Review Article

# The oncogenic landscape of the idiopathic pulmonary fibrosis: a narrative review

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**Background and Objective:** Translational research is a source of continuous innovation in medicine, more particularly for clinical research on new treatment modalities in idiopathic pulmonary fibrosis (IPF) patients. However, the heterogeneity of the disease is well recognized, and different pathological and molecular settings have been identified. The molecular mechanisms by which IPF proceeds in time and space remains poorly understood. Although some IPF features are reminiscent of cancer, the dynamics of malignant divergent clonal selective pressure and heterogeneity clearly differ from those occurring in IPF. This is reflected in the absence of patient proper selection and stratification to biological agents (pirfenidone, nintedanib) which limit therapeutic efficacy. Consequently, increased costs are related to the clinical management of advanced IPF patients. Steady collaboration and fluid communication between pneumo-oncologists, radiologists and molecular biologists is a clear priority for the correct interpretation of tests and the definition of effective personalized strategies against this orphan disease. The present work aims at providing the most relevant hints shared by cancer and IPF.

**Methods:** A systematic literature review was performed to identify all relevant data. The examined databases were Scopus, Web of Science, Cochrane, Google Scholar, and PubMed. The last search was run on January 5, 2022. We have primarily conducted separated research for lung cancer, IPF, genetics, epigenetics, surgery in IPF and cancer.

**Key Content and Findings:** The data here presented mainly focus on gene mutations, epigenetics and novel therapeutic approaches. Moreover, epidemiology, prognostic variables and in new treatment strategies adopted in patients with IPF and lung cancer are discussed as well.

**Conclusions:** Overall, the findings of this narrative review will be of help in defining the key molecular features that could applied in IPF setting with promising rationale to improve therapy and to better manage those cases carrying IPF and cancer concomitantly.

**Keywords:** Idiopathic pulmonary fibrosis (IPF); cancer; genetics; immunotherapy; personalized medicine

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## Introduction

Idiopathic pulmonary fibrosis (IPF) is characterized by a proliferative landscape, which recalls—under several aspects—that of cancer. This critical issue has been already exploited for therapeutic purposes taking advantage from know-how and expertise from cancer pharmacology. Moreover, IPF diagnosis is associated to a significantly higher risk of lung cancer development (1,2). Notably the coexistence of IPF is associated to a more unfavourable prognosis in lung cancer patients who generally experience severe disease exacerbation during antineoplastic therapy (3-5). Others and we already described bio-molecular similarities and differences between IPF and cancer (6-10) (*Figure 1*), however some points need deeper clarification and update.

The concept that interstitial lung diseases (ILDs) represent a relevant risk factor for lung cancer development is well documented and known (11-20). Within respect to IPF, reports indicated a cumulative incidence of cancer in IPF patients varying from 3.3%, 15.4%, and 54.7% after 1, 5, and 10 years of follow-up for IPF (21) to 41% and 82% at 1 and 3 years, respectively (5). Age and smoking habit act as known confounding variables since they impact on both lung cancer and IPF onset (19,20,22,23). Moreover, many occupational and environmental exposure toxics are common risks for the development of both the diseases. Notably, IPF patients are at higher risk of cancer development if compared to those affected by chronic obstructive pulmonary disease (COPD), another cancer predisposing pathologic entity (24). The Japanese Hokkaido registry data reports an unadjusted risk ratio of 7.8 for lung cancer in IPF patients *vs.* COPD ones (25,26). Most often tumors in IPF context arise in peripheral lung (27,28), although these data need further confirmation (19). The mechanistic explanation and the association between IPF and cancer are discussed in detail in the next sections of the manuscript. However, several issues deserve to be here underline. It is conceivable that the pro-proliferative landscape that characterizes IPF, should promote the selection of those cells carrying oncogenic mutations (29-31). Pirfenidone and nintedanib act as antifibrotic drugs through different mechanisms. The first essentially acts by deregulating a series of cytokines, including transforming growth factor (TGF)-β1, connective tissue growth factor (CTGF), platelet-derived growth factors (PDGF), and tumor necrosis factor (TNF)-α. Moreover, it behaves as scavenger of reactive oxygen species (ROS) and downregulate angiotensin-converting enzyme (ACE) expression (32,33). Nintedanib is a multikinase inhibitor which also down-regulates protein and mRNA expression of extracellular matrix (ECM) proteins, fibronectin, and collagen 1a1 and inhibits (TGF)-β1-induced myofibroblast differentiate (34). Notably, both drugs inhibited collagen I fibril formation (35). It should be underlined that a relationship exists between these main two treatments for IPF, namely pirfenidone and nintedanib, and lung as well. Several recent studies have shown a prophylactic effect of the use of pirfenidone perioperative setting against postoperative acute IPF exacerbations in patients with lung cancer (36-40). Notably therapy with pirfenidone seems

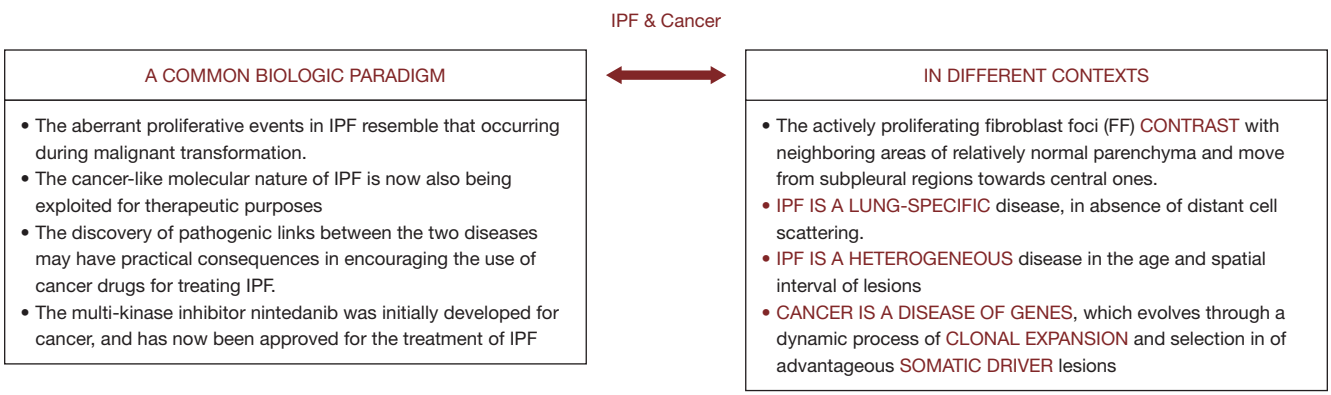


**Figure 1** IPF and cancer. The two diseases share common pathogenic pathways that should be exploited for novel therapeutic approaches. The oncogenic gain behaves as main driver of proliferative and invasive phenotypes. Heterogeneity which characterizes both diseases, refers to clonal selection (cancer) and histology (IPF). The specific IPF context impacts on the therapeutic exploitation of targeting oncogenes. IPF, idiopathic pulmonary fibrosis. IPF, idiopathic pulmonary fibrosis.

