Lung carcinogenesis and fibrosis taken together: just co-incidence?

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Abstract

Purpose of review—The pathogenesis of lung cancer and pulmonary fibrotic disorders partially overlap. This review focuses on the common features of the two disease categories, aimed at advancing our translational understanding of their pathobiologx and at fostering the development of new therapies.

Recent findings—Both malignant and collagen-producing lung cells display enhanced cellular proliferation, increased resistance to apoptosis, a propensity for invading and distorting the lung parenchyma, as well as stemness potential. These characteristics are reinforced by the tissue microenvironment and inflammation seems to play an important adjuvant role in both types of disorders.

Summary—Unravelling the thread of the common and distinct characteristics of lung fibrosis and cancer, might contribute to a more comprehensive approach of the pathobiology of both diseases and to a pathfinder for novel and personalized therapeutic strategies.

Keywords

fibroblast; carcinoma; scar; hallmarks; nuclear factor-κB

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive age- and smoking-related diffuse parenchymal lung disease believed to result from chronic alveolar epithelial cell injury and defective repair in response to yet unknown environmental insults [1]. IPF culminates from perpetual proliferation and migration of mesenchymal cells and from formation of fibroblast foci, in which activated myofibroblasts secrete increased amounts of extracellular matrix

(ECM) leading to remodelling and distortion of pulmonary structure and function [2]. The disease is rare, but its incidence increases worldwide [3]. Moreover, IPF unequivocally leads to death within 2-5 years after diagnosis and there is no effective etiologic cure, a fact that underlines the need for novel aproaches [4–6].

Lung cancer is the leading cause of cancer-related death in men and women worldwide [7]. This age- and smoking-related tumor results from chronic exposure of the airway and alveolar epithelium to environmental smoke leading to repetitive cycles of mutagenesis, apoptosis, defective DNA repair, mutation persistence, progressive hyperplasia and dysplasia, and frank lung occupation and dissemination [8]. Similar to IPF, death usually ensues within few years after diagnosis despite targeted therapies [9].

Several studies have highlighted the clinical risk factors associated with lung cancer development in IPF patients and examined the clinical characteristics and survival of patients having both IPF and lung cancer [11–20]. In terms of anatomy, fibrosis is present in IPF patients mainly in the lung periphery, as well as in the lower lobes, the same regions in which a great percentage of lung tumours are observed in tomography scans [14, 21]. Interestingly, patients who undergo lung transplantation for idiopathic pulmonary fibrosis have a 20-25 times higher incidence of primary lung cancer development than the general population [22, 23]. These observations have fueled a search for the molecular links between the two lung diseases [14, 15, 24–26].

Malignant properties of pulmonary fibroblasts

Upon injury, epithelial cells interact with mesenchymal cells and the ECM, promoting the progression of fibrosis [27, 28]. In a similar pattern, tumours behave like open wounds and activated mesenchymal cells are implicated in the pathobiology of both fibrosis and cancer [29]. The continuous process of tumorigenesis is characterised by evasion of cell death, sustained proliferative signalling, evading growth suppressors, enabling replicative immortality, activating invasion and metastasis, and tumour-promoting inflammation, among other features, but most strikingly, by unremitted growth and development of tumour niches supported by their interactions with stromal cells and the tumor microenvironment [30, 31]. Alike tumor-initiated tissues, fibrotic tissues are comprised by epithelial cells and fibroblasts/mesenchymal cells in close interaction with immune cells, angiogenic factors and the ECM [30, 32].

