Chapter 14
Common Pathways in IPF and Lung Cancer

Why Is Lung Cancer Highly Associated with IPF at a High Frequency?

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Abstract Lung cancer which is the leading cause of cancer death worldwide leads to poor clinical outcome, similar to idiopathic pulmonary fibrosis (IPF). Lung cancer and IPF are often characterized by high comorbidity, and IPF is therefore considered to be a risk factor for the incidence of lung cancer. On the other hand, its high comorbidity recalls the existence of a common pathway in the pathogenesis and progression of both diseases. However, lung cancer and IPF have distinct phenotypes in the clinicopathological characteristics and therapeutic strategies. Rather, the standard of care for lung cancer with IPF has not yet been established, as treatments for lung cancer are sometimes harmful for comorbid IPF and induce its exacerbation that results in death. In order to pursue the answer to the question, "Why is lung cancer highly associated with IPF at a high frequency?" this chapter focused on the common pathogenesis of IPF and lung cancer and reviewed possible common pathways that are associated with both diseases. Besides common causative factors such as physical changes and environmental exposure, genetic modifications, epigenetic aberrations, and dysregulation in signaling pathways have indeed been reported as possible biological mechanisms that commonly underlie both diseases. Diverse common pathways as described in this chapter may account for the high frequency of lung cancer with IPF. The approach to a better understanding of these pathways will invite a novel perspective on therapeutics for this comorbidity, leading to an improved prognosis.

Keywords Lung cancer • Common pathogenesis • Gene mutation • Epigenetics • Signaling pathway

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14.1 Introduction

Lung cancer is the leading cause of cancer death worldwide. Approximately 80 % of lung cancer consists of non-small cell lung cancer (NSCLC), more than three-quarters of which is diagnosed at an advanced stage, leading to a low 5-year survival rate of approximately 20 %. Thus, lung cancer, along with idiopathic pulmonary fibrosis (IPF), is associated with poor clinical outcome. Both diseases are often characterized by high comorbidity as it is reported that IPF concurred in 7.5 % of surgically resected lung cancer patients [1]. Furthermore, high rates of comorbidity have been reported; lung cancer occurred in 4.4–38 % of patients with interstitial pneumonia. Therefore, IPF is considered to be a risk factor for the incidence of lung cancer. Along with these epidemiologic data, IPF and lung cancer have possible common causative factors such as aging, environmental exposure, and infection from an etiological perspective. Indeed, squamous cell carcinoma, which is highly related to smoking, is the predominant histological type of lung cancer that is comorbid with IPF. On the other hand, gene mutations, epigenetic aberrations, activation of signaling pathways, dysregulation of apoptosis, and impaired expression of microRNA (miRNA) have been reported as possible biological mechanisms that commonly underlie lung cancer and IPF, particularly fibrosis that is considered as aberrant "wound healing" similar to cancer. These findings suggest the existence of a common pathway in the pathogenesis and progression of IPF and lung cancer. However, IPF that consists of a heterogeneous population is estimated to have numerous pathogenesis and courses. Its radiological severity has no correlation with the prevalence of lung cancer, which is not always developed in fibrotic lesions of IPF. Additionally, IPF demonstrates no increased risk of malignancies other than lung cancer. Lung cancer and IPF have distinct phenotypes in terms of the distribution of lesions and metastatic potential.

Aside from these pathogenetic implications, IPF is one of the morbidities that require the most careful attention when treated with lung cancer, because treatments for lung cancer such as antitumor drugs, thoracic radiation, and surgical resection sometimes lead to acute exacerbation of IPF. Given the limited number of clinical trials, the optimal treatment modality for lung cancer with IPF has not yet been established. A novel therapeutic strategy for lung cancer or IPF that differs from the conventional treatment modalities is being developed. This process is currently focusing on "molecular targeted drugs" such as nintedanib that selectively inhibit pathways that underlie the pathogenesis of these diseases.

In this chapter, possible common pathways of IPF and lung cancer are pleiotropically searched and reviewed to determine the reason for the high rates of comorbidity of both diseases. This approach for elucidation of the common pathogenesis of both diseases may consequently shed light on efficient and effective treatment for these comorbid refractory diseases with poor prognosis.

14.2 Gene Mutation, Amplification, and Deletion

Previous reports have suggested the association of many gene mutations with lung cancer, which generally contribute to the development and progression of the cancer. On the other hand, some cases of interstitial pneumonia are known to be inherited. Recent reports suggest that familial inherited interstitial pneumonia accounts for approximately 20 % of IPF [2]. To date, mutations in the genes encoding telomerase reverse transcriptase (TERT); the RNA component of the telomerase complex (TERC) [3]; surfactant protein A, SP-A (SFTPA); surfactant protein C, SP-C (SFTPC); and ATP-binding cassette transporter A3 (ABCA3) have been reported as genes responsible for familial interstitial pneumonia. Of these genes, *TERT* mutations, gene deletions of *SFTPA* and *SFTPC*, and gene amplification of *TERC* are also found in NSCLC.

There is very little information regarding single nucleotide polymorphisms (SNPs) as a common pathogenesis of lung cancer and IPF, although some gene mutations are often identified in sporadic IPF cases with lung cancer, suggesting that they may be associated with the development of lung cancer in IPF. This section focuses on common gene mutations in IPF and lung cancer.

14.2.1 Telomerase Reverse Transcriptase and the RNA Component of the Telomerase Complex

Telomerase is the enzyme complex that maintains telomeres, protecting chromosomes from degradation, end-to-end fusion, and atypical recombination. Once telomeres reach a critical length, RB and p53 signaling pathways initiate irreversible arrest of cell growth, cellular senescence, or apoptosis. Telomere dysfunction is associated with disease development. Telomeres require the telomerase enzyme complex to generate and maintain their structure and function. The telomerase complex has an enzyme and an RNA template component that are encoded by the *TERT* and *TERC* genes, respectively. The review by Gansner et al. indicated that *TERT* and *TERC* mutations were identified in both patients with familial interstitial pneumonia (8–15 %) and sporadic IPF (1–3 %) [4]. IPF caused by *TERT* and *TERC* mutations is inherited as an autosomal dominant pattern with haploinsufficiency, while these mutations associated with telomere shortening are also found in lung cancer, especially in small cell carcinomas [5]. Genome-wide association studies (GWAS) have identified the *TERT* locus on chromosome 5p15.33 as a lung cancer susceptibility marker [6], and recurrent TERT promoter mutation was found in 2.57 % of NSCLC patients [7]. In terms of *TERT* function, one of the targets of *TERT* regulation is the Wnt/β-catenin signaling pathway, whose activation via transforming growth factor-β (TGFβ) signaling promotes epithelial-mesenchymal transition (EMT) as well as myofibroblast differentiation [8]. Aberrant Wnt/β-catenin pathway signaling is tightly associated with carcinogenesis.

14.2.2 Surfactant Proteins

Of the surfactant proteins, germline mutations of the *surfactant protein A2* (*SFTPA2*) gene that interfere with protein trafficking have been identified in both IPF and lung cancer [9]. *Surfactant protein C* (*SFTPC*) gene mutations were also found in IPF [10], whereas deletion of its gene was identified in lung cancer [11].

