The Unfolded Protein Response in Chronic Obstructive Pulmonary Disease

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Abstract

Accumulation of nonfunctional and potentially cytotoxic, misfolded proteins in chronic obstructive pulmonary disease (COPD) is believed to contribute to lung cell apoptosis, inflammation, and autophagy. Because of its fundamental role as a quality control system in protein metabolism, the "unfolded protein response" (UPR) is of potential importance in the pathogenesis of COPD. The UPR comprises a series of transcriptional, translational, and post-translational processes that decrease protein synthesis while enhancing protein folding capacity and protein degradation. Several studies have suggested that the UPR contributes to lung cell apoptosis and lung inflammation in at least some subjects with human COPD. However, information on the prevalence of the UPR in subjects with COPD, the lung cells that manifest a UPR, and the role of the UPR in the pathogenesis of COPD is extremely limited and requires additional study.

Keywords: cigarette smoke; proteostasis; apoptosis; inflammation

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Chronic obstructive pulmonary disease (COPD) is combination of emphysema (i.e., lung parenchymal destruction) and chronic bronchitis (i.e., inflammatory narrowing and remodeling of the airways with mucous hypersecretion). The mix of emphysema and chronic bronchitis varies considerably across individuals, leading to distinct phenotypes (1–4). COPD is also associated with heightened oxidative stress in the lung and oxidative damage to a variety of lung macromolecules including proteins even in ex-smokers (5–8). Oxidatively damaged proteins are nonfunctional and, when misfolded, may even be cytotoxic (9).

Accumulation of damaged or misfolded proteins in the endoplasmic reticulum (ER), a condition termed "ER stress," induces a compensatory cellular response termed the "unfolded protein response" (UPR) (10–14). The UPR comprises a series of transcriptional, translational, and post-translational processes that reverse ER stress by slowing the flow of new polypeptides into the ER, increasing the ER capacity for protein folding and processing, enhancing the elimination of misfolded proteins, and expanding the size of the ER compartment. Moreover, when ER stress cannot be reversed, the UPR induces cell apoptosis. In fact, the various signaling pathways activated by the UPR determine whether cells restore protein homeostasis and survive or undergo apoptosis.

The UPR is known to play a role in lung diseases caused by the expression of genetically mutated, misfolded proteins (15–20). In cystic fibrosis, activation of the UPR in airway epithelial cells by mutant cystic fibrosis transmembrane conductance regulator (CFTR) delta F508 interferes with CFTR expression and activates the innate immune response (16, 17). In mutant surfactant protein C–induced interstitial pulmonary fibrosis (IPF), activation of the UPR in alveolar type II cells induces epithelial–mesenchymal transformation, extracellular matrix production, and type II cell apoptosis (18, 19).

Increasing evidence indicates that damaged proteins are present in the COPD lung, that elimination of these damaged proteins is impaired, and that the UPR may play a role in the pathogenesis of COPD (21–26). This paper reviews the role of the UPR in the maintenance of protein homeostasis, presents the data describing the potential role of the UPR in cigarette smoke–induced oxidant stress and COPD, and discusses those aspects of the UPR that are relevant to the pathogenesis of COPD.

The ER and the UPR

Protein folding in the ER, the "factory" where virtually all membrane and secretory proteins are post-translationally processed, is calcium-, energy-, and redox-state dependent and involves a variety of ER resident chaperones,

foldases, disulfide isomerases, and oxidoreductases (11).

Imbalance in the ER load of misfolded proteins relative to ER folding capacity causes ER stress and induces the UPR (10, 11, 13, 14, 27). A triad of ER resident membrane proteins, whose ER luminal domains sense misfolded proteins, activate complex signaling pathways designed to reestablish ER and global cell proteostasis. These three sensors are: a kinase, PERK (PKR-like ER kinase); a combination kinase/endonuclease, IRE1 (inositol requiring protein-1); and a proto-transcription factor member of the basic leucine zipper (bZIP) family, ATF6 (activated transcription factor 6) (Figure 1).

The precise manner in which misfolded proteins are sensed is not completely understood (28, 29). It is believed that dissociation of the major ER luminal chaperone, glucose-regulated protein of 78 kD (GRP78), from its binding sites on the luminal surface of the three sensors in response to the accumulation of misfolded proteins contributes. In addition, direct binding of misfolded proteins in peptide grooves on the luminal surface of IRE1 and PERK, which are similar to those of the major histocompatibility complex, also appear to be activating. ATF6 appears to lack such a binding groove.