Apoptosis

As opposed to normal wound repair, scar myofibroblasts escape apoptosis like cancer cells [33–38] and can be restrained upon inhibition of anti-apoptotic signalling pathways [39–44]. The mechanisms involved in mesenchymal cell resistance to apoptosis during IPF are multiple and are not fully understood [33, 34, 41–43, 45–47]. Apoptosis may be mediated by two pathways. The extrinsic pathway promotes apoptosis by stimulation of members of the tumor necrosis factor receptor (TNFR) family, and the intrinsic pathway induces apoptosis by certain cellular stressors like DNA damage or growth factor inhibition. Along the extrinsic pathway, death receptors like Fas are implicated in lung fibrosis both by enforcement of epithelial cell apoptosis during the injurious phase and through resistance of

fibroblasts to Fas-induced apoptosis during the resolution of lung injury. The Fas/Fas ligand (FasL) pathway is important in the attenuation of lung fibroblast survival during lung repair and fibrosis [47–49]. The expression of FasL by lung fibroblasts during IPF leads to continuous epithelial cell apoptosis and cell death escape by immune surveillance [50, 51] which can be reversed due to the low expression of Fas from fibrotic lung fibroblasts [52, 53]. Furthermore, lung fibroblasts express c-FLIP (cellular Fas-associated protein with death domain-like interleukin-1β-converting enzyme-inhibitory protein), which represses apoptotic signals downstream of Fas [47]. In addition, interleukin (IL)-6, a cytokine known to be involved in repair and remodelling, inhibits apoptosis and induces expression of the anti-apoptopic protein Bcl-2 in fibroblasts of patients with IPF who also exhibit inhibition of the mitochondrial depolarisation that is a critical component in the apoptotic programme [41, 54]. Finally, IPF fibroblasts overexpress IAP proteins which can inhibit apoptosis via blockade of caspase activation [41, 44, 46, 47]. In both tumorigenesis and fibrosis interplay with the ECM is important for apoptosis evasion [55–60]. Mechanical forces influence several biological processes, which involve cell adhesion and ECM organization where proteins and protein kinases have a critical role. Interactions like PTEN (protein phosphatase and tensin homologue) suppression, PI3K (phosphatidylinositol 3-kinase) negative regulation and AKT activation are capital for anti-apoptosis [56, 61]. Hippo and its interplay with TGF-β is also a key regulator of ECM remodelling and cell differentiation and are implicated in both lung fibrosis and cancer development through pro-tumour phenomena like apoptosis resistance [60]. Moreover, cell culture substrates that recapitulate the stiffness of fibrotic lungs are sufficient to decrease fibroblast apoptosis and increase pro-survival BCL-2 expression [41, 57, 62]. TGF-β1 also promotes MRTF-A (myocardin-related transcription factor-A) nuclear localisation where as a transcriptional co-activator of serum response factor it regulates myofibroblast differentiation and survival, further promoting lung fibrosis [41, 42, 62, 63]. MRTF-A has also been targeted as a partner of tumour progression and metastasis [64–66]. Apart from the ECM, several apoptosis signalling pathways are directly linked to fibrosis and malignancies. Protein kinases like AKT (also known as protein kinase B) and FAK (focal adhesion kinase) known for their active role in a variety of tumours, are also activated by profibrotic mediators like TGF-β1 and endothelin-1 in lung fibrosis [67–72]. These kinases induce the expression of downstream partners like IAP family members that are highly expressed in fibrotic lung fibroblasts and have also been shown to play a crucial role in cancer as they promote apoptosis escape [34, 44, 46, 67, 73–75].

Cellular proliferation

Another characteristic of malignant cells is their perpetual proliferative signalling which has also been described in fibrotic lung fibroblasts and represents a mechanistic similarity between the two diseases. In patients with IPF lung fibroblasts display high and heterogenic proliferative properties [76]. Although signals that enhance cell proliferation are reported in the pathogenesis of lung fibrosis in humans and murine models, the exact mechanisms by which this event is promoted are not yet fully understood. Several protein kinases, well known for their multifaceted role in malignancies, such as the receptors for vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF), were recently implicated in sustained proliferation of pulmonary