14.2.3 p53

The *p53* gene is widely known to function as a tumor suppressor by modulating DNA repair, cell division, and apoptosis induction, and its mutation alters the conformation of the p53 protein, which accumulates in the nucleus, resulting in carcinogenesis. *p53* mutation is found in many types of cancer as an early event of multistep carcinogenesis. *p53* mutations, which are mostly attributed to smoking, are implicated in 40–60 % of lung cancer, and transversion of GC to TA in *p53* was observed in 40 % of patients with smoking-associated cancer. On the other hand, TGFβ that is activated in IPF upregulates *p21*, which is highly expressed in IPF and is also upregulated by p53 and fibroblast-regulating cytokines. Intriguingly, *p53* mutations were detected in peripheral type squamous cell carcinoma within fibrotic areas of IPF. Smoking exposure that can cause *p53* mutations is commonly associated with squamous cell carcinoma and pulmonary fibrosis.

14.2.4 RAS

The *RAS* oncogene family includes *HRAS*, *KRAS*, and *NRAS*, which code for 21-kDa guanosine triphosphate (GTP)-binding proteins called p21. RAS proteins that are activated by binding with GTP elicit cellular proliferation via the RAS-dependent kinase cascade. Point mutations and overexpression of *RAS* lead to a loss of the intrinsic GTPase activity that inactivates RAS proteins, and consequently they activate RAS signaling. KRAS regulates cellular proliferation through signal transduction across cellular membranes. *KRAS* mutations are found in 12–57 % of adenocarcinoma and 2–9 % of squamous cell carcinoma of the lung and are furthermore associated with poor overall survival of lung cancer patients. Approximately 80 % of *KRAS* mutations in NSCLC involve codon 12 [12], and its point mutation, $KRAS^{G12D}$, was detected in lung tissue with interstitial pneumonia comorbid with lung cancer [13].

14.2.5 Fragile Histidine Triad

Fragile histidine triad (*FHIT*), a member of the histidine triad gene family, is a tumor suppressor gene that spans the FRAB3B common fragile site at chromosome 3p14.2. Homozygous deletions and loss of heterozygosity (LOH) at the *FHIT* locus leading to inactivation of the *FHIT* gene have been frequently reported in lung cancer cell lines and primary tumors. Aberrant *FHIT* mRNA transcripts have been identified in 40–80 % of tumor samples, and loss of FHIT protein expression is observed in approximately 70 % of primary tumors, mainly in smokers. Hypermethylation of the *FHIT* promoter region containing CpG islands was found in 36.7 % of tumor and 32.7 % of normal lungs, whereas LOH was detected in 61.9 % of tumors. Lost or reduced *FHIT* expression was found in 36.7 and 75.7 % of the tumor samples, respectively [14]. Consequently, the combination of methylation and LOH is considered to result in the loss of *FHIT*, and this phenomenon has been frequently identified in smokers with squamous cell carcinoma. In contrast, *FHIT* mutations have been rarely reported in lung cancer cells. However, *FHIT* gene mutations and protein reduction have been demonstrated in IPF, particularly in peripheral honeycomb areas. Accordingly, *FHIT* mutations may contribute to oncogenesis in some squamous cell carcinoma patients with a smoking history, although LOH of the *FHIT* locus and reduced FHIT protein were frequently found in metaplastic lesions in IPF.

These findings suggest that gene mutations may be at least partly associated with a common pathway of IPF and lung cancer, functioning as a trigger.

14.3 DNA Methylation by DNA Methyltransferase in Epigenetic Changes

Gene expression profiles are at least partly dependent on epigenetic changes, including DNA methylation, histone modifications, and regulation of noncoding RNA. Epigenetic changes can lead to changes in the expression of target genes without any changes in DNA sequence and are therefore potentially reversible. In this chapter, epigenetic changes are classified into three types of changes, DNA methylation, histone modifications, and noncoding RNA (microRNA).

Hypermethylation and hypomethylation of genes play an important role in epigenetic changes in gene expression. Modulation of gene transcription through DNA methylation is carried out directly by DNA methyltransferases (DNMTs) and is indirectly mediated through histone modifications. These epigenetic alterations are often caused by environmental exposure, tobacco smoke, diets, or aging. Hypermethylation of tumor suppressor genes and hypomethylation of oncogenes have been widely investigated, particularly in oncogenesis. Moreover, Rabinovich et al. have shown that the global methylation pattern in IPF is partly similar to that

in lung cancer, suggesting similar pathogenic mechanisms underlying the development of both diseases [15].

14.3.1 Phosphatase and Tensin Homolog

Phosphatase and tensin homolog deleted on chromosome 10 (PTEN), a dual-specificity protein and lipid phosphatase, inhibits cellular migration and proliferation, promotes cellular apoptosis, and is considered as an antifibrotic mediator, through inhibition of myofibroblast differentiation, as well as a tumor suppressor gene. PTEN dephosphorylates PI-3,4,5-trisphosphate, thereby inhibiting PI3K/AKT/mTOR signals. Inactivation of PTEN induced by rare gene mutations (5 %) and reduced PTEN protein expression (75 %) in NSCLC results in ligand-independent AKT/protein kinase B activation [16]. On the other hand, inhibition of PTEN that is negatively regulated by TGFβ promotes α-smooth muscle actin (αSMA) and collagen production, leading to induction of myofibroblast differentiation and development of pulmonary fibrosis [17].

14.3.2 Caveolin-1

Caveolin-1 (CAV1) is a 22-kDa scaffold protein that is one of three essential constituents of the flask-shaped (50–100 nm) invaginated membranes termed caveolae. CAV1 is considered to be associated with the development of various diseases, especially tumorigenesis, because it regulates diverse pathways of integrin, epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGF), MAPK, and PI3K/AKT/mTOR signaling. Wang et al. reported that CAV1 expression is reduced in lung tissues and in primary pulmonary fibroblasts from IPF patients and that TGFβ decreases CAV1 expression in pulmonary fibroblasts, whereas CAV1 can suppress TGFβ-induced ECM production in cultured fibroblasts through regulation of the c-JUN N-terminal kinase (JNK) pathway [18]. On the other hand, the role of CAV1 in cancers remains controversial. CAV1 expression was reportedly decreased in lung cancer [19], and exogenous CAV1 expression in cancer cell lines inhibited cellular growth and tumorigenesis [20]. In contrast, in other studies CAV1 expression was found to be upregulated in lung cancer, and its upregulation was associated with tumor metastasis and poor outcome [21, 22]. Li et al. reported that CAV1 maintains activated AKT, although this effect was observed in prostatic cancer cells [23]. Sunaga et al. reported that CAV1 reciprocally exerts oncogenic function in NSCLC and tumor suppressive function in SCLC [24].

14.3.3 Claudin-5

Hypermethylation and decreased expression of the *claudin-5* (*CLDN5*) gene encoding a transmembrane protein are found in IPF lung tissues [25]. The decrease in *CLDN5* expression found in bleomycin-induced pulmonary fibrosis may promote EMT [26]. Decreased or no expression of *CLDN5* is also observed in pulmonary squamous cell carcinoma [27], which is the most frequent histological type identified in lung cancer with IPF [28].