On activation, formation of IRE1 and PERK into higher-order oligomers leads to autophosphorylation of their cytosolic domains (28, 29). In contrast, activation of ATF6 induces a monomeric form of the protein, which is transported to the Golgi apparatus where it is cleaved into a smaller ~50-kD activated transcription factor, ATF6N by site-1 and site-2 proteases (S1P and S2P, respectively).

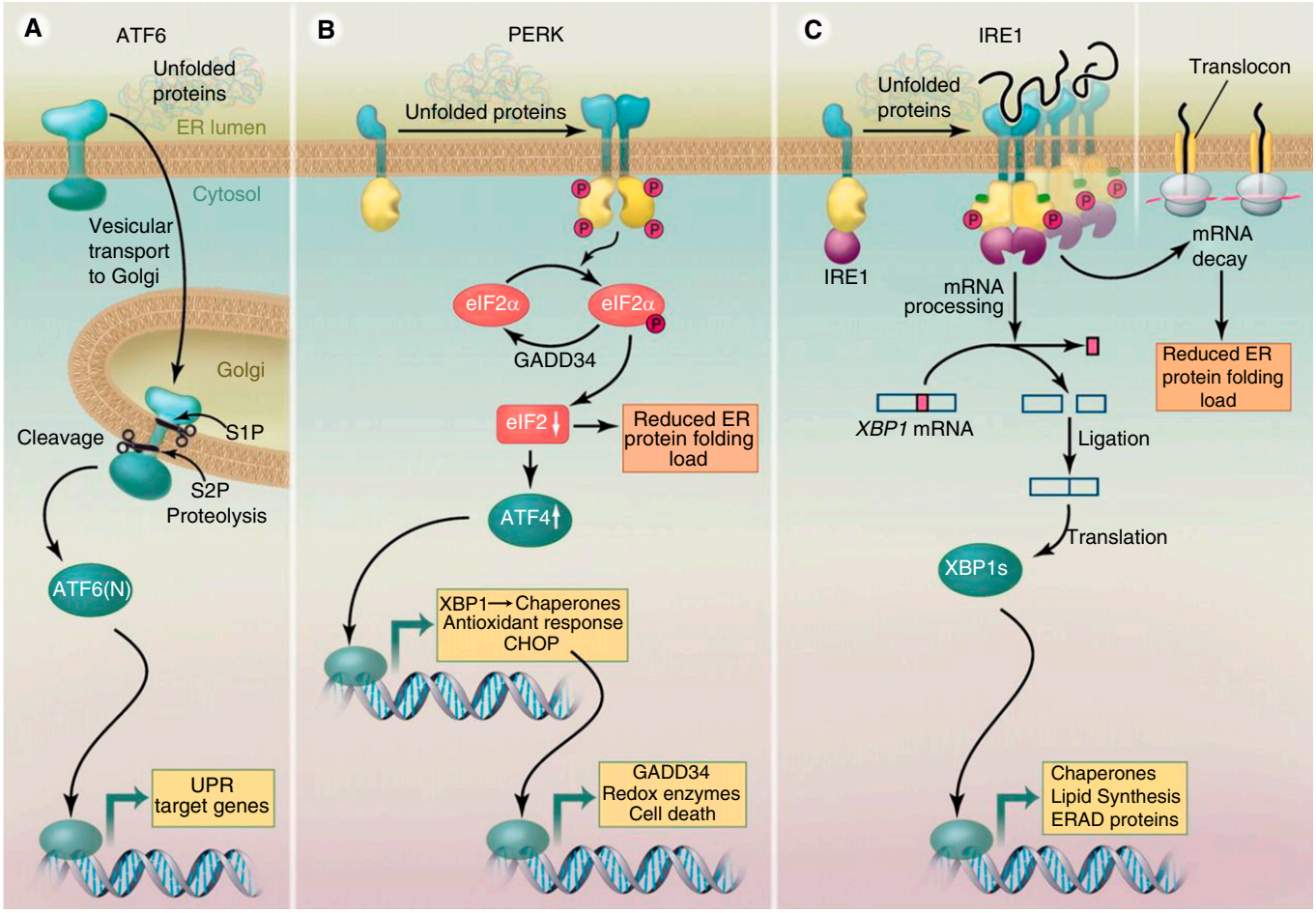

Figure 1. Schematic representation of the signaling pathways activated by the three endoplasmic reticulum (ER) sensors (i.e., PKR-like ER kinase [PERK], inositol requiring protein-1 [IRE1], and activated transcription factor 6 [ATF6]) that form the canonical unfolded protein response (UPR). The luminal domains of the three protein sensors respond to misfolded proteins in the ER lumen and produce bZIP transcription factors, which enter the nucleus to enhance transcription of UPR target genes. Different mechanisms are used by the several pathways to initiate signaling: PERK acts via its kinase activity to exert translational control; IRE1 acts via its endonuclease activity to form the transcription factor, spliced X-box binding protein 1 (XBP1s); and ATF6 forms an active transcription factor, ATF6N, from its amino terminus, by regulated proteolysis in the Golgi apparatus by site-1 and site-2 proteases (S1P and S2P, respectively). The transcription factors reduce ER stress primarily by increasing the protein-folding capacity of the ER. In addition, PERK and IRE1 reduce protein load in the ER by inhibiting translation and degrading ER-bound mRNAs, respectively. CHOP = C/EBP homologous protein; eIF2a = eukaryotic translation factor 2 alpha; ERAD = endoplasmic reticulum–associated degradation; GADD34 = growth arrest DNA damage protein 34. Reprinted by permission from Reference 27.

In addition to ATF6, activation of PERK and IRE1 also leads to the expression of several bZIP transcription factors (30, 31). In fact, the transcription factors induced by the three arms of the canonical UPR alter the expression of more than 1,700 genes, including those involved in protein chaperoning, folding, transportation, ubiquitination, antioxidant defense, cell-cycle regulation, apoptosis, inflammation, energy metabolism, immune function, membrane biogenesis, and so on (Table 1) (32). For example, PERK-induced phospho-eukaryotic translation factor 2 αp-eIF2α) facilitates translation of the mRNA coding for the transcription factor, ATF4, which, in turn, increases