Connecting GWAS Susceptibility Genes in COPD: Do We Need to Consider TGF-β2?

Chronic obstructive pulmonary disease (COPD) is a progressive inflammatory lung disease characterized by persistent respiratory symptoms and airflow limitation, leading to a poor quality of life. The airflow limitation is a consequence of chronic inflammation that causes structural changes to the lungs, resulting in parenchymal destruction (emphysema) and/or small airways diseases (obstructive bronchiolitis) (1). According to the World Health Organization, 251 million people worldwide suffer from COPD, and it is expected to become the third leading cause of death by 2030. This disease is therefore associated with a high personal, societal, and economic burden.

COPD is a complex disease, and its development is influenced by both genetic and environmental factors (2, 3). Although exposure to cigarette smoke is considered the main environmental risk factor for the development of COPD, other factors such as air pollution and occupational exposures also play a role in the etiology of the disease (4). Moreover, only ∼25% of smokers actually develop COPD, and 25–45% of patients with COPD have never smoked (5, 6). This heterogeneity indicates that there are differences in the individual susceptibility to develop COPD, pointing to a determining role of genetics in the development of COPD (7). Except for the example of α-1 antitrypsin deficiency, caused by genetic variants in one particular gene (*SERPINA1*) leading to severe early-onset emphysema (8), it has been widely accepted that COPD is a multigenic disease. The interplay among several genes is believed to be crucial in the development of COPD.

In the past decade, numerous studies have focused on the role of genetic variants in COPD using classical genome-wide association studies (GWAS). In these studies, genetic variants across the whole genome have been associated in a hypothesis-free manner with COPD and related traits such as lung function levels determined by spirometry. These studies have been highly successful in identifying genetic variants and their subsequent host genes that may play a role in the pathogenesis of COPD. Results of these analyses vary among studies as a consequence of ethnic differences, heterogeneity of the cohorts, and disparities in the definition of the particular traits. However, a number of variants have been consequently found across studies, including *FAM13A* (Family with Sequence Similarity 13 Member A), *TGF-β2* (Transforming Growth Factor β2), and *HHIP* (Hedgehog Interacting Protein) (2). *FAM13A* encodes a protein involved in Rho GTPase signaling that has been implicated in cytoskeletal changes, fatty acid oxidation, and mitochondrial function (9, 10). Variants in *FAM13A* have been associated with several chronic lung diseases, including COPD, asthma, and lung cancer (11). TGF-β2 belongs to the TGF-β family of proteins, which have a key role in normal lung development as well as tissue repair and remodeling in adulthood and are dysregulated in multiple lung diseases, including asthma, COPD, and lung fibrosis (12). *HHIP* interferes with the hedgehog signaling pathway, which plays an important role in embryonic development, including the branching morphogenesis of the lung. *HHIP* has frequently been associated with pulmonary function (13).

To gain more insight into the contribution of genes identified with GWAS in the pathogenesis of COPD, it is important to assess the functional role of these particular genes in cellular models that can unravel molecular mechanisms. These studies are still limited, and it is largely unclear how changes in the expression of COPD susceptibility genes translate into functionally different responses to environmental insults in lung tissue. In this issue of the *Journal*, Gong and colleagues (pp. 532–543) provide novel insight into the molecular mechanisms of *FAM13A* and *TGF-β2* in airway epithelial cells (14). Gong and colleagues selected the shortest network path between these two well-established COPD GWAS genes; functional characterization revealed that the transmembrane protein TGF-β2 is secreted through exosomes, which is mediated by a component of the adaptor protein 3 (AP-3) coat complex, AP3D1. This was found to be negatively regulated by *FAM13A* as demonstrated by silencing of *FAM13A*.

An interesting aspect of this study is that they did not focus on a single gene, but rather took a multiple gene approach. By selecting closely connected proteins from a protein–protein interaction network for COPD, they were able to select multiple genes with potentially related biological function to events involved in the pathogenesis of COPD. This fits well with the concept of COPD being a multigenetic disease.

A limitation of the study is the use of an immortalized human bronchial cell line, often with a low number of independent experiments. In addition, validation of the finding that *FAM13A* negatively regulates the secretion of TGF-β2 in an AP-3–dependent fashion recapitulated in primary airway epithelial cells is relevant for the translational value. Here, the preferred model would be fully differentiated primary airway epithelial cells cultured at the air–liquid interface to reflect the *in vivo* situation as closely as possible, although this could be challenging. Furthermore, it is of interest to investigate whether the findings are in line with changes observed in airway epithelial cells from patients with COPD. It may well be that FAM13A signaling is disrupted in cells derived from patients with COPD. We have recently shown that protein expression of FAM13A is significantly lower in the airways of patients with severe COPD than in those of control subjects without COPD (15). Consequently, the negative regulation of TGF-β2 excretion may be impaired, leading to increased TGF-β2 levels (Figure 1). So far, human studies in COPD have mainly focused on TGF-β1, showing increased levels of this protein in patients with COPD compared with control subjects (16). Although levels of TGF-β2 are increased in the bronchial epithelium of patients with asthma (17), this has, to the best of our knowledge, not

