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Review Article

IPF and lung cancer: homologous but different endings, the progress in the correlation research

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Abstract: Background: An increasing body of evidence has suggested that idiopathic pulmonary fibrosis is inclined to combine with lung cancer in recent years. Thus we studied the correlation of the two diseases to raise awareness of the risk of lung cancer in pulmonary fibrosis patients among doctors and patients. Methods: Data about the epidemiology, pathogenesis, clinical features and treatment strategies of idiopathic pulmonary fibrosis associated lung cancer cited in this review were obtained from major databases such as Pubmed, Web of Science, Embase, Scoups, Cancerlit and so on from 1957 to 2015. Results: The prevalence rate of lung cancer in pulmonary fibrosis patients is much higher than that in general population. Perturbed signaling pathways, epigenetic and genetic changes, and oxidative stress are all thought to be involved in the pathogenesis of idiopathic pulmonary fibrosis associated lung cancer. Hemoptysis and chest pain should be an alert for the presence of lung cancer in pulmonary fibrosis patients. The peripheral, lower, and highly fibrotic regions are the most common sites of lung cancer. Adenocarcinoma and squamous cell carcinoma are the most common types in idiopathic pulmonary fibrosis associated lung cancer patients. The treatment strategies including medication and surgery are controversial, complex and thorny. Conclusion: Idiopathic pulmonary fibrosis is associated with an increased lung cancer risk. It is necessary to raise awareness of lung cancer risk in idiopathic pulmonary fibrosis patients. Further research investigating the pathogenesis of idiopathic pulmonary fibrosis associated lung cancer could help develop newer therapeutic targets for treatment of idiopathic pulmonary fibrosis and lung cancer.

Keywords: Idiopathic pulmonary fibrosis, lung cancer, pathogenesis, clinical features, treatment

Introduction

Idiopathic pulmonary fibrosis (IPF) is the most common form of idiopathic interstitial pneumonia with a prevalence of approximately 20/100,000 and the cause is still unknown. The characteristic imaging findings include honeycombing in both lower lobes and under the pleura, while collagen bundles and fibroblast clusters are the main histological features. The disease typically has an insidious yet relentless progression and responds poorly to glucorticoids and other immunosuppressive therapies. The disease is associated with a poor prognosis, and respiratory failure is the most common cause of death in these patients. Therefore, IPF has become a highly lethal disease similar to lung cancer (LC). The role of pulmonary fibrosis in the pathogenesis of LC was first proposed in 1957 [1]. An increasing body of evidence has suggested that IPF patients have an increased risk of lung cancer and that lung cancer worsens the prognosis of patients with IPF. The correlation of IPF with LC has evoked much interest recently [2, 3]. Researches show that there are many similarities in the pathogenesis of the two diseases. In this systemic review, we aim to research the correlation of IPF and LC by searching abundant literatures from major databases such as Pubmed, Web of Science, Embase, Scoups, Cancerlit and so on. The references with regard to the aspects of the pathogenesis of IPF and LC, and the epidemiology, clinical features and treatment strategies of IPF-LC are selected for the review. References eventually cited in the review are mainly from Pubmed and Web of Science from 1957 to 2015. The recognition of common

pathogenic pathways between the two diseases would be attractive to the researchers to explore new clinical trials in terms of drugs and other effective interventions for the IPF and LC. Moreover, their correlation can raise awareness of the risk of lung cancer in IPF patients among doctors and patients.

Epidemiology of IPF-LC

Over the past 50 years, considerable research has been conducted on IPF-LC, however, the morbidity across studies is not comparable. Some scholars in China have reviewed IPF-LC related literature, coming to the conclusion that the morbidity is 4.8%-48% [4], while the studies conducted in other countries have revealed a morbidity rate of 9.8%-38% [5]. Although the data are different, the morbidities are obviously higher than that in the general population (about 2%-6.4%) [6]. It is apparent there is a wide variability in the reported prevalence, maybe a paucity of prospective cohort studies is an important reason for the difficult determination of accurate prevalence of lung cancer in IPF patients [4].

