

Current Opinion in Pulmonary Medicine

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

--Manuscript Draft--

Manuscript Number:	MCP230405
Full Title:	Lung carcinogenesis and fibrosis taken together: just co-incidence?
Article Type:	Review Article
Corresponding Author:	Georgios T. Stathopoulos, M.D., Ph.D. University of Patras Faculty of Medicine Rio, GREECE
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	University of Patras Faculty of Medicine
Corresponding Author's Secondary Institution:	
First Author:	Ioanna Giopanou
First Author Secondary Information:	
Order of Authors:	Ioanna Giopanou
	Kristina A.M. Arendt
	Georgios T. Stathopoulos, M.D., Ph.D.
Order of Authors Secondary Information:	

Title of review article: Lung carcinogenesis and fibrosis taken together: just co-incidence?

Authors: Ioanna Giopanou¹, Kristina A.M. Arendt², Georgios T. Stathopoulos^{1,2}.

Authors' affiliations:

- ¹ Laboratory for Molecular Respiratory Carcinogenesis, Department of Physiology,
Faculty of Medicine, University of Patras, 26504 Rio, Greece
- ² Comprehensive Pneumology Center (CPC), University Hospital, Ludwig-
Maximilians University and Helmholtz Zentrum München, Member of the
German Center for Lung Research (DZL), 81377 Munich, Germany

Author of correspondence: Georgios T. Stathopoulos; Laboratory for Molecular
Respiratory Carcinogenesis, Department of Physiology, Faculty of Medicine,
University of Patras, Rio, Achaia, 26504, Greece; Phone: 0030 2610 969154; Fax:
0030 2610 969176; E-mail: gstathop@upatras.gr.

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 pathobiology 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- κ B.

TEXT OF REVIEW

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 approaches [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-1 β -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-apoptotic 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- β 1 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- β 1 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- β 1, 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 β 1-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- β 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 $\alpha\text{v}\beta 6$. 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 parallels 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- β 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- κ B 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- β 1-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- β . 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- β . The TGF- β 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.

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.

FINANCIAL SUPPORT AND SPONSORSHIP

The authors' research is supported by European Research Council 2010 Starting Independent Investigator and 2015a Proof of Concept grants (grant numbers 260524 and 679345, respectively, to G.T. Stathopoulos).

CONFLICTS OF INTEREST

None declared.

REFERENCES AND RECOMMENDED READING

1. Xaubet A, Ancochea J, Molina-Molina M. Idiopathic pulmonary fibrosis. *Med Clin (Barc)*. 2016 Dec; 17(16): 30577-2.
2. Thannickal VJ, Henke CA, Horowitz JC, et al. Matrix biology of idiopathic pulmonary fibrosis: a workshop report of the national heart, lung, and blood institute. *Am J Pathol*. 2014 Jun;184(6):1643-51.
3. Hutchinson J, Fogarty A, Hubbard R, McKeever T. Global incidence and mortality of idiopathic pulmonary fibrosis: a systematic review. *Eur Respir J*. 2015 Sep;46(3):795-806.
 - A systematic, comprehensive, and current estimation of global IPF disease burden.
4. King TE, Jr., Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med*. 2014 May 29;370(22):2083-92.
5. Iwata T, Yoshino I, Yoshida S, et al. A phase II trial evaluating the efficacy and safety of perioperative pirfenidone for prevention of acute exacerbation of idiopathic pulmonary fibrosis in lung cancer patients undergoing pulmonary resection: West Japan Oncology Group 6711 L (PEOPLE Study). *Respir Res*. 2016 Jul 22;17(1):90.
 - A major clinical trial reflecting the clinical co-existence of the two diseases in question.

6. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med*. 2014 May 29;370(22):2071-82.
7. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015 Mar;65(2):87-108.
 - One of the most authoritative global estimates of cancer burden showing how lung cancer has become the number one cancer killer globally.
8. Chen Z, Fillmore CM, Hammerman PS, et al. Non-small-cell lung cancers: a heterogeneous set of diseases. *Nat Rev Cancer*. 2014 Aug;14(8):535-46.
9. Mok TS, Wu YL, Ahn MJ, et al; AURA3 Investigators. Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. *N Engl J Med*. 2016 Dec 6. [Epub ahead of print] PubMed PMID: 27959700.
10. Lee T, Park JY, Lee HY, Cho YJ, et al. Lung cancer in patients with idiopathic pulmonary fibrosis: clinical characteristics and impact on survival. *Respir Med*. 2014 Oct;108(10):1549-55.
11. Aubry MC, Myers JL, Douglas WW, et al. Primary pulmonary carcinoma in patients with idiopathic pulmonary fibrosis. *Mayo Clin Proc*. 2002 Aug;77(8):763-70.
12. Kawasaki H, Nagai K, Yoshida J, et al. Postoperative morbidity, mortality, and survival in lung cancer associated with idiopathic pulmonary fibrosis. *J Surg Oncol*. 2002 Sep;81(1):33-7.
13. Artinian V, Kvale PA. Cancer and interstitial lung disease. *Curr Opin Pulm Med*. 2004 Sep;10(5):425-34.

