Idiopathic pulmonary fibrosis is a devastating, age-related lung disease of unknown cause that has few treatment options. This disease was once thought to be a chronic inflammatory process, but current evidence indicates that the fibrotic response is driven by abnormally activated alveolar epithelial cells (AECs). These cells produce mediators that induce the formation of fibroblast and myofibroblast foci through the proliferation of resident mesenchymal cells, attraction of circulating fibrocytes, and stimulation of the epithelial to mesenchymal transition. The fibroblast and myofibroblast foci secrete excessive amounts of extracellular matrix, mainly collagens, resulting in scarring and destruction of the lung architecture. The mechanisms that link idiopathic pulmonary fibrosis with ageing and aberrant epithelial activation are unknown; evidence suggests that the abnormal recapitulation of developmental pathways and epigenetic changes have a role. In this Seminar, we review recent data on the clinical course, therapeutic options, and underlying mechanisms thought to be involved in the pathogenesis of idiopathic pulmonary fibrosis.

Introduction
Idiopathic pulmonary fibrosis (IPF), the most common form of the idiopathic interstitial pneumonias, is a chronic, progressive, irreversible, and usually lethal lung disease of unknown cause. IPF occurs in middle-aged and elderly adults (median age at diagnosis 66 years, range 55–75 years), is limited to the lungs, and is a disease of unknown cause. IPF occurs in middle-aged and elderly adults (median age at diagnosis 66 years, range 55–75 years), is limited to the lungs, and is a disease of unknown cause. IPF is autoimmune in nature and has a single and monogenetic vertical transmission. The annual incidence of IPF is rising and is estimated to be between 4·6 and 16·3 per 100 000 people and the prevalence is 13 to 20 cases per 100 000. There is a higher predominance of the disease in men (1·5 to 1·7:1) than in women and the frequency increases with age. The most important environmental risk factors are cigarette smoking and exposure to metal and wood dust. Genetic transmission occurs in about 0·5–3·7% of patients with IPF, although this frequency might be higher. Most affected families have an autosomal dominant vertical transmission pattern of inheritance with reduced penetrance. Familial cases of lung fibrosis are often missed. The effect of several comorbid conditions—obesity, diabetes mellitus, gastroesophageal reflux, pulmonary hypertension, obstructive sleep apnoea, coronary artery disease, and emphysema—on the clinical course of IPF remains to be fully defined.

Epidemiology and risk factors
The annual incidence of IPF is rising and is estimated to be between 4·6 and 16·3 per 100 000 people and the prevalence is 13 to 20 cases per 100 000. There is a higher predominance of the disease in men (1·5 to 1·7:1) than in women and the frequency increases with age. The most important environmental risk factors are cigarette smoking and exposure to metal and wood dust. Genetic transmission occurs in about 0·5–3·7% of patients with IPF, although this frequency might be higher. Most affected families have an autosomal dominant vertical transmission pattern of inheritance with reduced penetrance. Familial cases of lung fibrosis are often missed. The effect of several comorbid conditions—obesity, diabetes mellitus, gastroesophageal reflux, pulmonary hypertension, obstructive sleep apnoea, coronary artery disease, and emphysema—on the clinical course of IPF remains to be fully defined.

Diagnosis
The diagnosis of IPF often requires a multidisciplinary approach, involving pulmonologists, radiologists, and pathologists experienced in the field of interstitial lung diseases. A pattern indicative of usual interstitial

Search strategy and selection criteria
We searched PubMed from January, 1996, to April, 2011, using the search terms “idiopathic fibrosis”, “fibrosing alveolitis”, “usual interstitial pneumonia”, and “nonspecific interstitial pneumonia”. We also searched these terms alongside several subsets of terms as follows: definition and epidemiology; risk factors; natural history and acute exacerbation; staging and prognosis; and pathogenesis, treatment, and biomarkers. We mostly selected publications from the past 5 years although we also included highly regarded older publications. Reviews are cited to provide the reader additional detail and references. The search was limited to reports published in English.
emphysema, with shorter survival compared with patients with IPF alone. IPF = idiopathic pulmonary fibrosis.

