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REVIEW: IPF

Unravelling the progressive pathophysiology of idiopathic pulmonary fibrosis

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ABSTRACT: Idiopathic pulmonary fibrosis (IPF) is a life-threatening condition, with a median survival of <3 yrs. The pathophysiology is not fully understood, but chronic injury of alveolar epithelial type II cells (AECII) is considered key.

In IPF, disturbed folding and processing of surfactant proteins and impaired DNA repair may represent underlying reasons for maladaptive endoplasmic reticulum stress responses, increased reactive oxygen species production and/or DNA damage. Excessive AECII apoptosis occurs, leading to permanently perturbed epithelial homeostasis. The role of secondary hits also becomes evident. These may aggravate the disease and result in increased epithelial turnover, exhausting the regenerative capacity of progenitors and disturbing epithelial–mesenchymal interactions. Fibroblast proliferation, transdifferentiation and matrix deposition may be mediated through various mechanisms including epithelial–mesenchymal transition, fibrocyte invasion or expansion of a local fibroblast population.

Treatment modalities aiming to attenuate epithelial injury are currently in early pre-clinical development and may reach the clinical arena in only a few years. Meanwhile, novel drugs acting on highly activated fibroblasts such as pirfenidone, an anti-fibrotic drug authorised for IPF in the European Union, or BIBF 1120, a novel triple-kinase inhibitor (blocking vascular endothelial growth factor, platelet-derived growth factor and fibroblast growth factor) currently under clinical investigation, seem to attenuate the progression of IPF.

KEYWORDS: Alveolar epithelial type II cells, endoplasmic reticulum stress, fibroblast, idiopathic pulmonary fibrosis, pathophysiology

Idiopathic pulmonary fibrosis (IPF) is the most common form of chronic fibrosing idiopathic interstitial pneumonia (IIP). IPF is a fatal lung disease typically affecting older adults, with an estimated prevalence of 1.6 to 1.7 per 10,000 persons, and a median survival of 2–5 yrs [1–4]. A progressive decline in lung function increasingly restricts routine physical activity of the patient [1, 5]. While the mechanisms that result in IPF are still not fully understood, there is a strong suggestion of the involvement of epithelial alveolar cells.

MYERS and KATZENSTEIN [6] suggested the role of epithelial necrosis and alveolar collapse in the pathogenesis of usual interstitial pneumonia (UIP). However, this observation failed to gain a footing against the prevailing hypothesis that the development of IPF was due to a chronic inflammatory process and the resulting belief that therapeutic intervention should be directed toward arresting the inflammatory and immune response rather than the fibrotic process [7]. In 2006, SELMAN and PARDO [8] reintroduced the topic of the potential role of epithelial cells in IPF.

IPF is now thought to arise following recurrent injury to the epithelial alveolar cells, in particular the alveolar epithelial type II cell (AECII), thus, provoking responses associated with normal tissue repair and scar formation. In the pathogenesis of IPF, however, this scarring process continues unabated [9]. Risk factors for epithelial alveolar cell injury are thought to include smoking, exposure to metal or wood dust and genetic disposition, as well as age, amongst others [2].

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Indeed, chronic injury of AECIIs is now increasingly accepted as a key event in IPF. Injured AECIIs become susceptible to apoptosis. KORFEI *et al*. [10] showed that the cell markers pro-surfactant protein (SP)-C and p20 caspase-3, in stained sections of IPF lungs, revealed that 70-80% of the AECIIs demonstrated ongoing signs of apoptosis.

THE ROLE OF AECII IN IIPS

The function of the AECII in the lung has been known for many years [11–13]. These cells synthesise, secrete and recycle all components of surfactant (the active agent that covers the alveolar interface), thereby reducing surface tension and allowing breathing to take place at normal transpulmonary pressures. The surfactant produced by the AECIIs has been characterised in numerous biochemical studies of bronchoalveolar lavage and is known to be composed of ~90% lipid and ~10% protein. The surfactant proteins SP-B and SP-C, and phospholipid dipalmitoylated phosphatidylcholine are key components of surfactant [14]. The AECIIs also produce compounds of the innate immune defence system, such as defensins, collectins (of which the SP-A and SP-D are notable) and lysozyme, which all contribute towards the prevention of infections at a very low-recognition level. SP-A and SP-D, for example, are able to bind to the surface of various pathogens, thus facilitating their removal by alveolar macrophages [15–19]. The AECII cells also play a role in regulating the fluid balance in the lung, as well as having self-renewal characteristics (stem cell-like or progenitor cell) [20, 21]. Indeed, the AECIIs have a high potential to proliferate [14, 22, 23] and to transdifferentiate into alveolar epithelial type I cells [24].

The question that arises is why, with the capabilities of renewal and self-regulation possessed by the AECIIs, are they chronically injured in IPF? To help understand possible answers to this question, an important observation originating from familial forms of IPF and also nonspecific interstitial pneumonia is worthy of consideration. It has been found that in these families there are mutations in the surfactant proteins SP-A and SP-C, as well as in the telomeres, which appear to be associated with chronic AECII injury and apoptosis [25–30]. These mutations of the surfactant proteins seem to cause apoptosis largely through chronic stress of the endoplasmic reticulum (ER), which is the site of protein synthesis of the AECIIs. It is thought that the telomere mutations primarily cause DNA damage once the telomeres have been substantially shortened (fig. 1) [30].