14. Antoniou KM, Tomassetti S, Tsitoura E, Vancheri C. Idiopathic pulmonary fibrosis and lung cancer: a clinical and pathogenesis update. *Curr Opin Pulm Med*. 2015 Nov;21(6):626-33.
15. Le Jeune I, Gribbin J, West J, Smith C, et al. The incidence of cancer in patients with idiopathic pulmonary fibrosis and sarcoidosis in the UK. *Respir Med*. 2007 Dec;101(12):2534-40.
16. Tomassetti S, Gurioli C, Ryu JH, et al. The impact of lung cancer on survival of idiopathic pulmonary fibrosis. *Chest*. 2015 Jan;147(1):157-64.
 - An interesting paper that reflects on the mutually negative impact of IPF and cancer on prognosis.
17. Kanaji N, Tadokoro A, Kita N, et al. Impact of idiopathic pulmonary fibrosis on advanced non-small cell lung cancer survival. *J Cancer Res Clin Oncol*. 2016 Aug;142(8):1855-65.
18. Vancheri C. Idiopathic pulmonary fibrosis and cancer: do they really look similar? *BMC Med*. 2015 Sep 24;13:220.
19. Goto T, Maeshima A, Oyamada Y, Kato R. Idiopathic pulmonary fibrosis as a prognostic factor in non-small cell lung cancer. *Int J Clin Oncol*. 2014 Apr;19(2):266-73.
20. Isobe K, Hata Y, Sakamoto S, et al. Clinical characteristics of acute respiratory deterioration in pulmonary fibrosis associated with lung cancer following anti-cancer therapy. *Respirology*. 2010 Jan;15(1):88-92.
21. Khan KA, Kennedy MP, Moore E, et al. Radiological characteristics, histological features and clinical outcomes of lung cancer patients with coexistent idiopathic pulmonary fibrosis. *Lung*. 2015 Feb;193(1):71-7.

22. Hendriks LE, Drent M, van Haren EH, et al. Lung cancer in idiopathic pulmonary fibrosis patients diagnosed during or after lung transplantation. *Respir Med Case Rep.* 2012;5:37-9.
23. Daniels CE, Jett JR. Does interstitial lung disease predispose to lung cancer? *Curr Opin Pulm Med.* 2005 Sep;11(5):431-7.
24. Raghu G, Amatto VC, Behr J, Stowasser S. Comorbidities in idiopathic pulmonary fibrosis patients: a systematic literature review. *Eur Respir J.* 2015 Oct;46(4):1113-30.
25. Stella GM, Inghilleri S, Pignochino Y, Zorzetto M, et al. Activation of oncogenic pathways in idiopathic pulmonary fibrosis. *Transl Oncol.* 2014 Oct;7(5):650-5.
26. Konigshoff M. Lung cancer in pulmonary fibrosis: tales of epithelial cell plasticity. *Respiration.* 2011;81(5):353-8.
27. Horowitz JC, Thannickal VJ. Epithelial-mesenchymal interactions in pulmonary fibrosis. *Semin Respir Crit Care Med.* 2006 Dec;27(6):600-12.
28. Blackwell TS, Tager AM, Borok Z, et al. Future directions in idiopathic pulmonary fibrosis research. An NHLBI workshop report. *Am J Respir Crit Care Med.* 2014 Jan 15;189(2):214-22.
29. Schafer M, Werner S. Cancer as an overhealing wound: an old hypothesis revisited. *Nat Rev Mol Cell Biol.* 2008 Aug;9(8):628-38.
30. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell.* 2011 Mar 04;144(5):646-74.
31. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell.* 2000 Jan 07;100(1):57-70.

32. Hainaut P, Plymoth A. Targeting the hallmarks of cancer: towards a rational approach to next-generation cancer therapy. *Curr Opin Oncol*. 2013 Jan;25(1):50-1.
33. Thannickal VJ, Horowitz JC. Evolving concepts of apoptosis in idiopathic pulmonary fibrosis. *Proc Am Thorac Soc*. 2006 Jun;3(4):350-6.
34. Ajayi IO, Sisson TH, Higgins PD, et al. X-linked inhibitor of apoptosis regulates lung fibroblast resistance to Fas-mediated apoptosis. *Am J Respir Cell Mol Biol*. 2013 Jul;49(1):86-95.
35. Korfei M, Ruppert C, Mahavadi P, et al. Epithelial endoplasmic reticulum stress and apoptosis in sporadic idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2008 Oct 15;178(8):838-46.
36. Kuwano K, Kunitake R, Kawasaki M, et al. P21Waf1/Cip1/Sdi1 and p53 expression in association with DNA strand breaks in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 1996 Aug;154(2 Pt 1):477-83.
37. Lepparanta O, Pulkkinen V, Koli K, et al. Transcription factor GATA-6 is expressed in quiescent myofibroblasts in idiopathic pulmonary fibrosis. *Am J Respir Cell Mol Biol*. 2010 May;42(5):626-32.
38. Maher TM, Evans IC, Bottoms SE, et al. Diminished prostaglandin E2 contributes to the apoptosis paradox in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2010 Jul 01;182(1):73-82.
39. Hecker L, Logsdon NJ, Kurundkar D, et al. Reversal of persistent fibrosis in aging by targeting Nox4-Nrf2 redox imbalance. *Sci Transl Med*. 2014 Apr 09;6(231):231ra47.
40. Ashkenazi A. Targeting the extrinsic apoptotic pathway in cancer: lessons learned and future directions. *J Clin Invest*. 2015 Feb;125(2):487-9.