The pathogenesis of IPF-LC

Epithelial to mesenchymal transitions (EMT)

EMT is a complex phenomenon which is characterized by acquisition of markers of fibroblasts and myofibroblasts such as α-smooth muscle actin (α-SMA) and N-cadherin and the loss of epithelial markers including E-cadherin leading to the transformation of the epithelial cell into a motile mesenchymal cell. EMT is known to be an important mechanism of epithelial injury and fibrosis in several tissues [7, 8]. During the EMT process, the cell junctions of epithelial cells are lost and the cytoskeletons are remoulded, transforming the cells into spindles from polygonal shapes and acquiring invasive attributes due to loss of polarity and adhesive property. Besides, many signal molecules in EMT are thought to be related to the genesis of carcinomas. These phenomena indicate EMT process is associated with malignant transformation of epithelial cells and the metastasis of epitheliogenic tumors [9].

EMT can be induced by a variety of growth factors and cytokines including transforming growth factor β (TGF-β), fibroblast growth factor-2 (FGF-2), epidermal growth factor (EGF), insulin-like growth factor-2 (IGF-II), interleukin-1 (IL-1), and Wnt ligands [10]. The multifunctional cytokine TGF-β that is known to regulate cell proliferation, differentiation, apoptosis, survival and the production of matrix, is regarded as the "control switch" for fibrogenesis in several tissues including the lung tissue [11]. In addition, TGF-β-induced EMT can initiate carcinoma cell migration and invasion, and also allows the generation of stromal cells that support and instruct cancer progression [12, 13]. Therefore, we think TGF-β-induced EMT is highly likely an important mechanism for lung cancer in IPF. We will make a more detailed explanation below through the introduction of TGF-β signaling pathway and the associated signaling molecules.

Activated TGF-β combines with the receptors and initiates the downstream signaling pathways by the activation of some enzymes in the extra cellular matrix (ECM) such as matrix metalloproteinase (MMP) (**Figure 1**), including the Smad and non-Smad signaling pathways [14]. Activated Smad2 and Smad3 combines with Smad4 to form the Smad complex in the Smad pathway realizing the expression of mesenchymal markers including α-SMA, N-cadherin and MMP, and inhibiting the expression of epithelial markers known as E-cadherin via transcription factors such as Snail, ZEB and bHLH families [11, 15, 16]. In addition, Smad pathway can also activate protein kinase B(Akt) and glycogen synthase kinase-3β (GSK-3β) via non-genomic signaling molecules such as integrin-linked kinase (ILK), thus downregulate β-catenin expression and initiate EMT [17].

Many studies have suggested that the above molecules strongly relate to the onset, invasion and metastasis of lung cancer. ZEB1, a member of the Zinc finger E-box binding protein (ZEB) family, over expresses in lung cancer tissue, and is induced by the mutation of tumor inhibitor genes such as K-Ras and LKB1 gene. Besides, there is a negative correlation between the level of ZEB1 and LKB1 [18]. Snail, the zinc-finger transcription factor superfamily has a similar structure to ZEB family and can enhance malignant tumor invasion by overexpression [19]. Transcription factor Twist, an important member of the bHLH family, is a key regulator in EMT. It is known to induce malig-

