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***Corresponding Author**
Hammad Ghafoor

E-mail
hammadghafoor@seu.edu.cn

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Interaction of endoplasmic Reticulum stress responses to the vicinity of idiopathic pulmonary fibrosis: A potential target for a therapeutic approach

Hammad Ghafoor[1*], Farzana Nazir[2], Rabia Sabir[3], Muhammad Zubair[4], Muhammad Waqqas Hasan[5]

[1]Department of Microbiology and Immunology, School of Medicine, Southeast University, Nanjing, Jiangsu 2100096, China
[2]National University of Sciences and Technology PK & Guangzhou Municipal and Guangdong Provincial Key Laboratory of Molecular Target and Clinical Pharmacology, the NMPA and State Key Laboratory of Respiratory Disease, School of Pharmaceutical Sciences and the Fifth Affiliated Hospital, Guangzhou Medical University, Guangzhou, 511436, People's Republic of China
[3]MOE Joint International Research Laboratory of Animal Health and Food Safety, College of Veterinary Medicine, Nanjing Agricultural University, Nanjing, 210095, China
[4]Department of Laboratory Medicine, Wujin Hospital Affiliated with Jiangsu University, No. 2 North Yongning Road, Changzhou, 213017, Jiangsu, People's Republic of China
[5]Key Laboratory of Molecular Target & Clinical Pharmacology and the State & NMPA Key Laboratory of Respiratory Disease, School of Pharmaceutical Science & The Fifth Affiliated Hospital, Guangzhou Medical University, Guangzhou 511436, PR China

Abstract

Idiopathic pulmonary fibrosis (IPF) is a chronic lung disease characterized by scar formation in the lung's structure, progressive hypoxemia, dyspnea, body intolerance, and breathing difficulties. The diagnosis of IPF is difficult due to complex molecular mechanisms. In later stages, it will affect alveolar tissues, disrupt gaseous exchange, and ultimately lead to respiratory failure and death. The endoplasmic reticulum (ER) is essential for maintaining cellular homeostasis and protein secretions, lipid production, protein folding, and steroid synthesis or deposition. Numerous physiological and pharmacological conditions could affect ER homeostasis, which in turn influences the unfolded and misfolded protein responses that result in ER stress. The alveolar epithelium responds strongly to ER stress under IPF conditions, as evidenced by a biopsy of lung samples. Fibrotic disorders produce matrix-producing myofibroblasts. They have many wound-healing properties and may have distinct origins. The most often utilized marker is α-smooth muscle actin (SMA). However, the exact mechanism of ER stress in pulmonary fibrosis is still unknown. Therefore, in this review article, we have aimed to identify the disease-causing mechanism of IPF, understand the pathophysiology of alveolar cells during fibrotic response, and develop an effective drug to overcome this fibrotic disease. To develop logical strategies for modifying the senescent cell phenotype in the lung for therapeutic benefit, we have discussed the current understanding of the mechanism of IPF and the response of ER stress that regulates various aspects of cellular senescence related to chronic lung diseases.

Introduction

The term "pulmonary fibrosis" (PF) represents the pathological modification in the lung structure considered as slow progression, and irreversible deterioration of the lung architecture, which leads to the formation of scars on alveolar tissues. The later stages lead to organ malfunction, disruption of gaseous exchange, and respiratory failure due to the destruction of alveolar cells, which then leads to death [1, 2]. PF is an irreversible and chronic disease that comprises fibroblast and myofibroblast proliferation with the deposition of an extracellular matrix (ECM) that leads to respiratory failure. PF is a global disease with a prognosis due to unknown etiology and ineffective therapeutic strategies [3, 4]. After diagnosis, the median survival rate of the patients is about 2 to 6 years [5]. This lethal disease affects several types of lung cells and is characterized by continuous, irreversible injury, such as fibroblasts [6], endothelial cells, and epithelial cells [7]. IPF is characterized by progressive hypoxemia, dyspnea, unstable body intolerance, and severe respiratory complications [8]. Macrophages are the chief regulatory cells involved in the phagocytosis and degranulation of neutrophils during lung injury [9].

Various biological and pathological circumstances, such as fibroblast growth with lung extracellular matrix ECM components and epithelial cellular damage with interstitial inflammation, are involved in the pathophysiology of IPF [10]. Accumulation of activated (myofibroblasts) fibroblasts laterally to the epithelial surface, which can be composed of hyperplastic type II alveolar epithelial cells (AECs) or bronchiolar epithelium, is accompanied by collagen deposition [11]. Previous studies have shown that lung injury is closely related to inflammatory responses; the pathogenesis of pulmonary fibroblasts was caused by transforming growth factor beta-1 (TFG-b1) and myofibroblasts [12, 13]. IPF is more common in men (the likely age for the diagnosis is about 65 years) than women or rarely in younger people [14]. In addition to disease progression, several cell lines of AECs, fibroblasts, and different inflammatory mediators were involved [15]. Particularly, in IPF, parenchymal areas are host to macrophages with the M2 phenotype, which produce mediators that may influence fibrosis [15, 16]. After infection, respiratory cells stimulate and trigger the pathogen with the involvement of hyper-inflammatory cells and endoplasmic reticulum stress [17]. An elevated level of myofibroblasts in the lungs with the involvement of intermediate cells between the smooth muscle cells and fibroblasts suggests that these cells played a significant role in the progression of atypical fibrosis condition with the deposition of collagen and later developed IPF[13].

