triple-combination modulator therapy, which has shown greater efficacy than either dual combination and has been approved by the U.S. Food and Drug Administration. With the approval of the triple-combination drug, 90% of patients with CF will be eligible for a CFTR modulator (13). It is plausible that in the not-too-distant future, most infants diagnosed with CF will begin a highly effective CFTR modulator, such as the triple-combination treatment, shortly after birth, and continue receiving it indefinitely. This possibility highlights the continuing need for postmarketing observational analyses, such as this one by Burgel and colleagues, as we know relatively little about the long-term efficacy or safety of any CFTR modulator. ■

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Coming to "Grp(s)" with Senescence in the Alveolar Epithelium

According to the current paradigm of idiopathic pulmonary fibrosis (IPF) pathogenesis, injury to and dysfunction of the lung epithelium play a major role in driving the disease process (1). Over the past two decades, studies of families with PF implicated rare mutations in genes related to surfactant biology as monogenic causes of PF (2), and subsequent work from multiple groups has indicated that at least a subset of surfactant protein mutations lead to misfolding of the proprotein, leading to endoplasmic reticulum (ER) stress and activation of the unfolded protein response (UPR) (3–5). Although surfactant protein mutations appear to be rare causes of adult PF, evidence of UPR activation in the lung epithelium is a common, if not ubiquitous, feature of IPF lungs (6, 7). Studies using several different pharmacologic UPR inducers and transgenic mouse models have demonstrated links between UPR activation, epithelial cell death by apoptosis or necroptosis (4, 5, 8, 9), and chronic inflammation (10). Conceptually, these studies suggest that high-level expression of misfolded proteins can overwhelm ER chaperone function, promoting a proinflammatory epithelial cell phenotype and premature death of the alveolar epithelium. Consistent with this hypothesis, global haploinsufficiency for the ER chaperone Grp78 (glucose-related peptide 78, also known as the immunoglobulin heavy-chain chaperone protein, Bip) appears to

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worsen experimental fibrosis (11). However, a clear understanding of the mechanisms linking lung epithelial UPR activation to parenchymal fibrosis has remained frustratingly elusive.

In this issue of the *Journal*, Borok and colleagues (pp. 198–211) provide new insights into the mechanisms through which the ER chaperone Grp78 plays a homeostatic role in the lung epithelium and protects against alveolar inflammation and fibrosis (12). Focusing specifically on the role of Grp78 in type II alveolar epithelial (AT2) cells, the authors generated novel tamoxifen-inducible, AT2-cell–specific, Grp78-deficient mouse models. By day 14 after tamoxifen administration, these mice developed patchy histologic fibrosis, increased lung collagen content, and reduced lung compliance. Consistent with the authors' hypothesis, deletion of Grp78 in AT2 cells led to evidence of downstream UPR activation, including increased levels of Grp94 and Chop, and increased apoptosis in the lung epithelium. In most mice, by 90 days after tamoxifen treatment, there was resolution of injury and fibrosis. Lineage-tracing studies indicated that epithelial repair was mediated primarily by mobilization and proliferation of unlabeled (i.e., Grp78-competent) cells. This finding suggested a potential role of Grp78 in the regulation of AT2 progenitor potential.

The authors hypothesized that rather than being a direct effect of Grp78, this process could be mediated by UPR-driven induction of senescence. Using an elegant precision-cut lung-slice model, they demonstrated that mitigation of ER stress and apoptosis/senescence through administration of TUDCA, a pan-caspase inhibitor, and dasatinib/quercetin, respectively, led to enhanced resolution of hallmarks of fibrotic change and senescence. Although a protective role for TUDCA was previously demonstrated in mice (13), remarkably, these observations were also recapitulated in slices from human IPF lungs, suggesting that targeting these pathways may be an avenue for possible therapeutic intervention.