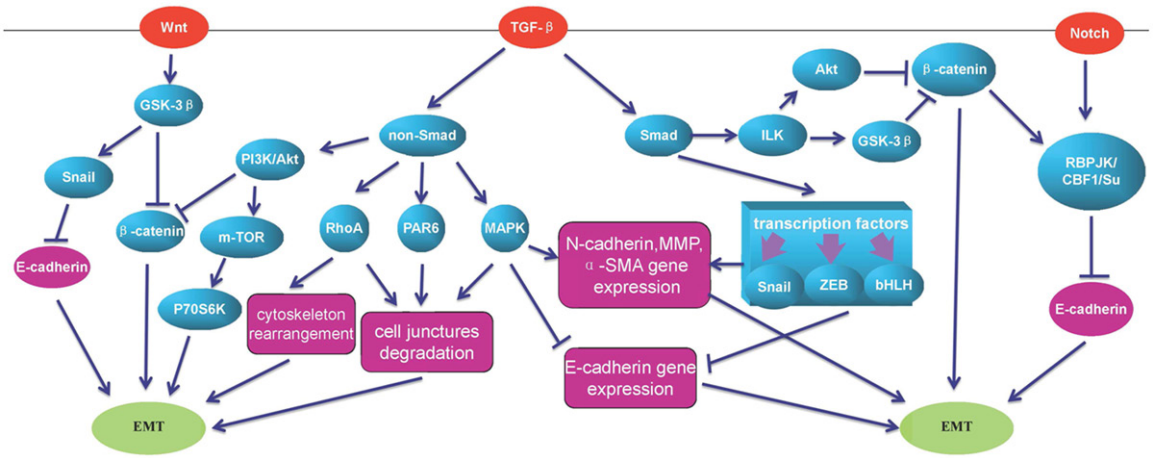

Figure 1. A complex of inducers and effectors involved in epithelial to mesenchymal transition. Activated TGF-β binds to the receptors and initiates the downstream biological effect by activation of Smad and non-Smad signaling pathways. Activated Smad pathway induces the upregulation of α-SMA, N-cadherin and MMP and downregulation of E-cadherin via transcription factors Snail, ZEB and bHLH families, which results in the EMT eventually. In addition, Smad pathway can also activate Akt and GSK-3β via ILK, thus induces the downregulation of β-catenin expression and EMT subsequently. PI3K/Akt, RhoA, PAR6 and MAPK involved in the non-Smad signaling pathway can downregulate β-catenin and prompt rearrangement of cytoskeletons and cell junction's degradation. Activated Wnt signaling pathway induces the downregulation of E-cadherin and β-catenin expression via GSK-3β, besides, activated Notch signaling pathways can also downregulate E-cadherin expression via transcription factors RBPJK/CBS1/Su. The above mentioned alteration of cytoskeleton rearrangement, cell junction's degradation, the increased expression of N-cadherin, MMP etc. and the decreased expression of E-cadherin will eventually lead to EMT.

nant transformation of alveolar epithelium into bronchial epithelium, and mediate angiogenesis via the vascular endothelial growth factor (VEGF) receptor. Therefore, the molecule appears to be instrumental in conferring invasive and metastatic properties to NSCLC [20]. ILK is a kind of Ser/Thr protein kinase and has the peculiarity of proto-oncogenes. It inhibits cell apoptosis and promotes tumor angiogenesis by the activation of PI3K/Akt and GSK-3β [21]. The activation of PI3K/Akt and GSK-3β has been shown to downregulate the expression of β-catenin on the surface of cells, and influence the function of the complex of β-catenin and E-cadherin via inducing cytoplasmic aggregation/nuclear translocation. The decrease of β-catenin weakens the adhesive ability of cells, and makes the lung cancer cells more invasive and with a greater predilection for metastasis [21-23].

The Smad signaling pathway is the main mechanism of EMT induced by TGF-β. However, in certain conditions, many non-Smad signaling pathways, including PI3K/Akt, RhoA (Ras homologue A), PAR6 (partitioning defective 6) and MAPK are also known to facilitate EMT [10]. PI3K/Akt can inhibit apoptosis and induce cell proliferation and angiogenesis by activating the downstream substrate m-TOR, and facilitate the genesis of lung cancer [24]. The Rho subfamily, a member of the Ras superfamily, is known to regulate the cytoskeletal structure and rearrange adherens junctions. RhoA is over-expressed in carcinomatous lung tissue according to the research made by Bhowmick et al. [25]. In addition, Ozdamar [26] found that phosphorylated PAR6 can induce RhoA ubiquitination and degradation, thereby prompting the rearrangement of cytoskeletons likewise. Since the rearrangement of cytoskeletons and the loss of cell polarity are indicative of EMT malignant transformation, RhoA and PAR6 are believed to be closely linked to the genesis and progression of lung cancer.

Activated Wnt signaling pathway (**Figure 1**) induces the downregulation of E-cadherin and β-catenin expression via GSK-3β, besides, activated Notch signaling pathways (**Figure 1**) can also downregulate E-cadherin expression via transcription factors RBPJK/CBS1/Su. The abnormal activated pathways are also known to lead to EMT and induce the onset, invasion and metastasis of lung cancer [27, 28].

In conclusion, EMT is not only an important intermediate mechanism for pulmonary fibrosis, but also appears to be a driver of the genesis and progression of lung cancer via the abnormally activated signaling pathways mentioned above and the cellular morphological changes.

