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Endoplasmic reticulum stress in pulmonary fibrosis

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Abstract

Endoplasmic reticulum (ER) stress is associated with development and progression of fibrotic diseases, including idiopathic pulmonary fibrosis (IPF). ER stress was first implicated in the pathogenesis of IPF >15 years ago with the discovery of disease-causing mutations in surfactant protein C, which result in a misfolded gene product in type II alveolar epithelial cells (AECs). ER stress and the unfolded protein response (UPR) have been linked to lung fibrosis through regulation of AEC apoptosis, epithelial-mesenchymal transition, myofibroblast differentiation, and M2 macrophage polarization. Although progress has been made in understanding the causes and consequences of ER stress in IPF and a number of chronic fibrotic disorders, further studies are needed to identify key factors that induce ER stress in important cell types and define critical down-stream processes and effector molecules that mediate ER stress-related phenotypes. This review discusses potential causes of ER stress induction in the lungs and current evidence linking ER stress to fibrosis in the context of individual cell types: AECs, fibroblasts, and macrophages. As our understanding of the relationship between ER stress and lung fibrosis continues to evolve, future studies will examine new strategies to modulate UPR pathways for therapeutic benefit.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a severe form of interstitial lung disease characterized by progressive dyspnea, exercise intolerance, hypoxemia, and respiratory failure [1]. The pathological equivalent of IPF, known as usual interstitial pneumonia (UIP), is identified by the presence of patchy areas of fibrotic remodeling in the distal lung parenchyma with fibroblastic foci [1,2]. Collagen deposition occurs in association with accumulation of activated (myo) fibroblasts in areas subjacent to the epithelial surface, which can be composed of hyperplastic type II alveolar epithelial cells (AECs) or epithelium with bronchiolar appearance [3]. Collapse of remodeled alveoli creates focal areas of fibrosis and stretches adjacent lung parenchyma, resulting in micro-honeycombing and traction bronchiectasis, which are characteristic of this disorder. In addition to AECs and fibroblasts, inflammatory cells are thought to contribute to the development of fibrosis [4]. Specifically,

macrophages with the M2 phenotype are found within parenchymal areas in IPF and secrete mediators that can impact fibrosis [4,5]. The current paradigm to explain IPF is that repetitive epithelial injury, along with genetic factors, results in persistent fibroblast activation and ongoing collagen and matrix deposition.

The endoplasmic reticulum (ER) is a specialized organelle responsible for maintaining protein homeostasis or “proteostasis”. The ER is primarily required for protein folding and performing quality control of proteins before they reach their intracellular or extracellular destinations. Any condition that perturbs protein processing can lead to accumulation of misfolded proteins in the ER – a condition termed ER stress. In response to ER stress, the cell launches a signaling cascade termed the unfolded protein response (UPR). The UPR initially aims to restore proteostasis, but may result in cell death under prolonged or severe ER stress [6]. Chronic ER stress is a key contributor to numerous diseases including neurodegeneration, diabetes, cancer, and metabolic diseases [7–10]. Current evidence points to a critical pathogenic role of ER stress/UPR in fibrosis in a number of organs, including kidney, heart, liver, gastrointestinal tract, and lung [8]. Potential mechanistic links between ER stress and lung fibrosis were first identified >15 years ago with the discovery that familial IPF can be caused by mutations in surfactant protein C (SFTPC), which is produced by type II AECs [11–14]. When mutant SFTPC constructs were expressed in lung epithelial cell lines, the result was accumulation of mutant protein in ER and induction of ER stress [15–20]. Subsequently, immunohistochemistry studies from our group [15] and others [21] showed that ER stress markers are common in the lungs of patients with both familial and sporadic IPF. This review will focus on progress in understanding the role of ER stress in lung fibrosis.