1950 With a rapidly progressive clinical course. Heavy smokers might develop pulmonary fibrosis combined with lung microinjuries that precede and possibly initiate the terminal phase of their disease. A few patients have a short duration of illness after the beginning of symptoms (cough and progressive dyspnoea). At presentation, patients have decreased lung volumes and capacities, with hypoxaemia at rest that worsens with exercise. In the placebo groups of large clinical trials, the mean annual rate of decline in forced vital capacity ranges from 0·13 L to 0·21 L.

Clinical phenotypes and prognosis
IPF has a heterogeneous clinical course, and patients have a median survival of 2·5–3·5 years after diagnosis. Clinical phenotypes with distinct patterns of comorbidities and survival are being defined (figure 2). Worse prognosis is associated with old age (>70 years of age), smoking history, low body-mass index, severe physiological impairment, large radiological extent of disease, and pulmonary hypertension.

Stable or slowly progressive course
Many patients with IPF have a relatively slow clinical course and usually consult doctors for months to years after the beginning of symptoms (cough and progressive dyspnoea). At presentation, patients have decreased lung volumes and capacities, with hypoxaemia at rest that worsens with exercise. In the placebo groups of large clinical trials, the mean annual rate of decline in forced vital capacity ranges from 0·13 L to 0·21 L.

Accelerated variant
A subgroup of patients, mainly male cigarette smokers, has a rapidly progressive course with shortened survival, known as accelerated IPF. In these cases, the transcriptional signature indicates the upregulation of several functional pathways, which mostly operate in alveolar epithelial and mesenchymal domains. Accelerated IPF differs in clinical course and transcriptional profile from the typical slowly progressive form, despite having similar lung function, chest imaging, and histological findings at the time of diagnosis. Boon and co-workers reported that the upregulated genes in the group whose disease progressed rapidly included members of the MAPK–EGR1–HSP70 (mitogen-activated protein kinase–early-growth response gene protein–heat shock protein 70) pathway, which regulate cigarette smoke-induced inflammation.

Acute exacerbation
Acute exacerbation of IPF is defined by rapid deterioration of the disease in the absence of infection, heart failure, pulmonary embolism, or other identifiable cause. Diagnosis is made by a combination of clinical (worsening of dyspnoea within days to few weeks), physiological (severe decrease of PaO2 in arterial blood), and radiographical findings (bilaterial ground-glass opacities and consolidation superimposed on a pattern typical of

pneumonia on high-resolution CT (figure 1) or on lung tissue obtained by surgical lung biopsy (figure 1) is crucial for the final diagnosis. The major differential diagnostic consideration is fibrotic nonspecific interstitial pneumonia,
usual interstitial pneumonia on high-resolution CT). Acute exacerbation of IPF is estimated to affect 5–20% of cases. Patients with this acute exacerbation have poor outcomes, with mortality exceeding 60% during admission to hospital, and among those who survive there is a >90% mortality within 6 months after discharge. Torque teno virus was detected in 27% of IPF cases during periods of acute exacerbation. Morphologically, diffuse alveolar damage superimposed on typical features of usual interstitial pneumonia can be seen. The pathogenic mechanisms are unknown, but widespread epithelial apoptosis has been reported. Circulating fibrocytes might be involved because the numbers of these cells increase during an acute exacerbation and return to pre-exacerbation concentrations in patients who recover.

**Pulmonary fibrosis and other lung disorders**

Diagnosis of combined pulmonary fibrosis and emphysema is based on high-resolution CT findings that show emphysematous lesions in the upper lobes and usual interstitial pneumonia-like lesions in the lower lobes (figure 3). Whether combined pulmonary fibrosis and emphysema is a distinct clinical condition, a different clinical phenotype in smokers developing IPF, or the presence of two different diseases running in parallel is unclear. Patients with combined pulmonary fibrosis and emphysema are commonly men who heavily smoke cigarettes and who have severe dyspnoea on exertion and have relatively conserved lung volumes associated with disproportionate impairment of gas exchange. These patients develop early and severe pulmonary arterial hypertension and they have a worse survival compared with patients with IPF who do not have emphysema.