expression of C/EBP-homologous protein (CHOP), a gene encoding a transcription factor involved in apoptosis. PERK also appears to promote expression of the master antioxidant transcription factor, nuclear factor erythroid 2–related factor 2 (Nrf2), by phosphorylating and inactivating its cytoplasmic inhibitor, kelch-like ECH-associated protein 1 (Keap-1) (33, 34). Phosphorylation of Keap-1 prevents Nrf2 degradation in the proteasome. In fact, ATF4 and Nrf2 interact combinatorially to increase transcription of more than 100 antioxidant genes, including those involved in glutathione synthesis and reduction and hydrogen peroxide scavenging (35). This aspect of the UPR enhances antioxidant defense and diminishes oxidant stress–induced cell injury.

IRE1, through its endonuclease activity, removes a 26-bp fragment from the transcription factor XBP1, thereby forming a shorter, functional transcription factor, spliced X-box binding protein 1 (sXBP1) (31). sXBP1, in combination with ATF6N, increases the expression of chaperones, foldases, and cytokines. sXBP1 also enhances genes involved in cholesterol synthesis and the formation of new lipid bilayers, which over time allow expansion of the ER membrane.

ATF6N and sXBP1 also interact cooperatively to enhance protein degradation by increasing expression of genes involved in ubiquitination and retro-translocation of misfolded proteins into the cytoplasm (36). This process has been termed endoplasmic reticulum–associated degradation (ERAD).

On the other hand, the PERK and IRE1 signaling pathways act translationally and post-translationally to decrease protein synthesis and the load of nascent proteins entering the ER. PERK inhibits translation by phosphorylating eIF2α, a regulatory component of the translational initiation complex, thereby inhibiting ribosomal function (10, 27). Of note, this kinase action of PERK on eIF2α is not unique but is also produced by several other stress kinases, such as protein kinase R. Of interest, phosphorylation of eIF2α decreases global protein synthesis but facilitates the translation of a small number of mRNAs with short open-reading frames in their 5′ upstream region, such as ATF4. IRE1, on the other hand, inhibits protein synthesis by degrading mRNAs, micro-RNAs (miRNAs), and 28S ribosomal RNA located in close proximity to the ER membrane. At least 37 known miRNAs are degraded by IRE1. This effect of IRE1 on mRNAs and miRNAs is termed regulated IRE-dependent decay (RIDD) (37).