Overview of ER stress and the UPR

A cell produces up to 4×10^6 proteins every minute with the ER bearing the responsibility of folding and processing at least a third of those [22,23]. Functions of the ER include orchestrating biogenesis, folding, assembly, and trafficking of proteins, as well as degradation of defective proteins [24–27]. ER function is tightly regulated by a combination of factors including protein load, metabolic demands of the cell, chaperone efficiency, redox balance, and calcium homeostasis [28–31]. Perturbations in any of these factors can lead to ER stress and activation of the UPR.

The UPR pathway consists of three ER transmembrane proteins: 1) PKR-like endoplasmic reticulum kinase (PERK), 2) activating transcription factor 6 (ATF6), and 3) inositol requiring enzyme 1 α (IRE1 α) [24,25,27]. In an unstressed cell, binding immunoglobulin protein (BiP), which is a chaperone that facilitates protein folding [26,27], remains bound to PERK, ATF6 and IRE1 α , and maintains these sensors in an inactive state. In a stressed cell with accumulation of proteins in the ER, BiP is sequestered away from the sensors, resulting in their activation and initiation of the UPR, which is designed to restore cellular homeostasis through reduction in overall protein translation along with selective increases in expression of critical chaperone and redox proteins [32,33].

PERK

On sensing ER stress, PERK is activated and undergoes auto-phosphorylation and dimerization [34]. PERK then phosphorylates the α subunit of eukaryotic translation initiation factor 2 α (eIF2 α) at Ser51, which is the only known direct target of PERK [35]. Phosphorylation of eIF2 α leads to overall inhibition of protein synthesis. Phospho-eIF2 α , however, can selectively up-regulate activating transcription factor 4 (ATF4), which is a transcription factor that induces expression of a set of genes required for cellular homeostasis [35–39]. ATF4 can also activate expression of pro-apoptotic factors, including growth arrest and DNA damage-inducible protein 34 (GADD34) [36,40] and C/EBP homologous protein (CHOP) [41,42].

ATF6

After its release from BiP, ATF6 translocates to the Golgi where it is cleaved into amino terminal and carboxy terminal (cytosolic) domains by site1 and site2 proteases [43,44]. Cleaved cytosolic ATF6 then translocates to the nucleus where it activates transcription of several chaperone proteins, such as BiP, calreticulin, and protein disulphide isomerase (PDI) [45]. Activated ATF6 also induces the expression of X-box binding protein 1 (XBP1), a downstream transcription factor activated through the IRE1 α pathway [46,47].

IRE1 α

When released from chaperone binding, IRE1 α undergoes oligomerization and auto-phosphorylation, resulting in activation of an RNase domain that cleaves XBP1 into an active form. Spliced XBP1 (XBP1s) then activates expression of target genes, including ER degradation enhancing α -mannosidase like protein (EDEP), which promotes protein degradation through the ER-associated degradation (ERAD) pathway [48]. In some settings, IRE1 α can be activated to degrade a wider range of ER-localized mRNAs through a process known as IRE1 α -dependent decay of mRNA (RIDD), thus affecting cell survival and other cellular phenotypes [49,50].

Factors influencing ER stress in IPF

In addition to genetically determined expression of mutant proteins, ER stress can be induced by: 1) exogenous factors that increase protein expression (e.g. viral infections) or produce reactive oxygen species (ROS) and/or impair redox balance in cells (e.g. cigarette smoke, inhaled particulates), and 2) intracellular processes that impair bioenergetics (e.g. hypoxia, aging), cause calcium shifts (e.g. mechanical stretch), or reduce clearance of misfolded proteins (e.g. proteasomal dysfunction, impaired autophagy) (Fig. 1).

In IPF, several groups have detected herpesvirus antigens in lungs of patients by PCR and immunohistochemistry [51]. Our group has reported concomitant expression of herpesvirus antigens and ER stress markers in AECs in IPF patients [15] as well as in asymptomatic relatives of patients with familial IPF [52], thereby suggesting a role of herpesvirus-induced ER stress in lung fibrosis. Also, increased expression of a repertoire of hypoxia-inducible genes has been reported in IPF lungs [53,54] and in single cell analysis of AECs in IPF [55] supporting the existence of cellular hypoxia, which can induce ER stress [56].