**Table 1** The search strategy summary

| Items | Specification |
|---|---|
| Date of Search (specified to date, month and year) | Last search January 5, 2022 |
| Databases and other sources searched | Scopus, Web of Science, Cochrane, Google Scholar, and PubMed. For the Google Scholar database, due to the excessive amount of data obtained, only the first 200 results for each search were considered, because further results rapidly lost relevance |
| Search terms used (including MeSH and free text search terms and filters) | Lung cancer, non-small cell lung carcinoma (NSCLC), idiopathic pulmonary fibrosis (IPF), epigenetic, genetic, surgery + IPF, ionizing radiation + IPF |
| Timeframe | 5 years |
| Inclusion and exclusion criteria (study type, language restrictions, etc.) | To obtain the highest search sensitivity, the keywords used to identify relevant articles were mainly: lung cancer OR NSCLC AND IPF AND genetics OR IPF AND NSCLC AND epigenetics; imaging AND IPF OR IPF AND CT AND ionizing radiation; IPF OR AND lung cancer AND surgery |
| Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.) | Two authors (GMS and SL) independently screened the titles of the identified studies. GMS, AGC and AB independently screened the titles and the abstracts of the studies; then, they read the full text of selected studies. Any disagreement was analyzed and overcome by discussion and reaching a mutual agreement |

Any additional considerations, if applicable.

to be associated to lower incidence of lung cancer in IPF patients if compared to non-pirfenidone treated cases (41), although this observation should be confirmed by more extensive analysis. Some recent observation also underlined a potential therapeutic role of pirfenidone against lung cancer. In detail, it has been reported *in vitro* and *in vivo* that it could suppressed activation of non-small-cell lung carcinoma (NSCLC) associated myofibroblasts (42), which are known to be involved in tumor progression (43-45) and impairs epithelial–mesenchymal transition (EMT) by acting on exogenous TGF-β1 and on paracrine TGF-β produced from NSCLC cells (46). Pirfenidone seems to play a synergic effect with conventional chemotherapy such as carboplatin (47), whereas studies evaluating effects of combination with immune checkpoint (IC) inhibitors are ongoing (the NCT04467723 trial evaluating the combination of pirfenidone with the programmed death-ligand 1 (PD-L1) and programmed cell death protein 1 (PD-1) inhibitor atezolizumab in second-line and beyond NSCLC, website at www.clinicaltrials.gov). The antiproliferative effect of nintedanib derives to its ability to block the vascular endothelial growth factor (VEGF), PDGF and the fibroblast growth factor receptor (FGFR). Nintedanib in combination with docetaxel is approved as second-line therapy for advanced NSCLC (48). It also promotes antitumor immunity and antitumor activity in combination with PD-1 blockade in mice by targeting cancer-associated fibroblasts (CAF) thus attenuating the immunosuppressive tumor microenvironment on one hand and promoting intratumoural activation of antitumor CD8+ T cells (49). Although some reports suggesting a positive effect (50-52), it is still unclear if nintedanib could play an effective role against lung cancer aroused in IPF patients. When associated with corticosteroids, it seems to be able to attenuate targeted drug (53) and IC inhibitor-related pneumonitis in cancer patients (54,55). Thus, we—here—report and discuss more recent advances from multidisciplinary contexts that will result in significant changes in the diagnosis and treatment of IPF patients. We present the following article in accordance with the Narrative Review reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-21-880/rc).

## Methods

A systematic literature review was performed to identify all relevant data. The examined databases were Scopus, Web of Science, Cochrane, Google Scholar, and PubMed. The last search was run on January 5, 2022. *Table 1* summarizes the search strategy.

## Advances on pathogenic mechanisms of IPF: what we could learn from molecular epidemiology linking lung cancer and fibrosis

### *Genetics*

Several already published data from genome-wide association and linkage studies have identified common genetic variants that are associated to increased risk of IPF onset and progression. Moreover, these IPF-related signature activation define a biologic context which essentially support clonal selection of transformed cells. Consequently IPF-related gene variants can be defined as: (I) IPF private; (II) favouring malignant transformation and (III) shared by IPF and lung cancer. The first gene set mainly affect genes encoding for proteins related to inflammatory and immune response, such as *TGF-β1* (56,57), interleukin-1 receptor alpha (*IL1RN*) (58,59), interleukin 8 (*IL8*) (60), toll-like receptor 3 (TLR3) (61) human leukocyte antigen (*HLA*) *DRB1*1501* (62), the cell-cycle progression related genes Cyclin Dependent Kinase Inhibitor 1A (*CDKN1A*) and tumor protein 53 (*TP53*) (63) and the Telomerase Reverse Transcriptase (*TERT*) genes. All these genes, known to confer a risk for IPF, are known to be associated to cancer as well. However, except for the tumor suppressor *TP53*, these genes do not behave as oncogenic drivers but rather their activation by genetic changes cooperates in sustaining malignant transformation. Telomerases are an enzyme that catalyse the addition of nucleotides on the ends of chromosomes and IPF is characterized by shortening of telomere lengths and consequent exhaustion of lung stem cells. Mutations in the genes encoding telomerase, *TERT* and telomerase RNA component (*TERC*), are pathogenetically associated to IPF. Mutational frequency affecting each gene is rare, but—overall—*TERT* mutations are the most common genetic defect found in FPF. The overall penetrance of pulmonary fibrosis in *TERT* mutation carriers is 40% in subjects with a mean age of 51 years (64-68). It could be hypothesized that the biologic landscape, which is linked to IPF, defined by pro-invasive, anti-apoptotic and pro-angiogenic features and properties of associated genes and molecules, could be exploited by tumour cells (already transformed) to optimize their malignant propensity, according to the biologic phenomenon already defined by "oncogene expedience" (69). In other words, the IPF genetic asset impacts on the risk of lung-cancer development although IPF-associated lung cancer does not derive from transformation due to mutation accumulation of IPF-related cells (70). With the expansion of genome-wide association studies (GWAS) novel biomarkers and actionable targets have been unveiled and new insights have been specifically derived by the integration of molecular techniques and conventional epidemiology, namely molecular epidemiology (71). This approach has been widely exploited in cancer, whereas few data are available for IPF (72). The identification of novel diagnostic and therapeutic endpoints, quantification of genetic damages, definition of genetic susceptibility for IPF could potentially derive from comparative studies on IPF-associated lung cancer. According to standard epidemiologic approach the two diseases share relevant environmental and occupational risk factors, such as tobacco smoke, dusts, and particulates, as well as some therapeutic agents. Moreover, IPF and lung cancer present lineage specifiers which underline a common cell-fate specification. The thyroid transcription factor-1 (TTF-1) also known as NK2 Homeobox 1 (NKX2.1) is a homeodomain-containing transcription factor, that is essential for the morphogenesis and differentiation of the thyroid, lung, and ventral forebrain. It controls the expression of select genes in the thyroid, lung, and the central nervous system. In the lung, TTF-1 is a critical regulator of the expression of surfactant proteins that are essential for lung morphogenesis, homeostasis, and host defence (73). TTF-1 is expressed in type II epithelial cells, less abundantly in non-ciliated respiratory epithelial cells and basal cells whereas it is not expressed in type I cells (29). TTF-1 is expressed lung after injury, and it may play a role in epithelial cell proliferation and differentiation during the repair processes, as fibrosis and cancer. In transgenic mice, increased TTF-1 expression caused severe inflammation, pulmonary fibrosis, respiratory failure, and death, associated with eosinophil infiltration and increased expression of eotaxin and interleukin 6 (IL-6). Increased expression of TTF-1 altered alveolarization and caused chronic pulmonary inflammation. In adults, TTF-1 is almost exclusively expressed in thyroid and pulmonary epithelial cells. Its expression, determined by immunohistochemistry, is a highly specific marker for primary lung adenocarcinomas (ADCs) and it must be used for the differential diagnosis between primary and metastatic ADCs (74,75). *TTF-1* gene amplifications can be detected in about 2–4% of primary lung and 13% of metastatic lesions (76-78); activated TTF-1 promotes epidermal growth factor receptor (EGFR) driven transformation (79,80). Overall *TTF-1* behave as oncogene in a lineage specific (ADC) context (81). However, opposing, and paradoxical effects have been reported in animal models carrying *TTF-1* haploinsufficiency being