At present, more than 30 different mutations of SP-C have been reported. This protein was the first to be deciphered in familial forms of IIP, and all, or most, of the mutations have been found

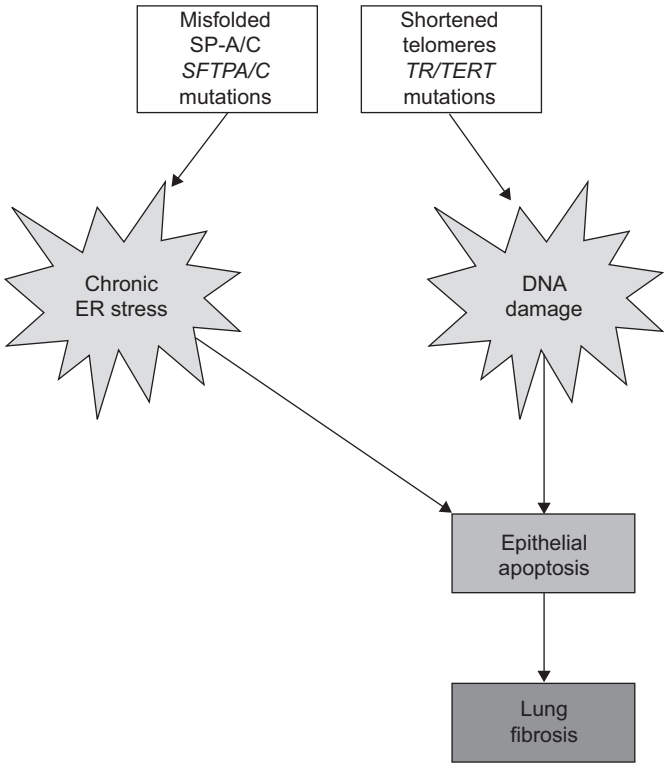

FIGURE 1. Possible mechanisms of famillial idiopathic interstitial pneumonia leading to lung fibrosis involves apoptosis caused mainly through chronic endoplasmic reticulum (ER) stress. Telomere mutations may primarily cause DNA damage once telomeres have been substantially shortened. SP-A/C: surfactant protein A/C; *SFTPA/C*: surfactant protein A/C gene; TR: telomerase RNA-component; TERT: telomerase reverse transcriptase.

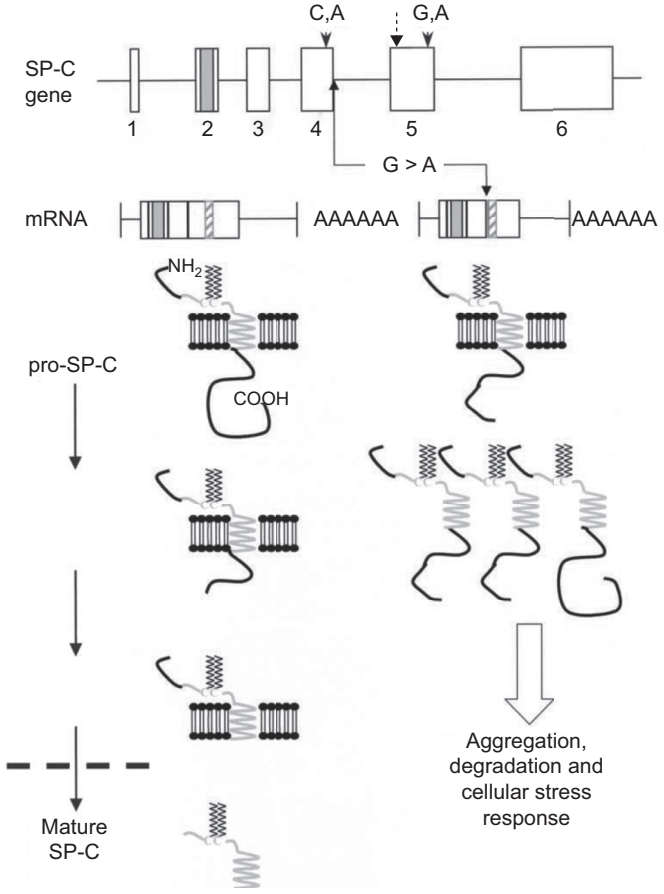

FIGURE 2. Surfactant protein (SP)-C mutations lead to protein misfolding. Pathomechanism of c.460+1G>A mutation, leading to alternate splicing of the SP-C mRNA and deletion of exon 4, and resultant production of a defective proprotein foreshortened by 37 amino acids. The mutated proSP-C protein cannot be folded and processed to its mature form, and so accumulates with the healthy SP-C proprotein. The deposition of unfolded aggregated surfactant proteins seems to cause chronic alveolar epithelial type II cell injury and eventually lung fibrosis [26].

