FKBP13: A New Player on the Block in Endoplasmic Reticulum Stress and Lung Fibrosis

Endoplasmic reticulum (ER) stress has long been recognized to play a direct role in the development and progression of lung fibrosis (1). Environmental insults, genetic mutations, and aging are among the causal factors of ER stress. Of the implicated genetic mutations, mutations in *SFTPC* result in the accumulation of misfolded protein in alveolar type 2 (AT2) cells (2). Transgenic mice with a knock-in *sftpc* gene carrying human mutations develop spontaneous lung fibrosis because of ER stress–induced AT2 cell apoptosis (3). In humans, *SFTPC* mutations have been reported in familial interstitial pneumonia (4). To date, ER stress has been linked to myofibroblast differentiation, T-cell differentiation, macrophage polarization, and apoptosis (1); each cell type serves a different role in fibrosis pathogenesis. For example, deletion of the ER chaperone Grp78 (78-kD glucose-regulated protein) in AT2 cells exacerbates lung fibrosis in aged mice (5). In contrast, macrophage-specific Grp78 knockdown prevents lung fibrosis by enhancing macrophage apoptosis (6).

Do all ER chaperones play roles in lung fibrosis and interstitial lung disease, as GRP78 does? In this issue of the *Journal*, Tat and colleagues (pp. 235–246) provide some mechanistic insight into another ER chaperone in lung fibrosis, FKBP13 (13-kD FK506-binding protein) (7). Previous studies have reported increased expression of the *FKBP2* gene (which encodes FKBP13) in fibrotic lungs and a correlation of expression levels with disease progression of lung fibrosis (8) and chronic hypersensitivity pneumonitis (9). The molecular function of FKBP13 is to transit between cisproline and transproline residues for proper protein folding in the ER lumen (10). FKBP13 is upregulated during ER stress (11) and is a part of the unfolded protein response, which is important in maintaining ER protein homeostasis (10).

The current study extends prior findings by demonstrating elevated FKBP13 protein expression in lung tissue of various fibrotic lung diseases, including idiopathic pulmonary fibrosis (IPF), hypersensitivity pneumonitis, rheumatoid arthritis–associated interstitial lung disease, and sarcoidosis. Elevated FKBP13 expression is correlated with worse lung function in patients with IPF measured by forced vital capacity and dyspnea scores. The expression of other ER stress markers, including GRP78, XBP1 (X-box binding protein 1) and CHOP (C/EBP homologous protein), was also positively correlated with FKBP13 concentrations in IPF lungs. Importantly, the mechanistic role of FKBP13 was examined in a knockout (KO) model. FKBP13-KO mice had exaggerated lung inflammation and increased susceptibility to AT2 cell apoptosis, and they developed fibrosis after both low and high doses of bleomycin. Furthermore, deficiency of FKBP13 prevented fibrosis resolution at a late stage because of elevated ER stress–induced lung epithelial cell apoptosis. The dual investigation of FKBP13 in both human and a murine model of lung fibrosis is a strength of this study that offers important information as to the role of FKBP13 in pulmonary fibrosis.

Important questions remain to be answered when considering the implications of these results. First, considering the differential inflammatory responses in wild-type and FKBP13-KO mice after low-dose bleomycin, it would be interesting to determine whether FKBP13 exerts similar protective effects in both suboptimal and optimal ER stress/unfolded protein response conditions using AT2 KO cells and ER stress–inducing agents. Second, do aged FKBP13-KO mice develop lung fibrosis spontaneously? In certain conditions, ER stress alone may not cause fibrosis but instead may sensitize tissue to secondary profibrotic insults, including aging (5, 8). Third, the results seem intuitively paradoxical, as FKBP13 is upregulated in end-stage fibrotic lungs but is protective against bleomycin-induced lung injury and fibrosis in KO mice. The authors conjecture that the upregulation of FKBP13 is a physiological response to buffer excessive ER stress. Alternatively, is it possible that the highly expressed FKBP13 cells in fibrotic IPF lungs arise from the newly discovered aberrant basaloid cells in late-stage IPF (12)? What if the increased expression in basaloid cells protects these aberrant cells from apoptosis, which, in turn, leads to detrimental profibrotic effects? As alveolar macrophages appear to play important roles in fibrosis resolution by secreting collagenases (13), the role of FKBP13 in alveolar macrophages needs to be further explored using cell type–specific conditional KO mice. In addition, whether or not FKBP13 in peripheral blood will be informative as to disease prognosis (and therefore serve as a viable biomarker for pulmonary fibrosis) remains to be determined.

Together, these findings extend prior data showing that ER stress is a common theme across different subtypes of pulmonary fibrosis, and they reveal FKBP13 to be another player in ER stress and lung fibrosis. The authors should be applauded for their efforts to identify molecular pathways driving increased ER stress, given its key importance in fibrosis pathogenesis. Adding new pieces to the puzzle of ER stress may enlighten us regarding therapeutic strategies for lung fibrosis by fine-tuning our understanding of the ER stress process. ■

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