14.3.4 $p14^{ARF}$

$p14^{ARF}$, a tumor suppressor gene, induces cell cycle arrest in both the G1 and G2 phases of the cell cycle and induces apoptosis in a p53-dependent and p53-independent manner. $p14^{ARF}$ silencing via DNA methylation has been reported in some tumor types. Nitric oxide (NO) upregulates $p14^{ARF}$ and, in turn, enhances p53 activity, resulting in apoptosis [29], whereas NO that is downregulated by TGFβ attenuates EMT in alveolar type II (ATII) cells, whose apoptosis can lead to pulmonary fibrosis [30].

14.3.5 $p15^{INK4B}$, Caspase Recruit Domain 10, and O-6-Methylguanine-DNA Methyltransferase

Huang et al. reported hypermethylation and reduced expression of the *cyclin-dependent kinase inhibitor 2B* (*CDKN2B*, $p15^{INK4B}$) gene and the *caspase recruitment domain 10* (*CARD10*) gene in IPF [31]. In particular, $p15^{INK4B}$, a tumor suppressor gene, is a member of the INK4 family, which includes the $p16^{INK4A}$ and $p14^{ARF}$ genes. This gene is induced by TGFβ through SMAD proteins, and aberrant methylation at the 5′ end of the $p15^{INK4B}$ gene was observed in 15 % of the neuroendocrine type of lung cancer [32], which includes small cell lung cancer that is frequently detected in IPF. Another report showed that *CARD10*, also known as *CARMA3*, was overexpressed in NSCLC [33]. The reason for the different *CARD10* expression profiles between IPF and lung cancer remains unknown and requires further investigation. Furthermore, the same group also reported that O-6-methylguanine-DNA methyltransferase (MGMT) was hypomethylated and overexpressed in IPF, whereas many articles have reported loss or decrease of *MGMT* expression through promoter methylation of this gene in lung cancer [34]. MGMT is a DNA repair enzyme that protects against DNA adduct formation of carcinogenesis, leading to a stabilized chromatin structure and prevention of apoptosis induction.

14.3.6 Prostaglandin E2 (PGE2)

Prostaglandin E2 (PGE2), a metabolite of cyclooxygenase-2 (COX2), is a lipid mediator derived from the COX pathway of arachidonic acid metabolism. COX2/PGE2 stimulates PI3K/AKT and extracellular signal-regulated kinase 1/2 (ERK1/2) signaling to induce tumor angiogenesis and invasiveness. COX2 expression and PGE2 production are increased in many tumor types including lung cancer [35]. On the other hand, PGE2 mediates many inhibitory signals in cells, thereby attenuating myofibroblast differentiation and potentially suppressing pulmonary fibrogenesis [36]. Lower levels of PGE2 in bronchoalveolar lavage fluid (BALF), and diminished PGE2 synthesis in fibroblasts, are found in IPF patients, suggesting its antifibrotic function [37]. PGE2 exerts its biological effects through the E-prostanoid 2 (EP2) receptor, the major G protein-coupled receptor for PGE2, and could thereby inhibit TGFβ-induced myofibroblast differentiation [38]. Decreased expression of the EP2 receptor confers PGE2 resistance on fibroblasts from mice with experimental fibrosis and from some patients with IPF. On the other hand, multiple signaling pathways can be associated with EP2-mediated oncogenesis: (1) activation of inducible nitric oxide synthase (iNOS)/guanylate cyclase (GC) and ERK1/2 via transactivation of the EGFR; (2) phosphorylation of the tyrosine-protein kinase SRC by β-arrestin 1 signaling, activation of the EGFR, and activation of PI3K/AKT and RAS/ERK pathways; (3) phosphorylation of JNK by β-arrestin 1 signaling and upregulation of profilin-1 (PFN1) to increase F-actin; (4) regulation of the cAMP/PKA/CREB pathway; or (5) increased expression of β-catenin-mediated cMYC and vascular endothelial growth factor (VEGF) [39]. Aberrant methylation of the promoter region of the *PTGER2* gene encoding the EP2 receptor is proposed as one plausible explanation for these phenomena. Hypermethylation of this region, which contains numerous CpG islands, was frequently observed in both IPF and lung cancer and is reported to be driven by PTEN suppression/AKT activation in fibroblast of IPF.

14.3.7 Thy1

Thy1 (CD90), a 25–37-kDa glycosylphosphatidylinositol (GPI)-anchored glycoprotein that is expressed mainly in leukocytes, is involved in cell-cell and cell-matrix interactions and may be a marker for lung cancer stem cells (CSCs) in NSCLC cell lines [40]. In IPF, hypermethylation of the promoter region of the *Thy1* gene causes loss or reduction of *Thy1* expression in fibroblasts [41]. Loss of this gene expression leads to myofibroblast differentiation within fibroblastic foci in IPF, whereas this alteration is associated with invasiveness in lung cancer.

14.3.8 Tumor Protein p53-Induced Nuclear Protein 1

In addition to evidence for hypermethylation, Sanders et al. have reported increased gene expression due to hypomethylation in IPF [25]. Tumor protein p53-induced nuclear protein 1 (TP53INP1), a major mediator of p53 antioxidant function that is localized on chromosome 8q22, is upregulated in IPF. Exposure to diverse stress agents enhances expression of *TP53INP1*, which encodes two nuclear isoforms, TP53INP1a and TP53INP1b. TP53INP1 transcriptionally activates p53-target genes such as *p21* and *p53-inducible gene 3* (*PIG3*), consequently leading to cell cycle arrest and apoptosis upon DNA damage stress in different cell types [42]. TP53INP1 in particular is considered as a tumor suppressor gene, because its expression is decreased in different tumor types.

These findings suggest that aberrant epigenetic alteration may be a potent candidate for a common pathogenesis of IPF and lung cancer through modification of corresponding gene expression.

14.4 Histone Modification in Epigenetic Changes

Histone modification that posttranscriptionally regulates gene expression is another epigenetic change. Histones are mainly modified by acetylation, methylation, phosphorylation, and ubiquitination. Of these changes, aberrant acetylation status that has been identified in many types of diseases is governed by histone acetyltransferase (HAT)-mediated acetylation and histone deacetylase (HDAC)-mediated deacetylation, which modulates the chromatin condensation status, thereby altering gene expression. HAT acetylates lysine residues of histones, which generally induces gene expression, whereas HDAC deacetylates these residues, resulting in chromatin condensation and consequently reducing gene transcription. Di- and trimethylated histone H3 lysine 9 (H3K9me2/3) and trimethylated histone H3 lysine 27 (H3K27me3) that repress gene transcription, and trimethylated histone H3 lysine 4 (H3K4me3) that enhances gene transcription, are well-known histone methylation modified forms. More than 50 histone lysine methyltransferases (HMTs) and demethylases regulate these methylations, resulting in epigenetic gene activation or silencing.