fibroblasts [77]. Moreover, TGF-β1, endothelin-1 and ECM ligation of cell-surface integrins activate the PI3K/AKT pathway which is highly observed in the IPF fibroblastic foci [68, 78–80]. PI3K/AKT activation induced by β1-integrin urges fibroblasts to abjure the antiproliferative signals [81]. Furthermore, inhibition of its signalling reduces lung fibroblast proliferation and fibrosis development both in vitro and in vivo [82–86]. Anticancer treatments have been shown to act suppressive in IPF patients, further amplifying the various consequences of proliferating signalling [87–89]. In addition, lung fibroblasts have been shown to abjure mediators for growth suppression, a main characteristic of malignant cells. IPF fibroblasts resist signals like prostaglandin (PG)E2, that inhibits proliferation and differentiation while enhancing susceptibility to apoptosis in normal lung fibroblasts or polymerised collagen growth [81, 90].

Aging

As noted above, age is highly related to lung diseases and is a risk factor for IPF and also for various cancers, but the mechanisms by which age contributes to each disease differ [91, 92]. Chromosome replication ageing is crucial for malignancies and as recently reported for IPF fibroblasts [39]. In contrast to cancer cells, where the enhanced telomerase activity lengthens telomeres and contributes to continuous cell proliferation, fibrotic lung fibroblasts exhibit accelerated telomere shortening and impaired telomerase function [93]. As a result, both increased fibrosis and decreased fibroblast apoptosis occur and predispose poor survival for patients with IPF [94–98].

Invasion and metastasis

One important hallmark of cancer is the ability to invade and metastasise. Among others, matrix metalloproteases are strongly related to invasion and migration of cells, as well as integrins, receptors which are a main regulator for the right cell adhesion [99]. The integrin expression activates the lung cancer related KRAS/RelB/NFkB pathway and leads to stem cell like properties like anchorage independent growth, tumor progression and drug resistance. Due to their function to create and maintain the communication between the extracellular matrix, inflammatory cells, fibroblasts and parenchymal cells, the integrins play not just a huge role in cancer, but also in IPF. They are involved in the processes of initiation, maintenance and resolution of tissue fibrosis. High expression of integrins was observed in myofibroblasts and in AECs after lung injury compared to untreated controls. It was also demonstrated that integrins are strong regulators of TGF-ß during lung fibrosis. The integrin family is therefore an interesting target for treatment of IPF. Different inhibitors are in preclinical and clinical phases, for example specific antibodies against αvβ6. Different kinds of these antibodies were tested in preclinical models of fibrosis among others bleomycin- models in mice. There is already one humanized antibody STX-100 in clinical trial phase 2 for treatment of IPF [100]. The paralleles of IPF and cancer concerning the aspects of migration could help finding therapeutic targets for both diseases.

Inflammation

Although the role of inflammation in IPF has been a contradiction, its participation as a promoting factor in the development and progression of tumorigenesis is frequently described [101]. Myeloid-derived suppressor cells (MDSC) are associated with poor

prognosis in malignancies and their expansion and accumulation in IPF is also correlated with disease progression [102]. Moreover, pulmonary fibrosis is characterized by the complex interaction with cells that are also involved in chronic inflammation. Overexpression of chemokines like CCL8 that attract monocytes has been recently associated with the disease [103]. Fibrosis-associated macrophages (FAMs) display an M2 phenotype, best characterised by strong expression of arginase, chitinase-like molecules, resistin-like molecule α and CD206 [104]. They facilitate the enhanced production of fibroblast growth factors [105], profibrotic cytokines [106, 107] and matrix metalloproteinases [108]. Their ablation by liposomal clodronate, or deletion of C–C-motif chemokine receptor 2 or PAI-1 protect against lung fibrogenesis [107, 109, 110].