associated with reduction of invasive and metastatic potentials because of a suppressive modulation on the genes implicated in cytoskeletal regulation, cell-cell organization, and motility. Interestingly, it is also associated to the enhancement of kirsten rat sarcoma (*KRAS*)-driven adenocarcinogenesis (82-84). TTF-1 is known to repress TGF-beta EMT by reducing TGF-beta and the TGF-beta related activation of Snail and Slug. On the contrary TGF beta represses TTF-1 through miR-365 (85). Lung cancer (LC) is genetically characterized by the presence of somatic mutations which are known to be selected by a variety of environmental exposures (among which tobacco smoke) on the background of specific germline mutations. Accumulation of somatic mutations affecting the RAS-RAF cascade has been reported with significantly higher prevalence of *v-raf* murine sarcoma viral oncogene homolog B1 (*BRAF*) mutations which define a novel potentially actionable target (86). Interestingly, growing evidence suggests that the occurrence of some germline mutations might predispose subjects to the development of IPF and to LC as well. The most intriguing changes that have been reported in lung tumors associated to IPF familial clusters refer to heterozygous missense mutations in pulmonary surfactant-associated proteins genes. It is well known that variants in the genes encoding for proteins A2 (*SFTPA2*) (87) and A1 (*SFTPA1*) (88) display pathogenic role and predispose to IPF (89) by impairing secretion of surfactant A proteins (SP-A) thus leading to protein instability and dysfunction of endoplasmic reticulum (ER). The latter induces stress and alter differentiation of resident alveolar type II (ATII) cells (45,90). Genetic variants of *SP-A* can, thus, interfere with intracellular protein trafficking and promoting cell proliferation in both lung fibrosis and malignant transformation (87). Similarly, mutations affecting genes encoding surfactant protein C (*SFTPC*) (91,92) are linked to lung fibrosis whereas protein-D gene variants (*SFTPD*) have been reported in paediatric cases of diffuse ILD (93). Inherited lung fibrosis is also associated to the occurrence of mutations affecting the gene encoding for the member A3 of the ATP-binding cassette family. Withing respect to the context of cancer, the ATP transporters are known to mediate chemoresistance (94) and, more recently, their role in all phases of disease onset and progression has been considered and documented (95). A comprehensive analysis retrieved from Gene Expression Omnibus (GEO) database reported the that genes encoding for peroxisome proliferator-activated receptor (PPAR) signalling pathway transducers were enriched in IPF associated to LC (96). The PPARs define a group of three nuclear receptor isoforms, PPAR-γ, PPAR-α, and PPAR-δ, encoded by different genes. They act as ligand-regulated transcription factors that control gene expression by binding to specific response elements (PPREs); they are known to play a critical physiological role as lipid sensors and regulators of lipid metabolism and are involved in cell proliferation. Deregulation of PPAR signalling has been reported in several disease including atherosclerosis, inflammation, cancer, infertility, and demyelination (97-99). Although the exact mechanism of PPARs in lung fibrosis and LC remains largely unknown, a PPARγ agonist, including a constitutively active PPAR-γ construct (VP16-PPAR-γ), has been found to exert antitumorigenic effects in both IPF and LC by inhibiting myofibroblast differentiation through the blockade of TGF-β and activating phosphatase and tensin homolog (PTEN) (100). The Acyl-CoA Dehydrogenase Long Chain (*ACADL*), cluster of differentiation 36 (*CD36*), Lipoprotein Lipase (*LPL*), and Matrix metalloproteinase-1 (*MMP1*) gene signatures in the PPAR pathway have been reported to be shared among IPF and LC (96). *In vivo* experiments demonstrated that silencing of *CD36* resulted in the inhibition of TGF-β activation in a rat silicosis model, ultimately blocking silica-induced lung fibrogenesis (101). Moreover, a population enriched in CD36+ macrophages has been reported in in the lungs of patients affected by IPF (102). CD36 promotes adipocytes genesis and differentiation (103); in lung fibrosis its expression is involved in the transformation of latent TGF-β1 to active form (101) and a CD36 synthetic peptide reduces fibrotic tissue alteration and collagen accumulation in a mouse model of silicosis (104). Increased *CD36* copy number has been related to tumor progression and increased risk of metastatic development (105). Interestingly, the IPF gene expression analysis indicates that the genes regulated by hypoxia are altered, suggesting a primary role of hypoxia-inducible factor 1-alpha (HIF-1α) in IPF onset (106). Overall, these data are coherent with most recent publications suggesting that a metabolic signature, linked to lipid mediators derived from phospholipids, sphingolipids, and polyunsaturated fatty acids play an important role in the pathogenesis of IPF (107-109). Coherently the *ACADL* gene, encoding for long-chain acyl-CoA dehydrogenase, an enzyme involved in fatty acid beta-oxidation and implicated in homeostasis of pulmonary surfactant (110), is known to be deregulated in IPF and to be a core signature gene that differentiates NSCLC from normal tissue. In cancer context *ACADL* seems to behave as tumor suppressor (111) and its

expression correlates with aggressive tumor phenotype (112) and poor prognosis (113). The LPL gene has been reported to be deregulated in IPF where it is significantly upregulated in NSCLC if compared to surrounding healthy tissue (52). In this context the matrix metalloproteinases MMPs, a family of 25 secreted and cell surface-bound neutral proteinases, play a crucial role. The *MMP1* seems to be the most significantly altered gene shared across IPF and LC. The human *MMP1* consists of 10 exons and is located on human chromosome 11q22.2-22.3. This gene is tightly linked to a cluster of eight MMP genes, including *MMP3*, *MMP7*, *MMP8*, *MMP10*, *MMP12*, *MMP13*, *MMP20*, and *MMP27*, and two pseudogenes (114). MMP1 participates in several processes which characterize both cancer and IPF such as ECM remodelling, cell plasticity, cell migration, and angiogenesis (115-117). MMP1 mutations are associated with COPD (118). A large amount of data reported that MMP1 is highly expressed in interstitial collagenase degrading fibrillar collagens as well as in cancer tissues, where it acts by promoting invasive potential and distant spreading (119). Several single nucleotide polymorphisms (SNPs) were identified to be individually significantly associated with risk of early-onset LC (120); notably MMP1 expression, measured by immunohistochemical (IHC), was reported to be higher in those NSCLC tissues associated with IPF, even in early-stage diseases. Most recent data emerge regarding the common genetic signature between IPF and cancer. Ammar *et al.* analysed samples from Lung Tissue Research Consortium (LTRC) and National Jewish Health (NJH) cohorts, identified genetic signature able to predict the IPF condition. Some genes were already known to be related to the pathogenesis of IPF such as matrix metalloproteinases, some others identified potentially targetable pathways such as the frizzled-related protein 2 (FRP2), a WNT-signalling (121) or identify predictive disease biomarkers as the Glutathione Peroxidase-3 (*GPX3*) gene, expressed in epithelial cell from bleomycin-induced fibrosis models and upregulated in IPF (122). Interestingly, maternal smoking and e-smoking negatively affects WNT signalling cascade in mouse models. It affects mRNA expression of the WNT transducers frizzled7 (Fzd7) and *Ctnnb1* (gene symbol of β-catenin) as well as the WNT target gene *Fn* (fibronectin) with significant implication lung development and homeostasis which could generate a favourable substrate for future onset of interstitial fibrosis (123-125). Moreover, a novel set of 12 disease-relevant translational gene markers (*C6*, *CTHRC1*, *CTSE*, *FHL2*, *GAL*, *GREM1*, *LCN2*, *MMP7*, *NELL1*, *PCSK1*, *PLA2G2A*, and *SLC2A5*) can split IPF *vs.* control patients (126). Another report on 35 matched tumor/IPF samples reported that somatic mutations occurred with predominant C/T transitions despite extensive smoking histories, thus suggesting more associations with *APOBEC3B*-related mutagenesis in the process of IPF-LC development, rather than smoking. *TP53* (62.9%) and *BRAF* (17.1%) genes were found significantly mutated in IPF-LC. Recurrent focal amplifications in 3 chromosomal loci (3q26.33, 7q31.2, and 12q14.3), and 9p21.3 deletion were identified, and genes associated with JAK-STAT signalling pathway were significantly amplified in IPF-LC (P¼0.012). Moreover, one case report on laser-assisted microdissected samples of IPF associated to lung cancer identified five mutations (*KDR*, *EPHA5*, *APC*, *CREBBP*, and *ERBB2*) proper of IPF, four mutations (*EPHA5*, *PKHD1*, *RB1*, and *KEAP1*) proper of IPF-associated cancer whereas the only mutated gene shared by both the diseases was *EPHA5* (118,127). The latter belongs to the ephrin receptor subfamily of the protein-tyrosine kinase family which are known to play a role in several developmental events and in cancer (128) as well as in modulating tumor surrounding microenvironment, being associated to enhanced infiltration of CD8+ T cells and M1 macrophages, reduced recruitment of immunosuppressive regulatory T cells (Tregs) into the tumor site, with prognostic and predictive value (129-131).