14.4.1 Histone Deacetylase

The 18 types of HDACs are subdivided into four major classes based on sequence homology and catalytic mechanism. HDACs are aberrantly activated in many tumor types and often reduce gene expression associated with lung tumorigenesis. Aberrant HDAC activity enhances cellular proliferation through a number of

signaling pathways including the MYC/MAD and RB/E2F pathways. HDACs have also been reported to be implicated in fibrogenesis in various organs. Guo et al. showed HDAC4-dependent differentiation of normal human lung fibroblasts (NHLFs) to myofibroblasts that requires AKT phosphorylation and demonstrated that AKT activation was indispensable for TGFβ-mediated lung fibroblast-myofibroblast transition [43]. Halder et al. reported that the loss of TGFβ type II receptor expression (TβRII) through histone deacetylation prevents TGF-β-mediated tumor suppressive function [44].

14.4.2 Histone Methyltransferase

HMTs generally contain the SET (suppressor of variegation, enhancer of zeste, trithorax) domain as the catalytic unit, and its dysregulation leads to aberrant histone methylation, resulting in tumorigenesis by oncogene activation and/or inactivation of tumor suppressor genes. Of *HMT* genes, the polycomb group protein *enhancer of zeste homolog 2* (*EZH2*) gene that has HMT activity is known to be overexpressed in many malignant tumors. Polycomb group proteins (PcG), which are transcriptional repressors, contain two distinct protein complexes: polycomb repressive complex (PRC) 1 and PRC2. PRC2 consists of EZH2, its catalytic subunit, the embryonic ectoderm development (EED) protein, and EED-associated HDAC1 and HDAC2. EZH2 acts as an HMT and trimethylates H3K27, thereby leading to epigenetic silencing of genes involved in development, differentiation, and growth. EZH2 also recruits DNMTs to target promoters. EZH2 thus inactivates tumor suppressor genes through both DNA methylation and histone methylation. Therefore, *EZH2* is considered as an oncogene. Indeed, we previously reported that EZH2 expression is associated with poor prognosis in patients with NSCLC and increases potentials of tumor growth and invasiveness in NSCLC cells [45]. Many PRC2 target genes contain CpG islands, and Vire et al. reported that EZH2 directly interacts with DNMTs and is necessary for de novo DNA methylation of PRC2 target gene promoters [46]. Regarding the association of IPF with HMTs, Coward et al. recently demonstrated that in fibroblasts from IPF, G9a HMT-mediated H3K9 methylation and EZH2-mediated H3K27 methylation were markedly increased at the *COX2* promoter, thereby resulting in epigenetic silencing of the *COX2* gene [47]. They also previously demonstrated that defective histone acetylation caused by decreased recruitment of HATs, and increased recruitment of the NCoR, CoREST, and mSin3a transcriptional corepressor complexes to the *COX2* promoter, is responsible for diminished *COX2* gene transcription in IPF. As described in the previous section, COX2/PGE2 function as key antifibrotic mediators by attenuating myofibroblast differentiation and potentially suppressing lung fibrogenesis, whereas these mediators, when overexpressed in lung cancer cells, are known to contribute to tumor angiogenesis.

14.4.3 Interferon-γ-Inducible Protein of 10 kDa/Chemokine C-X-C Motif Ligand 10

Interferon-γ-inducible protein of 10 kDa (IP10)/chemokine C-X-C motif ligand 10 (CXCL10) is secreted by diverse cells including monocytes, fibroblasts, and endothelial cells, and HDACs interact with HMTs that methylate H3K9 in order to maintain chromatin condensation at its promoter region. IP10 has been reported to inhibit tumor growth, metastasis, and angiogenesis in NSCLC [48], while Keane et al. reported that lung tissues and fibroblasts from IPF patients constitutively produced less IP10 than normal fibroblasts, suggesting that IP10 also attenuates angiogenic activity in IPF [49].

Given these findings, histone modification that interacts with diverse pathways and molecules may be directly and indirectly involved in the common pathogenesis of IPF and lung cancer.

14.5 MicroRNA in Epigenetic Changes

microRNAs (miRNAs) are a class of noncoding small RNAs that consist of approximately 20–25 nucleotides that bind to the 3′ untranslated region (3′ UTR) of the mRNA of target genes. Once bound to the target mRNA, the mRNA is degraded, and its translation is repressed. A single miRNA targets genes in different pathways, while a single gene is targeted by multiple miRNAs. Therefore, miRNAs play essential roles in numerous cellular and developmental processes, including in intracellular signaling pathways and organ morphogenesis, whereas aberrant miRNA expression is associated with the development and progression of a variety of diseases including cancer. Currently, miRNA is a major focus of research, and in this section, we extensively review the relationship between miRNA and the common pathway of IPF and lung cancer.

14.5.1 miR-21

miR-21, one of the best-characterized miRNAs in tumorigenesis, has been reported to be overexpressed in many types of cancer and to be particularly related to prognosis in never-smokers with NSCLC [50]. miR-21 has also been reported to be upregulated in the lungs of both mice with bleomycin-induced pulmonary fibrosis and in patients with IPF [51]. TGFβ, a key mediator of lung fibrogenesis, upregulates miR-21 expression, thereby promoting the activation of pulmonary fibroblasts, resulting in myofibroblast differentiation. Fibroblastic growth factor-2 (FGF2) also enhances miR-21 expression in human primary fibroblasts. In turn, enhanced miR-21 expression is primarily located in myofibroblasts in IPF.

TGFβ-induced fibrogenic activation of pulmonary fibroblasts through miR-21 is at least partly generated by negative modulation of SMAD7 and reduced SMAD2 phosphorylation. miR-21 is known to positively or negatively regulate the expression and function of diverse tumor-associated genes, including *tropomyosin 1* (*TPM1*), *programmed cell death 4* (*PDCD4*), *PTEN*, *TGFβ*, *nuclear factor I/B* (*NFIB*), a *serpin peptidase inhibitor* (*maspin*), *Sprouty-2* (*Spry2*), *myristoylated alanine-rich C-kinase substrate* (*MARCKS*), *matrix metalloproteinases* (*MMPs*), and *reversion-inducing cysteine-rich protein with kazal motifs* (*RECK*) that is an inhibitor of MMPs. Of these genes, *PDCD4*, *PTEN*, *TGFβ*, and MMP-mediated molecules are commonly associated with IPF and lung cancer.

PDCD4, which is considered as a tumor suppressor gene, inhibits the activation of activator protein-1 (AP1). In turn, AP1 that is activated through the RAS/MAPK pathway induces miR-21 expression, whereas RAS downregulates PTEN and PDCD4 in an AP1- and miR-21-dependent manner [52]. On the other hand, miR-21 in fibroblasts was associated with TGFβ-induced differentiation of fibroblasts into myofibroblasts through PDCD4, although this event was reported in cancer stroma [53].

PTEN expression, which is negatively regulated by TGFβ, is reduced in 74 % of NSCLC [54]. White et al. showed that PTEN expression is decreased in fibroblasts isolated from the lungs of IPF patients, that myofibroblasts in IPF have diminished PTEN expression, that inhibition of PTEN *in vivo* promotes fibrosis, and that PTEN prevents myofibroblast differentiation *in vitro* [17].