ER is a large perinuclear organelle that is responsible for protein secretion, modification, folding or unfolding, and transportation toward the appropriate sites. [18-20]. Homeostasis is essential for the normal functioning of cellular response, but different physiological or pathological factors could affect ER homeostasis, ultimately causing ER Stress [21, 22]. Numerous diseases are closely associated with misfolded proteins and cellular responses that create a signaling cascade, which is called an unfolded protein response. The Unfolded Protein Response (UPR) is activated by three transmembrane sensor proteins in the endoplasmic reticulum: IRE1 (inositol-requiring enzyme 1), PERK (protein kinase RNA-like endoplasmic reticulum kinase), and ATF6 (activating transcription factor 6) [23]. In the absence of endoplasmic reticulum stress, the luminal domains of these proteins are associated with BiP, or GRP78 (glucose-regulated protein 78 kDa), which inhibits the activation of the corresponding sensor proteins. During ER stress, BiP detaches from the sensor proteins, leading to their activation. Consequently, IRE1, PERK, and ATF6 "assess" if the functionality of the ER folding apparatus is adequate for the volume of newly produced proteins [23, 24].

The unfolded protein response is a cellular stress response that is closely linked with ER stress and is involved in proteostasis activity, which leads to cell death when ER stress persists. [25] and ER stress occurs when the ER's ability to fold proteins becomes saturated, which greatly contributes to the development of IPF [26, 27]. ER Stress is involved in different stress-related disease conditions including cancer, diabetes, neurodegenerative disease, and metabolic disorders [18, 28, 29], and different environmental factors such as stress, toxins, and silica

dust particles disrupt normal cell function (ER response), resulting in misfolded proteins in the ER lumen and activation. ER disturbance promotes different age-related disorders such as Alzheimer's and IPF [30, 31]. However, ER stress is involved in various types of pulmonary infections associated with the disease [32, 33]. ER stress/UPR fundamental role in fibrosis and a pathogenic role in various organs such as the liver, heart, kidney, gastrointestinal tract, and lung [28]. ER stress is potentially linked with IPF by the mutation of surfactant Protein C (SFTPC) in the alveolar epithelial cells [34, 35]. The Food and Drug Administration (FDA) approved pirfenidone and nintedanib, the first two pharmaceutical therapies for IPF, in 2014, after more than 10 years of ineffective clinical trials. These drugs are responsible for protecting lung function against pulmonary fibrosis patients, but they have no distinct effect on the quality of the mortality rate [36, 37]. In this review article, we will discuss the pathological process of IPF with several factors and explain the role of ER stress during pulmonary fibrosis, such as quantifying ER stress-associated proteins in blood specimens to detect early-stage idiopathic pulmonary fibrosis (IPF). Examining ER stress-related gene signatures in lung tissue biopsies or peripheral blood samples. This review article will be helpful for the strategic treatment of pulmonary fibrosis.

Pathophysiological process of idiopathic pulmonary fibrosis

Since the 1800s, in several reports on fibrotic lung disease, Liebow and Carrington's explained the description of "Usual Interstitial Pneumonia" (UIP), it is a distinct histopathologic form of diffuse lung parenchyma [38] that allowed for the formal establishment of idiopathic pulmonary fibrosis in late 1960s. Initially, the UIP correlates with histological findings such as "cryptogenic fibrosing alveolitis" [39]. Idiopathic pulmonary fibrosis **(**IPF) is a chronic inflammatory disorder, that slowly develops fibrosis [40, 41] and is related to various biological factors such as genetics, environment, exposure to dust, and several other risk factors, such as micro-injuries related to aging alveolar epithelium, playing an essential role. Katzenstein and his colleagues began research into the pathogenesis of IPF that demonstrated inflammatory cells were responsible for initiating this disease [42, 43]. Previous studies showed that, after histopathologic investigation and visualization in electron microscopy, few inflammatory cells, were responsible for epithelial damage or lung injury that was closely related to the formation of fibroblastic foci on the IPF patients [43]. IPF is associated with hereditary and several environmental risk factors, with repeated local micro-injuries to the elderly alveolar epithelium playing an important role. The initiating response in these micro-injuries is closely linked with the epithelial-fibroblast response, then the elevation of ECM and remodeling of the lung interstitium were monitored. These micro-injuries cause aberrant epithelial-fibroblast consciences, myofibroblast matrix synthesis, substantial extracellular matrix buildup, and lung interstitial remodeling.

Environmental factors

Environmental variables significantly influence the development and progression of pulmonary fibrosis (PF), including Idiopathic Pulmonary Fibrosis (IPF) and other variants. These factors may lead to lung damage, inflammation, and fibrosis due to recurrent exposure to deleterious substances. Several environmental factors were responsible for the development of this fibrotic disease. Occupational exposure and various infectious agents are likely to cause IPF, which is closely linked to environmental variables. However, environmental variables such as silica, viruses, germs, dust, industrial pollution, and agricultural practices are linked to various medical disorders. [14, 44]. Silicosis is a chronic, irreversible disease; this occupational disease is spreading all over the world [45]. Silicosis is a type of pulmonary fibrosis lung disease and is still untreatable due to ineffective treatment strategies. The best approach to preventing this fibrotic disease is early diagnosis, and a chest x-ray is recommended [46, 47]. Smoking is harmful to health and causes IPF in several patients [48]. Prolonged exposure to these environmental variables can result in recurrent lung damage, oxidative stress, and the activation of profibrotic pathways, ultimately leading

to pulmonary fibrosis.