Aging represents another ER stress-influencing factor in patients with IPF, whose median age of diagnosis is 66 years [57–59]. Aging can significantly impair ER function through reduction in chaperone production, increase in dysmorphic mitochondria (impacting bioenergetics), and inefficient proteasomal degradation of proteins [60–63]. Torres-Gonzalez et al. reported increased ER stress markers in type II AECs in old mice compared to young mice in an experimental model of lung fibrosis [64], thus supporting a connection between ER stress and aging. In addition to direct effects of aging, impairment in ER quality control mechanism (e.g. ERAD, autophagy) can contribute to ER stress [65,66]. In this regard, staining for microtubule-associated protein 1A/1B-light chain 3-II (LC3-II), which is reflective of autophagy, was shown to be absent in type II AECs in fibrotic lesions while expression was prominent in non-fibrotic areas [66].

Regulation of effector pathways by ER stress

ER stress and UPR signaling have been linked to fibrosis through apoptotic cell death, activation/ differentiation of fibroblasts, epithelial-mesenchymal transition (EMT), and activation or polarization of inflammatory responses [6,8,67].

Epithelial cell apoptosis is a key component of fibrotic diseases in a number of organs, including the lungs [3,6]. Prolonged or excessive ER stress can induce apoptosis in epithelial cells through several UPR-dependent downstream mechanisms, including induction of CHOP, activation of the ER bound caspase (caspase-4 in humans, caspase-12 in mice), or activation of c-Jun NH2 terminal kinase (JNK) [24–26,31]. Of these three pathways, apoptosis through induction of CHOP is best studied. CHOP is a member of the C/EBP family of transcription factors. It functions both as an inhibitor of C/EBP transcriptional activity and an inducer of gene targets through interactions with alternative enhancer sites [68,69]. CHOP regulates the apoptotic pathway through activation of pro-apoptotic genes and downregulation of anti-apoptotic genes, such as B-cell lymphoma 2 (BCL2) [70]. In most reports, CHOP is primarily induced downstream of PERK/ATF4, but all 3 arms of the UPR can participate in CHOP induction [71]. ER stress can also cause apoptosis through UPR-independent cell death mechanisms. For example, excessive ER stress releases calcium into the cytosol, which can trigger apoptosis through Bcl2-associated X protein (Bax) and Bcl2 homologous antagonist killer (Bak) [72].

In addition to effects on cell survival, ER stress can affect cell differentiation. In this regard, XBP1 contributes to plasma cell differentiation [73]. In the context of fibrosis, ER stress has been shown to affect differentiation of fibroblasts to myofibroblasts, which are an activated subset of fibroblasts common in fibrotic diseases that produce large amounts of collagen and other extracellular matrix components. For example, fibroblasts treated with ER stress-inducing agents are more susceptible to myofibroblast differentiation induced by TGF β [74,75]. In epithelial cells, ER stress has been shown to induce EMT, resulting in a cellular phenotype that may directly participate in fibrotic remodeling [19,20,76]. In addition to in vitro studies showing ER stress-induced EMT, treatment of mice with cyclosporine, which can induce ER stress in renal tubular epithelial cells, has been shown to cause EMT through both TGF β dependent and independent mechanisms [76,77].

Inflammation is linked to fibrosis in a number of organs, including lungs, and ER stress and the UPR pathway have been shown to regulate inflammatory signaling pathways, including nuclear factor kappa B (NF- κ B) and activator protein-1 (AP-1) [78]. In inflammatory bowel disease, ER stress has been observed in colonic mucosa and the IRE1 α pathway has been shown to regulate disease progression [79]. Accumulation of mutant muc2 (mucin in intestinal goblet cells) results in ER stress and inflammation in the large intestine with increased expression of interleukin-1 β (IL-1 β), tumor necrosis factor α (TNF α), and interferon- γ [80]. In bone marrow derived macrophages subjected to LPS stimulation, ER stress is able to drive production and processing of pro-IL-1 β [81].