TGFβ is a potent profibrotic cytokine and has been reported to play a critical role in the pathogenesis of IPF. While TGFβ also induces SMAD-independent signaling, TGFβ signaling that is dependent on SMAD proteins results from TGFβ binding to TβRII, which then phosphorylates and activates TGFβ type I receptor (TβRI) and consequently regulates tumor-associated gene transcription, including the regulation of diverse signaling pathways, the cell cycle, and EMT [55]. Interestingly, TGFβ signaling can exert either tumor suppressive or promoting function according to the conditions to which the cells are exposed.

MMPs, a protein family of zinc-dependent endopeptidases, are classified into subgroups. MMP-mediated degradation of many substrates leads to multiple biological and pathological conditions including wound healing, tumorigenesis, organ fibrosis, and inflammation. A functional imbalance between MMPs and their endogenous inhibitors, tissue inhibitors of metalloproteinases (TIMPs), can underlie the development of both pulmonary fibrosis and lung cancer [56]. MMP7 is overexpressed in both IPF and NSCLC [57, 58]. MMP2 and MMP9 were not only highly upregulated in the lungs of IPF patients but were also associated with tumor invasion and metastasis [59–61]. On the other hand, increased expression of TIMP1 was found in bleomycin-induced pulmonary fibrosis [62], and TIMP3 was upregulated in IPF patients [63]. Serum levels of TIMP1 and MMP9 were elevated in NSCLC tissues [64].

14.5.2 Let-7

The human lethal-7 (let-7) family, which contains 13 members, is another of the best-characterized miRNAs and contributes to development and carcinogenesis. Let-7 is considered as a tumor suppressor and is downregulated in both IPF and lung cancer. Among the let-7 family, a role for let-7d has been reported in many types of cancer and lung diseases. TGFβ reduces let-7d expression, which inhibits high mobility group AT-hook 2 (HMGA2), a target of let-7d that is highly expressed in alveolar epithelial cells (AECs) of IPF patients, thereby preventing EMT [65]. Pandit et al. also reported that SMAD3 binds to the putative let-7d promoter, which may be a potential mechanism by which let-7d inhibition of EMT is prevented [66]. Johnson et al. suggested that let-7 downregulation in lung tumors regulates RAS expression, which might function as a possible oncogenic mechanism [67]. The possible association of let-7 with RAS signaling through HMGA2 may result in antifibrotic phenotypes and oncogenesis.

Cell division cycle 25A (CDC25A) may be another target of let-7 that is associated with both IPF and lung cancer. CDC25A belongs to the CDC2 family of dual-specificity phosphatases and removes the inhibitory phosphates of cyclin-dependent kinases (CDKs), leading to their activation and consequently promoting cell cycle progression and cellular proliferation [68]. Let-7c targets the homeobox A1 gene (HOXA1), resulting in inhibition of CDC25A expression that is frequently increased in NSCLC [69, 70]. CDC25A expression was induced by keratinocyte growth factor (KGF), which also induces proliferation of AECs, whereas TGFβ, a key player in pulmonary fibrogenesis, has been reported to inhibit AEC proliferation induced by KGF [71]. TGFβ also reduces the increased let-7d expression that is found in the AECs of IPF. Let-7c and let-7d may exert reciprocal actions on the development of IPF and pulmonary tumorigenesis.

14.5.3 miR-155

miR-155 is produced from processing of the B-cell integration cluster (BIC), which is a noncoding transcript expressed in activated B cells, T cells, monocytes, and macrophages. miR-155 has also been reported to be upregulated in lung cancer and IPF [72, 73], and its expression is decreased by TGFβ. This miRNA reduces keratinocyte growth factor-7 (KGF7), resulting in fibroblast migration through activation of caspase 3 [74]. Coira et al. reported that miR-155 acts as an oncogene by inhibiting SMARCA4 (SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a, member 4), the catalytic subunit of the SWI/SNF chromatin-remodeling complex, in lung tumors [75]. miR-155 overexpression downregulates putative tumor suppressor genes including *TP53INP1*, *PTEN*, *PDCD4*, and *SH2 domain-containing inositol 5′-phosphatase 1* (*SHIP1*) [76, 77].

14.5.4 miR-29

The miR-29 family consists of miR-29a, miR-29b, and miR-29c and interacts with multiple profibrotic and inflammatory pathways, and its expression is significantly reduced in fibrotic lungs [73]. miR-29 is also one of the TGFβ-associated miRNAs involved in fibrogenesis and inhibits TGFβ-induced ECM synthesis through activation of the PI3K/AKT pathway in human lung fibroblasts [78]. miR-29 is negatively regulated by TGFβ/SMAD signaling through SMAD3 [79], whereas decreased miR-29 upregulates collagens and the genes encoding ECM proteins that are associated with the development of pulmonary fibrogenesis [80]. Therefore, miR-29 is considered to exert antifibrotic activity through regulation of the ECM and EMT. On the other hand, multiple studies have reported that miR-29 is downregulated in lung cancer [72, 81]. Furthermore, Fabbri et al. demonstrated that miR-29 exerts antitumor effects by directly targeting both DNMT3A and DNMT3B, thereby restoring the silenced expression of tumor suppressor genes in lung cancer [82].

14.5.5 miR-30

miR-30 downregulates RAB18, which belongs to the RAS superfamily, resulting in inhibition of NSCLC cell growth [83], whereas miR-30 is downregulated in IPF [66]. WNT1-inducible signaling pathway protein 1 (WISP1) is highly expressed in IPF, where it functions as a pro-fibrotic mediator, whereas miR-30a reverses TGF-β-induced WISP1 expression in lung fibroblasts [84].

14.5.6 miR-210

miR-210 is an intronic miRNA located within the genomic loci of transcripts. Its expression is increased in both IPF and lung cancer [85, 86]. Hypoxia-regulated miR-210 mediates gene expression implicated in diverse pathophysiological pathways, such as the cell cycle, apoptosis, angiogenesis, and oxidative metabolism. Bodempudi et al. reported that miR-210 expression is markedly increased in IPF fibroblasts in response to hypoxia, which stimulates fibroblast proliferation in IPF by repressing the cMYC inhibitor, MNT [87]. miR-210 overexpression directly downregulates MNT and indirectly activates cMYC, presumably thereby inhibiting hypoxia-induced cancer cell cycle arrest such as G0/G1 arrest and driving cellular proliferation [88]. On the other hand, Tsuchiya et al. reported that miR-210 overexpression in esophageal squamous cell carcinoma cells directly targets fibroblast growth factor receptor-like 1 (FGFRL1), resulting in induction of cell cycle arrest in both G0/G1 and G2/M phases and subsequent apoptosis [89].

14.5.7 miR-199a–5p

miR-199a–5p expression is increased in IPF patients, especially in myofibroblasts and fibroblastic foci. miR-199a–5p that is induced by TGFβ downregulates CAV1 that degrades the TGFβ/TβR complex, consequently promoting TGFβ signaling, ECM production, and myofibroblast differentiation, as well as cellular proliferation, migration, and invasion [90]. A recent report showed that miR-199 also regulates miR-155, which inhibits SMARCA4 that exerts a tumor suppressive function [75].