Furthermore, the several arms of the UPR interact cooperatively and may amplify the activity of a given pathway. For example, ATF6N promotes the expression of sXBP1 and dimerizes with it. ATF6N also interacts with ATF4 to enhance CHOP expression (27). Degradation of several miRNAs by IRE1-mediated RIDD enhances the expression of UPR effectors, including sXBP1, GRP78, etc. (37).

Of importance, a variety of negative feedback mechanisms attenuate signaling in all three pathways when ER stress is prolonged (27). For example, the PERK pathway is turned off via ATF4-induced expression of growth arrest DNA damage protein 34 (GADD34), the activator of the type 1 protein phosphatase 1C. GADD34-induced activation of protein phosphatase 1C dephosphorylates eIF2α, thereby reestablishing global protein synthesis. IRE1-mediated signaling can be reduced in several ways. First, RIDD-induced degradation of IRE1α mRNA decreases expression of IRE1 itself. In addition, sXBP1 promotes ubiquitination and enhanced degradation of IRE1α. The mechanism by which ATF6 is inactivated is not entirely clear, but negative regulation by other ER membrane proteins appears to play a role (38). Of interest, the time course of attenuation of signaling in the three UPR pathways differs. During prolonged ER stress, IRE1 signaling appears to be turned off first, followed by ATF6 and lastly PERK (39).

It has also been appreciated recently that that the several UPR sensors can be activated without an increase in misfolded proteins by changes in ER membrane lipid composition (40). Such activation suggests that under some circumstances the UPR may anticipate the increase in protein flux and, hence, act in a "feed-forward" manner.

Table 1. Cellular processes regulated by the transcription factors activated by the three canonical unfolded protein response signaling pathways

PERK Pathway (transcription factors: ATF4/CHOP/GADD34)
Protein synthesis
Amino acid metabolism
Cell survival
Autophagy
Oxidant defense
Inflammation
IRE1 pathway (transcription factor: sXBP1)
Protein synthesis
Protein chaperoning/folding
Protein transport/degradation
Cholesterol metabolism/cell membrane synthesis
Cell survival
Autophagy
Inflammation
ATF6 pathway (transcription factor: ATF6N)
Protein chaperoning/folding
Protein transport/degradation
Mitochondrial biogenesis
Energy metabolism
Inflammation

Definition of abbreviations: ATF6 = activated transcription factor 6; CHOP = C/EBP-homologous protein; GADD34 = growth arrest and DNA damage; IRE1 = inositol requiring protein-1; PERK = PKR-like ER kinase; sXBP1 = spliced X-box binding protein 1.

Interaction of the UPR with Other Pathways

The UPR interacts with a variety of cellular pathways of importance in COPD. For example, when activated, all three arms of the canonical UPR exert cell type–dependent proinflammatory effects (41–44). IRE1, when complexed with the adapter protein TNF receptor–associated factor 2 (TRAF2), activates the mitogen-activated protein kinases (MAPK), jun kinase (JNK) and p38 kinase, which in turn activate the proinflammatory transcription factors nuclear factor (NF)-κB and activator protein-1. The PERK pathway also activates NF-κB by decreasing expression of its short-lived inhibitor, IκB, and ATF6 activates NF-κB by inhibiting the kinase Akt. Moreover, spliced XBP1 increases expression of Th1 chemokines/cytokines that have been detected in the lung in COPD, such as IL-8 (CXCL8), IL-1β, and IFN-β. ATF6 also increases the expression of CXCL8, the IFN-γ–inducible chemokines IP-10 (CXCL10) and Mig (CXCL11), and the metalloproteinase MMP-9. The UPR also exerts a proinflammatory role indirectly by augmenting production of reactive oxygen species.