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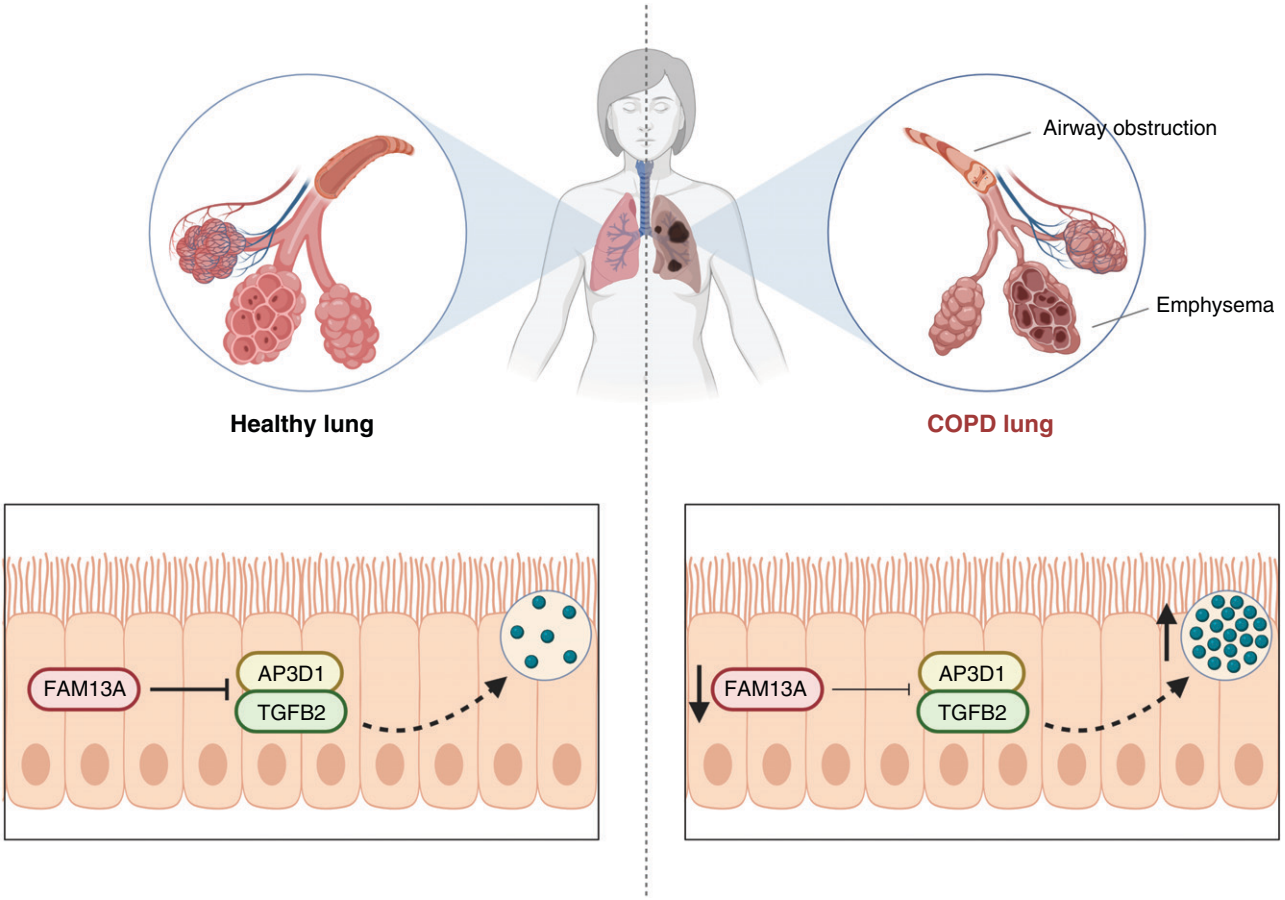

Figure 1. Schematic overview of the proposed FAM13A-AP3D1–TGF-β2 interaction in health and COPD. In healthy lungs, the exosomal release of TGF-β2 is negatively regulated by FAM13A. In COPD lungs, protein expression of FAM13A is decreased, leading to increased exosomal release of TGF-β2. This figure was created in BioRender. AP3D1 = adaptor related protein complex 3 subunit delta 1; COPD = chronic obstructive pulmonary disease; FAM13A = family with sequence similarity 13 member A; TGFB2 = transforming growth factor-β2.

yet been studied in COPD. Together with the established association of genetic variants in *TGF-β2* with COPD, the newly discovered network of FAM13A-AP3D1–TGF-β2 highly warrants further research into the role of TGF-β2 in COPD given the known function of TGF-β. This may not only lead to new insights in the pathogenesis of COPD but also yield new therapeutic strategies for its treatment. ■

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