14.5.8 miR-145

miR-145, a putative tumor suppressor, is downregulated in diverse tumors, and its overexpression suppresses the proliferation of human lung adenocarcinoma cells through the EGFR and NUDT1 [91]. On the other hand, Yang et al. reported that miR-145 expression is increased in TGFβ-treated lung fibroblasts and in the lungs of IPF patients and that miR-145 overexpression in lung fibroblasts increased TGFβ-induced αSMA expression by targeting Kruppel-like factor 4 (KLF4), a known negative regulator of αSMA expression [92]. miR-145 exerts reciprocal effects on tumorigenesis and IPF development.

14.5.9 miR-200

miR-200 expression downregulates ZEB1 and ZEB2 expression, thereby inhibiting EMT and consequently suppressing distant metastasis in lung cancer [93], although miR-200 enhances metastases in mouse breast cancer cell lines partly through miR-200-mediated downregulation of SEC23A [94]. miR-200 also targets the key pro-angiogenic cytokines, IL-8 and CXCL1, thereby inhibiting tumor angiogenesis. TGFβ decreased miR-200 expression in rat ATII cells, and indeed, miR-200 is downregulated in the lungs of IPF patients [95]. That study also showed that decreased expression of miR-200 regulates the expression of GATA3, ZEB1, and ZEB2 and promotes EMT in AECs.

14.5.10 miR-17–92

Reduced miR-17–92 expression interacts with DNMT1, contributing to IPF development [96]. miR-17–92 silencing via DNA methylation is found in lung tissue and fibroblasts from IPF patients, whereas reduced miR-17–92 expression is inversely

correlated with DNMT1 expression. Introduction of the miR-17–92 cluster into fibroblasts of IPF reduced both the expression of fibrotic genes and DNMT1 and DNA methylation of the cluster and normalized cellular phenotype. The review by Osada et al. indicated that cMYC, E2F1/E2F3, and STAT3, which are frequently activated in cancer, transactivate miR-17–92 that is overexpressed in lung cancer, especially in SCLC [97]. miR-17–92 also suppresses PTEN, BIM, TβRII, CTGF, RB, and p21. Increased miR-17–92 expression in tumors targets antiangiogenic and fibrotic genes, many of which are altered in IPF. The biological properties of miR-17–92 may differ between IPF and lung cancer.

14.5.11 miR-375

miR-375 is downregulated in squamous cell carcinoma and upregulated in adenocarcinoma of the lung. Its overexpression leads to inhibition of CLDN1 expression that suppresses cell migration, invasion, and metastasis [98]. On the other hand, miR-375 negatively regulates AEC transdifferentiation through inhibition of the Wnt/β-catenin pathway, and its expression was decreased in the lungs of IPF patients [99].

14.5.12 miR-185

miR-185 induces G1 arrest, thereby inhibiting cellular proliferation in lung cancer [100]. This arrest may be due to miR-185 suppression of *CDK6* and *AKT1* mRNA expression. The expression of miR-185 as well as of Argonaute subfamily proteins, AGO1 and AGO2, a core component of RNA-induced silencing complexes (RISCs), is increased in IPF.

14.5.13 miR-154

miR-154 may target several genes involved in the nuclear factor-κB (NFκB), hypoxia-inducible factor-1 (HIF1), MAPK, NOTCH, and autophagic molecular signaling pathways, and its expression is decreased in the sera of lung cancer patients [101]. In IPF, miR-154 induced by TGFβ inhibits *p15* (*CDKNB2*), a TGF-β-responsive gene, and the Wnt pathway repressors DKK2, DIXDC1, and PPP2CA and increases FZD 4/5/6, LRP, and KREMEN1, consequently inducing fibroblast proliferation and migration [102]. Therefore, miR-154 overexpression may be a positive regulator of the Wnt/β catenin pathway.

Although there are conflicting data regarding the role of miRNAs in pulmonary tumorigenesis and IPF development, miRNA interaction with other miRNAs may

Table 14.1 Association of microRNAs with tumorigenesis and the development of IPF

MicroRNA	Tumorigenesis	IPF development	Related molecules
miR-21	↑	↑	TPM1, PDCD4, PTEN,TGFβ, NFIB, mapsin, Spry-2, MARCKS
			MMPs, RECK, SMAD2, SMAD7, FGF2
Let-7	↓	↓	TGFβ, HMGA2, SMAD3, RAS, CDC25A
miR-155	↑	↑	TGFβ, KGF7, SMARCA4, TP53INP1, PTEN, PDCD4, SHIP1
miR-29	↓	↓	TGFβ, SMAD3, PI3K/AKT, DNMT3A, DNMT3B
miR-30	↓	↓	RAS, Rab18, TGFβ, WISP1
miR-210	↑?	↑	Hypoxia, MNT, FGFRL1
miR-199a–5p	↑	↑	TGFβ, CAV1, SMARCA4
miR-145	↓	↑	EGFR, NUDT1, TGFβ, KLF4
miR-200	↓	↓	ZEB1, ZEB2, Sec23a, IL-8, CXCL1, TGFβ, GATA3, PTEN
			BIM, TGFβRII, CTGF, RB, and p21
miR-17–92	↑	↓	DNMT-1, cMYC, E2F1/E2F3, STAT3
miR-375	↓	↓	TGFβ/SMAD, CLDN1, FZD8, Wnt/β catenin
miR-185	↓	↑?	CDK6, AKT1, AGO1, AGO2, RISCs
miR-154	↓?	↑?	NFκB, HIP-1, MAPK, Notch, TGFβ, p15, DKK2, DIXDC1
			PPP2CA, FZD 4/5/6, LRP, KREMEN1, Wnt/β catenin

be a strong candidate as a common pathogenesis of IPF and lung cancer as described in this section (Table 14.1). Further investigation is warranted.

14.6 Signaling Pathways

IPF is characterized by injured and hyperplastic alveolar epithelium, which releases diverse molecules including growth factors, cytokines, and MMPs, causing the activation and proliferation of mesenchymal cells, ECM deposition, and the accumulation of fibroblasts. These processes can lead to basal membrane disruption, fibrin formation, abnormal wound repair, and angiogenesis through multiple signaling pathways, thereby promoting cellular apoptosis or migration. In many lung cancers, these signals can also activate oncogenes or inactivate tumor suppressor genes, leading to oncogenesis through aberrant oncogenic pathways. These findings suggest that common signaling pathways may contribute to the development of both IPF and lung cancer. Indeed, some individual key molecules, as described in the previous sections, are associated with both oncogenesis and fibrogenesis