Fibroblast growth factor (FGF) signaling pathway

The name FGF comes from its function of stimulating fibroblast reproduction. It serves to exacerbate cell proliferation, differentiation and angiogenesis. A total of 22 FGFs had been documented in mammals, most of which are secretory glycoproteins and play a role via autocrine or paracrine signaling. FGFR is a member of the immunoprotein family which has four isoforms FGFR1-FGFR4. Each FGFR monomer consists of an extracellular domain, an acidic box, a transmembrane domain and a split tyrosine kinase domain. The extracellular domain includes a ligand binding site which is consisted of two or three Ig loops that arise by alternative splicing. Alternative splicing of the third Ig loop will generate the IIIb or IIIc isoform of the receptor. IIIc isoform is usually found to be expressed in the mesenchyme, while IIIb is mostly expressed in epithelial cells [29].

FGF1, also referred to as the heparin binding growth factor, is expressed in both epithelial and mesenchymal cells, and is known to interact with different isoforms of FGFRs, activate downstream signals, and play a role in restoration after lung damage [30]. Mackenzie et al. [5] reported an increased expression of FGF1, mesenchyme originating FGFR2c, FGFR3c, and a decrease in the levels of FGFR-1b and FGFR-2b in IPF patients. Further, findings reported by Ju [31] and Becerril [32] also indicate that up-regulation of FGFR-2b and the down-regulation of FGFR-2c accelerates the development of pulmonary fibrosis. The precise mechanism by which the FGFR signaling pathway affects IPF is still unclear. Abnormal activity of FGF/FGFR has been shown to induce MAPK, p-ERK, PI3K/Akt, polyomavirus enhancer activator (PEA3) and other downstream moieties, and subsequently facilitates EMT and the development of invasive properties and transfer of lung cancer [5, 33-35].

The expression of platelet-derived factor receptor a (PDGFRa) and vascular endothelial growth receptor 1 (VEGFR1) besides FGFR expression also appears to increase in IPF patients besides FGFR [36, 37]. Nintedanib is an orally administered tyrosine kinase inhibitor which inhibits the development of pulmonary fibrosis by the suppression of MMP-induced increase in the tissue inhibitor of metalloproteinase, followed by a reduction in matrix deposition. Moreover, the drug also exerts an antitumor action over FGFR, PDGFR, VEGF and downstream MAPK, ERK and other molecular pathways to inhibit the generation of tumor vasculature [38]. In Oct. 2014, the FDA authorized the use of nintedanib in patients with IPF. The EMA also admitted its function in IPF and recommends the combination therapy of nintedanib and docetaxel as a secondary option in cases of NSCLC metastasis and relapse [39]. Overall FGFR, FDGFR and VEGFR have been shown to be relevant to the link between IPF and lung cancer in a therapeutic context.

Epigenetic changes

Epigenetics is the study of changes in organisms caused by modification of gene expression rather than alteration of the genetic code itself, including DNA methylation, histone modifications (such as methylation and acetylation, etc.) and the expression of microRNA [40].

Thy-1 (CD90) is one member of the family of minimum cell surface immunoglobulins, which can regulate the reaction between cells and intercellular matrix expressed in normal fibroblasts. In a rat model of pulmonary fibrosis, methylation of gene promoter leads to down-regulation of Thy-1 expression. With the aggravation of fibrosis, the expression of Thy-1 is progressively decreased [41-43]. The down-regulated expression of Thy-1 has also been linked to the invasiveness of lung cancer [44]. P14ARF gene has been shown to prevent carcinogenesis by inhibiting the cell cycle and inducing apoptosis, thereby, acting as a tumor-suppressor gene. After its promoter 5'CpG island is abnormally methylated, the gene is in an inactive state and plays an important role in the development of lung cancer because cell proliferation is out of control [45]. Similarly, the silence of P14ARF gene mediated by hypermethylation has been proven to be an important mechanism of lung fibroblast apoptosis resistance, which leads to the occurrence and development of IPF [46].