Macrophages can be polarized into M1 (proinflammatory) or M2 (pro-fibrotic) subsets based on microenvironmental stimuli [82]. Based on available data, ER stress may be able to skew macrophage populations towards either a M1 or a M2 phenotype depending on the pathophysiological context. In obesity, IRE1 α deficiency has been reported to favor the M2 macrophage phenotype [83] and CHOP deficiency can increase both M1 and M2 macrophages [84]. However, in diabetes, pulmonary fibrosis, and allergic airway inflammation, ER stress has been reported to skew towards M2 polarization through JNK or CHOP dependent mechanisms [85–87].

Pro-fibrotic effects of ER stress in individual cell types in lung fibrosis

Pro-fibrotic effects of ER stress may be transduced through several different cell types in the lungs, including alveolar epithelial cells, fibroblasts, and macrophages (Fig. 2). The impact of ER stress on pro-fibrotic characteristics of each of these cell types is discussed below.

Alveolar epithelial cells

In lungs of IPF patients, ER stress markers have been identified primarily in type II AECs [15,21]. By immunohistochemistry, we identified increased expression of BiP, EDEM, and XBP1 in AECs from patients with both familial and sporadic IPF [15]. In addition, Korfei et al. reported increased expression of ATF4, ATF6, and CHOP in AECs from lung sections obtained from IPF patients, along with evidence of apoptosis by immunostaining for cleaved caspase 3 [21].

In type II AEC lines, over-expression of mutant SFTPC genes (either exon 4 deleted or L188Q SFTPC) results in ER stress and increased apoptosis [15,17,18]. Constitutive expression of exon 4 deleted SFTPC in mice resulted in fetal lethality with disrupted lung morphogenesis and defective surfactant protein processing [88]. We generated doxycycline inducible transgenic mice in which mutant L188Q SFTPC is expressed in type II AECs [89]. When this transgene was induced in type II AECs or when the ER-stress inducing agent tunicamycin was administered through direct intratracheal instillation into the lung, ER stress was observed in type II AECs; however, fibrosis did not develop and AEC apoptosis was not identified. In contrast, treatment with low dose bleomycin resulted in a substantial increase in fibrosis with greater AEC apoptosis than treatment with bleomycin alone [89]. Together, these data indicate that ER stress in AECs, at least at the levels achievable in these models, is not sufficient to induce lung fibrosis. Rather, ER stress appears to sensitize to development of fibrosis following epithelial injury.

The mechanisms by which ER stress regulates survival/apoptosis of AECs are incompletely understood and may be context dependent. In cultured type II AECs over-expressing mutant forms of SFTPC, Mulegeta et al. identified caspase 4/12 as an important mediator of apoptosis [18]. Similarly, activation of caspase-12 and cleaved caspase-3 was detected in lungs of mice expressing L188Q SFTPC in type II AECs following bleomycin treatment [89]. CHOP has also been implicated in ER stress-dependent AEC apoptosis [21], although current studies show inconsistent effects of CHOP deletion on lung fibrosis. Tanaka et al. [90] reported that CHOP deficient mice have reduced AEC apoptosis and lung fibrosis after bleomycin treatment. In contrast, Ayaub et al. [91] found that CHOP deficient mice had higher mortality and increased fibrosis compared to wild-type controls following bleomycin treatment.