41. Zhou Y, Huang X, Hecker L, et al. Inhibition of mechanosensitive signaling in myofibroblasts ameliorates experimental pulmonary fibrosis. *J Clin Invest.* 2013 Mar;123(3):1096-108.
42. Sisson TH, Ajayi IO, Subbotina N, et al. Inhibition of myocardin-related transcription factor/serum response factor signaling decreases lung fibrosis and promotes mesenchymal cell apoptosis. *Am J Pathol.* 2015 Apr;185(4):969-86.
43. Wynes MW, Edelman BL, Kostyk AG, et al. Increased cell surface Fas expression is necessary and sufficient to sensitize lung fibroblasts to Fas ligation-induced apoptosis: implications for fibroblast accumulation in idiopathic pulmonary fibrosis. *J Immunol.* 2011 Jul 01;187(1):527-37.
44. Ashley SL, Sisson TH, Wheaton AK, et al. Targeting Inhibitor of Apoptosis Proteins Protects from Bleomycin-Induced Lung Fibrosis. *Am J Respir Cell Mol Biol.* 2016 Apr;54(4):482-92.
45. Cisneros J, Hagood J, Checa M, et al. Hypermethylation-mediated silencing of p14(ARF) in fibroblasts from idiopathic pulmonary fibrosis. *Am J Physiol Lung Cell Mol Physiol.* 2012 Aug 15;303(4):L295-303.
46. Sisson TH, Maher TM, Ajayi IO, et al. Increased survivin expression contributes to apoptosis-resistance in IPF fibroblasts. *Adv Biosci Biotechnol.* 2012 Oct;3(6A):657-64.
47. Golan-Gerstl R, Wallach-Dayana SB, Zisman P, et al. Cellular FLICE-like inhibitory protein deviates myofibroblast fas-induced apoptosis toward proliferation during lung fibrosis. *Am J Respir Cell Mol Biol.* 2012 Sep;47(3):271-9.

48. Wallach-Dayana SB, Elkayam L, Golan-Gerstl R, et al. Cutting edge: FasL(+) immune cells promote resolution of fibrosis. *J Autoimmun.* 2015 May;59:67-76.
49. Huang SK, White ES, Wettlaufer SH, et al. Prostaglandin E(2) induces fibroblast apoptosis by modulating multiple survival pathways. *FASEB J.* 2009 Dec;23(12):4317-26.
50. Wallach-Dayana SB, Golan-Gerstl R, Breuer R. Evasion of myofibroblasts from immune surveillance: a mechanism for tissue fibrosis. *Proc Natl Acad Sci U S A.* 2007 Dec 18;104(51):20460-5.
51. Golan-Gerstl R, Wallach-Dayana SB, Amir G, Breuer R. Epithelial cell apoptosis by fas ligand-positive myofibroblasts in lung fibrosis. *Am J Respir Cell Mol Biol.* 2007 Mar;36(3):270-5.
52. Frankel SK, Cosgrove GP, Cha SI, et al. TNF-alpha sensitizes normal and fibrotic human lung fibroblasts to Fas-induced apoptosis. *Am J Respir Cell Mol Biol.* 2006 Mar;34(3):293-304.
53. Huang SK, Scruggs AM, Donaghy J, et al. Histone modifications are responsible for decreased Fas expression and apoptosis resistance in fibrotic lung fibroblasts. *Cell Death Dis.* 2013 May 02;4:e621.
54. Moodley YP, Misso NL, Scaffidi AK, et al. Inverse effects of interleukin-6 on apoptosis of fibroblasts from pulmonary fibrosis and normal lungs. *Am J Respir Cell Mol Biol.* 2003 Oct;29(4):490-8.
55. Parker MW, Rossi D, Peterson M, et al. Fibrotic extracellular matrix activates a profibrotic positive feedback loop. *J Clin Invest.* 2014 Apr;124(4):1622-35.