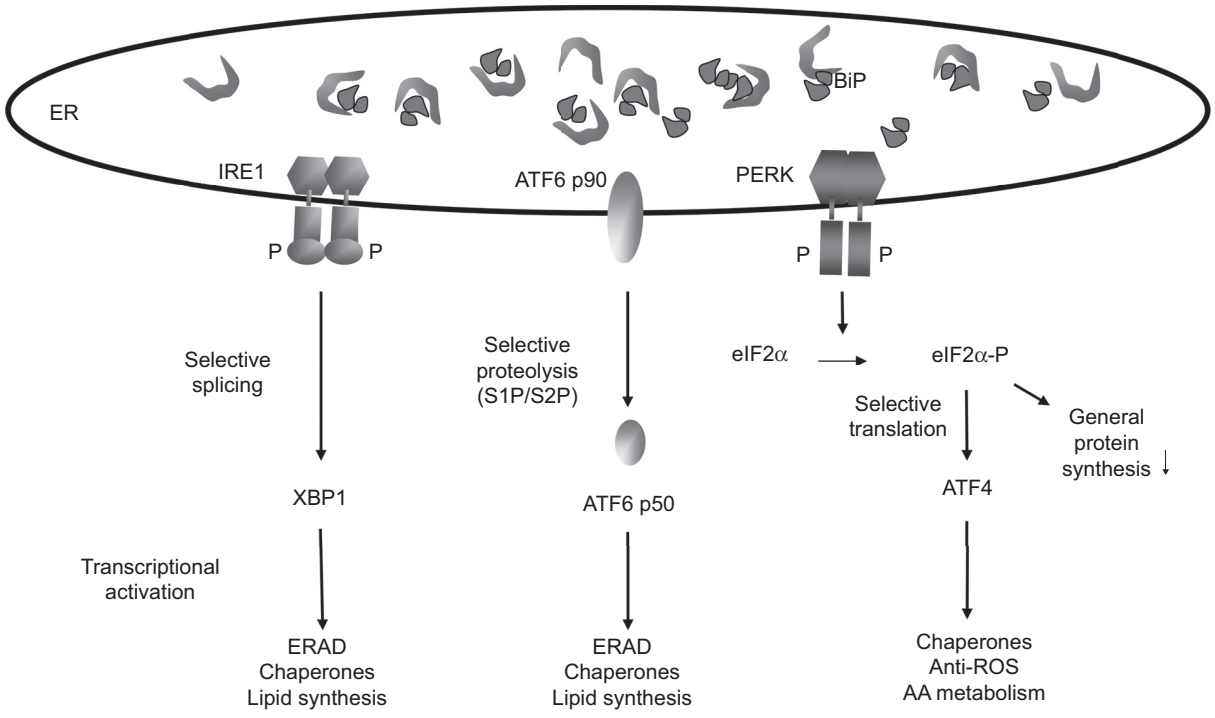

FIGURE 3. The cytoprotective endoplasmic reticulum (ER) stress mechanism [32]. BiP: immunoglobulin heavy chain-binding protein / 78 kDa glucose-regulated protein; IRE1: inositol-requiring protein 1; ATF: activating transcription factor; PERK: protein kinase R-like endoplasmic reticulum kinase; eIF: elongation initiation factor; XBP1: X-box binding protein 1; ERAD: ER-associated protein degradation; ROS: reactive oxygen species.