As the authors note, the impact of the *Sftpc-CreER* transgenic construct introduces complexity into interpretation of these studies. As demonstrated in the study, this construct leads to a functionally SP-C null allele, and therefore all Grp78-deficient mice were either haploinsufficient for SP-C or were SP-C null. It is difficult to ascertain how this impacts the findings. Loss or reduction of a highly expressed and processed protein may have reduced the burden on the ER quality-control systems and potentially mitigated the phenotypic severity and/or persistence to some degree. Conversely, prior work indicates that SP-C null mice have exaggerated injury responses and delayed injury repair (14). Regardless of these complexities, the net effect of simultaneously modulating levels of SP-C and Grp78 clearly alters the balance of the ER stress response in AT2 cells, leading to a profibrotic state.

Notably, it is becoming increasingly evident that the UPR pathway likely plays a significant role outside of the alveolar compartment in the context of fibrosis. For example, it was recently demonstrated that the UPR-regulated transcription factor XBP1 is critical for regulation of airway mucus secretion (15), and transgenic mice overexpressing Muc5b in the secretory cells appear to have increased fibrotic susceptibility in experimental models (16). A link between the UPR and senescence in the airway epithelium has not yet been established; however, several recent reports have described the presence of senescent basal-like cells in IPF lungs (17, 18), raising the possibility that this mechanism could play a broader role in the pathologic remodeling of the fibrotic lung epithelium.

This study has several significant implications. First, it adds to the growing body of evidence that widespread injury to AT2 cells is sufficient to trigger an acute inflammatory and fibrotic response in mice (10, 19–23). One question that has remained unresolved is why only a subset of models of AT2 injury lead to significant fibrosis; for example, LPS and influenza are both capable of causing severe alveolar injury but only minimal parenchymal fibrosis. This study suggests that the induction of a senescent phenotype in surviving AT2 cells may be one of the critical mechanisms that promote parenchymal fibrosis. Second, and perhaps more importantly, this work provides tantalizing evidence that alveolar epithelial senescence actively inhibits the resolution of fibrosis in a therapeutically targetable manner. Although further studies are clearly required to better elucidate the underlying mechanism, this finding suggests that cross-talk between the senescent epithelium and local mesenchymal populations is a central driver of lung fibrosis. With a growing understanding of the pathobiology linking epithelial senescence to fibrosis, there is reason to be optimistic that future therapies targeting senescence and its paracrine consequences in the lung epithelium will be able to improve outcomes for patients with PF. ■

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Hitting a HOMER: Epidemiology to the Bedside when Evaluating for Stereotactic Ablative Radiotherapy

In this issue of the *Journal*, Martinez-Zayas and colleagues (pp. 212–223) report and validate a novel prediction model (HOMER) to calculate the probability of patients with non-small cell lung cancer (NSCLC) having mediastinal lymph node involvement (1). Determining a patient's likelihood of lymph node metastasis is paramount in determining the stage of lung cancer and therefore appropriate treatment options. Clinical staging, including imaging modalities and biopsy techniques, remains a challenge and frequently falls short of surgical staging, depending on how aggressive the preoperative evaluation is (2). Accurate staging has been associated with improved survival and remains a huge emphasis in the care of patients with lung cancer (3). The study by Martinez-Zayas and colleagues is the first to derive and validate a risk model aimed at discriminating between the most clinically useful forms of nodal disease in patients who were both surgical and nonsurgical candidates: N0, N1, and N2/3 disease.

The authors should be commended for the statistical rigor used to derive and validate their model. Covariates used to develop the model were pragmatic, clinically relevant, and appropriately limited by the last common outcome. By externally validating their prediction model at other medical centers, the authors offer a model with the possibility of geographic stability for patients with NSCLC without T4 tumors or distant metastasis, after adjusting for the local institution's population. The authors further supported their model with temporal validation to show stability over time (4). HOMER therefore has the potential to be generalizable in both the short term and the long term for patients with NSCLC seeking treatment at well-practiced thoracic oncology centers that use systematic endobronchial ultrasound-guided transbronchial needle aspiration (EBUS TBNA) lymph node staging. To carry out the systematic EBUS lymph node staging that the output of HOMER applies to, an examination of the intrathoracic nodes is required by EBUS,

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