Genetic factors

Various genetic factors were engaged in initiating human disorders. A person can get inherited responses from the parents having a full set of genes. There is mounting evidence indicating the genetic role and response against the onset of IPF. Therefore, a direct strong association is not reported, however, other studies have described how host defenses such as MUC5B, ATP11A and TOLLIP maintain telomeres such as OBFC1, TERT, and TERC, Epithelial barrier function likely DPP9, and DSP were recognized [14, 49, 50]. A diverse range of diffuse parenchymal lung disorders with sporadic genetic variants make up interstitial pneumonia, containing genes involved in telomere biology and surfactant failure, such as SFTPC and SFTPA2, which include RTEL, TERT, TERC, and PARN. Later, it investigated how various individuals with Familial Interstitial Pneumonia (FIP) were related to mutations in SFTPC-containing genes, including SFTPC and SFTPA2, which are involved in surfactant dysfunction and telomere biology [51] and SFTPA2 [52]. Additionally, the entire SFTPC mutation occurred in human epithelial cells (A549 cells), which demonstrated elevated expression levels for activating ER stress. Several transcriptional factors associated with ER chaperones, including BiP (GRP78) or XBP-1, were confounded during ER stress [53]. Therefore, diverse membranous proteins like SFTPC and SFTPA2 were extremely expressed in lung cells called type II alveolar epithelial cells (AECs), proposing that AEC dysfunction is responsible for the disturbance in the protein's membrane that creates a strong link with the development of IPF, as shown in **Fig. 1**. As shown in **Table 1**, the SFTPC cell mutation revealed the activation of caspase 4, which starts the apoptotic cascade. As a result, a specific ER caspase (Caspase 4) was involved in the subsequent modification of genes in the membrane that were causing ER stress.

Maladaptive repair process

In the idiopathic pulmonary fibrosis (IPF) case, it is hypothesized that the activation of lung cells such as alveolar epithelial cells (AECs) after initial interstitial lung injury was involved in the maladaptive repair process [57]. During IPF, fibrogenesis response and pathological alteration in the lung structure were carried out by the involvement of the AECs. After lung injury, pathological disruption occurred, and then cellular homeostasis was disturbed. at that time, type 2 alveolar epithelial cells have been implicated in the renewal process to the type 1 alveolar epithelial cells [58, 59]. Type 1 and Type 2 alveolar epithelial cells participate in the IPF disease, these cells are involved in the fibrotic foci containing hyperplastic and apoptotic cells [40].

ER stress and the unfolded protein response

The ER is an intracellular organelle responsible for protein synthesis, modification, folding, and targeting proteins to their appropriate positions. Up to 4 x10^6 proteins are typically produced by each cell every minute for the ER-involved cellular modification process, and these numbers remain one-third of those at the processing level [60, 61]. ER plays a basic role in coordinating protein synthesis, folding, assembly, and trafficking, as well as the destruction of damaged proteins [62-65]. ER is involved in cellular homeostasis (ion balance) that is responsible for various proteins' folding and secretion, synthesis of lipids, and synthesis and storage of steroids [66]. Usually, the ER is in charge of secreting chaperone proteins like BiP (GRP78) and chop during the reaction to protein folding. However, under harsh circumstances, cells lack their equilibrium, making it difficult to maintain ionic balance and healthy metabolic processes for many cellular pathways. The depletion of calcium, decreased energy reserves, increased protein synthesis, frequent mutant protein expression, and activation of the unfolded protein response are only a few factors that could impact the ionic cell equilibrium [67]. Therefore, a variety of variables, such as protein load, cellular metabolism, chaperone effectiveness, calcium, and redox balance, strictly govern ER function [68-71].