MicroRNA (miRNA) is a noncoding single-stranded RNA molecule containing about 22 nucleotides, which participates in the transcriptional regulation of gene expression, both in flora and fauna. Abnormal regulation of miRNAs is known to induce abnormal expression of genes, and increases susceptibility to disease. The involvement of miRNAs in the pathogenesis of various lung diseases such as cystic fibrosis, asthma, lung cancer, COPD (chronic obstructive pulmonary disease) and IPF is well-documented [47]. The role of miRNA in the pathogenesis of IPF is of considerable interest. Approximately, 10% of miRNAs including miR-21, miR-29, miR-155, miR-26 a, miR-17~92, miR-96, miR-326 etc. have been implicated in the occurrence of IPF [48-53]. Upregulation of miRNA-21 expression has been shown to induce activation of TGF-β signaling pathway, which, in turn, is known to facilitate the occurrence and progression of pulmonary fibrosis [54]. A high level of miRNA-21 was also shown to promote proliferation, survival, invasion and metastasis in squamous cell lung carcinoma [55]. FOXO3A is an important member of the FOXO (forkhead box protein) family, which is involved in cell transformation, angiogenesis and tumor occurrence. The function of FOXO3A has been shown to be inhibited by upregulation of miRNA-96 expression causing IPF progression [50]. Further miRNA-96 has also been shown to promote apoptosis and inhibit progression of non-small cell lung cancer in the event of its downregulation [56]. Similarly, many other miRNAs have been implicated to be related to non-small cell lung cancer, approximately 50% of which are located in the cancer-associated genomic regions. The best-known is the let-7 family, which itself has an anticancer effect and is also known to inhibit Ras, HMGA2 protocarcinogenic gene expression [57]. Let-7 family also appears to play a role in the pathogenesis of pulmonary fibrosis. Ebrahimi et al. [47] have found that the let-7 located in the alveolar epithelial cells was downreguated in the EMT pathway induced by TGF-β, increasing α-SMA and N-cadherin expression, and causing alveolar interval thickening and collagen synthesis and deposition.

Genetic changes

Considering that patients with congenital dyskeratosis are often affected by pulmonary fibrosis, researchers set about studying the mutations of age related genes and pulmonary fibrosis from this perspective. In a study, mutations of telomerase genes (TERT and TERC) were found to be most common in patients with sporadic as well as familial IPF, especially in the distal alveolar epithelial cells [58]. The mutations in telomerases result in unsuccessful repeated additions of telomeres, and the gradual shortening of telomeres leads to dysfunction of tissue stem cells or initial cells and then restricts the engineering of tissues. On testing the domain of the TERT gene in the chromosome, R865H missense mutation and V747 frameshift mutation were found in 15% familial IPF patients, and likewise, similar mutations were also detected in a few patients with sporadic IPF [59, 60]. The above findings appear to implicate mutations of age-related genes TERT and TERC in the pathogenesis of IPF. However, in approximately 25% of IPF patients, shortened telomeres are detected in peripheral blood leukocytes without TERT and TERC mutations. Therefore, the involvement of other gene mutations inducing IPF appears likely [61]. The TERT gene which is instrumental in determining the telomerase activity is normally in a state of suppression. However, its over-expression can be induced by the mutation of this gene in the carcinomatous tissue (including lung cancer) [62]. The rs2736100 mutation from T to C in TERT gene is related to its over-expression in lung adenocarcinoma. Furthermore, suppression of TERT expression is shown to induce apoptosis of cancer cells and loss of carcinogenicity due to the shortening of telomeres [63]. The mechanism underlying telomere shortening, in the absence of mutations in TERT or TERC in known cases of IPF is unknown, as is the mechanism by which the TERT and TERC mutations or telomere shortening induces IPF. Nonetheless, the mutations of telomerases are likely to be the common pathway in the pathogenesis of IPF and lung cancer pathogenesis according to current studies.

The repeated cycles of epithelial insult and repair in IPF lung tissues was shown to induce P53 gene mutation. Kawasaki et al. [64] detected a P53 gene mutation and P53 protein change in 23% and 54% of patients with squamous metaplasia respectively; 40% and 60% of cases of squamous metaplasia with atypia; 57% and 62% of cases with squamous cell car-

cinoma; and 0% and 4% of other hyperplastic lesions. These findings suggest that P53 mutation is common in squamous metaplasia, and invariably occurs around the fibrotic tissues. These findings are particularly relevant and offer new leads for investigating the etiology of IPF complicating lung cancer. In addition to the mutations of tumor suppressor genes, the activation of proto-oncogenes is also detrimental to the genesis and development of lung cancer. The 12th codon point mutation of proto-oncogene K-Ras (GGT→GTT) in IPF has been shown to correlate with overexpression of Ras protein in type II alveolar epithelial cells and appears to induce development of lung cancer in IPF [65].