Conversely, the innate immune system exerts selective effects on the three signaling arms of the UPR (43, 44). For example, toll-like receptors 3 and 4 promote the activation of sXBP1 while simultaneously inhibiting ATF6 and the PERK pathway at the level of eIF2α and ATF4. In addition, cytokines have direct effects on the expression and activity of the three sensors. For example, Th2 cytokines like IL-13 enhance expression of ATF6.

Although initially adaptive and prosurvival, the UPR switches into antisurvival mode when ER stress is sufficiently severe or prolonged (10, 26, 45–47). Both the PERK and the IRE1 signaling pathways promote cell apoptosis by activating canonical mitochondrial mechanisms. PERK, acting via ATF4, induces the transcription of the proapoptotic transcription factor, CHOP. In turn, CHOP increases expression of the death receptor DR5 and caspases 8, 3, and 7; decreases expression of the antiapoptotic factor BCL2; and increases reactive oxygen species by enhancing expression of the ER oxidoreductase-1. The resultant CHOP-mediated increases in cytosolic calcium and reactive oxygen species enhance mitochondrial membrane permeability. In contrast, IRE1 promotes apoptosis via the RIDD-induced degradation of prosurvival mRNAs and by TRAF-induced activation of JNK kinase. Of interest, RIDD-mediated decreases in DR5 mRNA exert an antiapoptotic effect (47). Although the mechanism(s) by which the UPR switches from a survival to a death mode are not well understood, decreases in IRE1 activity in the face of maintained PERK activity have been suggested to play a role (47).

Autophagy, the cellular process that collects and delivers cytoplasmic proteins and organelles to lysosomes for degradation and recycling, is activated by the UPR (48–51). The UPR enhances autophagy chiefly by inhibiting the autophagy inhibitor, mammalian target of rapamycin complex 1 (mTORC1). In fact, the PERK-eIF2α pathway is essential for autophagy induced by ER stress. PERK, and to a lesser extent IRE1, stimulates autophagy by inhibiting Akt, the activator of mTORC1. In addition, PERK induction of ATF4 activates at least 12 ATG genes involved in autophagy (51). Interaction between the UPR and mTORC1 is bidirectional, however. For example, increases in mTORC1 activity may stimulate the three sensors directly and would appear to allow the UPR to act in anticipation rather than reactively in response to the accumulation of misfolded proteins. mTORC1-induced increases in the load of new proteins entering the ER may also activate the UPR by causing ER stress.

Finally, the process of protein folding and refolding generates reactive oxygen species (52). The UPR compensates and enhances antioxidant capacity chiefly by PERK-induced ATF4 and possibly by PERK-mediated phosphorylation of Keap-1, an inhibitor of the master antioxidant transcription factor Nrf2 (33, 34). Phosphorylation of Keap-1 prevents Nrf2 degradation in the proteasome, thereby enhancing its half-life and transcriptional activity. In fact, ATF4 and Nrf2 interact combinatorially to increase transcription of a large number of antioxidant genes, including genes involved in glutathione synthesis and reduction, heme-oxygenase 1, and catalase (35).

Lung-Specific UPR

Of considerable importance, the UPR is both cell- and tissue-specific (13, 53, 54). Several lung-specific aspects of the UPR have been recognized. For example, IRE1 exists in two isoforms, a universally expressed alpha isoform (IRE1α) and a beta isoform (IRE1β) that is selectively expressed in the lung and in the gastrointestinal tract (55, 56). Functionally, IRE1β is less capable of splicing XBP1 but better able to perform its RIDD function (57). Within the lung, IRE1β is expressed by airway goblet cells and plays a role in development of the mucous-secreting cell phenotype and production of the mucins MUC5AC and 5B (55). Of note, IRE1β immunoreactivity in the airway epithelium is increased in asthma and cystic fibrosis, which, like COPD, are associated with mucus hypersecretion (56).

Members of the large ATF6 family of ER regulators also demonstrate tissue-specific expression, and despite their structural similarity have different transcriptional targets (58, 59). Oasis, a member of the ATF6 family of bZHIP transcriptional activators, which is highly expressed in the lung, may contribute to collagen production and lung repair (59). In airway epithelial cells, ATF6 increases expression of the ER calcium pump, SERCA2b, which has been implicated in airway smooth muscle proliferation and airway remodeling in asthma (42). In airway epithelial cells, ATF6 is up-regulated by the Th2 cytokines IL-4 and -13.