Mesenchymal features of lung cancer cells

Mesenchymal cells are not only critical for lung development and fibrosis, but also for tumorigenesis [111, 112]. Stromal fibroblasts can effect tumor cell behavior in various manners. For instance, fibroblasts of the host environment interact with tumour cells and secrete in the ECM several growth factors like TGF-β, which next enhance a metastatic profile [113, 114]. Moreover, tumour-associated fibroblasts regulate matrix stiffness and, thereby, tumour cells promote angiogenesis [115, 116]. They also produce fibroblast activation protein (FAP), a serine peptidase whose expression has been associated with lymph node metastasis and overall poor prognosis [117, 118]. Additionally, while tumorigenesis is in progress fibroblasts induce a pretumoral phenotype of tumor associated macrophages, which plays a pivotal role in the immunosuppression induced within the tumor microenvironment [119].

Epithelial–mesenchymal transition

Epithelial–mesenchymal transformation (or transition; EMT) is a process of multiple phenotypic transitions including shape changes towards elongated and spindle-shaped cellular morphology, enhanced cytoplasmic cytoskeletal protein expression and activity, and the capacity for anchorage-independent growth, motility, migration and invasion, as well as an increased resistance to apoptosis [116, 120, 121]. This epithelial–mesenchymal phenotypic transition has been clearly observed during the malignant transformation of respiratory epithelial cells, and this link is supported by evidence suggesting that the same oncoproteins that drive lung cancer formation and progression (i.e. mutant KRAS) are responsible for EMT [122, 123]. It is clear, that EMT with its ability to invade, contribute to metastasis and therapeutic resistance plays a major role in tumorigenesis [121]. EMT is induced by multiple pathways like WNT, RTK and TGF-ß signalling, which are controlled by genetic and epigenetic mechanisms. In a tumor the cells are a heterogenic population created by instability of these processes. A major player in EMT is the NF-κB pathway, which can be activated by Notch, RTKs or KRAS [121–124]. Compared with the strong evidence of a major role of EMT in cancer development, it is controversially discussed whether "true" EMT contributes to lung fibrogenesis [116, 125–128]. While some may consider EMT to be partial or incomplete in pulmonary fibrosis, abundant evidence supports the plasticity of alveolar epithelial cells that can, in the context of lung injury, acquire a number of mesenchymal-like phenotypic behaviours [127, 129–132]. This phenotypic

transition is not limited to fibrotic lung injury, as airway epithelial cells were recently shown to migrate distally in response to influenza H1N1 infection of mice, thereby acquiring fibroblast phenotypes [133]. Unpublished observations from our laboratories indicate that similar processes occur both after tobacco smoke-contained carcinogen exposure, and after bleomycin-induced lung injury and fibrosis [133, 134]. In bleomycin-induced lung fibrosis it was shown that pleural mesothelial cells (PMC) start expressing an EMT phenotype with increased mesenchymal phenotypic markers and decreased epithelial phenotypic markers, as well as higher collagen-I synthesis, cell migration and activated TGF-ß1-Smad2/3 signalling pathway [135]. EMT in AECs was already proven over 10 years ago in primary cell culture, tissue samples of IPF patients, as well as mouse models. A main driving power and mediator thereby was TGF-ß. Multiple researchers could show the cell type transition by increases of typical mesenchymal markers like alpha-smooth muscle actin (alpha-SMA) or vimentin and decreases in epithelial markers thyroid transcription factor (TTF)-, e-cadherin and pro-surfactant protein-B (pro-Sp-B) in these samples [136–138]. Even so EMT is a common event in both IPF and cancer. In IPF, mesothelial cells can also undergo transition to mesenchymal cells, a process called mesothelial-to mesenchymal transition (MMT). After breakdown of healthy repair and regulatory pathways, mesothelial cells can in this way contribute to the development of tissue fibrosis. By lineage tracing of mesothelial cells in mice the EMT process was observed during development and was then named MMT. Later MMT was observed in mesothelial cells after exposure to different kinds of toxic agents, as well as TGF-ß. The TGF-ß treated mouse models underwent MMT and a transition from mesothelial cells to myofibroblasts resulting in fibrosis [139]. Principal in both cancer and IPF, the typical process of EMT with loss of cellular contacts, epithelial cell morphology and polarity, has a net negative outcome in disease progression.