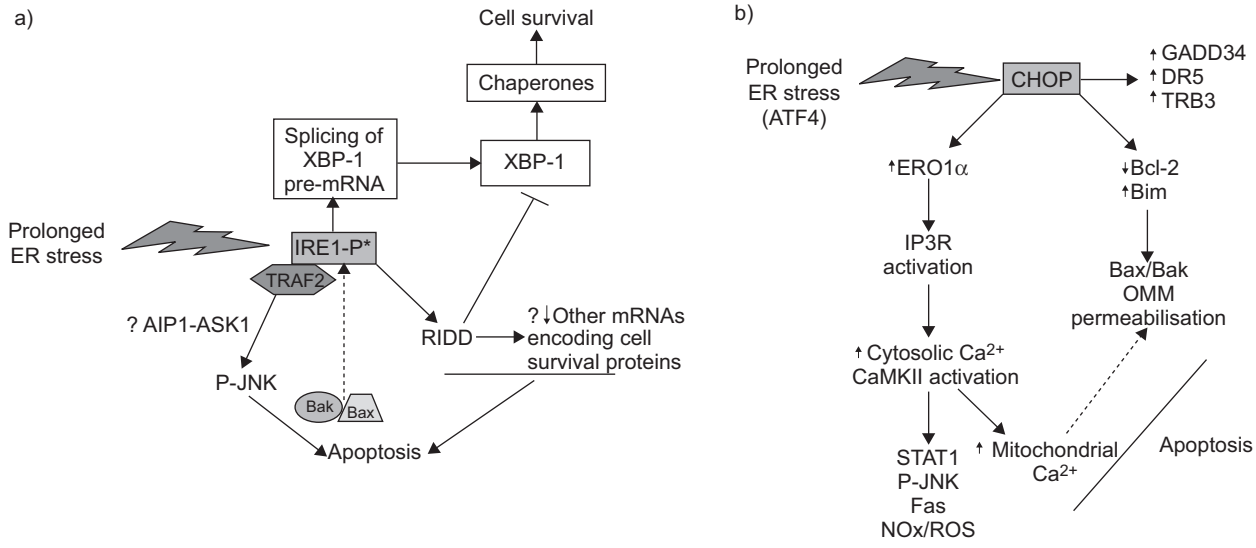

FIGURE 4. Maladaptive endoplasmic reticulum (ER) stress. This process generally helps the cell to survive, but if stress is overwhelming or prolonged, the cell will be driven to apoptosis. a) Prolonged activation of inositol-requiring protein (IRE)1 may promote apoptosis. b) Pathways through which prolonged activation of C/EBP homologous protein (CHOP) may promote apoptosis. XBP-1: X-box binding protein-1; TRAF2: tomour necrosis factor (TNF) receptor-associated factor 2; AIP1: ASK1-interacting protein 1; ASK1: apoptosis signal-regulating kinase 1; P-JNK: phosphorylated c-Jun N-terminal kinase; Bax: apoptosis regulator Bax; Bak: Bcl-2 homologous antagonist/killer; RIDD: regulated IRE1 dependent decay; ATF-4: activating transcription factor 4; ERO1α: ER oxidoreductin-1α; IP3R: inositol 1,4,5-triphosphate (Ip3) receptor; STAT: signal transducer and activator of transcription; Fas: TNF ligand superfamily member 6/Fas antigen ligand; NOx: nitric oxide; ROS: reactive oxygen species; GADD34: growth arrest and DNA damage-inducible protein GADD34; DR5: death receptor 5; TRB 3: Tribbles homolog 3; Bcl-2: B-cell lymphoma 2/apoptosis regulator Bcl-2; Bim: Bcl-2 like protein 11/Bcl2-interacting mediator of cell death; OMM: outer mitochondrial membrance. Reproduced from [33] with permission from the publisher.