### *Epigenetics*

The heterogeneous genetic background which characterized IPF cellular populations is and the possible presence of cells featuring characteristics of stemness define the genesis, maintenance, and plasticity of these cells. In this context the process of lung fibrogenesis is extensively regulated by epigenetic remodelling. Epigenetic mechanisms which modulate the expression of fibrotic genes are emerging as driver players in lung fibrogenesis (132-134). Indeed, several epigenetic regulators are deregulated in IPF: DNA methyltransferases, non-coding RNAs, histone demethylases, and histone acetyltransferases (135). Most studies aiming at analysing epigenetic profile of IPF have been conducted on DNA or mRNA extracted on fixed-formalin paraffin-embedded (FFPE) or frozen samples that are generally mixed before analysis. In this perspective it should be remarked that a relevant role is played not only by the epithelial cells and fibroblasts, but also by alveolar macrophages (AMs). Targeting epigenome represents

a potential strategy for fibrosis treatment. Changes in the epigenome are associated with the development and function of AMsin the IPF lung (136,137). Most methylation changes have been identified outside of CpG islands and several gene expression signatures have been reported known (e.g., collagens, *HDAC4*, *NOTCH1*, *PDGF*, *SERPINF1*, and *TOLLIP*) and novel candidate (*CASZ1*) genes. Moreover, environmental stimuli contribute to epigenetic changes. Several components of cigarette smoke have been reported to affect epigenome not only in lung cancer but also in IPF (138,139). Exposure to cigarette smoking has been associated to increased global levels of histone methylation (140). Overall, genes with differentially methylated CpG islands in their promoters are involved in key biologic processes which are implicated in IPF and cancer onset, such as cell assembly, morphology and organization, cell growth, proliferation, signalling, and apoptosis. Some alterations involve the *COL18A1* gene, known to be upregulated in IPF (141), genes that modulate myofibroblast differentiation and transition from pericytes to myofibroblasts as *NOTCH1* (142-144) and progressive IPF as *SMARCA4* (145) as well as the promoter of *CXCL3*, which is involved in bleomycin-induced fibrosis (146). Moreover the Serine/Threonine Kinase 17b (STK17B) and Serine/Threonine Kinase 3 (STK3) and the histone cluster 1 H2ah have been reported to be up-regulated in IPF, coherently with the hypo-methylated state of their promoter associated CpG islands (147). Moreover epigenetic regulation interferes in the capacity of fibroblasts from lung fibrosis to up-regulate cyclooxygenase-2 (COX-2) expression and COX-2-derived Prostaglandin E2 (PGE2) synthesis, through a mechanism involving hypermethylation of the transcriptional regulator, c8orf4 (148). Interestingly, hypermethylation of the *Thy-1* gene promoter region causes the loss of this molecule, which in more invasive behaviour of cancer and the transformation of fibroblasts into myofibroblasts within fibroblast foci in IPF.

Although DNA hypomethylation is a hallmark of cancer and common epigenetic traits are shared between IPF and cancer, some reported data suggest that the similarities in the differentially methylated CpG islands are unexpectedly limited global meth being less extensive in IPF (104). This observation points out methylation occurs in both diseases but should occur through different mechanisms. Excessive histone deacetylation is involved in the progression of pulmonary fibrosis through a complex interaction between histone deacetylases (HDACs) or histone acetyltransferases and fibrosis modulators TGF-beta1, small mother against decapentaplegic (Smad) 3, Smad7 and Snail (149). At this regard histone acetyltransferase EP300, upregulated by TGF-beta1, accumulates in lung fibroblasts and, in turn, promotes SMAD-mediated TGF-beta signalling. EP300 also activates discoidin domain receptor 1 (DDR1), a collagen receptor kinase which triggers ECM deposition (150) and promotes transcription of profibrotic molecules such as alpha-smooth muscle actin (α-SMA), Collagen I (COL1) and tissue inhibitor of metalloprotein, which further promote production of ECM (151). *EPP* is also frequently mutated in small cell lung cancer (SCLC) (152). Similarly to IPF, indeed, histone deacetylation is associated with lung cancer progression, resistance to chemotherapy and targeted therapy, and is harboured by nickel, chromate, arsenite present in smoke tobacco. Histone deacetylases I, I, III, VIII are the most common classes hyperexpressed in NSCLC and IPF and their deregulation is associated to poor prognosis in lung cancer (153). At higher level, histone acetylation is regulated by bromodomain and extra-terminal (BET) proteins, a family of chromatin readers (including BRD2, BRD3, BRD4, and BRDT) that bind acetylated histones, regulate gene transcription, and pass on epigenomic memory across cell divisions. BET proteins are implicated in cancer through activation of oncogenes like *c-Myc*, *IL-7R*, *FOSL1*, and *E2F*; among these, *BRD4* has shown to exert profibrotic action in a variety of organs, included lung, by regulating multiple gene programs and biochemical pathways in various cell types, although precise mechanisms have still to be elucidated. In IPF BDR4 probably activates specific enhancers and promoters that regulate transcription of downstream genes encoding ECM proteins such as α-SMA, COL1A1, fibronectin, and factors that stimulate trans-differentiation of fibroblasts (154). Moreover, BDR4 upregulates the pro-oxidant enzyme NADPH oxidase 4 (Nox4), promoter of oxidative stress and cellular ageing (155). The similarity between cancer and IPF is higher if referred to microRNA expression such as in the case of let-7d and hsa-miR-21, which are found to deregulated in both diseases (156-159). Let-7d inhibits EMT through modulation of signalling mediators downstream TGF beta, key orchestrator of fibrogenesis (160). Low levels of Let7d have been found in bronchoalveolar lavage-derived exosomes of IPF murine models compared with normal mice (161). Let-7d downregulates FoxM1, a transcription factor previously known to promote cell proliferation and resistance to apoptosis in cancer cells by activation of Wnt/beta catenin and TGF-beta/SMAD3 pathways (162). Intriguingly, also in IPF high levels of

FoxM1 have been found in lung fibroblasts where enhance differentiation of pericytes into myofibroblasts and collagen production, through activation of pathways common with carcinogenesis (70,163). The oncogene Mir-21 promotes cell proliferation, invasion, migration and radioresistance in various cancers, among which NSCLC, regulating nuclear factor kappa-light-chain-enhancer of activated B cells (NF-Kb), phosphatase and tensin homolog/akt murine thymoma viral oncogene homolog (PTEN/AKT), phosphoinositide 3-kinases (PI-3K)/AkT/mammalian target of rapamycin (mtor) pathways; moreover it induces EMT in cancer cells reducing the inhibitory effects of SMAD7 on fibrosis with upregulation of TGF-beta signalling (164). Similarly, in IPF, TGF-beta-induced overexpression of miR-21 in fibroblasts and myofibroblasts creates a positive loop mechanism in which negative modulation of SMAD7 and PTEN increases the expression of TGF-beta, promoting EMT and matrix collagen deposition (165,166). Both miR-29a and miR-185 have been found downregulated in bronchoalveolar lavage fluid (BALf) of IPF and lung cancer patients, probably in response to high levels of TGF beta. However, their hypoexpression produced different effects on the common target COL1A1, whose expression was increased in IPF but not in lung cancer, pointing out the peculiar fibrotic nature of IPF (167). Despite similarities, some microRNAs (miRNAs) are inversely expressed, suggesting the existence of disease-specific mechanisms, which complicate the identification of actionable targets effective in both conditions. For example, the hsa-miR-17-92 miRNA cluster, which encodes six miRNAs (hsa-miR-17, -18a, -19a, -19b, -20a, -92a), is overexpressed in various solid neoplasms, including lung cancer, where behaves as tumor promoter: its block by therapeutic agents, such as Docosahexaenoic acid, may limit cell proliferation, resistance to apoptosis and metastatization (168). However, miR-17-92 cluster has a crucial role for a balanced lung cell damage repair and for regulation of fibrotic genes such as *COL1A1*, *COL1A3*, *CTGF*, *VEGF*, *TGF beta*, *MMP-1*, *MMP-7* and *MMP-9*. Levels of the miR 17-92 cluster appear reduced in IPF lung tissue and fibroblasts for hypermethylation of promotor CpG islands by DNA methyltransferases (DNMTs), enzymes that may seem an effective actionable target to reduce lung fibrosis, as shown by Dakhlallah *et al.* (169). Unlike miRNA, whose action has been extensively studied, regulatory function of long non-coding RNAs (lnc-RNAs) is still largely unknown. Lnc-RNAs are single-stranded RNA sequences longer than 200 nucleotides, classified in 5 classes (intergenic, antisense, intronic, enhancers, and pseudogenes) according to the positional relationship with protein-coding genes (170). Lnc-RNAs form complexes with DNA, RNA, and proteins, regulating cellular processes such as chromatin modification, transcription, post-transcriptional modifications, scaffolding. Transcriptome sequences analyses reveal more than 1,800 lnc-RNAs deregulated in IPF (171). They upregulate mTOR and TGF-β1/Smad2/3 pathways, impair telomerase functions, alter mitochondrial, activate oxidative stress-related genes (ROS, superoxide dismutase, and catalase) and apoptosis-related genes (cytochrome-c, caspase-9, and caspase-3); they can directly bind to miRNAs silencing their expression (172). The complex scenario of epigenome is further modulated by exosomes, microvesicles and extracellular vesicles, membrane-derived vesicles of various diameter, released in extracellular microenvironment by a variety of cells such as B-cells, T-cells, mast cells, stem cells, dendritic cells, platelets, endothelial cells, epithelial cells. They convey proteins, lipids, miRNAs, long non-coding RNAs, DNA, enzymes and other factors responsible of cell-to-cell communication, epigenetic modifications. Composition of exosomes is influenced by microenvironment and determines the maintenance or the rupture of cellular homeostasis (173,174).