Stem cells

A cancer stem cell (CSC) is defined as that part of tumor which can constantly provide new cancer cells and also mobilize non-cancer cells, such as mesenchymal and vascular cells. This group of cells show increased telomere length controlled by highly active telomerase, have more active anti-apoptotic pathways, and a high activity of membrane transporters like ABC transporters, which can pump given drugs out of the cell [140–142]. The ABCG2 gene for instance is overexpressed in lung cancer stem cells and serves as a typical marker for this cell type [143]. In IPF similar mechanisms are involved. The ABCA3 gene, another member of the ABC transporter superfamily, is widely mutated in lung diseases and responsible for an abnormal surfactant metabolism and maybe a risk factor for IPF [144]. Taken together, in both lung diseases the typical features of stem cell-like behaviour play a major role in the pathogenesis, but instead of overlapping mechanisms they have a more opposite outcome. Having this in mind it is not surprising that the therapeutic approaches are different. It is clear that cancer stem cells have a negative impact in cancer progression and drug resistance and need to be targeted. In IPF, drug development focuses on mesenchymal stem cells (MSCS), a side population of stem cells originated from non-haematopoietic cells. These cells play significant roles in inhibition of T-cell proliferation and in secreting anti-inflammatory cytokines and growth factors, thus becoming a potential therapeutic target. Instead of the idea to inhibit the stem cell-like cell population in cancer therapy, researchers try to use the protective and repairative effects of the MSCs to treat IPF. After positive

results in mouse experiments, several clinical trials with MSCs in the treatment of IPF are ongoing [145].

IPF signaling pathways promoting cancer

Several studies demonstrate different signalling pathways that are strictly associated to fibroblasts and also play key roles in tumorigenesis. For instance, PI3K–Akt signaling substrate Girdin, an actin-binding protein that regulates cell migration, is expressed and activated by Akt phosphorylation in cancer-associated fibroblasts, thus promoting lung tumor progression [146]. Furthermore, the tumour microenvironment expresses survival and progression factors, that undergo a regulatory mechanism by the action of the mitogen-activated protein kinase 38 (p38MAPK) [147]. p38MAPK–leads in an hyaluronan-dependent reprogramming of the tumor microenvironment that promotes lung cancer growth [148]. Interestingly, STAT3 phosphorylation and induction of anti-apoptotic protein Bcl-2 and Survivin in lung cancer cells was found after cisplatin fibroblast stimulation and up regulation of interleukin-11 (IL-11). This effect confers lung cancer cells the advantage of chemoresistance [149]. S100A4, a fibroblast marker and activator of fibroblast-specific transcriptional programmes, has been shown to be expressed in IPF and to protect from metastasis [150]. FGF and TGF signalling in lung tumour cells, or mutations in their receptors, have been shown to be essential for lung adenocarcinoma development [151–153]. It is obvious that signalling pathways that are critical for fibrosis progression are also sensibly promoting tumor expansion and migration.

Conclusion

In conclusion, cancer and fibrosis are two discernible lung diseases that are impressively characterised and driven by similar biological pathways. Although their specific genetic and cellular mechanisms are not yet fully defined, several signalling pathways, anatomical compartments, and the microenvironmental behaviour corrupt tissue architecture and lead to its dysfunction [154, 155]. However, it is clear that lung tumorigenesis and fibrosis display a highly heterogeneous behaviour, which raises the need for a more personalised therapeutic approach [156–159]. Attenuation of lung fibrosis can be served by focusing on and exploring these overlapping mechanisms.

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Key points

- Mesenchymal properties of lung cancer cells are essential for lung tumor progression.

- Common signalling pathways are activated in both lung cancer and pulmonary fibrosis.

- The mechanistic overlap between lung fibrosis and cancer will hopefully lead to common therapies effective against both diseases.