Several other mechanisms have been implicated in ER stress-induced AEC apoptosis, including regulation of ER Ca^{2+} . Calmodulin-dependent kinase II (CAMKII) is an important regulator of ER Ca^{2+} and can modulate apoptosis [92]. Inhibition of CAMKII using a transgenic mice with AEC specific expression of the CaMKII inhibitor peptide AC3-I resulted in decreased intracellular Ca^{2+} , reduced CHOP, decreased AEC apoptosis, and protection from fibrosis following bleomycin treatment [92]. In addition, Bueno M. et al. [62] showed that the mitochondrial protective factor PTEN-induced putative kinase 1 (PINK1) is decreased in IPF lungs. In experimental models, ER stress induction resulted in decreased PINK1 in AECs, along with altered bioenergetics and increased AEC apoptosis [62]. PINK1 loss can also induce ER stress, indicating the possibility of a feedback mechanism linking ER stress, mitochondrial dysfunction, and fibrotic remodeling [93].

In addition to AEC apoptosis, another possible mechanistic link between ER stress and fibrosis comes from studies in which ER stress-inducing agents or expression of mutant SFTPC were shown to induce EMT in AECs with increased expression of mesenchymal markers such as α smooth muscle actin (α SMA), vimentin, N-Cadherin and reduction of epithelial markers like E-Cadherin, and zona occludens-1 (ZO-1) [19,20]. Further studies suggested the IRE1 α /XBP1 pathway is critical for regulating EMT in type II AECs [19]. Along these lines, induction of ER stress due to expression of mutant SFTPC (exon4 deletion) in A549 cells increased collagen production and secretion [94].

Fibroblasts

Myofibroblast differentiation is involved in wound healing and is characteristic of fibrotic diseases since these activated myofibroblasts produce increased amounts of collagen and matrix components [95]. In fibroblasts from IPF patients, pharmacological inhibition of ER stress through 4-phenylbutyric acid (4-PBA) treatment reduced TGF β 1-induced myofibroblast differentiation, α SMA expression, and collagen production [74]. Knockdown of the ER chaperone calreticulin using siRNA in mouse and human IPF fibroblasts reduced TGF β 1-induced collagen and fibronectin production [96]. Similarly, treatment of fibroblasts with an IRE1 α inhibitor reduced collagen 1 α 2 and fibronectin expression and reduced autophagy in IPF lung fibroblasts following TGF β treatment [75]. In addition, ER stress regulation of PI3K/AKT signaling has been implicated in fibroblast proliferation and differentiation [97]. Together, current data implicate ER stress in regulating myofibroblast

differentiation in the lungs; however, whether this is a critical pathogenic mechanism in IPF remains to be determined.

Macrophages

Macrophages can contribute to lung fibrosis through secretion of pro-fibrotic mediators (e.g. TGF β), chemokines, and matrix metalloproteases [4,98,99]. In the lungs, ER stress has been reported in macrophages obtained by bronchoalveolar lavage from asbestosis patients and alveolar macrophages from mice with asbestos-induced lung fibrosis [100]. In IPF, Yao et al. reported expression of CHOP in M2 macrophages in IPF patients [86].

Several groups have shown that ER stress can affect macrophage phenotypes; however, current studies are inconsistent regarding the impact of ER stress on M2 macrophage polarization. In mouse obesity models, genetic deficiency of IRE1 α or CHOP resulted in increased M2 macrophages [83,84]. On the other hand, several studies have shown that induction of ER stress skews towards M2 polarization. Specifically, ER stress-induced JNK activation has been shown to induce M2 polarization in mouse peritoneal macrophages [85]. In lung macrophages, CHOP has been reported to induce M2 polarization in the bleomycin model of pulmonary fibrosis and a model of allergic airway inflammation [86,87]. Similarly, treatment of murine bone marrow-derived macrophages with PBA was reported to prevent palmitate-induced M2 polarization [101]. Although available studies suggest that the effects of ER stress on macrophage polarization depend on the disease context, ER stress in lung macrophages appears to favor the M2 phenotype.

In addition to effects on macrophage polarization, ER stress may impact fibrosis by inducing macrophage apoptosis, thereby abrogating the effects of M2 polarization. Ayaub et al. showed that CHOP expression induced macrophage apoptosis and protected from bleomycin-induced lung fibrosis [91]. Similarly, silica has been shown to induce alveolar macrophages apoptosis via ER stress in vitro [102]. Taken together, these data reveal a complex interplay between ER stress and macrophage phenotype. Further studies are needed to clarify whether the net effect of ER stress in macrophages is pathogenic or protective in different models of lung fibrosis.