It should be remarked that not only smoke exposure can affect DNA methylation in both cancer and IPF. This issue is even more relevant for the cancer and the rare fibrotic cases that arise in non-smoker subjects. Indeed environmental or occupational exposure, pathogen infection and persistent tissue damage. For instance, polymorphisms in *CYP1A1* and *GTSM1*, xenobiotic metabolizing enzymes, have been reported to be associated to higher risk of lung cancer development whereas polymorphisms in *MLH1*, a mismatch pair enzyme should play a role in the onset of the disease in never smokers. Moreover, polymorphisms in genes involved in inflammatory cascade such as those encoding for interleukin (IL)-10, TNF, IL1-RN and IL-6 have been reported to be associated to lung cancer risk independently from cigarette smoke exposure (175). Within respect to IPF, previous reports suggested that SNPs in Mucin 5B *(MUC5B)* promotor region (rs35705950) are associated with prognosis of IPF and this fact may be related to the reduction of immune defense mechanism of *MUC5B* (176,177). Growing evidence suggests that lung microbiome plays a relevant role in maintaining lung immune homeostasis and that its alteration and disruption might be related to cancer onset by acting on epigenetic level such as by causing DNA damage, genomic instability, and inducing higher sensitivity to carcinogens (178).

Environment factors that can alter lung microbiota might promote, mainly through production of bacterial toxins and other pro-inflammatory factors, cancer onset and progression (179,180). A number of recent observations suggests a role for lung bacteria in IPF onset as well (181-184). First observation regarded the fact that bacteria (most often Streptococcus pneumoniae and Moraxella catarrhalis) are frequently isolated from BALF from IPF patients (185) and that patients enrolled in clinical trials have better outcomes in those arms encompassing treatment with antibiotics (186-188). Next generation analysis approaches more recently reported that changes in the lung microbiome are associated to IPF progression and acute phases (not in those patients treated with interferon (189); however, these data are too preliminary to define their potential predictive or prognostic role (190,191).

## Non-invasive diagnostic and monitoring tools

### *Is there a role for liquid biopsy in IPF setting?*

Liquid biopsy is a minimally invasive procedure that has been developed in molecular oncology. It allows the identification of circulating tumor-derived DNA (ct-DNA) that is shed from tumor cell in body fluids. Serial analysis of circulating tumor DNA (ctDNA) during treatment will provide a dynamic picture of molecular disease changes and could be used to monitor the emergence of secondary resistance and to identify heterogeneous subclonal populations developing during targeted treatments (192). This non-invasive sampling issue is overall simple to collect, although should present quantity and quality problems and representation bias. There is a strong rationale for application of this technique in early diagnosis and monitoring of IPF patients, although some key differences should be underlined. IPF landscape is enriched in neoplastic potential expressed in a context of complex genomic polyclonality and cellular heterogeneity. Smoking is strongly associated with IPF (193) and is a strong negative predictor for the occurrence of *EGFR* activating mutations in lung cancer according to previous reports (194). However, no somatic changes in coding sequences of driver known oncogenes. The latter observation, in therapeutic perspective, results in the absence of oncogenic addiction phenomenon. Thus, the oncogenic shock phenomenon cannot be exploited for therapeutic purposes in IPF. In cancer setting, the application of liquid biopsy: (I) ctDNA; (II) circulating tumor cells (CTC) for genetic analysis; (III) CTC. Interestingly, the level of circulating cell-free double-stranded DNA fragments (ccf-dsDNA) is increased in those IPF patients featuring rapid progression of the diseases if compared to stable IPF and health subjects. Moreover, the high expression of ccf-dsDNA is associated with that of amino acid, energy, and lipid metabolism pathways (195). Very recently, Pallante and colleagues (196) demonstrated the concordance between ccfDNA and genomic DNA by analyzing and detecting the rs35705950 polymorphism of MUC5B gene promoter, known to be involved in IPF onset (197). Overall, IPF is associated to increased tumor mutational burden (TMB) which, in turn, significantly contributes to the development of lung adenocarcinoma (198). However, data from TMB analysis from IPF-associated lung cancer are still controversial, being significantly higher than in lung adenocarcinoma alone (86,198). However, data from TMB analysis on lung cancer and concomitant ILDs are more controversial since some results reported that squamous cell carcinoma and adenocarcinoma with ILD do not have high TMB values (199). Due to the implication for therapy with IC inhibitors, since based on these data patients should not be addressed to immunotherapy (200), these preliminary observations deserve further validation data. Circulating cells have been studied to evaluate their possible role as predictive and prognostic markers. Elevated number of circulating fibrocytes, sorted by flow cytometry, is reported to be associated to higher mortality (201), rather than as validated marker of disease progression (202). Levels of circulating endothelial cells and endothelial progenitor cells have been found to be reduced in patients with IPF and treatment with nintedanib and pirfenidone further reduced their levels (203). Further validations are required regarding the role of circulating monocytes in prediction of disease progression (204).

### *Imaging*

The diagnostic algorithm for suspected lung tumor in the IPF setting is still unclear. The most recent ATS/ERS/JRS/ALAT guidelines, updated in 2015, do not address this issue (205). Also, more "*radiologically-oriented*" guidelines such as those from the Fleischner society do not specifically include management suggestions tailored for IPF patients. Since those patients can be considered at high-risk of developing a lung tumor the suggested management will therefore rely mostly on surgical lung biopsy and resection. These approaches can be way too aggressive for an IPF patients. For these reasons a recent editorial suggests the

following approach: high resolution computed tomography (HRCT) once a year in all patients with IPF. For patients with nodules less than 8 mm in diameter an HRCT every 3–6 months can be performed. If HRCT shows progression of the nodule, a PET-CT scan is recommended. For nodules with diameter of at least 8 mm, PET-CT scan is highly recommended. If PET indicates that a significant uptake is present, minimally invasive diagnostic procedures such as transthoracic needle biopsy or endoscopic approach are mandatory. If the patient is not suitable for biopsy, a multidisciplinary discussion is suggested (2). Even if nowadays early diagnosis of lung cancer mostly relies on HRCT and PET scans, which represent the cornerstone for timely therapeutic interventions, some new options may be available in the future. Magnetic Resonance (MR) and, especially, diffusion weighted imaging (DWI) has already shown that active lung inflammatory tissue in the IPF setting could be assessed effectively (206). It also has shown a capability of distinguishing between malignant and benign pathologies thanks to apparent diffusion coefficient (ADC) values (207). A promising tool may be IVIM (Intravoxel Incoherent Motion)-DWI which can also give information about perfusion. This may lead in the future to put aside data from PET-CT with those from MR. Another possible tool to optimize the management of IPF patients with a suspected lung cancer can be Radiomics. Radiomics is a quantitative approach to medical imaging, which aims, through mathematical extraction of the spatial distribution of signal intensities and pixel interrelationships, to quantify textural information by using analysis methods from the field of artificial intelligence. Radiomics has progressively gained attention for nodule characterization and, since no data are available in the IPF setting, more time is needed to distinguish the hope from the hype (208).