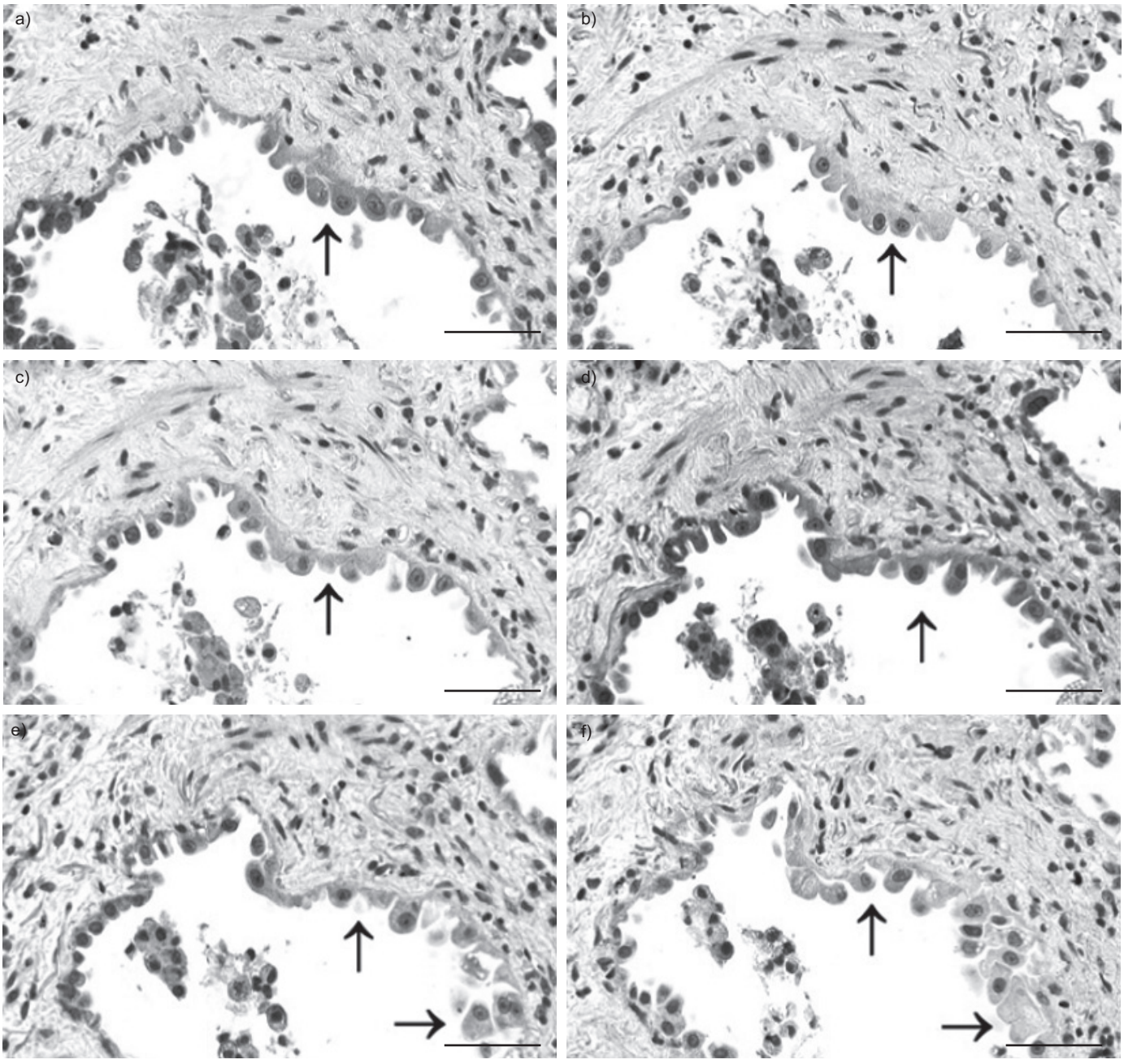

FIGURE 5. Hyperplastic alveolar epithelial type II cells show severe endoplasmic reticulum stress and consecutive apoptosis. Representative immunohistochemistry for a, d) pro-surfactant protein C, b) cleaved caspase 3, c) C/EBP homologous protein, e) activating transcription factor (ATF)-6 and f) ATF-4 in serial sections of idiopathic pulmonary fibrosis lung tissue. Scale bars=50 μm. Reproduced from [10] with permission from the publisher.

in the carboxyl-terminal part of SP-C [26, 31]. Due to its interaction with the surfactant lipids, SP-C is a very hydrophobic protein. If mature SP-C were expressed in AECIIs, the result would be immediate cell death, as this protein would attack the cell. To avoid this problem, the SP-C protein produced inside the AECII initially incorporates ''pro-protein'' parts on both the amino- and carboxyl-terminal ends, which are successively cleaved during the passage and transport of the protein through the lysosomal compartment of AECIIs. At the end of this process, the mature SP-C protein is co-secreted with the lipids comprising surfactant (fig. 2).

However, in the case of the mutated form of SP-C, the carboxyl-terminus is altered in structure and misfolded. Due to this misfolding, the mutated SP-C pro-protein cannot be further processed by the AECII and, thus, accumulates in the cell and appears to co-aggregate with the healthy SP-C. This deposition of unfolded aggregated surfactant proteins seems to cause chronic injury to the AECII (fig. 2) [26].

ER STRESS CAN BE PROTECTIVE AND DESTRUCTIVE

It is important to understand the mechanism of ER stress, which is usually a very cytoprotective mechanism (fig. 3). The