56. Liu F, Mih JD, Shea BS, et al. Feedback amplification of fibrosis through matrix stiffening and COX-2 suppression. *J Cell Biol.* 2010 Aug 23;190(4):693-706.
57. Booth AJ, Hadley R, Cornett AM, et al. Acellular normal and fibrotic human lung matrices as a culture system for in vitro investigation. *Am J Respir Crit Care Med.* 2012 Nov 01;186(9):866-76.
58. Cao Z, Livas T, Kyprianou N. Anoikis and EMT: Lethal "Liaisons" during Cancer Progression. *Crit Rev Oncog.* 2016;21(3-4):155-68.
59. Buchheit CL, Weigel KJ, Schafer ZT. Cancer cell survival during detachment from the ECM: multiple barriers to tumour progression. *Nat Rev Cancer.* 2014 Sep;14(9):632-41.
60. Saito A, Nagase T. Hippo and TGF-beta interplay in the lung field. *Am J Physiol Lung Cell Mol Physiol.* 2015 Oct 15;309(8):L756-67.
61. Xia H, Diebold D, Nho R, et al. Pathological integrin signaling enhances proliferation of primary lung fibroblasts from patients with idiopathic pulmonary fibrosis. *J Exp Med.* 2008 Jul 07;205(7):1659-72.
62. Huang X, Yang N, Fiore VF, et al. Matrix stiffness-induced myofibroblast differentiation is mediated by intrinsic mechanotransduction. *Am J Respir Cell Mol Biol.* 2012 Sep;47(3):340-8.
63. Bernau K, Ngam C, Torr EE, et al. Megakaryoblastic leukemia-1 is required for the development of bleomycin-induced pulmonary fibrosis. *Respir Res.* 2015 Mar 27;16:45.
64. Medjkane S, Perez-Sanchez C, Gaggioli C, et al. Myocardin-related transcription factors and SRF are required for cytoskeletal dynamics and experimental metastasis. *Nat Cell Biol.* 2009 Mar;11(3):257-68.

65. Kim T, Hwang D, Lee D, et al. MRTF potentiates TEAD-YAP transcriptional activity causing metastasis. *EMBO J*. 2016 Dec 27.
66. Kishi T, Mayanagi T, Iwabuchi S, et al. Myocardin-related transcription factor A (MRTF-A) activity-dependent cell adhesion is correlated to focal adhesion kinase (FAK) activity. *Oncotarget*. 2016 Nov 01;7(44):72113-30.
67. Horowitz JC, Ajayi IO, Kulasekaran P, et al. Survivin expression induced by endothelin-1 promotes myofibroblast resistance to apoptosis. *Int J Biochem Cell Biol*. 2012 Jan;44(1):158-69.
68. Horowitz JC, Rogers DS, Sharma V, et al. Combinatorial activation of FAK and AKT by transforming growth factor-beta1 confers an anoikis-resistant phenotype to myofibroblasts. *Cell Signal*. 2007 Apr;19(4):761-71.
69. Kulasekaran P, Scavone CA, Rogers DS, et al. Endothelin-1 and transforming growth factor-beta1 independently induce fibroblast resistance to apoptosis via AKT activation. *Am J Respir Cell Mol Biol*. 2009 Oct;41(4):484-93.
70. Zhao XD, Deng HB, Lu CL, et al. Association of EGFR and KRAS mutations with expression of p-AKT, DR5 and DcR1 in non-small cell lung cancer. *Neoplasma*. 2017 Jan 03;64(2).
71. Sulzmaier FJ, Jean C, Schlaepfer DD. FAK in cancer: mechanistic findings and clinical applications. *Nat Rev Cancer*. 2014 Sep;14(9):598-610.
72. Martini M, De Santis MC, Braccini L, et al. PI3K/AKT signaling pathway and cancer: an updated review. *Ann Med*. 2014 Sep;46(6):372-83.
73. Fulda S, Vucic D. Targeting IAP proteins for therapeutic intervention in cancer. *Nat Rev Drug Discov*. 2012 Feb 01;11(2):109-24.

- 74.** Hikami S, Shiozaki A, Kitagawa-Juge M, et al. The Role of cIAP1 and XIAP in Apoptosis Induced by Tumor Necrosis Factor Alpha in Esophageal Squamous Cell Carcinoma Cells. *Dig Dis Sci*. 2017 Jan 03.
- 75.** Dizdar L, Oesterwind KA, Riemer JC, et al. Preclinical assesement of survivin and XIAP as prognostic biomarkers and therapeutic targets in gastroenteropancreatic neuroendocrine neoplasia. *Oncotarget*. 2016 Dec 26.
- 76.** Jordana M, Schulman J, McSharry C, et al. Heterogeneous proliferative characteristics of human adult lung fibroblast lines and clonally derived fibroblasts from control and fibrotic tissue. *Am Rev Respir Dis*. 1988 Mar;137(3):579-84.
- 77.** Grimminger F, Gunther A, Vancheri C. The role of tyrosine kinases in the pathogenesis of idiopathic pulmonary fibrosis. *Eur Respir J*. 2015 May;45(5):1426-33.
- Mechanistic insights are provided by this publication on how kinases involved in tumorigenic signaling are involved in IPF pathogenesis.
- 78.** Manning BD, Cantley LC. AKT/PKB signaling: navigating downstream. *Cell*. 2007 Jun 29;129(7):1261-74.
- 79.** Vittal R, Horowitz JC, Moore BB, et al. Modulation of prosurvival signaling in fibroblasts by a protein kinase inhibitor protects against fibrotic tissue injury. *Am J Pathol*. 2005 Feb;166(2):367-75.
- 80.** Conte E, Gili E, Fruciano M, et al. PI3K p110gamma overexpression in idiopathic pulmonary fibrosis lung tissue and fibroblast cells: in vitro effects of its inhibition. *Lab Invest*. 2013 May;93(5):566-76.