## A perspective on novel cancer-related therapies in IPF

### *Rationale for immunotherapy in fibrotic lung*

It is well known that inflammation plays a relevant pathogenic role in IPF even though anti-inflammatory drugs as steroids do not impact significantly on disease progression (209). This observation points out that the role on inflammatory reactions might not be a driver of IPF, or more properly, the complex IPF context requires a deeper characterization of the inflammatory pathways involved to identify effective targets. The inflammatory profile of IPF is characterized by type 2 inflammation (210,211) involving the interleukin (IL)-13 and IL-4, produced by T helper 2 (Th2) cells and type 2 innate lymphocytes; both are suggested to play a prominent role in fibrosis development (212). Type 2 immune cascade is known to drive pathogenic events in allergic asthma and several inhibitory molecules have reached the clinical use. Among them anti IL-13 monoclonal antibody (mAb) lebrikizumab has been recently tested in the randomized, multicenter, double-blind, placebo-controlled, parallel-group study NCT01872689 trial aimed at evaluating its efficacy and safety as monotherapy or with pirfenidone in IPF subjects. Although the pharmacodynamic biomarkers indicated a certain activity of lebrikizumab in association to the already known safety profile, lebrikizumab alone or in combination with pirfenidone showed no additional advantages since it was not able to improve functional parameters (213). Similar results have been reported using the anti-IL-13 mAb tralokinumab which safety profile resulted acceptable in absence of significant advantages (NCT01629667, NCT02036580) (214) and the study evaluating the mAb dectrekumab in IPF was discontinued in absence of significant results (215). These observations suggest that IL-13/type 2 immunity might not be the right target in IPF onset although a potential role of type 2-driven immune response is conceivable in acute exacerbation (AE) of disease. Growing evidence point out that many important fibrogenic steps should be orchestrated by both innate and adaptive immunity and that the innate response prevails (216) or, more properly, that the epithelial damage plays an important role in inducing immune system dysregulation which acts as critical driver for disease progression (217). This specific feature is a common denominator to cancer (218-220) and sustain a rationale for IC blockade therapeutic strategy. Immunotherapy has substantially changed the therapeutic strategies for cancers such as melanomas, lymphomas, and lung tumors. Unfortunately, only 20–50% of patients with advanced solid tumors respond to treatment. There is therefore a need for the development of methods to identify patients who are most likely to respond to immunotherapy. ICs are molecules located on the surface of cells that can send inhibitory stimuli to attenuate immune responses. Tumors express IC proteins on their cell surface to escape detection from the immune system. Thus, targeted inhibition towards these receptors enhances T cell response against the tumor. Tumor cells express checkpoint proteins on their surface to evade host immune response. Targeted inhibition towards

these receptors enhances T cell response towards the tumor (221,222). Cytotoxic T-lymphocyte antigen 4 (CTLA-4), PD-1, and PD-L1 are key negative regulators of anti-tumor T cell reactivity. The development of IC inhibitors has revolutionized the treatment of a variety of cancers. Several studies have shown that pre-existing tumoral and peritumoral immune infiltration correlates with patient response to PD-1 and PD-L1 immunotherapy. Three distinct immune phenotypes have been described: immune-inflamed, immune-excluded, and immune-desert. Immune-inflamed tumors are characterized by dense, functional CD8 cell infiltration, increased interferon-γ signaling, expression of cell checkpoint markers (such as PD-L1), and a high mutational burden. These tumors tend to respond to immunotherapy. The detailed description of cancer microenvironment and sensitivity to IC inhibitors (ICIs) goes beyond the scope of this paper. It should be underlined that the cellular heterogeneity which characterizes IPF complicates data interpretation and can make elusive data interpretation when obtained from tissue homogenates. The recently completed study entitled "*Immunopathologic Profiles and Blood Biomarkers in Patients With IPF*" (NCT04187079) aimed at IPF tissue and blood profiling also investigating the cellular expression of ICs (namely PD-L1) in lung epithelial cells. It is known that PD1-PDL1 are expressed in IPF lymphocytes (223), AMs (224) and myofibroblasts (159) through IHC stain and RNA sequencing. The PD-1/PD-L1 axis is likely to contribute to lung fibrogenesis (225) anti PD-L1 Abs significantly reduces pulmonary fibrosis (226). PD-1 expression on CD4+ T cells is known to lead to activation of Signal Transducer and Activator of Transcription (STAT) 3 which, in turn, induces IL-17A and TGF-β expression (227). *Ex vivo* blockade of the PD-1/PD-L1 axis is associated to STAT3-mediated IL-17A and TGF-β production by $CD4^+$ T cells (223). PD-L1 inhibitors should not be used in conjunction with mesenchymal stromal cell (MSC) therapy (228). CTLA-4 is strongly overexpressed in IPF CD4- and CD28 null IPF lymphocytes if compared to health cells and anti-CTLA-4 antibody treatment was shown to aggravate fibrosis in a humanized IPF model (173,225,229). Notably, a high level of hypoxia and immune activity is associated to worst prognosis in IPF, whereas those patients featuring high level of oxygen and low immunogenic reactions the best prognosis (230). These preliminary findings point out a novel strategy to effectively select patients for immunotherapy. Overall, the expression of IC molecules in lung fibrotic tissues sustain a rationale for a deeper investigation of their pathogenic role and as actionable targets. Durable responses to nivolumab in a lung cancer patient withs idiopathic pulmonary fibrosis (231-233). This observation suggests that in those cases, ICI treatment should be considered a potentially effective option even though the occurrence of ILD has been identified as a rare but potentially severe event induced by immunotherapy (234). In this perspective the already reported activation of the MET oncogene in IPF should become relevant (9). IPF resembles cancer in two critical MET-associated behaviors: invasive phenotype and pro-coagulant status. In cancer, MET activation occurs as a late event, consequently to transcriptional up-regulation driven by unfavorable microenvironmental conditions MET (mainly hypoxia) amplified cancer clones are selected under therapeutic pressure in a context of molecularly heterogeneous lesions exposed to targeted therapies or radiotherapy (235,236). Thus, this oncogenic expedient (69) can be exploited for therapeutic purposes in IPF. Moreover, it has been already reported that, in lung cancer mutations occurring in several oncogenes among which MET, modulate tumor microenvironment and a positive correlation between MET amplification and PDL1 overexpression has been already reported (237,238). Thus, in a context-specific regulation of its expression, MET might become a functional marker of IPF and an actionable target, positively associated to response to ICIs (*Figure 2*).

### *Radiotherapy in lung cancer with IPF*

Radiation induced lung injury (RILI) represents one of the major issues in the setting of thoracic radiotherapy (239); it generally corresponds to radiation-induced pneumonitis, an intermediate phase injury after exposure to ionising irradiation, which in most cases paves the way for the development of late fibrosis. Both pneumonitis and fibrosis are dose-limiting toxicities of great concern to the radiation oncologist, especially in the scenario of a combined chemoradiotherapy approach or in high dose hypo-fractionated radiotherapy.

