Pulmonary fibrosis and lung cancer: not the same disease, but not so different

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Summary

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrosing interstitial pneumonia characterized by a poor survival, even worse than many cancers. Recent studies have demonstrated that IPF and cancer share several cellular and molecular alterations related to epigenetic and genetic changes, altered regulation of apoptosis, abnormal response to regulatory signals, abnormal expression of microRNAs (miRNAs), reduced cell-to-cell communication and activation of specific signaling pathways. This leads to the hypothesis that IPF can be considered, in some respects, a cancer-like disease. This correlation may help in understanding the pathogenesis of IPF by exploiting the great knowledge of the biological mechanisms studied in cancer but it may also help in increasing the awareness of this disease at public, political and even at healthcare level. In addition, the identification of common pathogenic pathways between the two diseases may stimulate new clinical trials with cancer drugs, as in the case of nintedanib, and drugs combinations or different lines of drugs as largely experimented in cancer.

KEY WORDS: interstitial lung diseases, idiopathic pulmonary fibrosis, cancer, epigenetic alterations, cell to cell communications, signal transduction pathways, myofibroblasts, TGF-β, tyrosine kinases.

Introduction

Idiopathic pulmonary fibrosis (IPF) is defined as a “specific form of chronic, progressive, fibrosing interstitial pneumonia of unknown cause, occurring in adults, limited to the lungs and associated with the histopathological and/or radiological pattern of usual interstitial pneumonia” (1). Incidence and prevalence have not been easy to estimate because previous studies have only recently had a uniform definition of IPF. The annual incidence of IPF in the USA is estimated at 6.8 to 16.3 per 100,000 (2), while in Europe there is not a single global value but only data from individual countries (3).

For a long time, IPF was considered the result of a chronic inflammatory process of the lung caused by an unknown agent. However, this hypothesis has been discarded because IPF is characterized from early phase by the presence of variable degree of fibrosis with mild or no inflammation at histology (4). This supports the idea that there are two pathways that lead to fibrosis: the “inflammatory route” and the “epithelial-fibroblastic route” (5). The first one, common to non-IPF interstitial lung diseases (ILDs), is characterized by an early phase of alveolitis accompanied by the recruitment and activation of inflammatory cells which in turn may activate lung fibroblasts, ultimately causing fibrosis. The second route is typical of IPF. Here, damaged alveolar epithelial cells without the participation of inflammatory cells, are able to stimulate the migration and activation of mesenchymal cells via the production of a number of growth factors and chemokines, leading to the formation of aggregates of fibroblasts and abnormal deposition of collagen and extracellular matrix components. This abnormal repairing process is driven by a series of pathogenic events that are described in other chronic degenerative diseases and interestingly also in cancer.

Some authors have in effect defined cancer as a wound that does not heal with a series of other analogies with IPF including the etiology, which is often unknown, similar risk factors such as smoking and/or environmental or professional exposure, and the presence of a specific genetic background considered im-
imported for the occurrence of the disease. Interestingly, IPF and cancer have in common a series of cellular and molecular alterations related to epigenetic and genetic changes, altered regulation of apoptosis, abnormal response to regulatory signals, abnormal expression of microRNAs (miRNAs), reduced cell-to-cell communication and activation of specific signaling pathways. Based on this evidence we have hypothesized that IPF may be considered in some respects a cancer-like disorder of the lung. The purpose of this short review is to analyse the main reasons supporting the concept of IPF as a cancer-like disease (6, 7).

Epigenetic and genetic alterations

Epigenetic disorders are alterations by which the environment alters the degree of activity of genes without changing the DNA sequences and the information contained therein. Therefore, epigenetic alterations are related to aging, cigarette smoke, nutritional, chemical and physical factors. It has been recently shown that such alterations are involved not only in the initiation and progression of cancer but also in the pathogenesis of IPF (8, 9). In cancer, the most frequent epigenetic disorders are represented by methylation of suppressor genes and hypomethylation of oncogenes. According to Rabonwich, similar alterations may be present in IPF. Thy-1 is a glycoprotein expressed by normal fibroblasts, where the hypermethylation of its promoter region causes the reduction of the expression of the related Thy-1 glycoprotein (10). The loss of expression of this glycoprotein facilitate the differentiation of fibroblasts into myofibroblasts (11, 12). Similarly, in cancer, the same alteration is associated with a more invasive behavior of the neoplasia. In addition to epigenetic alterations, several genetic alterations have been identified in IPF affecting specific cellular mechanisms, such as cell cycle, differentiation, and apoptosis.