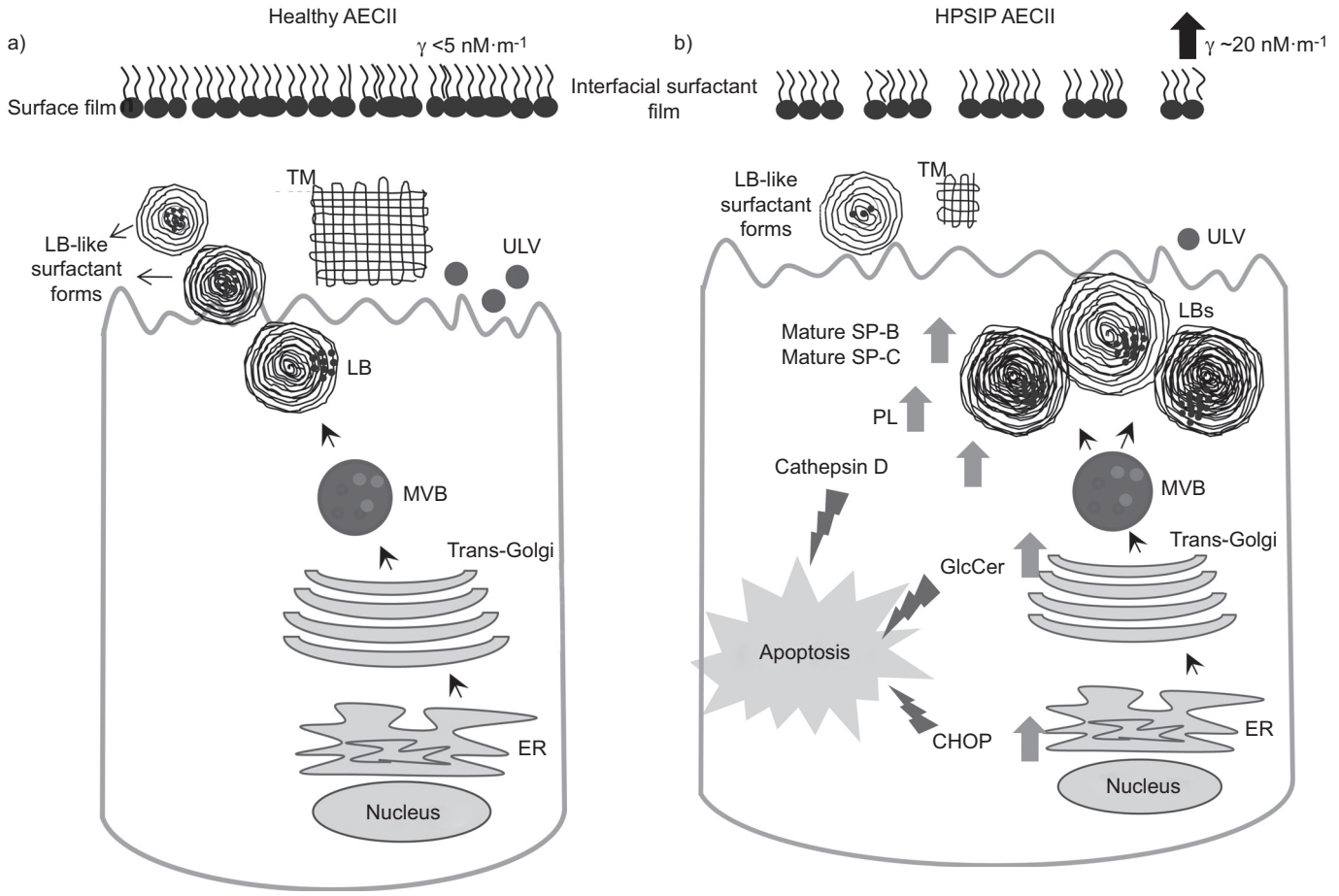

FIGURE 6. a) Healthy alveolar epithelial cells type II (AECII) and b) Hermansky–Pudlak syndrome-associated interstitial pneumonia (HPSIP) AECII. Disturbed intracellular surfactant transport in AECII occurs. The mature forms of surfactant proteins are blocked inside the late lysosomal compartment of the cell, but not primarily in the endoplasmic reticulum (ER) or Trans-golgi. The AECIIs become swollen due to the accumulation of the mature surfactant proteins, which in turn causes lysosomal stress reactions through activation of cathepsin D, glycerol ceramides and eventually C/EBP homologous protein (CHOP). GlCcer: glucosylceramides; LB: lamellar bodies; MVB: multivesicular bodies; PL: phospholipids; SP: surfactant protein; TM: tubular myelin; ULV: unilamellar vesicles.

ER contains chaperones that help protein folding, of which the most important is BiP, along with three other key signalling molecules: IRE1, ATF6 p90 and PERK. BiP usually interacts with these three key signalling molecules, keeping them in an inactivated state. If BiP is required to dissociate from the signalling molecules, to help client proteins to fold, IRE1, ATF6 p90 and PERK are activated and cause a redundant signalling process in the cell, with the primary purpose of aiding the cell to improve the folding of any misfolded proteins and to attain homeostasis again [32]. These 'redundant' signalling processes involve pathways that eventually affect lipid synthesis, overexpression of chaperones and compounds of the ER-associated protein degradation pathway (mainly proteasomal compounds), anti-reactive oxygen species signalling and arachidonic acid metabolism. This ER stress reaction generally helps the cell to survive; however, if the stress condition is overwhelming or prolonged, the cell will be driven to apoptosis *via* the activation of the two main factors; CHOP and ATF-4. ER stress may help the cell to survive or, under prolonged conditions, can drive the cell to apoptosis (fig. 4) [33].

PATHOMECHANISMS OF SP-C MUTATIONS

BRIDGES and co-workers [34, 35] examined the comparative effect of wild-type SP-C and mutated SP-C proteins on cell conditions. HEK-293 cells were transfected to express either wild-type SP-C or mutated SP-C. The wild-type SP-C was found to co-localise in the lysosomal compartment, whereas mutated SP-C co-localise in the ER. It was demonstrated that a significant increase in ER-stress reaction occurred within the cells expressing mutated SP-C. Subsequent secondary injury of the cells, through infection with a virus or blockage of proteasomal function, showed that the cells with mutated SP-C rapidly underwent apoptosis, whereas the cells with wild-type SP-C were not driven to cell death.

The clinical relevance of these observations is that respiratory infections tend to occur easily and may explain why many patients report infection prior to the exacerbation of IPF.

SPORADIC IPF

As with familial forms of IPF, a significant ER stress reaction driving the AECII to apoptosis is also seen in sporadic IPF and may be related to disturbed processing of surfactant compounds (fig. 5). Along with these intracellular changes, the composition of the alveolar surfactant pool is greatly altered and, thus, the surface tension of the alveolus is increased. As a result, higher pressure is needed to inflate the lungs; therefore, compliance is reduced, probably resulting in stretching of the distal lung [10].

