

# Research Progress on Pathogenesis of Idiopathic Pulmonary Fibrosis Complicated with Lung Cancer

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## Abstract

Idiopathic Pulmonary Fibrosis (IPF) is a fatal disease characterized by abnormal pulmonary fibroblast proliferation and excessive muscle fibroblast deposition in the extracellular matrix. Although it is not a malignant tumor, the prognosis is similar to many tumors or even worse. Sixty to seventy percent of IPF patients die from the disease. Without treatment, the average life expectancy after diagnosis is about 3-5 years. Other causes of death may be related to complications, with cardiovascular disease and Lung Cancer (LC) being the most significant contributors to mortality. At present, the pathogenesis of IPF-LC is not clear. Several studies have indicated the existence of a common pathway in the pathogenesis of IPF combined with LC. This review aims to provide a reference for the etiological treatment of IPF by examining relevant literature on the common pathogenesis and molecular pathways of IPF-LC, focusing on epigenetics, cellular communication, signaling pathways, and environmental factors.

## Keywords

Idiopathic pulmonary fibrosis, lung cancer pathogenesis, treatment

## Introduction

Idiopathic pulmonary fibrosis and lung cancer have similar pathogenesis: In IPF, activated myofibroblasts promote the deposition of ECM, leading to acute deterioration of IPF, similar to myofibroblasts of IPF. In LC, cancer-associated fibroblasts (CAF) are key players in the cell and activated CAF drives cancer [1, 2]. This article reviews the co-pathogenesis between IPF and LC.

## 1. Pathogenesis of idiopathic pulmonary fibrosis combined with lung cancer

### 1.1 Epigenetic inheritance and genetic abnormalities

Lung cancer and idiopathic pulmonary fibrosis have common risk factors such as environmental exposure (smoking, dust, environmental particles), genetic risk factors, and aging, which can lead to significant genetic and epigenetic changes in the human genome. The established pathogenesis of most tumors is attributed to hypermethylation of tumor suppressor genes and hypomethylation of oncogenes. Genome-wide DNA methylation studies have shown that islands of differentially methylated cytosine guanine phosphate (CpG) overlap in lung cancer and IPF, suggesting a common pathogenic pathway between the two diseases [3] that abnormal DNA methylation can contribute to the development and progression of both pulmonary fibrosis and lung cancer. Specific gene mutations also play an important role in the origin and development of tumors. Genetic mutations associated with the development and

progression of lung cancer have been found in familial pulmonary fibrosis and about 10%-20% of sporadic IPF cases, including mutations encoding telomerase (PARN, PARN, RTEL1). These genes cause telomere shortening by regulating telomere length. Induce malignant tumor. In addition, the expression of p53 and p21 genes is up-regulated in the bronchial and alveolar epithelial cells of IPF patients [4], such gene mutations have been confirmed by microsatellite DNA detection, and are commonly found in the peripheral honeycomb lung region unique to IPF [5]. Patients with lung cancer and IPF have increased concentrations of free-circulating DNA compared to patients with other secondary pulmonary fibrosis, and circulating and cell-free DNA is considered diagnostic and prognostic biomarkers for cancer [6]. In addition to circulating DNA, abnormal mRNA expression levels are also associated with the onset of both diseases. Short non-protein-coding RNAs regulate oncogenes involved in growth, invasion, and metastasis. Studies have shown that 10% of mRNAs are abnormally expressed in IPF patients, in which miR-30, let-7, miR-29, and miR-200 are down-regulated, and miR-21 and miR-155 are up-regulated. These changes correspond to DNA associated with interstitial fibrosis, ECM deposition, induction of EMT, and apoptosis, resulting in accelerated deterioration of lung function in patients with IPF.

## 1.2 Abnormal intercellular communication

Intercellular gap junction (GJ), composed of connexin (CX) family proteins, provides a channel for direct information exchange between cells, and Cx43 is the most abundant in the fibroblast cell membrane, which plays an important role in cell proliferation and synchronous tissue repair [7]. Downregulation of Cx43 expression is associated with increased expression of transforming growth factor- $\beta$ , collagen production, and accelerated differentiation of myofibroblasts. These changes lead to the proliferation and migration of stromal cells and fibroblasts, which may be conducive to wound repair and wound healing. Meanwhile, these changes may also lead to abnormal proliferation of fibroblasts, induced abnormal repair, and interstitial fibrosis. Low expression of Cx43 is usually associated with tumor progression and loss of intercellular communication. J can increase the immunogenicity and immunomediated cytotoxicity sensitivity of tumor cells. Cx43 is related to tumor suppression through different heterocellular GJ-mediated communication inhibition, which occurs at different points in the tumor immune cycle. CHENQ et al. [8] confirmed that human lung cancer cells promote the formation of cancer-astrocytes gap junction through the expression of protocadherin (PCDH7), enabling cancer cells to transfer to astrocytes through gap junction channels under the action of the second messenger cGAMP, and activate STING pathway to produce IFN $\alpha$ , TNF and other inflammatory factors, leading to the proliferation and development of malignant tumors. Interstitial fibrosis, therefore, abnormal intercellular communication will promote the occurrence of tumors and interstitial fibrosis.