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Altered cell to cell communications

Cells continuously interact through junctional communication to coordinate normal tissue functions, to maintain homeostasis and to obtain a synchronized tissue behavior. Gap junctions are specialized intercellular connections formed by connexon proteins, hexameric oligomers of transmembrane proteins called connexins. Gap junctions have a critical role in the lungs. They regulate secretion of pulmonary surfactant mediated by alveolar cell and prevent lung injury by improving barrier function. Some studies have shown that inhibition of gap junctions cause a barrier function reduction in mouse models developing...
Symptoms similar to pulmonary fibrosis (25, 26). Cancer is characterized by a loss of cell to cell communication mediated by gap junctions and by a reduction in connexin expression suggesting that in order to progress, tumor cells need to isolate themselves from the influence of surrounding normal cells. Lower levels of Cx43 have been identified for example in lung cancer and in gastric cancer cells (27). Cx43 is also involved in the wound-healing of the skin. In this process cell to cell communication and gap junctions have an important role in modulating inflammation and tissue repair. It has been demonstrated that the down regulation of Cx43 protein foster the proliferation and migration of keratinocytes and fibroblasts (28). We have hypothesized that the loss of proliferative control in IPF cells could be caused by an altered fibroblast to fibroblast communication mediated by a reduced expression of connexin 43, very similar to what happens in cancer. Effectively, we have demonstrated that IPF fibroblasts, as observed in cancer cells, have a reduced ability to express connexin 43 (29).

Uncontrolled proliferation: the role of myofibroblasts

One of the distinctive characteristics of IPF is the presence in lung biopsy of fibroblastic foci, formed by myofibroblasts whose origin is still unclear. Three different theories have been proposed to explain their origin. According to the first, myofibroblasts arise from resident fibroblasts and organize themselves into fibroblastic foci, producing excessive amounts of extracellular matrix (ECM) proteins. It has been supposed that injured alveolar cells produce mediators responsible for migration of local fibroblasts to the injured site and for their differentiation in myofibroblasts (30). The second hypothesis describes myofibroblasts as derived from resident epithelial cells through a process of migration and cellular differentiation called epithelial mesenchymal transition (EMT). Epithelial cells lose cell to cell attachment and adhesion molecules like E-caderin, reorganize cytoskeleton and assume mesenchymal markers like fibronectin and alpha-smooth-muscle actin. This transition is a form of metaplasia and is very similar to what happens in cancer (31). It has been hypothesized that EMT also contribute to cancer progression and metastasis. This process is supported by extracellular factors like TGF-β, growth factors and metalloproteinases that promote cancer progression. TGF-β is also produced by cancer cells and stimulates fibroblasts differentiation and migration to the cancer site.

According to the third hypothesis, myofibroblasts derive from circulating fibrocytes originated from bone marrow and express typical markers of mesenchymal cells such as fibronectin (32). It has been shown that some of the myofibroblasts in the tumor stroma originate from circulating fibrocytes. Consequently, they have an important function in cancer development. Cancer associated fibroblasts produce different mediators, such as metalloproteinases and growth factors to support their own growth. Metalloproteinases are a group of zinc-dependent endopeptidases, which act by destroying extracellular matrix and remodeling tissues. In cancer their role is to break down connective tissue barriers permitting cancer cells to infiltrate the surrounding tissues (33). This is very similar to what happens in IPF: myofibroblasts sustain their own growth producing cytokines like TGF-β, which stimulates fibroblasts proliferation and collagen production. Cancer progression is also facilitated by the expression of some molecules, such as laminin, heat shock proteins and fascin. Laminin is an extracellular matrix protein (expressed on the basement membrane) and it is overexpressed at the invasive front of different cancers (34). Laminin stimulates cancer progression and many studies have shown that laminin high expression is linked to a more invasive behaviour of cancer. Heat shock protein (HSP) are a family of proteins whose overexpression is linked to cancer capacity of metastasize. HPS are involved in many cellular processes such as protein folding and are a powerful regulator of cell apoptosis, that interacts with specific signaling pathways. In particular, HP 27 expressed in cancer cells is associated with a poor prognosis and high capacity to metastasize. Fascin is usually not expressed in normal epithelial cells but it is present in human carcinoma. Many studies have indicated fascin as a candidate biomarker for aggressive carcinomas (35). In IPF, epithelial cells surrounding fibroblasts foci also express fascin, HSP 27 and laminin suggesting, once again, an important similarity between IPF cells and cancer cells (36).

Activation of signal transduction pathways

A large variety of signal transduction pathways are activated both in cancer and in IPF and many studies have also demonstrated their involvement in the pathogenesis of these two diseases. The Wnt signaling pathways are a group of signal transduction pathways made up of proteins that pass signals from the outside of a cell, through cell surface receptors, to the inside of the cell. It has been demonstrated that the alterations of this pathway may have clinical relevance in a variety of diseases, including lung cancer, mesothelioma and...
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hibition of p110 isoforms on IPF fibroblast proliferation in vitro lipid substrate specificity. Recently, we as-

ally is divided into three different classes: Class I, Class II, and Class III based on primary structure, regulation and in vitro lipid substrate specificity. Recently, we as-

cessed the expression of class I PI3K p110 isoforms in IPF lung tissue as well as in tissue-derived fibrobl-

ast cell lines evaluating the effect of the selective inhi-

bition of p110 isoforms on IPF fibroblast proliferation and fibrogenic activity. The expression of PI3K p110α, β and γ isoforms does not differ between normal and IPF tissue/tissue-derived fibroblasts whereas p110γ was more expressed in both IPF lung homogenates and ex vivo fibroblast cell lines with a strong im-