Cigarette Smoke-induced Alterations in Protein Metabolism and the UPR

Oxidant stress in the form of cigarette smoke irreversibly damages a variety of lung proteins, thereby requiring their degradation by the ubiquitin–proteosome system or via autophagic vacuoles (26, 60–62). Cigarette smoke–induced accumulation of insoluble, polyubiquitinated proteins has been demonstrated *in vitro* in alveolar epithelial cells, airway epithelial cells, and alveolar macrophages (AMs). Similar findings have been demonstrated *in vivo* in the lungs of cigarette smoke–exposed mice (26, 60). The identity of these misfolded proteins is not well delineated. However, at least one protein of considerable functional importance to ER function, protein disulfide isomerase (PDI), an ER-resident foldase, has been shown to be oxidized and misfolded by cigarette smoke both *in vivo* and *in vitro* (26). Accordingly,

cigarette smoke not only increases the load of misfolded proteins in the ER but simultaneously may impair ER folding capacity.

Concomitantly, cigarette smoke inhibits elimination of misfolded proteins in human lung cells by impairing proteosome function (61, 63). For example, acute treatment of human alveolar epithelial cells with cigarette smoke extract decreases the trypsin, chymotrypsin, and caspase activities of the proteasome (61, 63).

The autophagy–lysosomal pathway, a complementary degradative pathway that is particularly useful in degrading macroaggregates of terminally misfolded proteins, also appears to be impaired by cigarette smoke exposure (63, 64). AMs from chronic cigarette smokers demonstrate increased numbers of autophagic vesicles *in vivo* compared with AMs obtained from nonsmoking subjects (63). Moreover, acute exposure of human AMs to cigarette smoke increases the number of autophagosomes and impairs their elimination. Accumulation of autophagic vacuoles and their impaired elimination appears to be explained by defective fusion of autophagic vacuoles with the lysosomal membrane as evidenced by accumulation of p62, the ubiquitin and LC3-binding adaptor protein, which promotes fusion of these membranes. Similar findings have been obtained in cigarette smoke–exposed cultured human airway epithelial cells (22). Autophagosomes are also present in the lungs of cigarette smoke–exposed mice (22).

Not surprisingly, given its effects on protein misfolding, cigarette smoke induces a UPR in a variety of human cell types *in vitro* (61, 65–67). For example, in human airway epithelial cells, alveolar epithelial cells, and lung fibroblasts, acute cigarette smoke exposure up-regulates expression of the chaperones, GRP78, calnexin, and calreticulin; the foldase PDI; and molecules involved in the PERK pathway (i.e., p-eIF2a, ATF4, and CHOP).

Chronic cigarette smoking is also associated with activation of the UPR in the human lung as evidenced by increased expression at the protein level of the chaperones GRP78, calnexin, calreticulin, and PDI (66) (Figure 2). Chaperone levels are lower in ex-smokers than in active smokers, suggesting that the UPR is partially reversible with cessation of smoking.