BRCA1 (Breast Cancer 1) has been used to define the susceptibility linked to breast and ovarian cancers. However, in recent years, this gene has been implicated in tumorigenesis and angiogenesis in several tumors besides being of prognostic relevance in NSCLC [66]. BARD1 (BRCA1 related loop domain 1) can combine with and stabilize P53 gene, and thereby controls cell proliferation, promotes cell apoptosis, and inhibits tumorigenesis. Therefore, BRCA1 appears to have the characteristics of tumor suppressor genes [67]. BARD1β is one of BARD1 alternative splicing isoforms, and loses the ability to suppress tumors owing to the lack of the N-terminal loop domain linking to BRCA1. On the contrary, it is considered to be a driving factor of malignant tumors, and the level of its expression has been shown to correlate with the progression of malignant tumors. Overexpression of BARD1β has been shown to promote the genesis and invasion of lung cancer besides being of prognostic relevance [68, 69]. Further, a lack of BARD1β expression in normal individuals, its overexpression in IPF patients, as well as its role in fibroblast proliferation in EMT induced by TGF-β have been documented [70].

In conclusion, mutations of the P53 and K-Ras genes and the over expression of BARD1β appear to induce lung cancer in IPF patients. Furthermore, the risk for lung cancer is remarkably higher in IPF patients as compared to those without IPF.

Oxidative stress

The role of oxidative stress in inducing mitochondrial DNA (mtDNA) damage and mutations and causing alveolar epithelial cell apoptosis, interstitial lung fibrosis and other pulmonary diseases, such as lung cancer and COPD, has been well-documented [71, 72]. The underlying mechanism by which oxidative stress-induced mt-DNA damage causes lung fibrosis is not known. Catalase has been shown to attenuate IPF fibroblast activity [73] and reduce GSH in IPF alveolar epithelial cell surface liquid; NAC may blunt the degree of lung fibrosis in a mouse model of bleomycin-induced lung fibrosis [74]. These findings indicate that oxidative stress accelerates lung fibrosis. Compared to nuclear DNA (nDNA), mtDNA is more sensitive to oxidative damage and may sustain 10-fold higher mutation rate as compared to that of nDNA. Owing to the respiratory chain, mitochondria tend to acquire an affinity for reactive oxygen species (ROS), which appears to be the main reason for this phenomenon, given that mt-DNA lacks the protection of histone [72]. Mitochondrial insult or mutation leads to respiratory chain dysfunction, abnormal cell metabolism, the acceleration of aerobic glycolysis and malignant transformation, which all reflect the observations made by Warburg [75]. Wang et al. [76] reported the existence of mt-DNA mutation in more than 40% of NSCLC patients. Therefore, blocking the oxidative stress and protecting the integrity of mt-DNA appears to be a potential strategy for treatment of IPF-LC.

In summary, the above factors of epithelial mesenchymal transitions, gene mutations, epigenetic changes, oxidative stress and FGFR signaling pathways, are all increasing the risk of carcinogenesis in IPF patients. However, the reasons for the different endings, IPF or LC, by the common mechanisms are unknown. Therefore, further research with regards to the different endings underlying more detailed mechanisms is required in order to help develop targeted preventive interventions.

Clinical features and treatment

IPF usually occurs in people older than 50 years, with the main clinical symptoms being irritant cough and dyspnea. 25%~63% of the IPF patients have clubbed fingers. Besides the features above, IPF-LC is common in elderly males with a history of heavy cigarette smoking, and hemoptysis and clubbing are more common [77]. Therefore, in an IPF patient having an exacerbation of cough, sputum produc-

tion and dyspnea, and who presents with hemoptysis and chest pain, should alert the treating physician to the possibility of lung cancer. The common location and pathological types in patients with IPF-LC are not insistent, however, most studies suggest that the peripheral, lower, and highly fibrotic regions tend to be more affected [6, 77, 78]. Nevertheless, there are studies that suggest a low propensity for cancer developed in the fibrosed areas, and have reported carcinoma as being more common in the upper lobes [79]. According to Oh et al. [80] when IPF patients are diagnosed with lung cancer, more patients tend to be in the early stages, manifest circular or oval-shaped nodules on chest radiograph, with an average diameter of 17 mm. Further, the first average tumor doubling time is 77 days and the second is about 53 days. Studies conducted by Lee et al. [78] in 2000 and 2005 also reported that adenocarcinoma was observed to be the most common type of lung cancer. However, others have reported squamous cell carcinoma as the most common pathological type [77, 81]. Turner and Mizushima et al. [82, 83] found squamous cell carcinoma to be the most common type in male patients with IPF-LC, and adenocarcinoma as the most common type in their female counterparts. We have some speculations about theses contradictory results found in the literature above. It is known that squamous cell carcinoma has a higher correlation with smoking than adenocarcinoma, and smoking is much more common in male than female. Therefore, it may be the reason why some researchers claimed squamous cell carcinoma is the most common type of lung cancers in IPF patients. There is literature claiming adenocarcinoma is the most type of lung cancers in female IPF patients. In consideration of researches showing estrogen receptor is relevant to the genesis of the pulmonary adenocarcinoma, therefore we think estrogen receptors also participate in the genesis of lung cancer in IPF patients. In addition, the different size and composition of samples may be one of the important reasons why contradictory results are found in the literature, therefore it is very necessary to expand the sample size and research further.

