shortness of breath. Cigarette smoking is a major cause of emphysema, but there are also less common genetic causes of emphysema, such as alpha-1 antitrypsin deficiency (1). The mechanisms underlying the induction and progression of emphysema are believed to involve an imbalance in lung proteases and antiproteases, chronic inflammation and oxidative stress, alveolar wall cell death, and failure of alveolar wall maintenance (2, 3). A better understanding of the cellular and molecular mechanisms that drive emphysema may lead to novel therapeutic strategies to prevent its development or halt its progression, resulting in better health outcomes for patients.

There is a growing body of evidence showing that FSTL-1 ( follistatin-like 1) plays an important role in lung development and respiratory diseases, including asthma and pulmonary fibrosis (4–8). In a study presented in this issue of the Journal, Henkel and colleagues (pp. 934–945) examined the consequences of reduced FSTL-1 expression on postnatal lung homeostasis (9). For this
In summary, Henkel and colleagues have identified a novel role of FSTL-1 in protecting against the development of emphysema in mice, which is independent of cigarette smoke exposure. This appears to be achieved by FSTL-1 affecting NF-κB (nuclear factor-κB) signal transduction in macrophages via modulation of Nr4a1. Although the exact nature of an FSTL-1/Nr4a1/NF-κB pathway in human emphysema remains to be defined, this study has important clinical implications, as it may pave the way for novel therapeutics that can prevent or halt the progression of emphysema.

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**TMEM16A Potentiators: Is There a Need for New Modulators in Cystic Fibrosis?**

On October 21, 2019, the U.S. Food and Drug Administration approved a highly effective triple combination therapy (eloxacaftor, tezacaftor, and ivacaftor) for patients with cystic fibrosis (CF) with at least one copy of the F508del mutation in CFTR (CF transmembrane conductance regulator). This combination therapy improved lung function, sweat chloride, weight, and quality of life in an unprecedented fashion for a folding mutation (1, 2). Thus, the currently available highly active modulators have the potential to reach ~90% of the population of patients with CF. This raises the question whether additional therapies for CF or other airway diseases related to CFTR dysfunction are still needed.

Given the remaining patients with CF without current highly effective treatment modalities, patients who cannot tolerate or who respond poorly to available modulators and the uncertainty of the treatment efficacy over time, the answer is a resounding yes. The question then is which mechanisms to target. Because lung disease is a major contributor to morbidity and mortality, a main aim of CFTR modulators is to hydrate mucus by restoring airway surface liquid volume to facilitate mucociliary clearance (MCC). Homoeostasis of airway surface liquid is tightly regulated and maintained by the balance of ion channel activities in the airway epithelium, including chloride secretion by CFTR and calcium-activated chloride (CaCC) channels, potassium secretion by large-conductance calcium-activated and voltage-dependent potassium (BK) channels, and sodium absorption by the epithelial sodium (ENaC) channels (3, 4). Ion channels that compensate for defective CFTR therefore represent an important therapeutic target group.

Restoring airway surface hydration in CF by modulating ion channel function alternative to CFTR has shown promise as a therapeutic option in vitro and in animal studies, but strategies targeting these proteins had limited success in clinical trials. So far, no therapeutics have been developed for BK channel activation. Approaches to down-regulate the expression and/or function of ENaC have been proposed as a means to improve mucus hydration. Unfortunately, prototypical ENaC blockers such as amiloride showed no clinical efficacy, whereas amiloride analogs and other approaches provided thus far no measurable clinical benefit (5, 6), possibly because of low dosing to avoid toxicity.

Therapeutic strategies to enhance apical chloride secretion alternative to CFTR have been attempted even before the molecular identification of TMEM16A (transmembrane member 16A), also known as ANO1 (anoctamin 1), as one of the CaCCs (7–9). Early studies in vitro and in normal subjects provided evidence that stable uridine-5′-triphosphate analogs stimulate CaCC via increases in cytosolic calcium and improve MCC (10, 11). However, these selective P2Y2 purinergic receptor agonists also stimulated mucin secretion (12) and ultimately failed to demonstrate any clinical benefit in the large phase 3 clinical trial TIGER-2 (Transport of Ions to Generate Epithelial Rehydration).

TMEM16A is a highly conserved member of a larger family of proteins that comprise Ca2+-dependent ion channels and phospholipid scramblases. Although TMEM16A is thought to be a significant contributor to CaCCs in the airways, the exact function of TMEM16A in airway disease remains controversial. This largely stems from findings that TMEM16A is expressed at low levels in the airway epithelium under normal conditions, and that its expression is highly induced by proinflammatory cytokines, including IL-4 and IL-13 that drive goblet cell hyperplasia (7, 13). Furthermore, the possible prossecretory effect of TMEM16A on mucin secretion (13) led to speculations that augmentation of TMEM16A activity may have adverse effects on MCC in CF.

In this issue of the *Journal*, Danahay and colleagues (pp. 946–954) describe the identification of a novel TMEM16A potentiator, ETX001, that enhances anion secretion and improves MCC both in primary CF bronchial epithelial cells in vitro (unstimulated and stimulated with IL-13) and in an in vivo sheep model of CF-like airway disease (14). ETX001 failed to stimulate TMEM16A activity in the absence of calcium, but rather...