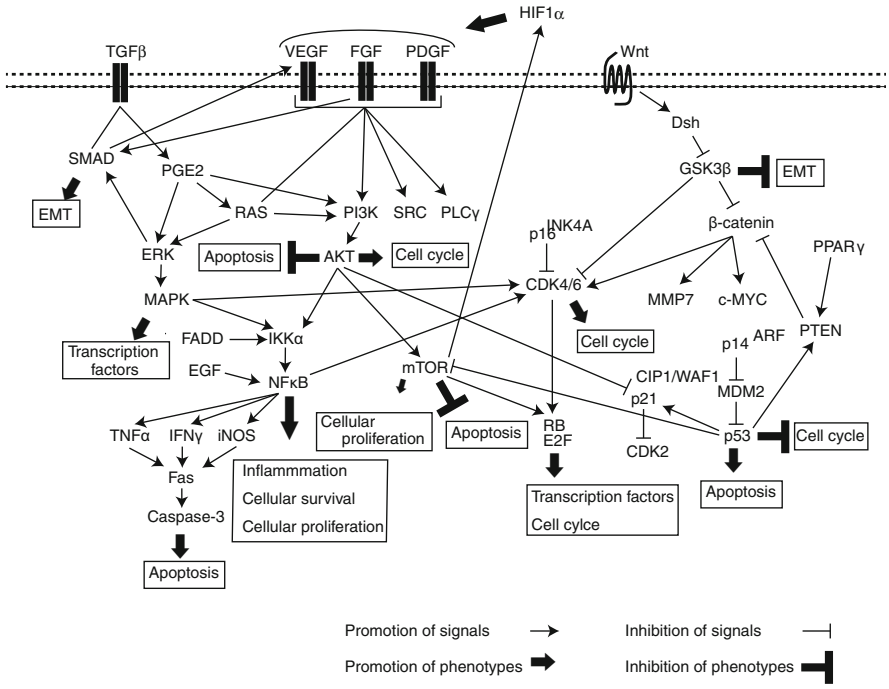

Fig. 14.1 Potential signaling pathways underlying the common pathogenesis of IPF and lung cancer

through common signaling pathways (Fig. 14.1). Therefore, we further describe noteworthy signaling pathways mentioned in the previous sections.

14.6.1 Transforming Growth Factor-β Signaling

As described in the previous sections, the TGFβ signaling pathway plays important roles in wound healing and fibrogenesis through its cross talk with other signaling pathways and diverse mediators. TGFβ-induced EMT and accumulation of myofibroblasts can be promoted by integrin-dependent activation of SMAD and Wnt/β-catenin signaling [103]. Myofibroblasts are resistant to apoptosis, which promotes fibrogenesis, partly through reduction of the anti-fibrotic prostaglandin E2 (PGE2) in IPF [104]. The features of these phenomena that lead to EMT appear to be similar to those of tumor cells, and myofibroblasts promote cellular infiltration and progression through multiple mediators in a tumor environment.

14.6.2 Wnt Signaling

The Wingless-type protein (Wnt) family, which consists of 19 secreted proteins, transmits its signal through activation of multiple pathways. One major Wnt pathway, termed the canonical pathway, inhibits GSK3β, leading to the stabilization and accumulation of β-catenin in the cytosol and its translocation into the nucleus, consequently resulting in enhanced expression of target genes that are associated with diverse diseases. As described in the previous Sect. 14.3.1, the Wnt/β-catenin pathway is one target of TERT regulation. β-catenin transmission of Wnt signals to the nucleus regulates diverse oncogenic genes including *cyclin D1* and *cMYC*, and its overexpression and stabilization can promote oncogenesis. The review by Stewart et al. indicates that expression of WNT1, a Wnt ligand, is correlated with aberrant β-catenin expression and increased expression of cMYC, cyclin D1, VEGFA, MMP7, Ki67, and survivin, resulting in proliferation of NSCLC [105]. The other Wnt pathway, termed the noncanonical pathway, which does not involve β-catenin, is mainly comprised of two types of pathways, the planar cell polarity pathway (Wnt-PCP pathway) and the Wnt-calcium pathway (Wnt/Ca2+ pathway). The combined expression of WNT7A and FZD9 in NSCLC cell lines leads to ERK5 activation, which in turn leads to increased PPARγ expression and activation of Sprouty-4. Sprouty-4 inhibits EMT, consequently inhibiting tumor growth [106, 107]. Indeed, aberrant expression of Wnt ligands and Wnt signaling mediators has been frequently found in NSCLC.

The Wnt/β-catenin pathway also promotes EMT and myofibroblast differentiation that is mediated through TGFβ, thereby contributing to pulmonary fibrogenesis. The Wnt/β-catenin signaling pathway was upregulated in lung tissues of IPF patients. Moreover, β-catenin targets cyclin D1 and MMP7, both of which are considered to be associated with pulmonary fibrogenesis [108].

14.6.3 PI3K/AKT/mTOR Signaling

Phosphoinositide 3-kinases (PI3Ks) regulate cellular proliferation, survival, adhesion, and motility. These kinases stimulate PIP3 synthesis on the cell membrane, thereby promoting the PI3K/AKT/mTOR pathway, a downstream signaling pathway composed of multiple receptor tyrosine kinases. The PI3K/AKT/mTOR pathway is activated early in the pathogenesis of pulmonary tumorigenesis through the modulation of multiple signals as follows, resulting in inhibition of apoptosis and cell survival: (1) mutations in *PI3K* or *PTEN* as well as in the *EGFR* or *KRAS* and (2) *PIK3CA* amplification, *PTEN* loss, or *AKT* activation [109]. In fibroblasts of IPF, PI3K/AKT/mTOR signals are aberrantly activated, while PTEN activity is lower than that of normal cells [110]. Furthermore, the PI3K/AKT/mTOR pathway interacts with many other signaling pathways, including those of MAPK and VEGFR, in IPF cells [111].

14.6.4 Nuclear Factor-κB Signaling

Cross talk between the NFκB and PI3K/AKT/mTOR signaling pathways may contribute to lung cancer cell survival and proliferation [112]. PI3K/AKT promotes NFκB activity in an IKKα-dependent manner [113], while NFκB is activated by Fas-associated death domain protein (FADD) phosphorylation through IKK, thereby promoting proliferation in lung adenocarcinoma [114]. Furthermore, EGF induces IKK-independent NFκB activation through IκBα phosphorylation in lung adenocarcinoma cells [115]. NFκB activation was associated with *KRAS* mutation, and both lost p53 function and active $KRAS^{G12D}$, the major *RAS* point mutation in lung cancer, constitutively activate NFκB as well as downstream signaling pathways, such as PI3K and MAPK, in lung cancer cells [116]. NFκB activation is also found in the IPF-associated inflammatory process. NFκB-dependent inflammatory mediators, including tumor necrosis factor (TNF)-α, TGFβ, interleukin (IL)-1, inducible nitric oxide synthase (iNOS), and interferon (IFN)-γ, were highly expressed in IPF patients and in animal models of pulmonary fibrosis [117–119]. Previous *in vivo* studies showed that suppression of the NFκB signaling pathway can attenuate bleomycin-induced pulmonary fibrosis, while *in vitro* studies also found that the NFκB signaling pathway contributed to the regulation of TGFβ [119–121].

14.6.5 Fibroblast Growth Factor Signaling

Fibroblast growth factors (FGFs) are a family of homologous polypeptide ligands that bind to their cognate FGF receptors (FGFRs) [122]. There are 22 FGF ligands comprising six subfamilies and four FGFR isoforms that are differentially activated by FGF ligands in conjunction with the scaffold protein heparan sulfate proteoglycan. Binding of FGF ligands to FGFRs transmits signals associated with angiogenesis as well as with cellular migration and proliferation, and the FGF signaling pathway is involved in the pathogenesis of diverse diseases. However, FGF signaling exerts reciprocal effects on tumor promoting and suppressive activities, which are dependent on the tumor type. Regarding IPF, TGFβ released from AECs induces the proliferation of pulmonary fibroblasts through FGF2, which promotes phosphorylation of p38 MAPK and JNK [123], and high FGF2 levels have been found in the bronchoalveolar lavage fluid and serum of IPF patients [124]. Many NSCLC cells showed elevated FGF2 levels, which in turn promote the growth of these tumor cells by intracrine mechanisms [125]. FGF2 also contributes to angiogenesis and tumor proliferation in many types of cancer, and FGF2-mediated autocrine and paracrine signaling can potently promote oncogenesis.