## 1.3 Abnormal activation of signaling pathway

Abnormal activation of major signaling pathways exists in both IPF and lung cancer. Wnt/ $\beta$ -Catenin signaling pathway is involved in tumor metaplasia, lung remodeling, and epithel-to-mesenchymal transformation (EMT) by promoting the overexpression of tissue invasions related molecules [9] such as cyclin-D1, laminin, and matrix metalloproteinase (MMP)-7, which has been found in lung cancer. Abnormal activation of the Wnt/ $\beta$ -catenin pathway is found in fibroproliferative diseases of liver and kidney, pulmonary mesothelioma, and hepatorenal tissue. The Wnt/ $\beta$ -catenin pathway is strongly activated in the lung tissue of patients with idiopathic pulmonary fibrosis, and dehydrosingone (DHz) alleviates pulmonary fibrosis by regulating the Wnt/ $\beta$ -catenin pathway to inhibit inflammation and epithel-mesenchymal transformation [10]. The most important target of Wnt/ $\beta$ -catenin pathway is to up-regulate the expression of TGF- $\beta$  and activate extracellular signals-regulating protein kinase (ERK1/2) and phosphatidylinositol 3-kinase (PI3K)/protein kinase B(AKT) signaling pathways to regulate cell proliferation and apoptosis. In IPF patients, TG- $\beta$ 1 induces myofibroblast differentiation,  $\alpha$ -SMA expression, and collagen fiber production, and affects the proliferation of lung fibroblasts. Fibroblasts and myofibroblasts are expected to be potential therapeutic targets for IPF. In the tumor microenvironment, activation of the PI3K pathway is involved in the termination of uncontrolled cell proliferation. Candidate biomarkers of PI3K inhibitors have predictive value in pre-clinical models and show histologically specific changes in primary tumors, so inhibition of PI3K is considered a treatment for IPF and lung cancer. In addition, tyrosine kinases are key receptors in a variety of signaling pathways and play important roles in cell differentiation, growth, motility, adhesion, and regulation of cell death. In recent years, studies on the role of tyrosine kinase receptors in wound healing and fibrosis formation have shown that tyrosine kinase activity is affected by tyrosine kinase receptor ligands, such as TGF- $\beta$ , VEGF, PDGF, and FGF, which mediate carcinogenesis and fibrosis. Studies have shown that platelet-derived growth factor regulates the

expression of vascular endothelial growth factor in non-small cell lung cancer through an auto-secretory mechanism, and is involved in the recruitment of tumor-associated fibroblasts (CAFs) in tumors. It has been demonstrated that crenolanib (PDGF receptor inhibitor) can be dose-dependent in a model system of non-small cell lung cancer using A549 cells. The way inhibits cell proliferation and induces apoptosis [11]. In addition, in a bleomycin-induced rat fibrosis model, the multiple tyrosine kinase receptor inhibitor Nidanibinetedanib has shown significant advantages in the treatment of IPF and has been approved for the treatment of idiopathic pulmonary fibrosis. In two Phase 3 placebo-controlled INPULSIS trials, Nidanib has demonstrated controllable safety and tolerability in long-term use, and Nidanib in combination with docetaxel is currently being used in patients with advanced non-small cell lung cancer (NSCLC) following first-line chemotherapy, as shown in a recent case report. Nidanib alone effectively inhibited the progression of pulmonary fibrosis and the spread of primary tumor in a 69-year-old late-stage IPF-LC patient. The programmed death ligand-1/Programmed Cell death 1 (PD-L1/PD-1) axis is a major checkpoint pathway for maintaining systemic immune balance and self-tolerance, which cancer cells use to evade the surveillance of the immune system. Targeted programmed cell death 1 (PD-1) and programmed cell death ligand-1 (PD-L1) immune checkpoint inhibitors have shown effective clinical efficacy and revolutionized treatment options for multiple tumor types, especially non-small cell lung cancer (NSCLC). PD-1/PD-L1 monoclonal antibody has become the first-line drug in the treatment of advanced NSCLC. Recently, human observational studies have found that PD-L1 is overexpressed in IPF patients compared with non-IPF lung tissue samples, and inhibition of PD-L1 can reduce experimental pulmonary fibrosis. It is further suggested that the PD-1/PD-L1 axis plays an important role in the occurrence and development of pulmonary fibrosis. In future research and clinical trials, PD-1 inhibitor-related drugs may be beneficial to the remission of IPF-LC.