Combined pulmonary fibrosis and pulmonary hypertension has a negative effect on prognosis in patients with IPF. This combined disorder is associated with low diffusing capacity for carbon monoxide, shorter walk distances, desaturation during exercise, and an increased risk of death. Bronchogenic carcinoma commonly occurs in patients with IPF (9.8–38%). The mechanisms underlying the apparent association of IPF and cancer are unclear. There is an association with cigarette smoking; however, most lung cancers in patients with combined pulmonary fibrosis and cancer are in peripheral areas involving fibrosis and severe epithelial abnormalities, implicating the fibrotic process itself in the pathogenesis of lung cancer. Chronic DNA damage leading to p53 gene mutation and allelic loss of the gene that encodes the fragile histidine triad (FHIT) might be involved in carcinogenesis associated with IPF. Additionally, the Torque teno virus has been implicated. Intriguingly, some cases of lung cancer occurred in patients with familial IPF associated with rare mutations in the gene that encodes surfactant protein A2 (SFTPA2).

**Pathogenesis**

From an inflammatory-driven to an epithelial-driven disease

Inflammation has a pivotal role in most interstitial lung diseases and, if chronic, evolves to fibrosis. However, with the redefinition of IPF as a distinct condition characterised by the pattern typical of usual interstitial pneumonia, the progressive fibrotic reaction in IPF was associated with an epithelial-dependent fibroblast-activated process (figure 4) and a poor response to anti-inflammatory therapy. However, deregulated adaptive immune mechanisms and subsequent inflammation could have a role in the onset or progression of the disease in a subgroup of patients with IPF. Therefore, at least two different cellular routes—the inflammatory pathway and the epithelial pathway—could lead to lung fibrosis.

**Epithelial injury and activation: genetic and environmental interactions**

Several environmental factors might contribute to epithelial injury and apoptosis, including cigarette smoking and chronic silent microaspiration. Additionally, chronic viral infection, mainly herpes virus infection, might contribute to the pathogenesis of IPF.
There are no genetic factors consistently associated with sporadic IPF. Alterations in unfolded protein response occur in some familial cases of pulmonary fibrosis that have mutations in surfactant protein C, a hydrophobic protein expressed exclusively by AEC type II (AEC II). Missense or short-deletion mutations of this protein result in the production of misfolded protein, which, by accumulation or complex formation, can cause epithelial cell injury. A common polymorphism in the promoter region of mucin 5B gene (MUC5B) is associated with familial interstitial pneumonia and sporadic IPF. MUC5B is a gel-forming mucin expressed by bronchial epithelial cells. Dysregulated MUC5B expression is associated with chronic airway disease and these findings suggest a role in the pathogenesis of pulmonary fibrosis.

Data from a genome-wide scan in six families with familial IPF identified a shared haplotype on chromosome 4q31, which was significantly more frequent in patients than in population-based controls. This haplotype harboured ELMOD2, a gene expressed in lung, however, it was expressed significantly less in IPF lung when compared with that of the healthy lung. ELMOD2 is essential for cellular processes and might have an antiviral effect in AECs. Mutations of
telomerase have been implicated in familial pulmonary fibrosis (see below).

Despite epithelial injury and apoptosis, an increased number of hyperlastic and hypertrophic type II pneumocytes is a notable feature of lungs affected by IPF. Additionally, large and elongated or attenuated epithelial cells are observed. Bronchiolar-type epithelium and squamous metaplasia lining the honeycomb lesions are also reported. Epithelial cells are highly active, leading to a dysregulated repair process that seems to be perpetually turned on even in the absence of the primary stimulus.41

Emerging evidence indicates that deregulation of some embryological pathways might explain the abnormal behaviour of AECs and perhaps of fibroblasts in IPF.19 Wnt ligands comprise a large family of secreted glycoproteins essential to morphogenetic processes. Results from several studies indicate that alveolar epithelium and fibroblasts overexpress members of the Wnt/wingless pathway in lungs affected by IPF.56–59

The Wnt–β-catenin pathway is switched on in both cell types.60 β1 integrin–collagen interaction in normal fibroblasts activates PTEN, which is also a negative growth regulator, whereas this negative feedback mechanism is defective in IPF fibroblasts.63