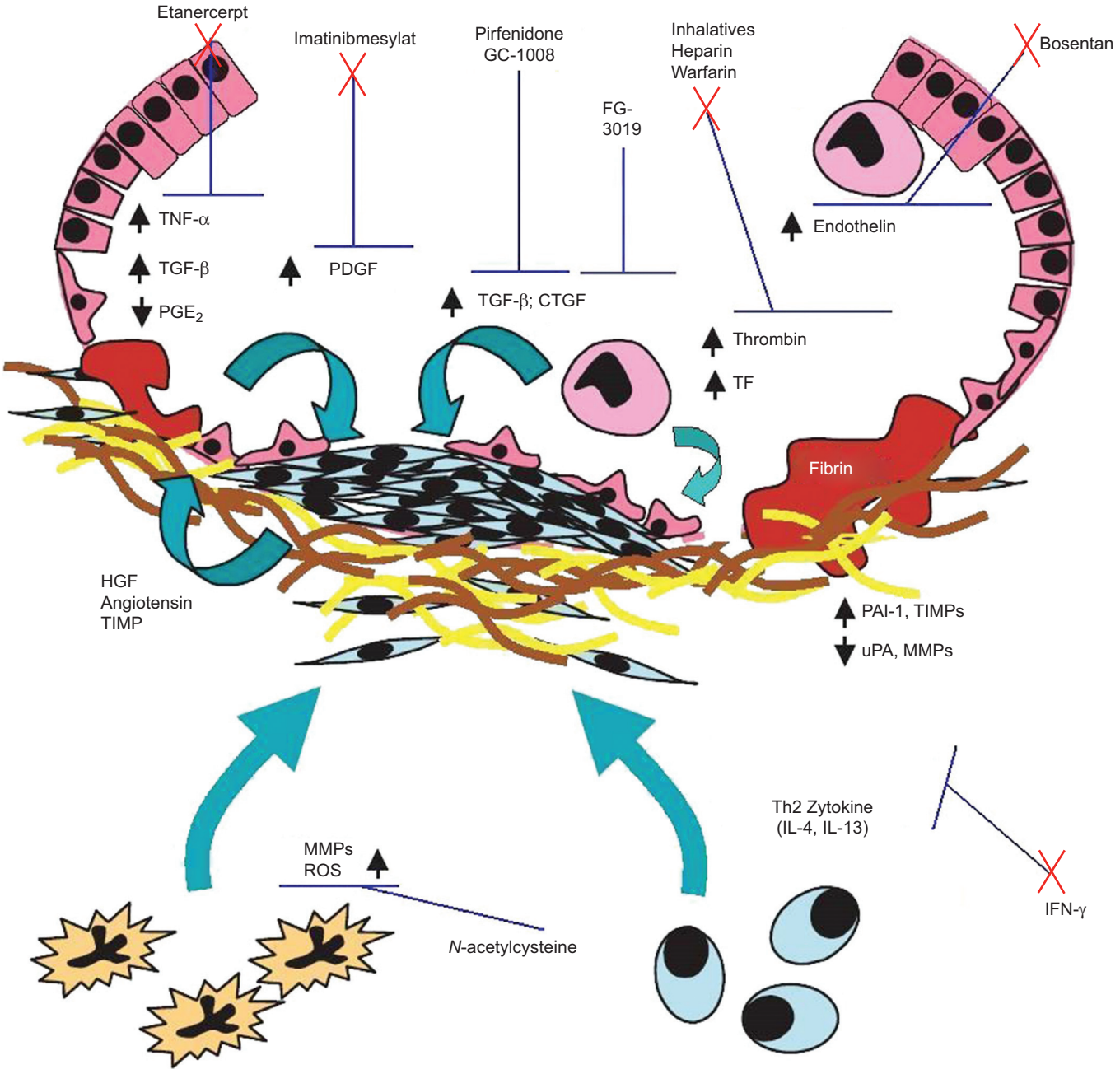

FIGURE 7. Current therapeutic approaches targeting profibrotic signalling pathways. Those pathways potentially leading to fibrosis have been used to develop targeted therapies for idiopathic pulmonary fibrosis treatment. Some potential therapies, which have had success in other disease areas, have failed. For example, tumour necrosis factor (TNF)-α blockers (*e.g.* etanercept) have been shown to be ineffective, and it appears that there is no significant role for agents that act on the endothelin pathway (*e.g.* bosentan). Therapies targeting anti-fibrotic and growth factor pathways are currently being developed. TGF-β: transforming growth factor-β; PGE_2: prostaglandin E_2; PDGF: platelet-derived growth factor; CTGF: connective tissue growth factor; TF: transcription factor; HGF: hepatocyte growth factor; TIMP: tissue inhibitor of metalloproteinases; PAI-1: plasminogen activator inhibitor-1; uPA: urokinase-type plasminogen activator; MMP: matrix metalloproteinases; ROS: reactive oxygen species; TH2: T-helper 2 cell; IL: interleukin; IFN: interferon. Reproduced from [48] with permission from the publisher.

In IPF a key histological pattern that is observed is UIP, which may also be observed in other conditions. A rare example is Hermansky–Pudlak syndrome-associated interstitial pneumonia (HPSIP), which occurs in ~40% of patients with Hermansky–Pudlak Syndrome (HPS); a lysosomal transport deficiency disease affecting the whole body. HPSIP has the same UIP pattern, histopathology and high-resolution computed tomography appearance as IPF. Therefore, the underlying molecular mechanism of this disease may help in the understanding of IPF. In fact, MAHVADI *et al.* [36] studied murine analogues of HPS and, surprisingly, again found that disturbances with regard to intracellular surfactant transport in AECII are involved [36]. In this case, the mature forms of SPs ready to be excreted are blocked inside the late lysosomal compartment of the cell but not

primarily in the ER or trans-Golgi network. The AECIIs become swollen due to the accumulation of the mature SPs, which seems to cause a lysosomal stress reaction through activation of cathepsin D, glycerol ceramides and, eventually, CHOP (fig. 6).