munoreactivity for p110γ. Furthermore, both p110γ pharmacological inhibition and gene silencing were able to significantly inhibit proliferation rate as well as a-SMA expression in IPF fibroblasts. This suggests that PI3K p110γ isoform may have an important role in the pathogenesis of IPF and can be a specific pharmacological target (41). In this regard, a recent study has demonstrated that oral administration of p110γ inhibitor prevents bleomycin-induced pulmonary fibrosis in rats (42). More recently researchers have focused on another signal transduction pathway in IPF: the JAK-STAT signaling pathway. This system is a major signaling alternative to the second messenger system such as Cyclic AMP, Cyclic GMP, Inositol Triphos-

ate, Diaacglycerol and Calcium. It transmits informa-

tion from chemical signals outside the cell, through the cell membrane, and into gene promoters on the DNA in the cell nucleus, which causes DNA transcription and activity in the cell. JAK-STAT signaling path-

way is frequently altered in many cancers. One of the regulatory mechanisms of JAK-STAT signaling pathway is represented by the SOCS family (suppressor of cyto-

tokine signaling proteins). The role of SOCS1 in IPF pathogenesis has been recently studied by Bao et al. According to this author, a lower expression of SOCS1 was identified in IPF patients and this finding has been related to severe manifestations of disease and to a worse prognosis (43).

Another key signaling pathway strongly activated in many cancers but also in IPF is represented by tyro-

sine kinases pathway. Tyrosine kinases catalyze the phosphorylation of tyrosine residues in some proteins. They are involved in cell growth, differentiation, adhe-

sion, motility and regulation of cell death. Mutations can make tyrosine kinases a nonstop functional state. This may lead to initiation or progression of cancer. An important activity of this pathway has been also studied in wound healing and fibrogenesis (44, 45). Platelet-derived growth factor (PDGF), a ligand of tyro-

sine kinase receptor, is a potent growth factor for fi-

broblasts in vitro and some fibrogenic mediators like TGF-β and basic fibroblast growth factor (FGF) have PDGF-dependent profibrotic activities. There is evidence that PDGF protein and mRNA are increased in IPF. In particular high levels of PDGF (A-D) isoforms have been shown in irradiated mice and the use of a PDGF receptor inhibitor has attenuated the development of pulmonary fibrosis in animal models induced by radiation (46, 47). As well as PDGF, fibroblast growth factor (FGF) is largely involved not only in carcinogenesis but also in fibrogenesis. FGF receptors are present on epithelial cell and fibroblasts and medi-

ate EMT and fibroblast transition into myofibroblasts (48). The use of tyrosine kinase receptors inhibitors have been widely used in non small cell lung carcino-

ma and other cancers. These growth factors have poten-
tent mitogenic effects, so their inhibition is expected to reduce fibrosis in IPF, as already happens in cancer therapy where they are widely used. Imatinib-mesy-
late, a specific PDGFr inhibitor, was evaluated for its potential antifibrotic effects in preclinical and clinical studies. It was able to inhibit fibroblast proliferation and collagen deposition in vitro and in vivo but when it was evaluated in a clinical trial, no benefits in slowing progression were found (49, 50). Triple inhibition seems to be associated to a more potent antifibrotic effect. On this basis, BIBF 1000, an inhibitor of PDGFr, VEGFr and FGFr, was evaluated in a mice model of bleomycin-induced pulmonary fibrosis and in an ex vivo fibroblast differentiation assay. It was found to attenuate fibrogenesis by reducing the expression of pro fibrogenetic factors and by decreasing collagen deposition (51). On the same line, BIBF 1120 (nintedanib), a triple kinase inhibitor with potent suppressing effects on VEGFr, PDGFr and FGFr, was also evaluated. More recently, nintedanib was studied in few clinical trials as a potential antifibrotic therapy in IPF demonstrating that treatment with this drug may reduce of about 50% the decline in lung function of IPF patients. Based on these results, nintedanib has been approved as a new and additional therapeutic
ability together with pirfenidone in patients with IPF (52-54).

Conclusions

In spite of the great progress observed in diagnosing, managing and treating IPF during the past few years, the disease is still marked by a disappointing survival and the diagnosis is too often made late when the disease is already in advanced stages. Worsening the situation is the lack of valid diagnostic and/or prognostic biomarkers and above all the poor awareness of this disease at public, political and even at the healthcare levels. The awareness of cancer as a potentially fatal disease is instead well understood and the need for supporting cancer research well established at any level of the public opinion. In virtue of this, during the last few years we have witnessed to progressive improvement in the diagnostic and therapeutic strategies against cancer. The idea of IPF as a cancer-like disease burdened by a survival even worse than many cancers may help in increasing the awareness of this disease. In addition the identification of common pathogenic pathways between the two diseases may stimulate new clinical trials with cancer drugs, as in the case of nintedanib, and hopefully with combinations or different lines of drugs as largely experimented in cancer.

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