- 81.** Nho RS, Hergert P, Kahm J, et al. Pathological alteration of FoxO3a activity promotes idiopathic pulmonary fibrosis fibroblast proliferation on type I collagen matrix. *Am J Pathol.* 2011 Nov;179(5):2420-30.
- 82.** Le Cras TD, Korfhagen TR, Davidson C, et al. Inhibition of PI3K by PX-866 prevents transforming growth factor- α -induced pulmonary fibrosis. *Am J Pathol.* 2010 Feb;176(2):679-86.
- 83.** Korfhagen TR, Le Cras TD, Davidson CR, et al. Rapamycin prevents transforming growth factor- α -induced pulmonary fibrosis. *Am J Respir Cell Mol Biol.* 2009 Nov;41(5):562-72.
- 84.** Kang HR, Lee CG, Homer RJ, Elias JA. Semaphorin 7A plays a critical role in TGF- β 1-induced pulmonary fibrosis. *J Exp Med.* 2007 May 14;204(5):1083-93.
- 85.** Conte E, Fruciano M, Fagone E, et al. Inhibition of PI3K prevents the proliferation and differentiation of human lung fibroblasts into myofibroblasts: the role of class I PI3K isoforms. *PLoS One.* 2011;6(10):e24663.
- 86.** Lu Y, Azad N, Wang L, et al. Phosphatidylinositol-3-kinase/akt regulates bleomycin-induced fibroblast proliferation and collagen production. *Am J Respir Cell Mol Biol.* 2010 Apr;42(4):432-41.
- 87.** Hostettler KE, Zhong J, Papakonstantinou E, et al. Anti-fibrotic effects of nintedanib in lung fibroblasts derived from patients with idiopathic pulmonary fibrosis. *Respir Res.* 2014 Dec 12;15:157.
- 88.** Roth GJ, Binder R, Colbatzky F, et al. Nintedanib: from discovery to the clinic. *J Med Chem.* 2015 Feb 12;58(3):1053-63.

89. Conte E, Gili E, Fagone E, et al. Effect of pirfenidone on proliferation, TGF-beta-induced myofibroblast differentiation and fibrogenic activity of primary human lung fibroblasts. *Eur J Pharm Sci.* 2014 Jul 16;58:13-9.
90. Bozyk PD, Moore BB. Prostaglandin E2 and the pathogenesis of pulmonary fibrosis. *Am J Respir Cell Mol Biol.* 2011 Sep;45(3):445-52.
91. Selman M, Pardo A. Revealing the pathogenic and aging-related mechanisms of the enigmatic idiopathic pulmonary fibrosis. an integral model. *Am J Respir Crit Care Med.* 2014 May 15;189(10):1161-72.
92. Thannickal VJ, Murthy M, Balch WE, et al. Blue journal conference. Aging and susceptibility to lung disease. *Am J Respir Crit Care Med.* 2015 Feb 01;191(3):261-9.
93. Kropski JA, Blackwell TS, Loyd JE. The genetic basis of idiopathic pulmonary fibrosis. *Eur Respir J.* 2015 Jun;45(6):1717-27.
94. Dai J, Cai H, Li H, et al. Association between telomere length and survival in patients with idiopathic pulmonary fibrosis. *Respirology.* 2015 Aug;20(6):947-52.
95. Castriotta RJ, Eldadah BA, Foster WM, et al. Workshop on idiopathic pulmonary fibrosis in older adults. *Chest.* 2010 Sep;138(3):693-703.
96. Naik PK, Moore BB. Viral infection and aging as cofactors for the development of pulmonary fibrosis. *Expert Rev Respir Med.* 2010 Dec;4(6):759-71.
97. Sueblinvong V, Neujahr DC, Mills ST, et al. Predisposition for disrepair in the aged lung. *Am J Med Sci.* 2012 Jul;344(1):41-51.
98. Povedano JM, Martinez P, Flores JM, et al. Mice with Pulmonary Fibrosis Driven by Telomere Dysfunction. *Cell Rep.* 2015 Jul 14;12(2):286-99.