FROM AECII INJURY TO LUNG FIBROSIS

There are three different theories under discussion regarding the mechanisms through which injury to the AECIIs results in lung fibrosis. The first involves epithelial–mesenchymal transition (EMT), with epithelial cells undergoing transdifferentiation into fibroblasts and consecutive activation. While this process has clearly been shown to occur *in vivo* in mice [37], there is still debate with regard to the importance of this pathway in IPF patients [38, 39]. According to a recent paper, not many mesenchymal cells seem to have originated from epithelial cells through EMT [39]. The second theory proposes that the dying AECII loses control over the mesenchymal cells and, as a result, the mesenchymal cells proliferate and produce more collagen. In detail, prostaglandin (PG)E_2 has been shown to be a key factor controlling fibroblast differentiation and proliferation [40]. In IPF, PGE_2 levels are greatly reduced and, therefore, the absence of control of fibroblastic proliferation due to excessive epithelial apoptosis may be of importance. Moreover, it has been shown that chronically injured alveolar epithelial cells release a number of pro-fibrotic compounds, such as transforming growth factor-β, connective tissue growth factor, tissue factor, factor VII and factor X, that together activate mesenchymal cells [41–44]. A third putative mechanism may be that the dying AECII release factors such as stromal cell-derived factor-1 attracting circulating fibrocytes, which in turn invade the lung and locally expand the fibroblast pool [45]. In this regard, the number of circulating fibrocytes has been shown to be greatly increased in acute exacerbations of IPF [46].

Currently, it is not fully understood to what extent these proposed mechanisms actually play a part in the transition to lung fibrosis; however, each mechanism results in fibroproliferation, expansion of the fibroblast pool and the accumulation of collagen.

In terms of mediators of lung fibrosis, it is important to understand that different mechanisms lead to AECII apoptosis (ER stress *via* protein misfolding, DNA damage through telomerase shortening and lysosomal stress as seen in HPS) and that there are a multitude of different pathways that may result in fibrosis (for example pathways involving chemokines, pro-coagulant factors, anti-fibrinolytic factors, growth factors, leukotrienes and endothelin). With regard to the pathways potentially leading to fibrosis, these have been used to develop targeted therapies for the treatment of IPF (fig. 7) [47, 48]. Some of the potential therapies previously studied, and which have had success in other disease areas, have failed. For example, tumour necrosis factor-α blockers (*e.g.* etanercept) have been shown to be ineffective, and it appears that there is no significant role for agents that act on the endothelin pathway (*e.g.* bosentan) [49]. Therapies targeting the anti-fibrotic and growth factor pathways are currently being developed.

TARGETING THE ANTI-FIBROTIC PATHWAY IN PATIENTS WITH IPF

Pirfenidone is an orally available molecule that has demonstrated both anti-fibrotic and anti-inflammatory activity *in vitro* and *in vivo*. It appears to decrease fibroblast proliferation and reduce collagen formation and has been shown to be effective in different *in vivo* models of organ fibrosis; not only the lung, but also in the heart and kidney [50, 51].

In a pre-clinical mouse model of bleomycin-induced lung fibrosis, pirfenidone was shown to significantly reduce the extent of lung fibrosis, as well as reduce the number and magnitude of myofibroblast responses [52]. Indeed, the pre-clinical data show that pirfenidone exerts anti-fibrotic actions, and it has recently been demonstrated to be effective in clinical trials of patients with IPF [53–55]. The primary end-point of change in percentage predicted forced vital capacity was found to be significantly increased in one of the two larger randomised, placebo-controlled trials, and a recent Cochrane meta-analysis of the available data from pirfenidone studies suggested that treatment with pirfenidone appears to slow down, but not completely arrest, the natural course of the disease [56].

Moreover, data from a recent phase II trial employing a novel triple-kinase inhibitor (BIBF 1120) targeting the receptors of fibroblast growth factor, vascular endothelial growth factor and platelet-derived growth factor, suggest that this compound may be similarly effective in IPF, although this has yet to be proven in currently ongoing phase III trials [57].

SUMMARY AND CONCLUSIONS

As we increase the understanding of the pathophysiological mechanisms involved in IPF, it is clear that there is evidence linking chronic AECII injury to the development of UIP/IPF. AECII injury is primarily mediated through ER stress, lysosomal stress, and mitochondrial and DNA damage. Secondary injuries, due to factors such as smoking or infection, may also have an important role in the development of the disease.

There are multiple pathways for chronic AECII injury to convert to fibrosis and, thus, many potential targets for developing new treatments for IPF. The growth factor and anti-fibrotic pathways seem to be important current targets, as demonstrated with the anti-fibrotic pirfenidone, which has shown strong pre-clinical anti-fibrotic activity and has been shown to be effective in clinical trials of patients with IPF.

STATEMENT OF INTEREST

P. Markart has received fees for speaking from Roche and InterMune.

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