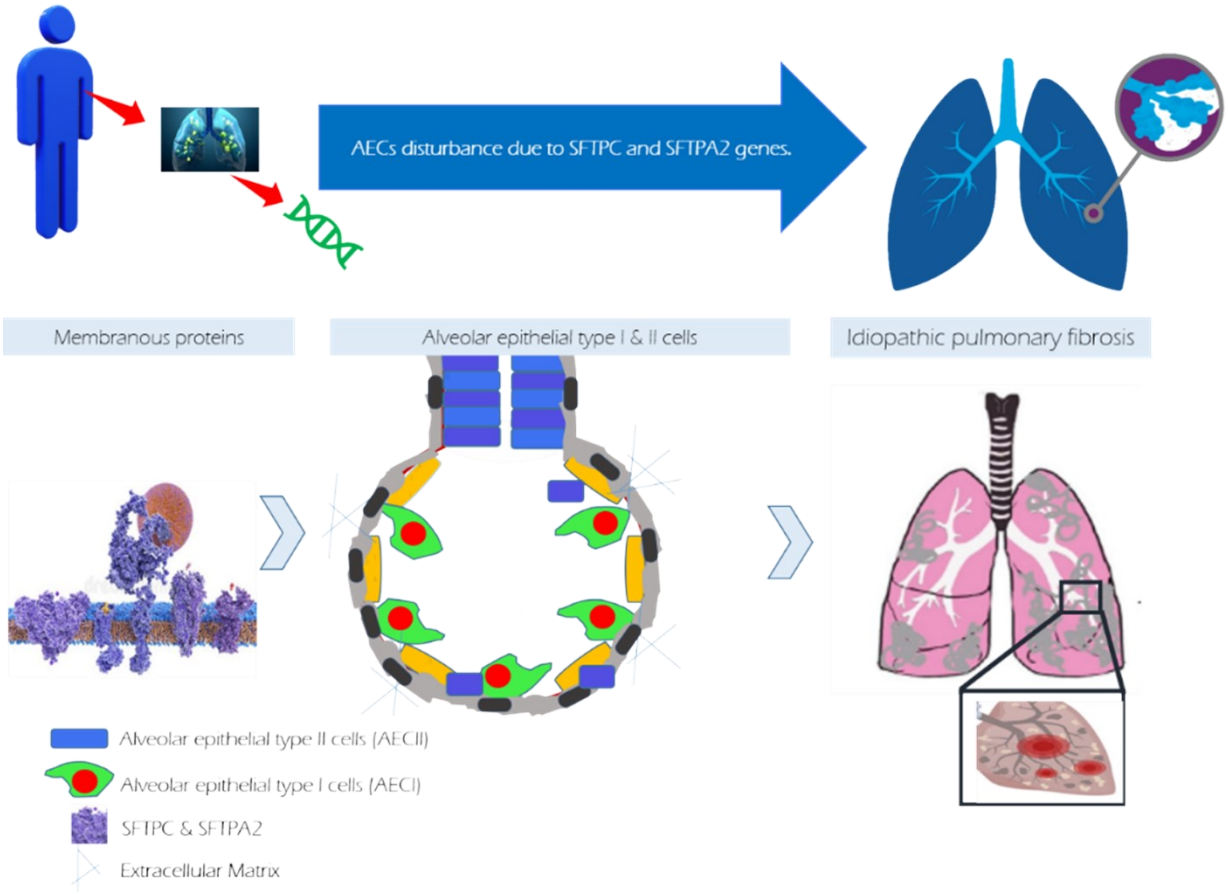

Fig. 1: The proportion of SFTPC and SFTPA2 genes were higher in the Type II alveolar epithelial cells (AECs) that propose AECs disturbance due to SFTPC and SFTPA2 genes in the idiopathic pulmonary fibrosis.

Table 1: Idiopathic pulmonary fibrosis represented a mutation percentile with the involvement of different genes.

Disease	Gene	Mutation percentile	References
Idiopathic pulmonary fibrosis sporadic (80 percent of IPF cases)	Unidentified	NOT YET	[54]
Familial Interstitial Pneumonia (20 percent of IPF cases)		8-15	[49, 55]
	TERT		
	TERC	Less than 1	[49, 55]
	SFTPC	2-25	[51, 56]
	SFTPA2	Less than 1	[52]

In mammalian cells, the primary proteins that initiate this evolutionarily conserved response are activating transcription factor 6 (ATF6), inositol-requiring 1α (IRE-1α), and double-stranded RNA-dependent protein kinase-like ER kinase (PERK) [62, 63, 65]. BiP is a chaperone that facilitates protein folding in the unstressed state for proper cellular function and numerous metabolic activities [64, 65]. UPR response sensors such as IRE1, PERK, and ATF6 remain bound and inactive. The UPR is stimulated by cellular stress, protein accumulation in the ER, and BiP sequestration away from the sensors. It is intended to restore cellular homeostasis through a reduction in overall protein translation as well as selective increases in the expression of important chaperone and redox proteins. Apoptosis and cell repair are associated with ER [72, 73]. Protein kinase R-like endoplasmic reticulum kinase (PERK), inositol-requiring enzyme 1 (IRE1), activating transcription factor 6 (ATF6), and glucose-regulating protein 78 (GRP78 or Bip) are all

upregulated in response to ER stress, which can improve the ER's ability and unfolded proteins have played an essential role in the cytoprotective effect.

ER transmembrane proteins

A specific class of integral membrane protein known as a transmembrane protein (TP) covers the entire cell membrane. The production of lipids and proteins is closely dependent on the ER. The ER, the Golgi apparatus, lysosomes, endosomes, secretory vesicles, and the plasma membrane are all organelles that produce transmembrane proteins and lipids. The ER transmembrane proteins PERK, ATF6, and IRE1 are intimately linked to the UPR pathways [74, 75]. During the cellular stress response, these proteins are bound by BiP and stable inactive conditions [71]. The synthesis of membrane proteins with multiple transmembrane domains at the endoplasmic reticulum is poorly understood, despite further study being necessary for the importance of these proteins to cell physiology.

PKR-like endoplasmic reticulum kinase

PKR-like Endoplasmic Reticulum Kinase (PERK) serves as one of the three primary sensors of endoplasmic reticulum stress within the Unfolded Protein Response (UPR). It is essential for sustaining protein homeostasis; however, extended activation leads to inflammation, apoptosis, and fibrosis in conditions such as idiopathic pulmonary fibrosis (IPF), neurodegeneration, and cancer.