Potential therapeutic approaches

There is substantial interest in targeting ER stress and UPR in many diseases; however, blocking the UPR should be approached with caution because of the adaptive and homeostatic nature of this system, as evidenced by prenatal or neonatal lethality of PERK, ATF6, IRE1, or XBP1 knockout mice [6,103–107]. Therefore, targeting primary UPR components could result in cellular toxicity rather than reduction of pathogenic effects. Despite these concerns, a small molecule inhibitor has been reported to allosterically modulate the RNAase activity of IRE1 α oligomers (but not dimers) leading to cell survival under ER stress [108], thus suggesting that fine-tuned and nuanced targeting of upstream UPR mediators might prove beneficial. Downstream or terminal UPR effectors (e.g. CHOP) are not necessarily crucial for maintaining homeostasis in normal physiological conditions, as evidenced by CHOP knockout mice being perfectly viable [109]. Therefore, a productive

strategy could be to target ER stress-downstream effectors that regulate cell survival and fibrotic remodeling.

An alternative approach to reduce ER stress could be to improve protein processing by improving chaperone functions through pharmacological agents. For example, the chemical chaperones 4-PBA and taurohyodeoxycholic acid (TUDCA) have been shown to have beneficial effects in mouse models of fibrotic diseases [90,110–114]; however, determination of the usefulness of these chaperones in IPF requires further work. Since ER stress and the integrated UPR require interplay of numerous intracellular factors, moving forward it would be important to take this biological complexity into account while choosing and targeting “druggable” nodes.

Future directions

Although current evidence suggests that ER stress-induced apoptosis in type II AECs is an important determinant of fibrosis susceptibility, further studies will be needed to delineate other potential pro-fibrotic effects of ER stress in these cells. Senescence biomarkers p16 and p21 have been observed in epithelial cells in IPF [115,116]. Therefore, the connection between ER stress and senescence, which has been reported in some cultured cells [117,118], represents an important area for future investigations. Secondly, in addition to ER stress caused by specific factors in individual cells, non-cell autonomous functions of UPR (transmissible ER stress) is another interesting area for future investigations. Recently, transmission of ER stress from one cell type to another has been reported in several settings, including diet-induced obesity and diabetes [119], viral myocarditis [120], and cancer [121–124]. Finally, while a combination of in vivo and in vitro studies have revealed signaling pathways involved in mediating the pro-fibrotic effects of ER stress, moving forward it will be critical to determine which of these pathways are predominantly dysfunctional in IPF patients. With upcoming technological advances, studies aimed at defining the genomic, transcriptomic, and proteomic signature of single cells isolated from IPF patients will likely fill knowledge gaps pertaining to the relative importance of different arms of the UPR and downstream pro-fibrotic pathways in this disease. A nuanced understanding of causes and mechanisms of ER stress in different cell types will hopefully better inform clinical studies aimed at targeting this important disease-modifying pathway.

Conclusions

A variety of studies implicate ER stress as an important factor in progression of a variety of chronic, fibrotic diseases, including IPF. In the lung, ER stress appears to primarily localize in AECs, where this pathway has been linked to increased AEC apoptosis, as well as other pro-fibrotic phenotypic characteristics. In addition, ER stress in other cell types, including fibroblasts and macrophages, can affect pro-fibrotic responses by these cells. Further studies are required to define the upstream factors that induce ER stress in IPF and identify the effector molecules that mediate ER stress-related phenotypes. This information will facilitate new strategies to modulate these pathways for therapeutic benefit.

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Fig. 1.
Potential causes of ER stress.

Fig. 2.
Pro-fibrotic effects of ER stress in different cell types in lung fibrosis.