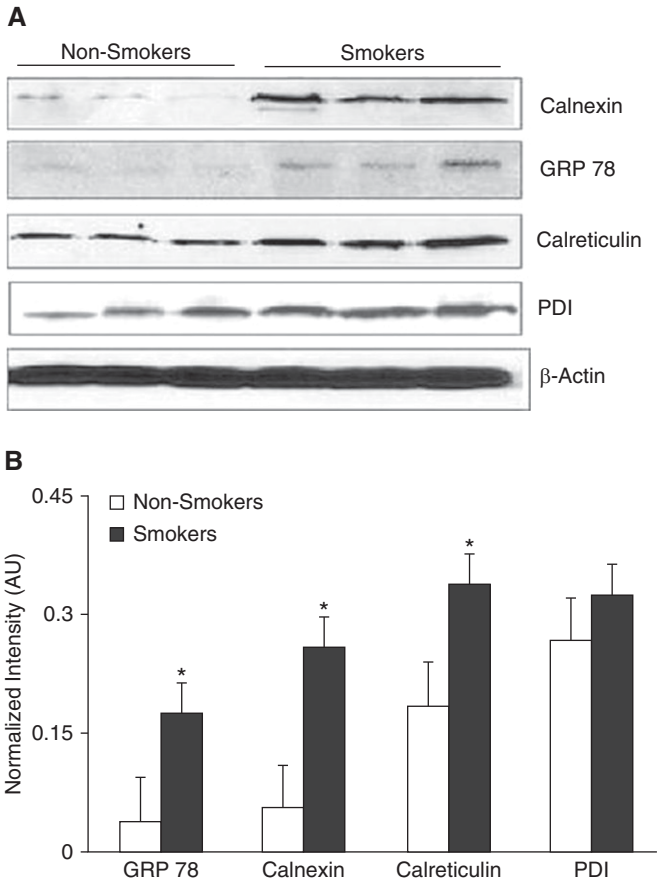

Figure 2. Expression of endoplasmic reticulum (ER) chaperones (GRP78, calreticulin, calnexin) and a foldase (protein disulfide isomerase-PDI) is increased in the lungs of smokers. Western blot in lungs of individual smokers and nonsmokers. (*A*) Results for individual subjects are shown as separate lanes. (*B*) Group mean ± SE data of bands scanned and quantitated. *$P < 0.05$ compared with nonsmokers. Data from Reference 66.

Cigarette smoke exposure of mice *in vivo* also induces a UPR in the lung, but changes are complex (25, 26). For example, Kenche and colleagues (26) demonstrated increased expression of p-eIF2α, CHOP, and p50 ATF6N proteins and small (less than twofold) changes in sXBP1 mRNA in mouse lung lysates after acute exposure to smoke from a single cigarette. Changes were less apparent 12 hours after exposure. Of interest, Geraghty and colleagues reported only a trend toward increased ATF4 and CHOP mRNA in mouse lung lysates after 4 weeks of smoke exposure and significant decreases below control values at 1 year of exposure (25). Geraghty and colleagues reported that ATF4 and CHOP mRNA were increased in AMs from mice exposed to smoke for 10 days (25). The results of these two studies in the mouse suggest the possibility that changes in the UPR are rapid, transient, and cell type–dependent.

Alterations in Protein Metabolism in COPD

The lungs of humans with COPD, like those of cigarette smoke–exposed mice, demonstrate increased amounts of insoluble polyubiquitinated, high-molecular-weight proteins (21, 22). However, because most subjects with COPD are ex-smokers, accumulation of terminally misfolded proteins is not explained by the acute effects of cigarette smoking. In subjects with COPD, several proteins involved in the ERAD process are increased (21, 22). Expression of ERAD proteins correlates with the severity of COPD and is greatest in subjects with Global Initiative for Chronic Obstructive Lung Disease 4 severity airflow obstruction. In addition, increased expression of p62 in the COPD lung suggests that elimination of autophagosomes

via the lysozyme is defective, as is the case with cigarette smoke exposure (22). Of considerable interest, the importance of defects in autophagy in COPD is supported by the observation that carbamazepine treatment, which stimulates autophagy, decreases both p62 and the severity of emphysema in the smoking mouse model (22). These several findings suggest that the function of both the proteosome and autophagy–lysosome pathway of protein degradation are impaired in COPD.

UPR and COPD

Apoptosis of lung structural cells, NF-κB–induced inflammation, and autophagy are believed to contribute to the process of lung destruction and remodeling in COPD (3, 68, 69). The diverse functions of the UPR are of particular interest in COPD in this regard because they have the potential to play a role in its pathogenesis. However, the role of the UPR in COPD remains unclear. Moreover, the few studies available are not entirely in agreement (20–23). For example, Min and colleagues (21) and Malhotra and colleagues (23) demonstrated increased expression of phospho-eIF2α and CHOP, key proteins in the PERK pathway, in the lungs of subjects with COPD. The IRE1 and ATF6 arms of the UPR were not assessed. Changes in phospho-eIF2a and CHOP expression correlated directly with the severity of airflow obstruction. Moreover, Malhotra and colleagues (23) reported that the increase in CHOP in COPD was associated with increases in caspase 3 and 7, suggesting that the PERK pathway was contributing to heightened apoptosis in COPD. Of importance, most subjects with COPD were ex-smokers, indicating that changes in expression were not explained by active cigarette smoking. Rather, heightened ER stress in COPD was attributed mechanistically to decreases in proteosomal activity and proteosome gene expression. In turn, reductions in proteosomal activity were explained in part by decreased expression of Nrf2, which promotes expression of key components of the 20 S proteosome under oxidant stress conditions. Of note, decreased Nrf2 expression and decreased expression of key Nrf2/ATF4 regulated antioxidant enzymes such as heme-oxygenase-1 in COPD have also been reported by others, suggesting that signaling pathways other than PERK exert predominant effects on antioxidant gene expression in COPD (70–72).