Owing to the compromised cardiopulmonary reserve, treatments of lung cancer in IPF-LC patients require several considerations. Although more IPF patients are diagnosed with lung cancer in the early stage than the late stage, it is prudent to carefully assess the indication for surgery. Pneumonia, ARDS and AEIPF are the common post-operative complications that may lead to respiratory failure which is associated with a high mortality rate [79, 84]. Lee et al. [79] found no correlation in basal lung function, sex, smoking, surgical factors and pathological type between IPF-LC patients who died of post-operative respiratory failure and the survivors, suggesting that IPF may be an independent predictor for survival in these patients. However, the reported survival rates have widely varied in different studies. Watanabe et al. [85] pointed out that IPF should not be considered as a contraindication for surgery in patients with stage I lung cancer, and cited a five-year survival rate of 61.6% in patients with IPF-LC as against 83% in patients without IPF. Lee et al. [78], however, reported a post-operative five-year survival rate of 37.5% in IPF-LC patients as against 72.5% in patients without IPF. Owing to the contradictory findings, the question about the five-year survival rate after surgery requires further examination. In addition, several studies have indicated that the application of radiotherapy and targeted drugs (e.g., gefitinib and Icotinib) often aggravates pulmonary fibrosis and exacerbate respiratory failure. The restricted therapeutic option is the key contributor to the poor prognosis in IPF-LC patients.

Drugs for treatment of IPF are rather limited. The appearance of nintedanib should prompt further research into the common mechanisms in IPF and lung cancer, which could help unravel novel therapeutic targets and help prevent IPF-LC and improve its prognosis.

Conclusion

The prevalence of lung cancer in IPF patients is much higher than that in general people, which prompts an obvious correlation between the two diseases. Recognition of the correlation can raise awareness of the risk of lung cancer in IPF patients among doctors and patients. Our study find epithelial to mesenchymal transition, FGFR signaling pathway, gene mutations, epigenetic changes and oxidative stress are the common pathogenesis of IPF and lung cancer. However, the reasons for the different end-

ings, IPF or LC, by the common pathogenesis are unknown. Therefore, further studies in terms of the more detailed mechanisms are required. Although there are no acknowledged and enough effective treatments aiming at IPF associated lung cancer at present, the recognition of the correlation between the two diseases will be attractive to the researchers with regards to the new clinical trials for drugs and other effective interventions.

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Disclosure of conflict of interest

None.

Abbreviations

IPF, idiopathic pulmonary fibrosis; LC, lung cancer; IPF-LC, idiopathic pulmonary fibrosis complicating lung cancer; EMT, epithelial to mesenchymal transition; α-SMA, α-smooth muscle actin; TGF-β, transforming growth factor β; FGF-2, fibroblast growth factor-2; EGF, epidermal growth factor; IGF-II, insulin-like growth factor-2; MMP, matrix metalloproteinase; Akt, protein kinase B; GSK-3β, glycogen synthase kinase-3β; ILK, integrin-linked kinase; ZEB, Zinc finger E-box binding protein; VEGF, vascular endothelial growth factor; NSCLC, non small cell lung cancer; RhoA, Ras homologue A; PAR6, partitioning defective 6; FGF, Fibroblast growth factor; PEA3, polyomavirus enhancer activator; PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor 1; COPD, chronic obstructive pulmonary disease; FOXO, forkhead box protein; BRCA1, breast cancer 1; BARD1, BRCA1 related loop domain 1; mtDNA, mitochondrial DNA; n DNA, nuclear DNA.

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