FAM13A, A Fatty Acid Oxidation Switch in Mitochondria Friend or Foe in Chronic Obstructive Pulmonary Disease Pathogenesis?

Mitochondria are the main source of ATP in the lung, and type 2 epithelial cells have a rich mitochondrial content. These cells have progenitor capacities and continuously secrete surfactant proteins, which explains their high metabolic demand. Lung mitochondria preferentially use glucose-derived substrates for oxidative energy production, but type 2 cells also require acetyl-coenzyme A for fatty acid (FA) synthesis necessary for the production of surfactant components. Increases in FA oxidation (FAO) in alveolar type 2 cells have been reported as a response to stresses such as starvation or altered glycolysis (1–3). These responses to stress might be important for maintaining the survival of the epithelium in physiological and pathological conditions.

Chronic obstructive pulmonary disease (COPD) is a phenotypically complex disease. The number one environmental factor that increases COPD risk is cigarette smoking. However, a small subset of never-smokers do develop COPD. During the past decade, genome-wide association studies have identified multiple candidate genes that associate with COPD risk and severity, and a handful of these candidate genes have been confirmed in multiple replication studies in independent cohorts.

One of the most replicated COPD-associated genes is *FAM13A*. *FAM13A* was first linked to lung function by Hancock and colleagues; later studies by Cho and colleagues identified it as a COPD risk gene (4, 5). In both studies, the associated polymorphism was located in an intronic region, indicating this was not a case of a functional polymorphism. In fact, all significant associations in *FAM13A* have been found in noncoding regions of the gene. In 2014, further insight was provided by Kim and colleagues, who showed that noncoding *FAM13A* polymorphisms were correlated with gene expression levels, and thus were probably in linkage disequilibrium with genetic loci that regulated the expression of *FAM13A* (6).

In this issue of the *Journal*, Jiang and colleagues (pp. 738–748) provide new insight related to *FAM13A* gene expression and increased COPD risk (7). Using cell-based assays and animal models, these investigators show that cigarette smoke (CS) induces up-regulation of the gene *CPT1A* (carnitine palmitoyltransferase-1A), a key enzyme that controls FAO in mitochondria (Figure 1). The up-regulation of *CPT1A* led to increased cell death through the increased production of reactive oxygen species (ROS). Interestingly, in mice with genetic deletion of *FAM13A*, the effects of CS on cell death were mitigated, indicating that *FAM13A* plays a critical role in

regulating not only *CPT1A* expression but also FAO in mitochondria. They also observed that *FAM13A* does not act alone in this regulatory process, but instead acts through an intermediary protein, SIRT1, to control *CPT1A* expression. These functional observations suggest there is a link between mitochondrial function and COPD, in that increased expression of *FAM13A* leads to an increase in FAO and subsequent increases in ROS.

Agarwal and colleagues previously reported that *CPT1A* expression and FAO were amplified in alveolar type 2 cells exposed to CS or acrolein, a toxic component of CS (8). However, in contrast to the findings of Jiang and colleagues, they interpreted the increase in FAO as an adaptive and protective response initiated by CS-induced glycolytic impairment and the consequent decrease in ATP production. The switch in metabolic substrate usage from glucose to fatty acids was postulated to maintain ATP levels and delay the CS-induced alveolar cell damage. Enhanced FAO associated with cellular survival and resistance to metabolic stress has also been observed in cancer cells. This effect was related to FAO-mediated generation of nicotinamide adenine dinucleotide phosphate reduced, which provides redox power to counteract oxidative stress (9). In contrast, a recent kinetic model shows that the ratio between electrons entering the respiratory chain via flavin adenin dinucleotide versus nicotinamide adenine dinucleotide reduced determines oxygen radical formation, suggesting FAO can increase ROS levels. During FAO, the FADH₂/nicotinamide adenine dinucleotide reduced production ratio is high, resulting in greater ROS generation compared with oxidative metabolism of pyruvate produced by glycolysis (10). In either case, some evidence suggests a similar switch in metabolic substrate usage might occur in patients with COPD. In support of this, free fatty acids in plasma are lower in patients with COPD, suggesting fatty acid use could be higher (11).

Metabolic studies in COPD have been conducted primarily in airway epithelial cell lines and in mice exposed to CS. These approaches fail to completely recreate the chronic stress and the inflammatory milieu that could have important metabolic consequences for type 2 cells in COPD lungs. It is well recognized that weight loss, skeletal muscle dysfunction, and nutritional abnormalities are frequently associated with COPD. The contribution of skeletal muscle and systemic metabolic alterations might be recapitulated in COPD animal models. Patients with COPD show high glucose production, glycolysis, and glucose oxidation (12), in contrast to the decreased glycolysis reported

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Figure 1. *FAM13A* regulates the CPT1A–FAO pathway in chronic obstructive pulmonary disease (COPD). *FAM13* locus has been shown to be associated with increased expression of *FAM13A* and higher risk for COPD. *FAM13* in association with SIRT1 induces the expression of *CPT1A*, a key enzyme that regulates fatty acid oxidation (FAO) in the mitochondria. Up-regulation of CPT1A promotes FAO and high production of ROS, leading to lung epithelial cell death; this is an important pathogenic mechanism that might lead to COPD. CAT, carnitine translocase; CoA, coenzyme A; CPT1A, carnitine palmitoyltransferase 1; CPT2, carnitine palmitoyltransferase 2; FACS, fatty acyl-CoA synthase; FADH2, flavin adenin dinucleotide; *FAM13A*, family with sequence similarity 13 member A; NADH, nicotinamide adenine dinucleotide reduced; ROS, reactive oxygen species; SIRT1, sirtuin 1; TCA, tricarboxylic acid cycle.

in isolated type 2 epithelial cells from mice exposed to CS (8). In addition, cell and mouse models often fail to consider that COPD is frequently a disease of the elderly, and metabolic changes occur in the lung and other tissues with aging. Thus, studies in alveolar epithelial cells derived from patients with COPD might confer better understanding of the metabolic adaptations to chronic stress, as well as their consequences in cell survival.

The studies by Jiang and colleagues solidify the link between mitochondrial function and COPD that has been previously suggested. Cloonan and colleagues showed that another commonly replicated COPD risk gene, *IREB2*, also has links to mitochondrial function (13). As with *FAM13A*, *IREB2* expression is increased in the lungs of patients with COPD, and mice without an *IREB2* gene were protected from CS-induced COPD. Exposure to CS has also been linked to other alterations in mitochondrial function and homeostasis, including increased ROS production, reduced biogenesis, disrupted mitochondrial fusion, and altered mitophagy (14, 15).

FAM13 has previously been shown to negatively regulate β -catenin activity, promoting its degradation (16). However, inhibition of β -catenin in airway epithelial cell lines did not alter FAO, suggesting *FAM13* promotes tissue destruction and impaired repair capacity by a different mechanism. The work by Jiang et al represents a step forward in the identification of pathogenic mechanisms in COPD and the correlation with genetic susceptibility to this disease. Future studies are required to fully clarify the cellular and metabolic responses of human lung cells to chronic stress and disease (Figure 1). ■

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