Another FGF, FGF1, exerts antifibrotic activity through downregulation of collagen expression and antagonization of some TGFβ-mediated profibrotic functions [126]. FGF1 was also shown to restore TGFβ-induced EMT in AECs through

dephosphorylation of the SMAD2 phosphorylation that was induced by the MEK/ERK pathway. FGF1-mediated activation of FGFR signaling induces the recruitment and activation of SRC homology (SH2)- or phosphotyrosine (PTB)-containing proteins, thereby activating multiple signaling pathways including PI3K/AKT, MEK1/2-ERK, and p38MAPK [127]. Recently, Daly et al. reported that low levels of FGF1 are associated with favorable outcomes in stage I lung adenocarcinoma [128].

14.6.6 Fas/FasL Signaling

Fas, a cell surface death receptor of the TNF receptor (TNFR) superfamily, paradoxically promotes both survival/differentiation and apoptosis through the modulation of immune responses. Low to absent staining of Fas was detected in fibroblastic cells of fibroblast foci from IPF patients [129]. Exposure to the proinflammatory cytokines, TNF-α and IFNγ, increases Fas expression in an NFκB- and MAPK-dependent manner, thereby sensitizing fibroblasts to Fas-induced apoptosis and reversing the resistance of lung fibroblasts to apoptosis, which is mediated by a prosurvival effect of TGFβ. Aberrant Fas/Fas ligand (FasL) expression is found in many lung cancer cells and samples [130], suggesting its contribution to lung carcinogenesis.

14.6.7 Vascular Endothelial Growth Factor Signaling

The vascular endothelial growth factor (VEGF) signaling pathway is well characterized. VEGF ligands (VEGFA to VEGFE and placental growth factor) induced by hypoxia, growth factors, and cytokines interact with VEGF receptors (VEGFR1–3), especially with VEGFR2 that activates the PI3K/AKT pathway; promotes cellular proliferation, migration, and survival as well as angiogenesis; and inhibits apoptosis. VEGF is highly expressed in lung cancer, and its expression is associated with poor prognosis [131]. While normal wound healing requires angiogenesis, aberrant neovascularization is often found in IPF tissues, suggesting that VEGF signaling is associated with the development of IPF. Furthermore, Kobayashi et al. showed that SMAD3 signaling mediates TGFβ-induced VEGFA production in human lung fibroblasts [132].

14.6.8 Platelet-Derived Growth Factor Signaling

The platelet-derived growth factor (PDGF) family, which consists of PDGFA to PDGFD, promotes cellular proliferation, invasion, and angiogenesis as well as

wound healing and proliferation of mesenchymal cells. Enhanced PDGF expression and activation of its signaling have been reported in different types of cancer and in fibrotic disorders. Dimeric PDGFs bind to the receptors PDGFRα and PDGFRβ, thereby transmitting signaling through PI3K, SRC, phospholipase C-γ, and RAS pathways in both an autocrine and a paracrine manner [133]. PDGFA and PDGFC paracrine signaling was associated with fibroblastic tumor infiltration in NSCLC cell lines [134]. Furthermore, PDGF signaling, which partly overlaps with VEGF signaling, activates cancer-associated fibroblasts (CAFs) and recruits VEGF-producing stromal fibroblasts, leading to both tumorigenesis and angiogenesis [135]. PDGF that is synthesized by alveolar macrophages is a potent mitogenic and chemotactic factor for fibroblasts. Previous *in vitro* studies showed that PDGF interacts with several fibrotic mediators including TGFβ, IL-1, TNF-α, FGF, and thrombin, thereby promoting fibrogenesis. Macrophages and fibroblasts from IPF patients produce PDGF, whereas PDGFB and PDGFR mRNAs are highly expressed in hyperplasic ATII cells in IPF [136]. PDGF/PDGFR signaling can at least partly interact with VEGF/VEGFR and FGF/FGFR signaling pathways, and the intricate cross talk between these pathways may contribute to the common pathogenesis of IPF and lung cancer.

14.6.9 RAS/RAF/MEK/MAPK Signaling

Signaling of the RAS/RAF/MEK/MAPK pathway is one of the most extensively characterized signals and modulates cellular migration, proliferation, and apoptosis; its aberrant signals are therefore involved in the development of diverse diseases. In particular, this pathway is frequently activated in lung cancer, most commonly via *KRAS* mutations in approximately 20 % of lung cancers, particularly in adenocarcinomas in smokers [137]. The RAS/RAF/MEK/MAPK pathway has also been associated with the development of IPF. Many molecules and pathways, as well as most signals described in this section, can converge, regulate, or interact with the RAS/RAF/MEK/MAPK pathway.

14.6.10 Signaling Through Connexin

Gap junctions are composed of protein complexes including connexins that characterize cell-cell communication, and their alteration is tightly associated with cellular proliferation, tissue repair, and tumor growth. Vancheri et al. reported the possible role of connexins, especially connexin 43 (CX43), in the common pathogenesis of IPF and lung cancer [138].

Multiple pathways that are mutually dependent interact with one another, thereby regulating the signals that can lead to inflammatory processes and tumorigenesis. Therefore, a possible common pathway of IPF and lung cancer may

provide a therapeutic perspective on these comorbid disorders. For example, nintedanib that targets PDGFRα and PDGFRβ, VEGFR1 to VEGFR3, and FGFR1 to FGFR3 has therapeutic potential for both IPF and NSCLC based on the phase III trials, INPULSIS-1 and INPULSIS-2, for IPF and LUME-Lung 1 for NSCLC [139, 140].

14.7 Conclusion

Both IPF and lung cancer are heterogeneous disease groups, and furthermore, multiple pathways and diverse molecules that interact with one another can be associated with both diseases, raising the complexity of the pathogenesis of these diseases. However, we often encounter patients with lung cancer comorbid with IPF in clinical practice, and as described in Sect. 14.1, lung cancer occurs in 4.4–38 % of patients with interstitial pneumonia according to previous reports. Possible commonality in the pathogenesis of IPF and lung cancer has been discussed in this chapter, suggesting that in this context, there may be a common pathway that contributes to the development of IPF and lung cancer. Diverse signals and molecules can transmit individual signaling pathways, converge on a common pathway, and promote inflammatory processes in IPF and lung tumorigenesis. These phenomena may lead to a high frequency of comorbid IPF and lung cancer. Therefore, an efficacious therapeutic strategy for both diseases that targets such a possible common pathway may be exploited in the future, although it has already been attempted, in part. In particular, although the incidence of lung cancer with IPF is steadily increasing, there are few reports regarding its treatment. For more efficacious and efficient therapy for IPF and lung cancer, a more fundamental pathway that underlies the development of both diseases needs to be determined.

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