Phosphatase and tensin homologue (PTEN) is crucial for development. In adults, PTEN participates in the regulation of physiological processes such as cell polarity, proliferation, and apoptosis.61 In patients with IPF, PTEN expression is downregulated in myofibroblasts within fibroplastic foci, which might account for their assumed resistance to apoptosis.62 β1 integrin–collagen interaction in normal fibroblasts activates PTEN, which is also a negative growth regulator, whereas this negative feedback mechanism is defective in IPF fibroblasts.83

Sonic hedgehog (Shh) is an essential morphogen for patterning during embryogenesis. This developmental ligand enables cells to evade apoptosis and cell cycle arrest, conferring a proliferative advantage. In lungs affected by IPF, a strong expression of Shh was reported, mainly in epithelial cells lining honeycomb cysts.64,65

Bone morphogenetic proteins belong to the transforming growth factor β (TGFβ) superfamily and have an essential role in embryonic and postnatal development.66 In adults, reactivating the expression of bone morphogenetic protein antagonists can contribute to the progression of some chronic degenerative diseases. Increased expression of gremlin, a strong bone morphogenetic protein antagonist, has been reported in fibroblasts in lungs affected by IPF.67 Increased concentrations of gremlin could attenuate phosphorylation mediated by bone morphogenetic protein signalling in lungs, leading to increased TGFβ1-induced epithelial to mesenchymal transition (EMT) and decreased myofibroblast apoptosis.

In summary, some developmental programmes are probably activated during normal tissue repair. However, this process must be tissue specific and temporally modulated. Conversely, sustained deregulation might contribute to the pathogenesis of IPF. The upregulation of Wnt, Shh, and gremlin 1 and the downregulation of PTEN are important pieces of evidence indicating that IPF could occur as part of recapitulation of developmental pathways, thus contributing to a maladaptive repair process.

Profibrotic effects of aberrantly activated AECs in the lung microenvironment

An important pathological process in IPF is the activation of the coagulation cascade, which has several profibrotic effects (figure 5).46–50 In IPF, the tissue factor–Factor VIIa–Factor X complex assembles on the alveolar epithelium, allowing activation of Factor X, which in turn stimulates fibroblasts within the underlying fibrotic regions. Provisional matrix, formed by fibrin and fibronectin, could stimulate EMT even in the absence of TGFβ1.68 Additionally, thrombin and activated Factor X induce the differentiation of lung fibroblasts to myofibroblasts via the proteinase-activated receptor 1.69,70 These findings provide compelling evidence that procoagulant signalling is activated in IPF and that deficient function of alveolar fibrinolysis, mainly caused by the epithelial cells, has an important role in driving the fibrotic lung response.

In injured tissues, fibroblasts are activated and differentiate into myofibroblasts, which are specialised contractile cells with higher profibrotic potential than fibroblasts. In the fibroblastic foci, these cells cause the exaggerated extracellular matrix deposit—the hallmark of the scarring process that leads to the destruction of the lung architecture. The origin of fibroblasts and myofibroblasts and the reasons why they organise in morphologically distinct foci in IPF is unclear (figure 6).
Overview of the sources of recruitment of fibroblasts during the development of idiopathic pulmonary fibrosis

Activated alveolar epithelial cells secrete CXCL12—the sole ligand for the chemokine receptor CXCR4, which is the main receptor of human fibrocytes. Fibrocytes are, in turn, chemotacted from the peripheral blood to the injured areas. Additionally, epithelial cells secrete strong chemotactic and mitogen growth factors such as PDGF, inducing the migration and proliferation of resident mesenchymal cells. Finally, under different stimuli, including TGFβ1 and wound clotting, epithelial cells might evolve to fibroblasts through an epithelial to mesenchymal transition process. In the local microenvironment, fibroblasts form small clusters (fibroblast foci) and differentiate to myofibroblasts that have a more aggressive profibrotic phenotype. CXCL=chemokine ligand. CXCR=chemokine receptor. PDGF=platelet-derived growth factor. TGFβ=transforming growth factor β.