#### 1.4 Abnormal migration and invasion of cytokines

TGF- $\beta$  is currently believed to play a major role in accelerating pulmonary interstitial fibrosis and carcinogenesis, especially TGF- $\beta$ 1 [12], and myofibroblasts in IPF patients regulate tumor proliferation, progression, immunosuppression, angiogenesis, and vascular remodeling [12] through autocrine TGF- $\beta$ . TGF- $\beta$  represents a key driver signal for fibroblast and CAF trans-differentiation [13], and is essential for tumor progression and therapeutic resistance [14]. In the lung cancer microenvironment, TGF- $\beta$  is primarily derived from tumor epithelial cells, induces myofibroblast recruitment during cancer cell invasion, and protects myofibroblasts from apoptosis. CAFs, mediated by inflammatory mediators and metalloproteinases (MMPs), destroy the basal membrane of the surrounding tissue and accelerate the proliferation of malignant tumors [15]. In addition, MMPs and integrins are strongly associated with cell invasion and migration [16], with integrins activating cancer cells via the KRAS/RelB/NF- $\kappa$ B pathway and stimulating tumor cell stem cell properties such as independent growth and drug resistance characteristics. These properties provide intercellular communication between inflammatory cells, fibroblasts, and parenchymal cells through the extracellular matrix, resulting in abnormal proliferation of tumor cells. Under IPF conditions, the integrin expression of myoblasts and vascular endothelial cells in damaged lung tissue is up-regulated, which promotes the initiation, maintenance, and regression of pulmonary fibrosis. Clinical studies targeting  $\alpha$ v $\beta$ 6 specific antibodies have shown that these antibodies significantly upregulate integrin expression in preclinical fibrosis models and bleomycin-induced mouse pulmonary fibrosis models [17]. Due to the undetectable level of integrin  $\alpha$ v $\beta$ 6 expression in normal healthy tissues and its high prevalence in aggressive tumor cells, it may become a potential target for tumor imaging and clinical examination to facilitate early diagnosis and treatment.

#### 1.5 Inflammatory environment

Mononuclear macrophages are important regulatory cells in tissue regeneration, repair, and fibrosis. Dysfunction of macrophages can produce a large number of inflammatory mediators and growth factors, leading to abnormal tissue repair, fibrosis, and carcinogenesis. Macrophages are highly plastic and their functional phenotype depends on different microenvironments, with M2 macrophages being the most prominent macrophage type in pulmonary fibrosis. Pirfenidone regulates macrophage polarization and improves radiation-induced pulmonary fibrosis by inhibiting the TGF- $\beta$ 1/Smad3 pathway [18]. M2 macrophages are widely believed to be trigger cells for tumor progress [19]. Myeloid derived suppressor cells (MDSCs) are most commonly used to describe cells produced during chronic inflammation, especially advanced cancer, and are defined by their T cell immunosuppressive function [20]. The poor prognosis of malignant tumors caused by immune escape can be identified as a valid biomarker of disease progression, and MDSCs are only negatively correlated with lung function in IPF [21], therefore, by controlling the expansion and accumulation of MDSC, or blocking their T cell inhibition, they are expected to be a new approach for IPF

treatment.

## 2. Peroration

The pathogenesis of idiopathic pulmonary fibrosis complicated with lung cancer involves genetics, cell communication, signaling pathways, cytokines, and inflammatory environment, which are intertwined, and the overall prognosis is poor. The early symptoms of IPF-LC are mainly mild, non-specific symptoms such as dyspnea and dry cough, and are often combined with multiple diseases and are easy to cover up. Velcro rales, clubbing fingers, and other specific manifestations can be heard during physical examination when the disease progresses gradually. Pulmonary function examination (PFT) indicated insufficient restrictive ventilation function, such as decreased carbon monoxide diffusion function (DLCO), forced vital capacity (FVC), and one-second volume (FEV1). Histopathological features of IPF were common manifestations of interstitial pneumonia (UIP). In patients with UIP/IPF-LC, lung cancer tended to occur in the honeycomb-dense peripheral lung zone. The most common histological subtypes are peripheral squamous cell carcinoma and adenocarcinoma. At present, there is no clear biological marker for the diagnosis and prognosis of IPF-LC. The treatment of such patients should be combined with IPF, LC stage, and pathological classification, and an individualized treatment plan should be developed taking into account both. Currently, there are no clear biological markers for the diagnosis and prognosis of patients with IPF-LC, and the treatment of such patients should be combined with IPF, LC staging, and pathological classification, and an individualized treatment regimen should be developed taking into account both Case measures. At present, there is no clear conclusion in RCT studies on the efficacy of IPF-LC. This paper reviews the latest pathogenesis of IPF-LC, hoping to contribute to the clinical research of researchers and the best management of such patients by clinicians.

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