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Stress in the ER (Endoplasmic Reticulum) A Matter of Life and Death for Epithelial Cells

Idiopathic pulmonary fibrosis (IPF) is believed to result from aberrant repair of chronic or recurrent alveolar epithelial injury (1). Fibroblastic foci, aggregates of myofibroblasts that underlie injured epithelial cells, are the prevailing “active” lesions of fibrosis (2). Alveolar epithelial cells overlying fibroblastic foci show evidence of a regenerative response to injury, with hyperplasia and proliferation, as well as evidence of apoptosis (3). In animal models, alveolar epithelial cell apoptosis is sufficient to induce fibrogenesis, whereas blockade of epithelial apoptosis can attenuate fibrosis (4, 5). The mechanisms of alveolar epithelial cell apoptosis in IPF have not been defined.

Apoptosis is a critical component of tissue homeostasis and wound repair (6, 7). Recent studies have defined alternative forms of programmed cell death, such as autophagy, which overlap with apoptosis and share the apoptotic machinery (7, 8). Endoplasmic reticulum (ER) stress has been identified as a stimulus of programmed cell death through both classic apoptosis and autophagic pathways (9). Stimuli such as nutrient deprivation, hypoxia, oxidative stress, and defective protein secretion induce ER stress, leading to impaired post-translational processing of secretory proteins, which accumulate within the cell (10). This triggers a cytoprotective “unfolded protein response” that decreases global protein synthesis while increasing production of cellular chaperones and other mediators of protein folding and secretion (10). If the unfolded protein response fails to control the cytotoxic effect of these accumulated proteins, cells will commit to a pathway of regulated cell death (11). Accordingly, chronic ER stress is implicated in the pathogenesis of several chronic diseases, including amyloidosis, Alzheimer’s disease, and diabetes. Until recently ER stress had not been investigated in the context of chronic lung disease.

In this issue of the *Journal* (pp. 838–846), Korfei and colleagues provide information regarding ER stress in the pathogenesis of IPF (12). The major finding of this study is the strong association between ER stress and type II alveolar epithelial cell apoptosis in IPF. Importantly, this study examined tissue and primary cells from patients with sporadic IPF and compared them with tissue from patients with chronic obstructive pulmonary disease (COPD) or with tissue and cells from normal lungs. The findings

demonstrate that epithelial cells from both IPF and COPD lungs are undergoing apoptosis, as evidenced by caspase-3 activation and Bax dimerization. The IPF specimens also show activation of ER stress responses mediated by activating transcription factor (ATF)-4, ATF-6, and CAAT/enhancer binding protein homologous protein (CHOP) (10). The COPD specimens, in contrast, reveal that type II cell apoptosis occurs in the absence of ER stress. Through evaluation of primary epithelial cells from IPF and normal lungs, the authors further demonstrate that ER stress markers colocalize with the type II epithelial cell markers surfactant protein (SP)-B, SP-C, and thyroid transcription factor-1 (TTF-1) in the IPF specimens, but not in the COPD or normal specimens.

Although this study confirms the association between ER stress and type II cell apoptosis in IPF, it does not address the mechanisms triggering ER stress. Lawson and colleagues recently reported similar findings of ER stress in the epithelium of patients with sporadic and familial IPF (13). Within the familial IPF subpopulation, evidence of ER stress was observed in patients with and without mutations in SP-C (14). The finding of ER stress in sporadic and non-SP-C familial IPF demonstrates that a variety of mechanisms apart from failure to secrete SP-C can induce ER stress and contribute to the loss of epithelial cells in IPF. The significance of this particular finding remains to be seen, but it raises the possibility that different causes of ER stress may account for the heterogeneity of clinical outcomes seen in this disease.

The current study shows that ER stress is not restricted to areas of “mature” or “active” fibrosis, but that it is also present in histologically normal areas of the IPF lung. This finding supports several potential pathogenic mechanisms of IPF, including the presence of a diffuse process causing ongoing epithelial cell stress, an intrinsic defect that is variably expressed within the epithelial cells, or a “two-hit” process by which susceptible epithelial cells are exposed to multiple stimuli of ER stress. Insight into the potential causes of ER stress is provided by Lawson and colleagues’ study linking herpesvirus infections with ER stress in IPF and previously reported associations between viral infections and IPF (13, 15).

However, if ER stress is caused by a viral infection, how do we explain the temporal and spatial heterogeneity of usual interstitial pneumonia? As an alternative possibility, oxidative stress has been implicated in IPF pathogenesis and is also associated with ER stress. The profibrotic cytokine, transforming growth factor- β 1, incites myofibroblast production of reactive oxygen species, which induces epithelial cell apoptosis (16). But, if ER stress in IPF is caused by reactive oxygen species generated by mesenchymal cells within fibroblastic foci, how can we explain ER stress in histologically normal lung? It seems likely that several different causes of ER stress, alone or in combination, might contribute to the development of IPF.

In a broader context, the differences between IPF and COPD in the current study provide insight into reparative responses to lung injury. The concept of an apoptosis paradox, by which epithelial cells undergo excessive apoptosis and mesenchymal cells resist apoptosis, has been proposed in the pathogenesis of IPF (3). Interestingly, this study shows that alveolar epithelial cell apoptosis is a feature of both IPF and emphysema. Yet, in IPF, apoptosis is associated with accumulation of connective tissue, whereas in emphysema it is associated with the destruction of connective tissue. The dichotomy of apoptotic mechanisms, in light of the pathologic differences between IPF and emphysema, suggests that epithelial-mesenchymal cross-talk may differ in the context of ER stress compared with other stimuli of apoptosis. Might there be something specific to the ER stress response that stimulates the mesenchymal cell reparative response?

The studies by Korfei and colleagues and Lawson and associates provide intriguing hints into the pathogenesis of IPF. Yet, these studies represent only the beginning of a novel line of mechanistic investigation, and they raise many important questions that will be the focus of IPF research for years to come. The most important of these is, can targeted modulation of ER stress pathways influence the outcome of lung injury and repair, and therefore serve as a novel strategy for treatment of IPF?

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Gefitinib First or Gefitinib Second Is Timing Everything in the Treatment of EGFR Mutant Non-Small Cell Lung Cancer?

Somatic mutations in the epidermal growth factor receptor (EGFR) have emerged as important biomarkers in predicting the likelihood of tumor response to the EGFR tyrosine kinase inhibitors gefitinib and erlotinib in patients with advanced non-small cell lung cancer (NSCLC). EGFR mutations were originally described in 2004 in several retrospective studies and subsequently led to a number of prospective phase II clinical trials where NSCLC patients with EGFR mutations were treated with either gefitinib or erlotinib (1–6). In these prospective studies, tumor responses have

been observed in 60–80% of patients and the median times to progression range from 8 to 12 months (4–6). These findings are substantially different from those typically observed with systemic chemotherapy in patients with advanced NSCLC (7). This has prompted the initiation of phase III clinical trials comparing gefitinib or erlotinib with chemotherapy in NSCLC patients with EGFR mutations or in NSCLC patient populations, such as those with Asian ethnicity or never or former light smokers with adenocarcinoma, that are heavily enriched for EGFR mutations.