- 99.** Kidera Y, Tsubaki M, Yamazoe Y, et al. Reduction of lung metastasis, cell invasion, and adhesion in mouse melanoma by statin-induced blockade of the Rho/Rho-associated coiled-coil-containing protein kinase pathway. *J Exp Clin Cancer Res.* 2010 Sep 16;29:127.
- 100.** Collisson EA, Campbell JD, Brooks AN, et al. Comprehensive molecular profiling of lung adenocarcinoma. *Nature.* 2014 Jul 31;511(7511):543-50.
- 101.** Behr J, Kolb M, Cox G. Treating IPF--all or nothing? A PRO-CON debate. *Respirology.* 2009 Nov;14(8):1072-81.
- 102.** Fernandez IE, Greffo FR, Frankenberger M, et al. Peripheral blood myeloid-derived suppressor cells reflect disease status in idiopathic pulmonary fibrosis. *Eur Respir J.* 2016 Oct;48(4):1171-83.
- 103.** Lee JU, Cheong HS, Shim EY, et al. Gene profile of fibroblasts identify relation of CCL8 with idiopathic pulmonary fibrosis. *Respir Res.* 2017 Jan 05;18(1):3.
- 104.** Mantovani A, Biswas SK, Galdiero MR, et al. Macrophage plasticity and polarization in tissue repair and remodelling. *J Pathol.* 2013 Jan;229(2):176-85.
- 105.** Barron L, Wynn TA. Fibrosis is regulated by Th2 and Th17 responses and by dynamic interactions between fibroblasts and macrophages. *Am J Physiol Gastrointest Liver Physiol.* 2011 May;300(5):G723-8.
- 106.** Ballinger MN, Newstead MW, Zeng X, et al. IRAK-M promotes alternative macrophage activation and fibroproliferation in bleomycin-induced lung injury. *J Immunol.* 2015 Feb 15;194(4):1894-904.
- 107.** Osterholzer JJ, Olszewski MA, Murdock BJ, et al. Implicating exudate macrophages and Ly-6C(high) monocytes in CCR2-dependent lung fibrosis

- following gene-targeted alveolar injury. *J Immunol.* 2013 Apr 01;190(7):3447-57.
- 108.** Craig VJ, Zhang L, Hagood JS, Owen CA. Matrix metalloproteinases as therapeutic targets for idiopathic pulmonary fibrosis. *Am J Respir Cell Mol Biol.* 2015 Nov;53(5):585-600.
- 109.** Osterholzer JJ, Christensen PJ, Lama V, et al. PAI-1 promotes the accumulation of exudate macrophages and worsens pulmonary fibrosis following type II alveolar epithelial cell injury. *J Pathol.* 2012 Oct;228(2):170-80.
- 110.** Murray LA, Chen Q, Kramer MS, et al. TGF-beta driven lung fibrosis is macrophage dependent and blocked by Serum amyloid P. *Int J Biochem Cell Biol.* 2011 Jan;43(1):154-62.
- 111.** McCuaig R, Wu F, Dunn J, et al. The biological and clinical significance of stromal-epithelial interactions in breast cancer. *Pathology.* 2017 Feb;49(2):133-140.
- 112.** Kalluri R, Zeisberg M. Fibroblasts in cancer. *Nat Rev Cancer.* 2006 May;6(5):392-401.
- 113.** Stuelten CH. How Little Is Too Much? - How Transient Tumor-Stromal Crosstalk Can Control Tumor Progression. *J Clin Cell Immunol.* 2016 Oct;7(5).
- 114.** Bhowmick NA, Chytil A, Plieth D, et al. TGF-beta signaling in fibroblasts modulates the oncogenic potential of adjacent epithelia. *Science.* 2004 Feb 06;303(5659):848-51.

- 115.** Bremnes RM, Donnem T, Al-Saad S, et al. The role of tumor stroma in cancer progression and prognosis: emphasis on carcinoma-associated fibroblasts and non-small cell lung cancer. *J Thorac Oncol.* 2011 Jan;6(1):209-17.
- 116.** Puig M, Lugo R, Gabasa M, et al. Matrix stiffening and beta1 integrin drive subtype-specific fibroblast accumulation in lung cancer. *Mol Cancer Res.* 2015 Jan;13(1):161-73.
- 117.** Errarte P, Guarch R, Pulido R, et al. The Expression of Fibroblast Activation Protein in Clear Cell Renal Cell Carcinomas Is Associated with Synchronous Lymph Node Metastases. *PLoS One.* 2016;11(12):e0169105.
- 118.** Wen X, Xie Y, He X, et al. Fibroblast activation protein-alpha positive fibroblasts promote gastric cancer progression and resistant to immune checkpoint blockade. *Oncol Res.* 2016 Oct 26. doi: 10.3727/096504016X14768383625385.
- 119.** Takahashi H, Sakakura K, Kudo T, et al. Cancer-associated fibroblasts promote an immunosuppressive microenvironment through the induction and accumulation of protumoral macrophages. *Oncotarget.* 2016 Dec 30. doi: 10.18632/oncotarget.14374.
- 120.** Kleaveland KR, Moore BB, Kim KK. Paracrine functions of fibrocytes to promote lung fibrosis. *Expert Rev Respir Med.* 2014 Apr;8(2):163-72.
- 121.** Polyak K, Weinberg RA. Transitions between epithelial and mesenchymal states: acquisition of malignant and stem cell traits. *Nat Rev Cancer.* 2009 Apr;9(4):265-73.
- 122.** Bartis D, Mise N, Mahida RY, et al. Epithelial-mesenchymal transition in lung development and disease: does it exist and is it important? *Thorax.* 2014 Aug;69(8):760-5.