Recent studies indicate that changes in miRNAs that regulate the UPR also alter the expression of key UPR proteins in COPD (24, 73, 74). Hassan and colleagues (24) reported that decreased expression of miR199a-5p in peripheral blood mononuclear cells from subjects with usual COPD as well as the ZZ phenotype of alpha-1 antitrypsin deficiency act to increase expression of GRP78, ATF6N, and sXBP1. Decreased miR199a-5p expression in peripheral blood mononuclear cells was associated with heightened methylation of the miR199a-5p promoter region in subjects with COPD and ZZ.

In contrast to the above studies, Korfei and colleagues (20) failed to detect expression of the UPR markers GRP78, sXBP1, CHOP, and ATF6N in the explanted lungs of subjects with end-stage COPD expression. These UPR markers were increased in the lungs of subjects with IPF and in alveolar type II epithelial cells isolated from these subjects, however. Of note, IPF was the primary focus of the study. The COPD data were used as a control.

These several studies suggest that the UPR can be activated by several potential mechanisms, including direct oxidation of client proteins or chaperones (e.g., PDI), impaired function of the proteasome or autophagosomes, and decreased expression of miRNAs that regulate the UPR. They also suggest that the canonical UPR may be activated in only a subset of subjects with COPD. In fact, individual differences in the behavior of the UPR may explain the variable results reported by the several studies in COPD (32).

Gaps in Our Knowledge

A key unanswered question is whether the UPR acts as a susceptibility factor for the development of COPD. That is, does the behavior of the UPR either predispose to or prevent the development of COPD. Heightened UPR activity may contribute to lung cell apoptosis in COPD (21, 23). Conversely, it seems possible that diminished UPR activity may contribute to the accumulation of misfolded protein aggregates and impaired antioxidant defense observed in COPD. It is of interest in this regard that UPR gene expression varies considerably across individuals and appears to be genetically determined (32). Moreover, because COPD appears to be a syndrome with diverse phenotypes (1–4), it seems possible that the UPR may play a pathogenetic role in some subjects but not in others.

It has been suggested that the PERK arm of the UPR is activated in at least some subjects with COPD (21, 23). The role of the remaining UPR canonical pathways, IRE1 and ATF6, in COPD is unknown. Given the decades-long period of the disease, the tendency of the several arms of the UPR to turn off with prolonged stress, and the ability of immune mechanisms to modify the activity of the PERK and IRE1 signaling arms, it would be surprising if the canonical UPR is manifested.

Of note, the several studies performed in COPD have used whole lung tissue, which is composed of a mix of lung structural and inflammatory cells. As a result, the identity of the lung cell types that demonstrate increased UPR activity in the COPD lung is not known. It seems intuitive that cells with the highest rates of protein synthesis (e.g., airway epithelial cells, alveolar type 2 epithelial cells, AMs, and B cells in lymphoid follicles) would be most likely to demonstrate a UPR. The role of the UPR in individual lung structural and inflammatory cell types is unstudied.

Finally, mucous hypersecretion contributes to symptomatology and morbidity in COPD (75). IRE1β expression in airway epithelial cells promotes mucus cell development and mucin production. Whether IRE1β is overexpressed in subjects with COPD with chronic bronchitis and contributes to this process requires further study.

Conclusions

Oxidative stress in the form of cigarette smoke exposure induces protein misfolding and a UPR in the lung and isolated lung cells. Because of its role in protein metabolism, inflammation, autophagy, cell survival, and antioxidant defense, the UPR is potentially of great importance in the pathogenesis of COPD.

Several studies have suggested that the UPR contributes to lung cell apoptosis and lung inflammation in at least some subjects with human COPD. However, information on the prevalence of the UPR in subjects with COPD, the lung cells that might manifest a UPR, and the role of the UPR in the pathogenesis of COPD is extremely limited and requires additional study. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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