Thoracic radiotherapy plays a role in enhancing the occurrence of AEs in IPF, even when baseline symptoms are trivial. Pre-existing IPF is a well-known risk factor for pulmonary toxicity after ionising irradiation (240); previous reports have shown that it can raise the risk of severe and even life-threatening pneumonitis, whose rates in such patients range between 6.3% and 18.2%, in relation to different radiotherapy techniques (241). Nevertheless, IPF does not constitute an absolute contraindication for thoracic

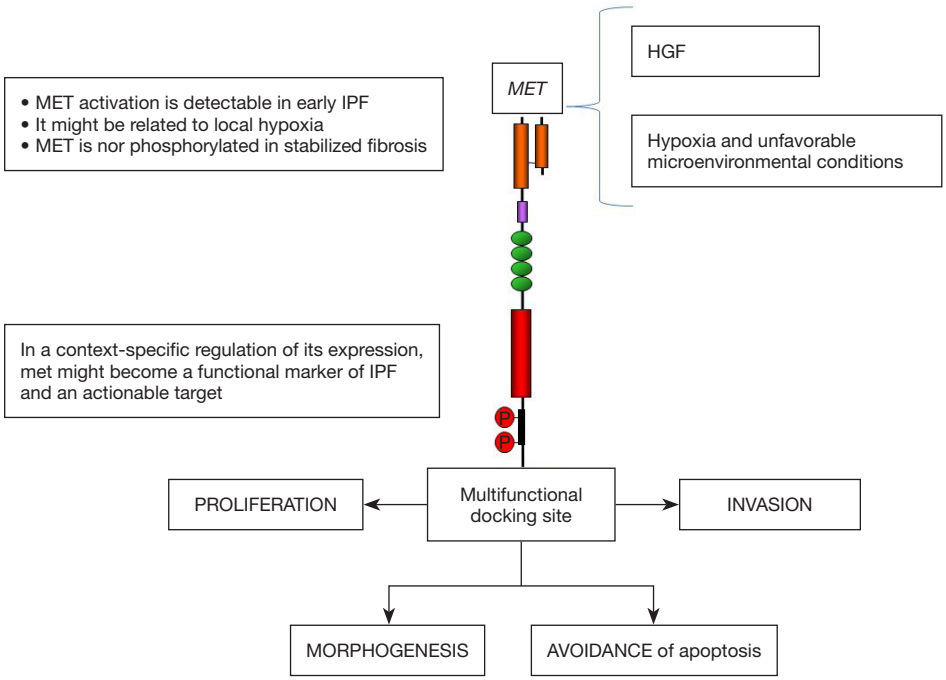


**Figure 2** Functional annotation of the MET oncogene as an actionable target of IPF. MET-mediated events in IPF rely on qualitative differences among physiological signals. No driver genetic lesions, causally implicated in the disease can be clearly demonstrated ("Fibrogenic Expedience"). The MET blockage falls among those therapeutic strategies aimed at impairing the "aberrant recapitulation of developmental programs". The hypoxia-induced MET up-regulation might cooperate in triggering IPF regenerative/reparative processes. HGF, hepatocyte growth factor; IPF, idiopathic pulmonary fibrosis.

radiotherapy, even if European Organisation for Research and Treatment of Cancer (EORTC) guidelines suggest avoiding irradiating lung cancer patients with IPF (242). While some encouraging data come from some preliminary experiences with proton therapy (241), the decision to offer radiotherapy to these patients should be made after a multidisciplinary approach in which patient's individual risk is evaluated, especially in terms of his/her clinical status, disease specific survival and therapeutic index.

### *Surgery in lung cancer with IPF*

Lung resection plays a role in the treatment of patients affected by IPF with resectable NSCLC. However, in this scenario, two major issues influence significantly the surgical procedure and the survival outcomes: the high risk of postoperative AEs of IPF in the short-term, and the death due to cancer in the long-term (243). Surgery is a defined risk factor for AE in IPF patients (16) and since its incidence in this group of patients is estimated to be approximately 9.3% (244) and no preventive measure is known, it is crucial to carefully select the patients to properly refer treat the patients. In a study by T. Sato and colleagues, a simple scoring system to identify high risk patients for AE was derived in order to help in the decision-making process for surgery selection and predict the patients requiring intensive observation postoperatively (245). Among the surgical procedures of lung resection, wedge resection is associated to the lowest risks of postoperative AE compared to segmentectomy, lobectomy, bilobectomy and pneumonectomy, since AE risk increases according to the resected lung parenchyma volume (244). Death due to cancer is the major concern in the long-term: it represents the main cause of death in lung cancer patients affected by IPF, mostly attributable to cancer recurrence after surgery. Contrary to AE risk, lobectomy shows better results for death due to cancer in patients with stage IA, while wedge resection and segmentectomy were associated to poor outcomes (244).

Lung resection in patients with IPF is challenging but required for several patients. The choice of surgical procedure must be tailored based on several criteria, such as pulmonary function, cancer stage and recurrence risk,

postoperative AE risk, and the natural course of IPF.

### *Percutaneous thermal ablation in lung cancer with IPF*

Alternative treatments such as radiofrequency ablation could be of therapeutic benefit with relatively minimal complications, particularly in patients who are not fit enough for surgical interventions. On the other hand, the risk of severe complications with stereotactic body radiation therapy (SBRT) when treating patients with IPF is widely recognized. For these reasons, in the IPF setting, thermal ablation procedure, generally performed under CT guidance, can be a viable therapeutic option. Radiofrequency ablation and SBRT in patients with inoperable stage I NSCLC had similar overall survival rates while local progression rates were higher for radiofrequency ablation (246). No specific comparison had been performed over different types of ablative procedures (radiofrequency, microwave, cryoablation) while the largest experience came from radiofrequency ablations. Every technique has its own advantages and disadvantages (e.g., cryoablation is safer near the airways while microwaves are powerful and faster than radiofrequency) that can be a further strength of minimally invasive procedure. At the same time this heterogeneity creates severe difficulties in obtaining large databases of procedures outcome and procedures performances. For these reasons a multidisciplinary advice and centre preferences and expertise are fundamental for alternative treatment choice and management.

### *Advanced cell therapies*

Based on the U.S. Food and Drug Administration (FDA) cell therapy includes cellular products for immunotherapies, cancer vaccines, and other types of both autologous and allogeneic cells for certain therapeutic indications (www.fda.gov). According to this definition, the most clinical implications regard clearly cancer, but the recent progresses in the knowledge of molecular mechanisms responsible of IPF with the evidence of biologic similarities between IPF and malignant proliferation give a strong rationale for the investigation and development of cell therapeutic strategies and tissue engineering to impair fibrotic damages. MSCs feature the pluripotent capacity of and their ability to differentiate to important lineages that can modulate on immunity, impair inflammatory reactions, and promote epithelial tissue repair (247); the clinical application of MSC therapy has been shown to be feasible and safe in humans with IPF (www.clinicaltrial.gov) and several data have been already published (248-252). A schematic representation of the application of MSCs in lung fibrosis is reported in *Figure 3*. MSCs and fibrocytes can be generated from the bone marrow and home to the injured lungs in response to several secreted chemokines and growth factor receptors (253,254). Lung resident MSCs (LR-MSCs) and mainly myofibroblasts precursors have been detected as well (255,256). Allogenic MSCs derived from unrelated donors seems to be safe as homologous obtained cells when infused in patients carrying mild-moderate disease (257). MSCs communicate with their surrounding microenvironment and in particular, the alveolar niche cells promote alveolar epithelial progenitors to regenerate the damaged epithelium (258). Different strategies have been explored to the development of advanced cellular therapy in IPF. The MSCs quiescence or dormancy is a key feature of stem cells; thus, a potential target of therapeutic intervention is that of inducing stem cells into the cell cycle to start differentiation. In this perspective, the Wnt/β-catenin signalling is known to be implicated IPF pathogenesis since its activation inhibits MSCs to differentiate into epithelium. The pharmacological inhibition of the Wnt cascade might be exploited to impair myofibroblasts differentiation and proliferation (259,260). Moreover, MSCs in IPF become rapidly senescent (261-263) and strategies to ameliorate this process are beneficial in reducing disease progression. miRNAs are involved in mediating MSC senescence by modulating the expression of several pathways. Very recently, miR-200 family members (miR-200b-3p and miR-200c-3p) and miR-199a-5p has been reported to regulate MSC senescence in IPF patients with by acting on the Sirtuin 1/AMP-activated protein kinase signalling cascade; thus, they emerge as a novel potential target to rejuvenate IPF-MSCs and to prevent fibrotic damages and to restore proper differentiation (264,265). MSCs display immunomodulatory properties and can secrete anti-fibrotic factors (*Figure 4*). It has been reported that lung resident MSC can be in IPF lungs and their secretome is able to damage fibroblast proliferation while promoting enhanced epithelial wound repair via several growth factors, among which hepatocyte growth factor (HGF) (266,267). Interestingly, inhaled lung spheroid cell-secretome (LSC-Sec) and exosomes (LSC-Exo) have been shown to attenuate bleomycin and silica-induced fibrosis in experimental models in a more effective manner that those derived from resident MSCs. They seem block EMT acting on WNT/beta catenin, Rho/Rock and TGFbeta 1/SMAD pathways (268). Other therapeutic targets in the context of cell therapy in IPF are represented by MSC-derived growth