The UPR uses PKR-like endoplasmic reticulum kinase (PERK) as a master regulator of protein synthesis under ER stress to stop an additional influx of client proteins. The eukaryotic translation initiation factor 2A (eIF2) subunit of the elongation initiation factor 2 (eIF2) complex, PERK's sole established substrate, is phosphorylated at serine-51, preventing the start of translation [76-78]. The transmembrane protein PERK regulates oxidative stress and contributes to the accumulation of misfolded proteins in the ER. PERK receptors sense the presence of unfolded proteins and reduce the activity of the ribosomal initiation factor (eIF2a) to attenuate the translation of proteins by phosphorylation of its α-subunit. PERK signaling cascades (ER Stress) depend on CHOP, and many disorders that result in ER stress are related to CHOP-induced apoptosis [79]. A prior work showed that PQ-induced epithelial mesenchymal transition (EMT) was significantly impacted by PERK-regulated ER stress, but the underlying mechanism was not obvious[80]. Loss of epithelial markers and the development of mesenchymal markers are characteristics of EMT [81].

Activating Transcription Factor 3

Activating Transcription Factor 3 (ATF3) is a member of the ATF/CREB family of transcription factors and induces a wide range of stress responses (toxin-injured liver, blood-deprived heart, and post-seizure brain). Cyclic AMP-dependent transcription factor ATF-3 (ATF-3) protein is encoded by the *ATF3* gene [82] and it is involved in numerous transcriptional activities. During various physiological stress conditions in the tissues, ATF-3 response is induced [83]. PERK activates eukaryotic translation-initiation factor 2 (eIF2), which results in selective translation of ATF4 and enhanced expression of ATF3 while decreasing overall translation [84]. ATF3 is a crucial stress-responsive transcription factor implicated in multiple clinical diseases, including pulmonary fibrosis. It serves a dual function contingent upon the biological setting, acting as either a transcriptional repressor or activator.

Activating Transcription Factor 4

Activating transcription factor 4 (ATF4) is regulated by various cellular gene expressions [85]. ATF4 is a protein that is encoded by the *ATF4* gene in humans [86, 87]. The eIF2 complex is required for the beginning of protein synthesis in eukaryotic cells and suppresses the process by which eIF2 is phosphorylated. ATF4-dependent expression of the genes ATF3 and CHOP, which are involved in metabolism, amino acid balance, and glutathione production, is regulated by EIF2 phosphorylation [88-91]. In prolonged ER stress conditions, ATF4 arrested growth induction and DNA damage-inducible gene 34 (GADD34) showed translational recovery (eIF2α)

[92]. In addition, ATF4 controls 254 genes' expression without the assistance of CHOP. Different cellular activities, such as the body's reaction to ER stress (chaperones), protein synthesis, translation, and amino-tRNA synthetase activity, are regulated by CHOP and ATF4 [85].

Activating Transcription Factor 6

An unfolded protein response is carried out by Activating Transcription Factor 6 (ATF6), a transmembrane protein that is encoded by the ATF6 gene. ATF6 occurs in two isoforms, ATF6α and ATF6β. In mammalian cells, this protein is responsible for the induction of X-box binding protein 1 (XBP-1) and a transcription factor activated by IRE-1 [93, 94]. During ER stress, BiP is released from ATF6 at protease-cleaving sites (71, 88), the cytoplasmic domain is released into the cytosol. The cleaved domain moves to the nucleus and binds to cis-acting ER stress response elements (ERSE), activating ER protein-folding chaperones like BiP, GRP94, calreticulin, calnexin, and protein disulfide isomerase [94-97].

Inositol-Requiring Enzyme 1

The Inositol-Requiring Enzyme 1 (IRE-1) protein is a transmembrane protein with two functional domains. IRE-1 includes protein kinase and endoribonuclease activities that are activated during ER stress. IRE-1 exists in 2 forms in mammals, including IRE1-a, and released from BiP, IRE1-b homodimerizes and cleaves up to a 26-nucleotide intron region from the transcription factor XBP-1. Spliced XBP-1 translocates to the nucleus, where it binds to ERSE (a different binding site than ATF6), stimulating transcription of ERAD target genes and restoring protein homeostasis [98, 99].

GADD153/C/EBP homologous protein

Prolonged ER stress conditions could induce apoptosis via ER-related apoptosis molecules such as GADD153/C/EBP homologous protein (CHOP), c-Jun N-terminal kinase (JNK), and caspase-12 [100]. The transcription factor C/EBP homologous protein (CHOP) is activated by ER stress, and CHOP knockout protects against its deadly consequences. CHOP is involved in the transcriptional activity that is activated during the ER stress pathway with the regulation of three UPR pathways that are linked with apoptosis. The CHOP gene promoter contains binding sites for ATF4, ATF6, and XBP-1 [101]. ER, signaling cascade leads to cell death under pathological situations [102].

Glucose-Regulated Protein 78 (GRP78/BiP)

ER homeostasis is controlled by the chaperone protein Glucose-Regulated Protein 78 (GRP78/BiP), also known as glucose-regulated protein 78 [103]. Aged rodent tissues have decreased GRP78 expression, suggesting that GRP78 may be involved in the maturation process [104, 105]. GRP78 is linked with the maturation process of rodents, as shown in Figure 3. GRP78 inhibition causes ER stress/UPR activation and liver-specific inflammation. The deletion of GRP78 degenerates fibrosis injury [106]. The inappropriate functioning of epithelial pulmonary fibroblasts that is associated with ER stress is likely a mechanism related to the aging of IPF patients [107, 108] (**Fig. 2**).