Strong evidence indicates that AECs are the primary source of mediators that function as chemotactic factors or mitogens for mesenchymal cells, including platelet-derived growth factor, TGFβ, tumour necrosis factor α, and endothelin 1.66 These factors probably contribute mostly to the migration, proliferation, and differentiation of resident mesenchymal cells.

There is an influx of circulating fibrocytes into lungs affected by IPF.79 Fibrocytes are a unique subpopulation of leucocytes characterised by the expression of haemopoietic (CD45, CD34) and mesenchymal (collagen I, fibronectin) cell markers.79 Most human circulating fibrocytes express the chemokine receptor CXCR4, suggesting that the CXCR4–CXCL12 axis is crucial for trafficking into IPF lungs. AECs from these patients strongly express CXCL12, which probably forms the chemotactic gradient needed for trafficking of CXCR4-positive fibrocytes.79

The epithelium might directly contribute to the expansion of the population of fibroblasts and myofibroblasts through the EMT. In this process, epithelial cells acquire mesenchymal properties through which they increase their capability to move and to synthesise interstitial matrix.13,14 Evidence that supports the EMT as a source of IPF myofibroblasts include co-localisation of epithelial (prosurfactant proteins) and mesenchymal (alpha-smooth muscle actin [alpha-SMA], N-cadherin) markers in AECs from IPF lungs,75,76 the expression of typical epithelial proteins (ie, keratin 18) in IPF fibroblasts,75 and alveolar type II cells from fibrotic human lungs have increased expression of genes encoding mesenchymal proteins and potential regulators of EMT.77

Additionally, there are strong drivers of EMT in lungs of patients with IPF. SNAIL transcription factors, key regulators of TGFβ1-induced EMT in the lung, are increased in hyperplastic AECs.78 Depletion of SNAIL and SNAI2 with small interfering RNA inhibited TGFβ1-induced EMT. Twist, another driver of EMT, was reported in hyperplastic AECs from the lung of patients with IPF. Interestingly, IPF tissue with high Twist protein levels was also positive for the herpesvirus, EBV. In IPF, EBV infection might be a source of injury precipitating EMT through the expression of Twist.80

Thus, local mesenchymal cells, circulating fibrocytes, and EMT participate in the expansion of fibroblasts and myofibroblasts in IPF. However, the relative quantitative contribution of each process in the onset, progression, or perpetuation of IPF is unknown. In experimental lung fibrosis in mice, EMT accounted for about 33% of fibroblasts, and bone marrow progenitor recruitment accounted for about 20% of fibroblasts.81 We can assume that, at least in this model, the remaining 50% of fibroblasts originate from resident mesenchymal cells (or another undisclosed source [eg, pericytes, and endothelial or mesothelial to mesenchymal transition]).

Differentiation of fibroblasts to myofibroblasts

Three main factors drive the differentiation of fibroblasts to myofibroblasts and guarantee maintenance of the contractile phenotype: high mechanical stress (that induces the differentiation to proto-myofibroblasts), local increase of active TGFβ1 (mainly produced by AECs in IPF), and the presence of specialised matrix proteins, such as the extra domain A (ED-A) splice variant of fibronectin.82 Myofibroblasts cause the exaggerated accumulation of extracellular matrix (fibrosis) and contribute to basement membrane disruption and epithelial cell death (figure 7).83,84

Elimination of myofibroblasts by apoptosis is essential during normal wound healing; this process does not seem to occur in the fibrolastic foci of IPF. Microenvironmental signals such as TGFβ1 and endothelin 1 (mostly synthesised by AECs in IPF) might promote fibroblast resistance to apoptosis through signalling pathways involving PI3K/AKT.85 However, there is no convincing evidence that reduced susceptibility to apoptosis can cause the persistence of myofibroblasts in vivo.86 Moreover, the reasons why fibroblasts and myofibroblasts apparently survive while epithelial cells die within the same microenvironment (the apoptosis paradox) is unclear.87 A potential explanation might be related to prostaglandin E2 deficiency (usually observed in IPF), which increases AECs sensitivity to apoptosis but decreases fibroblast sensitivity to apoptosis.88

The absent type I pneumocytes

AECs type I cover more than 90% of the alveolar surface area of the peripheral lung and, interfacing with
pulmonary capillaries, provide a surface readily permeable to gases. Patients with IPF have an important loss of type I pneumocytes, although the putative effect of this pathological process on the fibrotic response is unclear. Furthermore, transdifferentiation of type II pneumocytes into type I pneumocytes, indispensable to re-establish a functional alveolar epithelium, is profoundly altered in IPF because of the severe abnormalities of the extracellular matrix and interrupted epithelial basement membrane.

