ATP12A: Connecting Mucus and Fibrosis in Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a lung disease of rare classification, characterized by epithelial injury, remodeling, and irreversible loss of function, usually leading to death within 3–5 years after diagnosis (1). The disease is marked by classic honeycombing on computed tomography and histologic examination marking areas of reepithelialized air spaces (2). Although termed idiopathic, indicating that the cause is unknown, the past two decades have seen the generation of a wealth of genetic studies indicating association with a wide variety of gene variants, including genes such as surfactant protein C (SFTPC) (3), surfactant protein A (SFTPA2) (4), and MUC5B (the gene encoding mucin 5B) (5, 6). The identified variant rs35705950 in the MUC5B promotor has been validated as a risk factor in a number of independent studies (7). This protein is one of the primary secreted mucins that make up the bulk of the solid content of airway mucus (8). Accumulation of MUC5B has been detected in lungs collected from patients with IPF (9). Additionally, overproduction of MUC5B in mouse lungs has been shown to be detrimental, causing decreased mucociliary transport and persistence of bleomycin-induced fibrosis (10). However, despite the breadth of data connecting these two factors, the mechanisms underlying the link between accumulation of mucus and development of IPF remain unclear.

Mucus accumulation is more commonly associated with diseases of the bronchial structures such as cystic fibrosis (CF) (8). In CF, mucus accumulation is abundant, leading to overtly plugged small airways, dominated largely by MUC5B (11). In the CF airway, additional pathologic processes worsen the overproduction of mucus, including an abnormal airway pH, largely suggested to be due to a lack of bicarbonate transport through the defective CF transmembrane conductance regulator (CFTR). In the human large airways in CF, the absence of bicarbonate leads to unchecked H^+ secretion via activation of the nongastric H^+/K^+ adenosine triphosphatase (ATP12A), reducing mucus pH and increasing mucus viscosity, likely preventing adequate mucociliary transport. When ATP12A is added exogenously to the mouse lung through recombinant adenovirus expression, $CFTR^{-/-}$ mice develop mucus hyperviscosity that is not present in the absence of ATP12A (12). Extensive work from the CF field has determined that the increased viscosity, followed by reduced transport and accumulation of mucus in the lung, including the small airways, leads to many of the resulting pathologic processes (8) even though small airways do not express ATP12A. In IPF, however, although MUC5B accumulation in the small airways and the signaling pathways that lead to increased expression of MUC5B is well documented, the involvement of CFTR and ATP12A have not been assessed.

In this issue of the *Journal*, Abdelgied and colleagues (pp. 638–650) identify the role of ectopic expression of ATP12A in the development of IPF (13). Their study has several significant findings: *1*) ATP12A is expressed not only in the large airways and submucosal glands, but also in the small airways of human IPF lungs, and it is colocalized with accumulated MUC5B; *2*) viral vector–mediated ATP12A expression in mouse lungs worsens bleomycin-induced fibrosis, apoptosis of alveolar epithelium, and mucus accumulation; and *3*) inhibition of ATP12A by the competitive proton pump blocker vonoprazan reversed these effects in bleomycin-treated mice. These experiments elegantly demonstrate the abnormal appearance of ATP12A in the human diseased lung and show that it induces the phenotype in an experimental model to confirm the link to disease. In particular, the authors show that the aggravation of fibrosis by the presence of ATP12A occurs through the activation of TGF-β1 (transforming growth factor-β1), a commonly known mechanism of fibrotic progression in human IPF disease (14). The authors posit that ATP12A is not a "bystander" in the development of disease but rather a driver, an assertion that is bolstered by the appearance of ATP12A in areas of MUC5B accumulation. This association suggests that the microenvironment surrounding increased ATP12A, and likely decreased pH, may aggravate an increase in MUC5B and contribute to the lack of transport out of the airway.

Although the experimental model tested in this study is convincing, the results do rely on the administration of bleomycin to mice, a model that has been used heavily in mechanistic and biomedical laboratory studies of IPF (15) but may not be entirely consistent with the human disease presentation. In particular, the development of therapeutics targeting IPF has been challenging when this model is used to determine efficacy (15), which may complicate any future studies directed at therapeutic interventions involving ATP12A using the bleomycin-induced mouse model. Additionally, even though the detection of ATP12A in the human small airways is likely to worsen the progression of IPF, based on the animal experiments conducted here, it is still not clear if the increase in ATP12A is present before the appearance of disease or whether it is regulated in response to epithelial changes.

In summary, the results presented by Abdelgied and colleagues (13) reveal a significant new mechanism of disease progression in IPF. The inappropriate expression of ATP12A in small airways in IPF lungs likely leads to decreased pH, increased mucus accumulation, and more severe apoptosis through the canonical TGF-β1 pathway. The strength of human and experimental data indicate that ATP12A may be a viable therapeutic target in the amelioration of fibrosis development, potentially filling an important gap in the field. ■

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