Regulation of effector pathways by ER stress

ER stress is involved in several disease complications such as cancer, obesity, diabetes, and inflammation [109, 110]. ER stress is also responsible for alveolar infection and creating lung fibrosis through the regulator for fibroblast proliferation and myofibroblast differentiation [111]. ER Stress is associated with fibrosis through apoptotic pathway (cell death), activation and differentiation of fibroblasts, epithelial-mesenchymal transition (EMT), and stimulation or polarization of inflammatory responses [25, 28, 32]. During pathogenic load, macrophages are the first line of defense soldiers that are responsible for overcoming harsh situations with the polarization of M1 (pro-inflammatory) or M2 (pro-fibrotic) separations based on micro-environmental stimuli [112]. Chronic AEC II

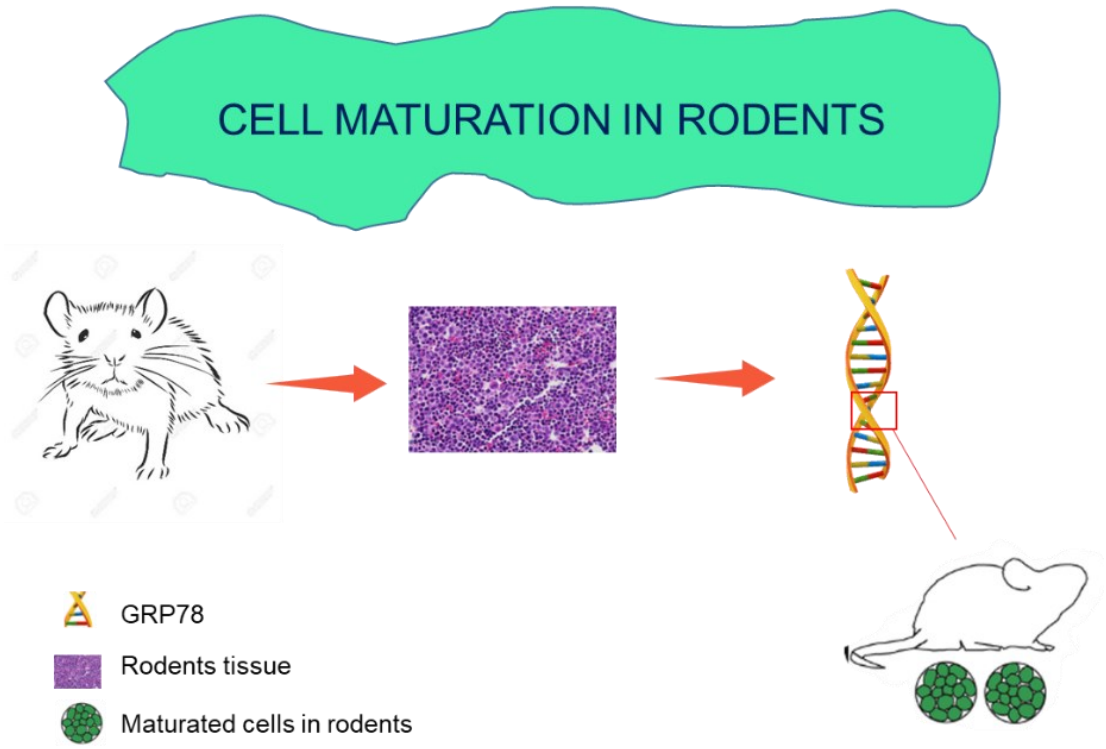

Fig. 2: GRP78 linked with the maturation process of rodents.

dysregulation is thought to play a key role in IPF. AEC IIs are stem cells that help to renew type I AECs during normal lung homeostasis or after lung injury. AEC IIs were discovered to be aberrant in the tissues of IPF patients. Activated AEC II cells help PF by inducing lung fibroblasts to secrete extracellular matrix proteins and collagen [5]. However, during diabetic conditions, ER stress is responsible for the activation of pulmonary fibroblasts and allergic inflammatory responses through CHOP or JNK pathways [113]. Furthermore, ER stress is caused by a decrease in PINK1 activity, suggesting a possible feedback mechanism between ER stress, mitochondrial failure, and fibrotic remodeling. [114].

Prospective mechanisms of ER stress linked with pulmonary fibrosis

ER stress is closely linked with pulmonary fibrosis, including multiple cell lines and the bleomycin-induced animal model of IPF [25, 32]. ER stress is responsible for fibrosis by the strong evidence of human alveolar epithelial cells (AECs type II). These pneumocytes showed an induced expression level of CHOP (ER Stress marker) [113] and the activation of ATF4, ATF4, and XBP1 [26]. Hence, the activation of the unfolded-protein response (UPR) has been responsible for the sporadic transmission of IPF associated with viral infection and inherited related IPF [27]. A higher level of fibroblast was also observed in the lungs of IPF patients, which was connected to an increased ER stress response to TGFb [115]. IPF is associated with the mutation of two genes (SFTPC and SFTPA2) that lead to ER stress in type II pneumocytes and misfolding response in the encoded surfactant proteins, serving as a direct molecular driver for the ER stress in these forms of IPF [27, 116] (**Fig. 3**).