- 123.** Huber MA, Azoitei N, Baumann B, et al. NF-kappaB is essential for epithelial-mesenchymal transition and metastasis in a model of breast cancer progression. *J Clin Invest.* 2004 Aug;114(4):569-81.
- 124.** Serresi M, Gargiulo G, Proost N, et al. Polycomb Repressive Complex 2 Is a Barrier to KRAS-Driven Inflammation and Epithelial-Mesenchymal Transition in Non-Small-Cell Lung Cancer. *Cancer Cell.* 2016 Jan 11;29(1):17-31.
- Excellent research work highlighting the importance of EMT, first identified in fibrosis, in cancer. This paper also dwells on the importance of mutant KRAS in driving tumor-associated inflammation.
- 125.** White RA, Neiman JM, Reddi A, et al. Epithelial stem cell mutations that promote squamous cell carcinoma metastasis. *J Clin Invest.* 2013 Oct;123(10):4390-404.
- 126.** Chapman HA. Epithelial-mesenchymal interactions in pulmonary fibrosis. *Annu Rev Physiol.* 2011;73:413-35.
- 127.** Rock JR, Barkauskas CE, Cronic MJ, et al. Multiple stromal populations contribute to pulmonary fibrosis without evidence for epithelial to mesenchymal transition. *Proc Natl Acad Sci U S A.* 2011 Dec 27;108(52):E1475-83.
- 128.** Duffield JS, Luytens M, Thannickal VJ, Wynn TA. Host responses in tissue repair and fibrosis. *Annu Rev Pathol.* 2013 Jan 24;8:241-76.
- 129.** Kage H, Borok Z. EMT and interstitial lung disease: a mysterious relationship. *Curr Opin Pulm Med.* 2012 Sep;18(5):517-23.

- 130.** Kim KK, Wei Y, Szekeres C, et al. Epithelial cell alpha3beta1 integrin links beta-catenin and Smad signaling to promote myofibroblast formation and pulmonary fibrosis. *J Clin Invest.* 2009 Jan;119(1):213-24.
- 131.** Borok Z, Whitsett JA, Bitterman PB, et al. Cell plasticity in lung injury and repair: report from an NHLBI workshop, April 19-20, 2010. *Proc Am Thorac Soc.* 2011 Jun;8(3):215-22.
- 132.** Iwano M, Plieth D, Danoff TM, et al. Evidence that fibroblasts derive from epithelium during tissue fibrosis. *J Clin Invest.* 2002 Aug;110(3):341-50.
- 133.** Zuo W, Zhang T, Wu DZ et al. p63(+)Krt5(+) distal airway stem cells are essential for lung regeneration. *Nature.* 2015 Jan 29;517(7536):616-20.
- Seminal research paper identifying airway progenitors in alveolar repair.
- 134.** Roman J, Ritzenthaler JD, Gil-Acosta A, et al. Nicotine and fibronectin expression in lung fibroblasts: implications for tobacco-related lung tissue remodeling. *FASEB J.* 2004 Sep;18(12):1436-8.
- 135.** Chen LJ, Ye H, Zhang Q, et al. Bleomycin induced epithelial-mesenchymal transition (EMT) in pleural mesothelial cells. *Toxicol Appl Pharmacol.* 2015 Mar 01;283(2):75-82.
- 136.** Kim KK, Kugler MC, Wolters PJ, et al. Alveolar epithelial cell mesenchymal transition develops in vivo during pulmonary fibrosis and is regulated by the extracellular matrix. *Proc Natl Acad Sci U S A.* 2006 Aug 29;103(35):13180-5.
- 137.** Yao HW, Xie QM, Chen JQ, et al. TGF-beta1 induces alveolar epithelial to mesenchymal transition in vitro. *Life Sci.* 2004 Nov 19;76(1):29-37.