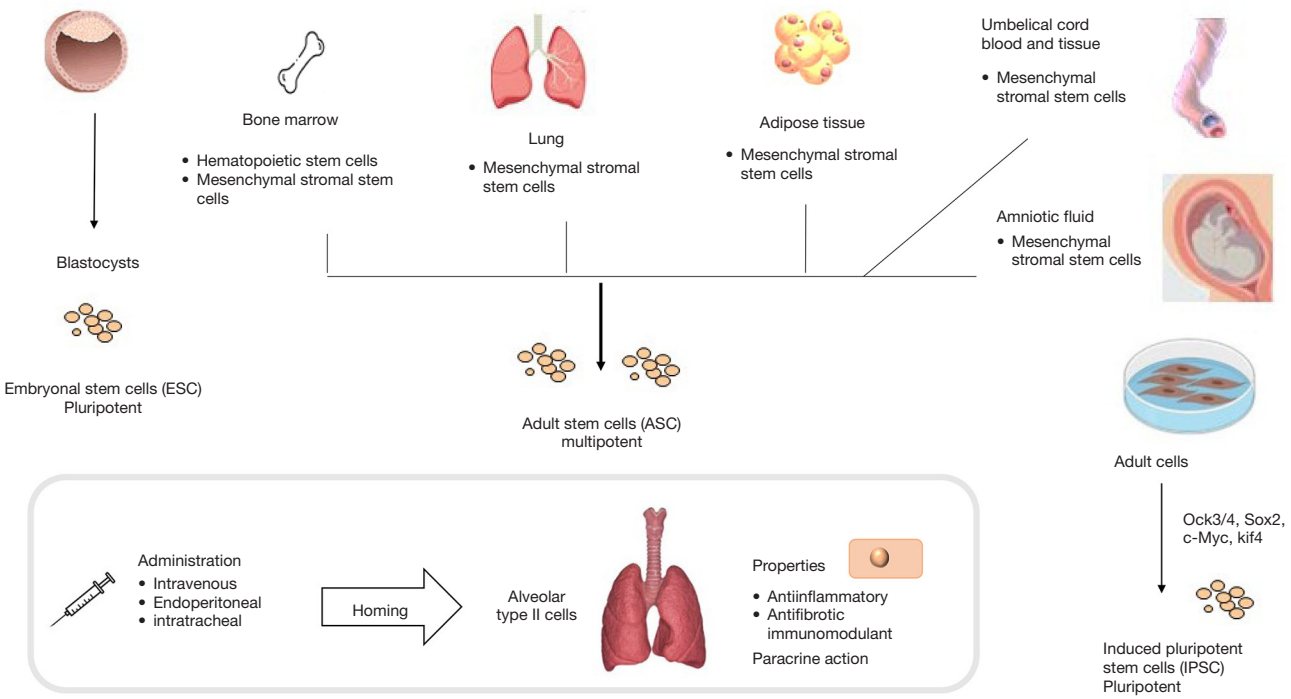


**Figure 3** Stem cells and their application in lung fibrosis. Stem cells can be classified into embryonal stem cells (ESC), adult stem cells (ASC) and induced pluripotent stem cells (IPSC) according to their origin. ESCs derive from embryo blastocysts, ASC can be isolated from various tissues, such as bone marrow, lung, adipose tissue, umbilical cord blood, umbilical cord tissue and amniotic fluid. IPSC are obtained from somatic cells using reprogramming factors (OCT3/4, SOX2, C-MYC, KLF4), responsible for re-programming to pluripotency. Stem cells can be administrated intravenously, intratracheally or intraperitoneally. They migrate to the injured sites of the lungs where they differentiate in alveolar type II cells and exert anti-inflammatory, antifibrotic and immunomodulant actions. IPF, idiopathic pulmonary fibrosis.

factors, as HGF, which play relevant roles in the repair of alveolar epithelial cells, actively contrasts myofibroblasts activation and the abnormal deposition of ECM (269). Growing evidence indicates that the changes in ECM composition and mechanical properties which characterize IPF can be exploited for therapeutic purposes. Synthetic materials as polyacrylamide, hydrogels, highly cross-linked polymer networks as well as liposomes, polymeric nanoparticles represent engineered platforms which can be decorated with cell-adhesive ligands, signalling factors, drugs which can modulate lung remodelling (270-272).

## Concluding remarks

IPF identifies a specific entity characterized by chronic, progressive fibrosing interstitial pneumonia of unknown cause, still lacking effective therapies. Growing evidence points out that aberrant proliferative events in IPF recall malignant transformation given a specific temporal and cellular heterogeneity. To look at IPF through cancer glass can help in stratifying and addressing patients to personalized approaches as well as in analyzing the mechanisms of abnormal cell/matrix interactions which characterize the disease. Moreover, the advances in cancer immunotherapy and the improvement in imaging and radiotherapy techniques open the way for treatment of those patients carrying both lung cancer and IPF that till now have represented a sort of therapeutically orphan population. Translational research is a source of continuous innovation in medicine more particularly for clinical research on new treatment modalities in IPF patients and will contribute to improve mechanistic explanation of disease onset and progression. To reach this goal, the real efficiency of next future studies and trials will depend on the integration of proper sample collection, gene expression analysis and functional and bio-informatic annotation as well as on the coordination of multidisciplinary know how and technical platforms.

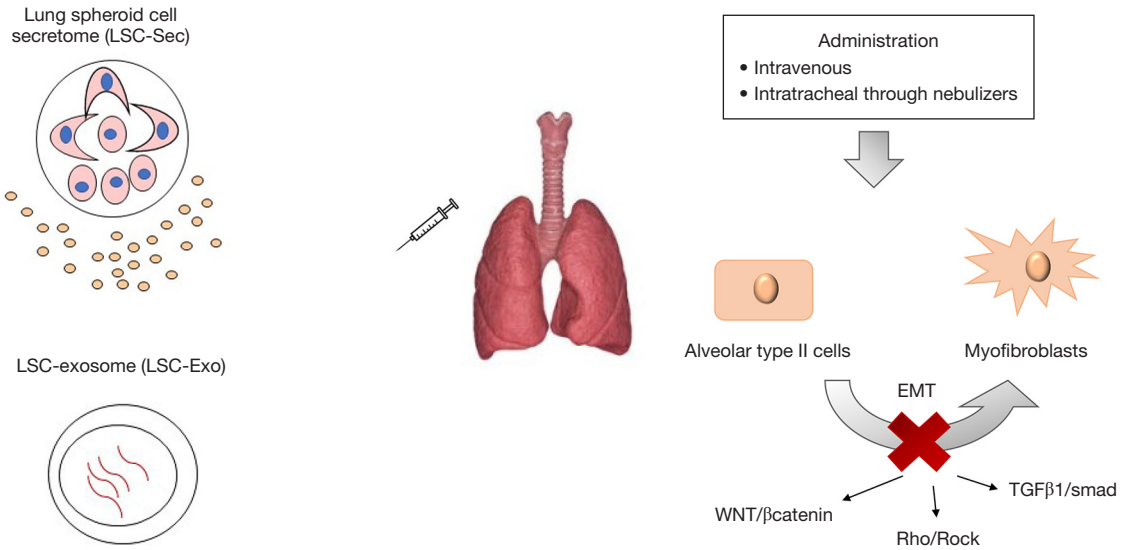


**Figure 4** Stem cells and secretoma. Lung spheroid cells are round aggregates composed by stem cells and stromal cells. They produce a complex of proteins and growth factors, complexify named as secretoma, also including exosomes. Lung spheroid cell-secretome (LSC-Sec) and exosomes (LSC-Exo) reproduce a regenerative microenvironment and promote differentiation of stem cells towards epithelial phenotypes. EMT, epithelial mesenchymal transition.

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