Therapeutic approaches

Endoplasmic reticulum stress and the Unfolded Protein Response (UPR) are associated with various diseases, including pulmonary fibrosis, neurological disorders, metabolic disorders, and cancer. Given that UPR regulates cellular homeostasis, apoptosis,

inflammation, and fibrosis, targeting its pathways presents interesting therapeutic methods. According to the obvious homeostatic response and adaptive nature of this system, it will lead to prenatal and neonatal lethality like PERK, ATF6, IRE1, and XBP1 knockout mice. UPR is activated after the accumulation of unfolded or misfolded proteins in the lumen of the endoplasmic reticulum [25, 101]. The unfolded protein response is a signaling cascade that is triggered by ER stress and is responsible for various cellular processes. The UPR increases the ER to properly accomplish protein folding or initiate apoptosis or autophagy pathway in cells that are irreversibly damaged by differences in gene expression level and translation of protein. As a result, instead of reducing pathogenic effects, specific UPR systems may be involved in cellular toxicity. Despite this, a small molecule inhibitor has been described that allosterically modifies the RNAase activity of IRE1a oligomers (but not dimers), resulting in cell survival under ER stress [117].

Another approach to reducing ER stress would be to improve protein processing by pharmacologically increasing chaperone activity. Targeting ER stress-downstream effectors that control cell survival and fibrotic remodeling may therefore be a successful technique. Downstream or terminal UPR effectors (e.g., CHOP) are not essential for sustaining homeostasis under normal physiological settings, as demonstrated by the viability of CHOP knockout mice. Interference with protein processing and folding produces ER stress, which leads to an increase in unfolded protein response. In cases of pulmonary fibrosis, ER stress controls the differentiation of myofibroblasts. These findings suggest that pulmonary fibrosis treatment and control using ER stress inhibitors may be possible.

Discussion

There is a growing interest in figuring out which proteins or signaling pathways are involved in the pathophysiological process of pulmonary fibrosis. Chronic pulmonary fibrosis causes diffuse parenchyma in the lung tissue, which is made up of excessive extracellular matrix deposition and alveolar architecture loss, ultimately leading to respiratory failure [3, 4]. In the last few decades, IPF has been considered a life-threatening disease. Although, previous reports demonstrated that pulmonary fibrosis is closely associated with ER Stress [111]. ER stress has been involved in different cellular pathways and disease conditions. ER stress is initiated due to the disturbance of processing and folding proteins, ultimately responsible for an unfolded protein response (UPR) [118]. ER Stress is involved in the upregulation of myofibroblast differentiation in pulmonary fibrosis [111]. Various pathological conditions and molecular mechanisms were elaborated that led to scar formation in the lung tissue and decreased function. Therefore, the spontaneous transmission of IPF has been caused by the activation of the unfolded protein response (UPR). IPF is linked with the mutation of genes that cause a misfolding response in the encoded surfactant proteins.

It is vital to look into the mechanism of IPF, especially because it is one of the most prevalent adverse effects of lung remodeling and lung function impairment. With the mutation of genes (SFTPC and SFTPA2) that result in a misfolding response in the encoded surfactant proteins and ER stress in type II pneumocytes, ER stress is closely linked to the development of IPF, providing a direct mechanistic driver for ER stress in these forms of IPF. Numerous diseases have been linked to ER stress, and some mechanisms connect ER stress to cell death. The plethora of parallel pathways that may lead to downstream cell death mechanisms poses the biggest obstacle to any technique for preventing cell death brought on by ER stress. However, it has been reported that a small molecule inhibitor can repress or reduce the RNAase activity of IRE1a oligomers (but not dimers), allowing cells to survive under ER stress.

Conclusion

Numerous studies identify endoplasmic reticulum stress as a significant contributor to the advancement of various chronic fibrotic illnesses, including idiopathic pulmonary fibrosis (IPF). In the lung, endoplasmic reticulum stress predominantly localizes in alveolar epithelial cells, where this route has been