138. Willis BC, Liebler JM, Luby-Phelps K, et al. Induction of epithelial-mesenchymal transition in alveolar epithelial cells by transforming growth factor-beta1: potential role in idiopathic pulmonary fibrosis. *Am J Pathol*. 2005 May;166(5):1321-32.
139. Mutsaers SE, Birnie K, Lansley S, et al. Mesothelial cells in tissue repair and fibrosis. *Front Pharmacol*. 2015;6:113.
140. MacDonagh L, Gray SG, Breen E, et al. Lung cancer stem cells: The root of resistance. *Cancer Lett*. 2016 Mar 28;372(2):147-56.
141. Signore M, Ricci-Vitiani L, De Maria R. Targeting apoptosis pathways in cancer stem cells. *Cancer Lett*. 2013 May 28;332(2):374-82.
142. Serrano D, Bleau AM, Fernandez-Garcia I, et al. Inhibition of telomerase activity preferentially targets aldehyde dehydrogenase-positive cancer stem-like cells in lung cancer. *Mol Cancer*. 2011 Aug 09;10:96.
143. Dean M, Fojo T, Bates S. Tumour stem cells and drug resistance. *Nat Rev Cancer*. 2005 Apr;5(4):275-84.
144. Zhou W, Wang Y. Candidate genes of idiopathic pulmonary fibrosis: current evidence and research. *Appl Clin Genet*. 2016;9:5-13.
145. Wecht S, Rojas M. Mesenchymal stem cells in the treatment of chronic lung disease. *Respirology*. 2016 Nov;21(8):1366-75.
146. Yamamura Y, Asai N, Enomoto A, et al. Akt-Girdin signaling in cancer-associated fibroblasts contributes to tumor progression. *Cancer Res*. 2015 Mar 01;75(5):813-23.
147. Alspach E, Flanagan KC, Luo X, et al. p38MAPK plays a crucial role in stromal-mediated tumorigenesis. *Cancer Discov*. 2014 Jun;4(6):716-29.

148. Brichkina A, Bertero T, Loh HM, et al. p38MAPK builds a hyaluronan cancer niche to drive lung tumorigenesis. *Genes Dev.* 2016 Dec 01;30(23):2623-36.
149. Tao L, Huang G, Wang R, et al. Cancer-associated fibroblasts treated with cisplatin facilitates chemoresistance of lung adenocarcinoma through IL-11/IL-11R/STAT3 signaling pathway. *Sci Rep.* 2016 Dec 06;6:38408.
150. O'Connell JT, Sugimoto H, Cooke VG, et al. VEGF-A and Tenascin-C produced by S100A4+ stromal cells are important for metastatic colonization. *Proc Natl Acad Sci U S A.* 2011 Sep 20;108(38):16002-7.
151. Pardo OE, Latigo J, Jeffery RE, et al. The fibroblast growth factor receptor inhibitor PD173074 blocks small cell lung cancer growth in vitro and in vivo. *Cancer Res.* 2009 Nov 15;69(22):8645-51.
152. Hammerman PS, Lawrence MS, Voet D et al. Comprehensive genomic characterization of squamous cell lung cancers. *Nature.* 2012 Sep 27;489(7417):519-25.
153. Tchaicha JH, Akbay EA, Altabef A, et al. Kinase domain activation of FGFR2 yields high-grade lung adenocarcinoma sensitive to a Pan-FGFR inhibitor in a mouse model of NSCLC. *Cancer Res.* 2014 Sep 01;74(17):4676-84.
154. Chaudhuri O, Koshy ST, Branco da Cunha C, et al. Extracellular matrix stiffness and composition jointly regulate the induction of malignant phenotypes in mammary epithelium. *Nat Mater.* 2014 Oct;13(10):970-8.
155. Bonnans C, Chou J, Werb Z. Remodelling the extracellular matrix in development and disease. *Nat Rev Mol Cell Biol.* 2014 Dec;15(12):786-801.
156. Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med.* 2015 Feb 26;372(9):793-5.

- 157.** Clarke DL, Murray LA, Crestani B, Sleeman MA. Is personalised medicine the key to heterogeneity in idiopathic pulmonary fibrosis? *Pharmacol Ther.* 2017 Jan;169:35-46.
- 158.** Saber A, Hiltermann TJ, Kok K, et al. Mutation patterns in small cell and non-small cell lung cancer patients suggest a different level of heterogeneity between primary and metastatic tumors. *Carcinogenesis.* 2016 Dec 17. pii: bgw128. doi: 10.1093/carcin/bgw128.
- 159.** Schwaederle M, Zhao M, Lee JJ, et al. Impact of Precision Medicine in Diverse Cancers: A Meta-Analysis of Phase II Clinical Trials. *J Clin Oncol.* 2015 Nov 10;33(32):3817-25.

EDITORIAL MANAGER - MS CHECK FORM

MS Number	MCP230405
Corresponding Author name	Georgios T. Stathopoulos
Review title	Lung carcinogenesis and fibrosis taken together: just co-incidence?
Section	Neoplasms of the Lung with Imaging
Author address on MS?	Y
Author phone number on EM?	Y
Author email (if not on MS)	Y

Structured abstract	Y
Key words	Y
Introduction	Y
Headings in text	Y
Conclusion	Y
Keypoints	Y

Word count: abstract	134
Word count: text	2947

Bullets/annotations	Y
Refs. in sequence?	Y

Conflicts of Interest	Y
-----------------------	---

Format of references

# Colour figures	-
# Half tones	-
# Line drawings	-
# Tables	-
Supplementary Digital Content	-
Figures/Tables cited in text?	-
Figure legends and titles?	-
Figures to be printed in colour?	-

Comments for copyeditor :