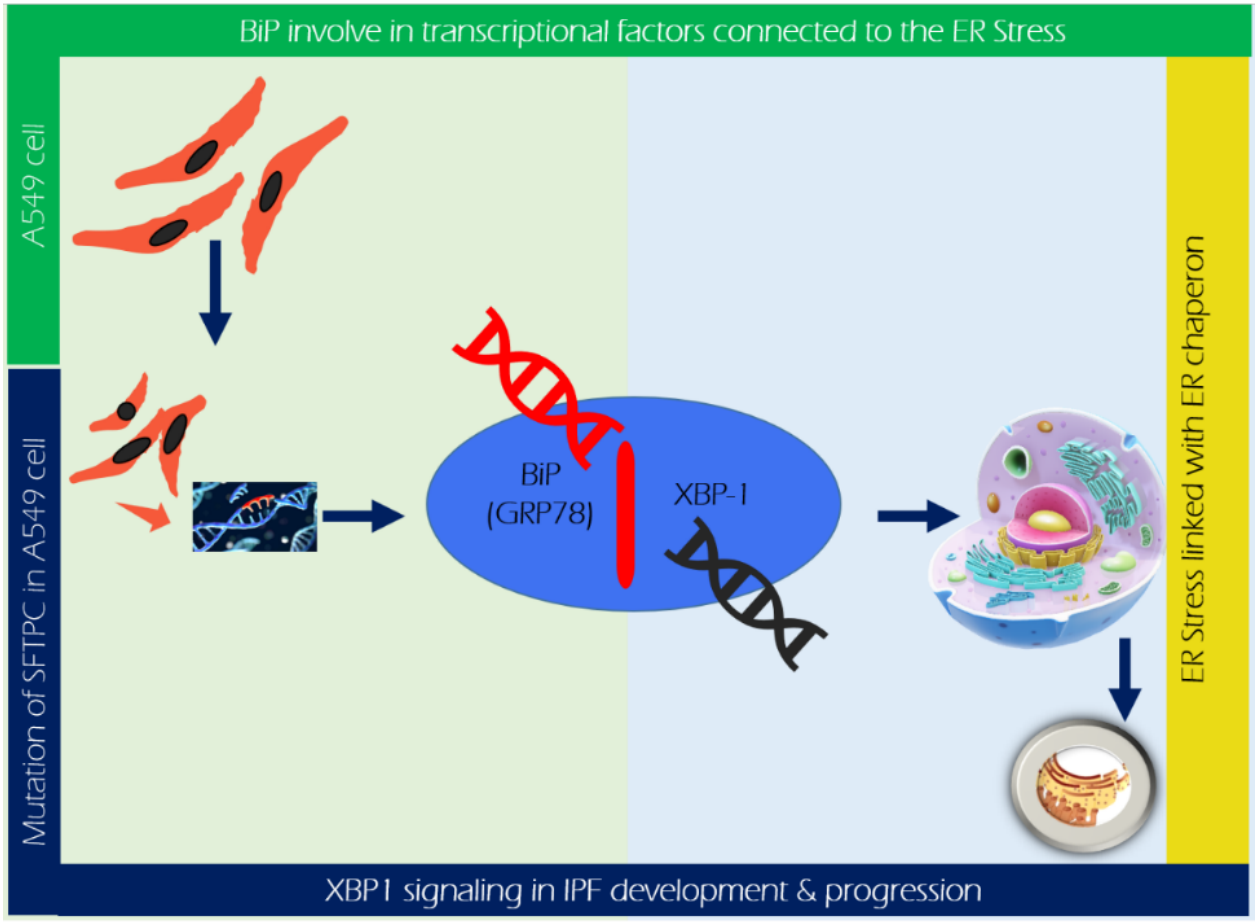

Fig. 3: The Mutation of SFTPC that occurred in the human epithelial cells (A549 cell) showed ER Stress activation that is closely linked with ER chaperones including BiP (GRP78) and XBP-1.

associated with heightened apoptosis of these cells and other pro-fibrotic phenotypic traits. As a result, human respiratory epithelial cells (AECs type II) seriously recommend that ER stress is to blame for fibrosis because these pneumocytes displayed elevated CHOP expression levels. The apoptotic pathway (Cell death) is closely linked with ER stress; therefore, they participate and engage in different activities of the differentiation and activation of fibroblasts and then stimulate the inflammatory cells during epithelial-mesenchymal transition (EMT).

Future prospectives

Respiratory illnesses are among the most mysterious and lethal diseases that disturb the entire world through health-related issues. PF is a life-threatening disease that, after prolonged, sustainable infection, leads to irreversible damage of the lung tissue and later respiratory organ failure. Ultimately, this leads to the profuse deposition of extracellular matrix inside the alveolar duct and causes respiratory failure. Although the present study suggests that ER stress-induced pulmonary fibrosis through the involvement of alveolar epithelial cells. Any disruption in the ER causes ER stress. ER stress has been linked to several diseases and cell death. As a result, the link between ER stress and senescence, which has been found in several lung cells, is an important element for future research. Pulmonary fibrosis is closely linked with the involvement of the ER stress pathway that is connected to a wide variety of respiratory illnesses having different onsets of respiratory failure with the acute and chronic stages, and there is significant evidence for the pathogenesis of this occupational sickness.

ER stress is responsible for UPR, which has been described in a variety of disorders, and essential aspects to manage this associated mechanism for future research. Previously, different *in-vivo* and *in-vitro* studies determined that ER stress may be involved in the regulation of cellular pathways and the progression of several diseases. Then, these pathways are severely impacted by ER chaperons, which are responsible for the development of IPF. Currently, advanced technologies finding an exact genomic sequence evaluation with transcription and proteomic strategies of single cells isolated from IPF patients will fill the knowledge gaps relating to different factors to overcome UPR and downstream pro-fibrotic factors associated with pathways. So far, the prospects have been concerned with determining the sequence of a gene such as chaperone, which has been implicated in the spread of fibrosis and other respiratory illnesses. The effectiveness of antifibrotic medications in treating IPF has been demonstrated, but it is unknown whether these results will generalize to other fibrotic disorders with limited therapeutic options [119]. Addressing these issues and creating tailored therapeutics for use in conjunction with existing therapies will be the task of the upcoming decade to stop the advancement of fibrosis and preserve the quality of life for patients with IPF.

Authors' contributions

Hammad Ghafoor conceptualized and collected data, designed the figures, and prepared the first draft of the manuscript. Farzana Nazir and Rabia Sabir reviewed and edited the manuscript. All the authors carefully read, discussed, and approved the final manuscript.

Conflict of interest

The authors declare no conflict of interest.

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