The loss of AEC type I might provoke the reduction of some important antifibrotic molecules (eg, caveolin 1). However, whether decreased concentrations of caveolin 1, specifically attributable to the loss of type I pneumocytes, is involved in IPF pathogenesis is not known. Furthermore, the receptor for advanced glycation end products (RAGE) is also decreased in IPF. RAGE is a member of the immunoglobulin superfamily of cell surface receptors that is highly expressed by normal AECs (figure 7). Activated myofibroblasts secrete angiotensinogen and H$_2$O$_2$ that induce alveolar epithelial cell death. They also produce matrix metalloproteinases such as MMP2 and MMP9, which are implicated in the disruption of the epithelial basement membrane.

**Matrix metalloproteinases in idiopathic pulmonary fibrosis**

MMPs have an important role in the pathogenesis of idiopathic pulmonary fibrosis. Most are localised in aberrant alveolar epithelial cells, with very few in the fibroblastic foci. Strong cytoplasmic staining of MMP1 in epithelial cells (A) and MMP2 in fibroblasts (B) is shown. MMP=matrix metalloproteinase.

**Angiogenesis and vascular remodelling**

Neovascularisation is a fundamental process in tissue repair after injury and is affected by the balance between various factors—mainly chemokines that promote or inhibit angiogenesis. There is increased angiogenesis in experimental lung fibrosis; however, the role of this angiogenesis in IPF is unclear. An aberrant vascular remodelling occurs in lungs affected by IPF but fibrotic areas have fewer blood vessels, whereas adjacent nonfibrotic tissue is highly vascularised. There are almost no...
capillaries within the fibroblastic foci, indicating that the fibrotic process in IPF does not need neovascularisation.105 Thus, under certain pathological settings, increased angiogenesis seems to have a fibrogenic role, whereas, in other settings, decreased angiogenesis enhances fibrosis.

Processes that link ageing with IPF

The mechanisms that link ageing with IPF remain elusive. High-resolution CT findings usually associated with IPF are frequently seen in asymptomatic elderly individuals (75 years or older) and are absent in younger patients.24 One possible mechanism is related to an accelerated shortening of telomeres.106 Telomeres shorten successively with each cell division—when they achieve a critical length, they activate a p53-dependent checkpoint that leads to apoptosis or replicative senescence.26 Short telomeres are expected to compromise the replicative potential of progenitor cells that remain in tissues after injury.

The results from two studies identified loss-of-function mutations of telomerase in 8–15% of patients with familial IPF.106,107 Subsequently, it was found that patients with sporadic IPF had short leucocyte telomeres; short telomeres were also detected in the alveolar epithelium.108 Thus, such individuals might be at increased risk for developing IPF. Some patients with other forms of IPF also had shortened telomeres, raising the possibility of shared mechanisms.26

However, shortening of telomeres is also observed in chronic obstructive pulmonary disease, another age-related but completely different lung disease.25 Moreover, telomerase-deficient mice that have sequential shortening of telomeres develop spontaneously emphysematous-like lesions. AECs from these mice show activation of the stress response pathway and spontaneous apoptosis,109 indicating that, in this model, telomere shortening causes epithelial cell damage, but the consequence is an emphysema-like disorder not fibrosis. Additionally, evidence of epithelial alveolar apoptosis has been also reported in human emphysema.110–113 Nevertheless, the whole population shift in the distribution in the telomere length suggests that telomere shortening might be a pathogenic co-factor for IPF.

Ageing is also associated with increased oxidative stress as a result of an imbalance of pro-oxidants (reactive oxygen and nitrogen species) and antioxidants (eg, superoxide dismutases, glutathione).114 The consequences include direct damage to DNA, oxidation of polyunsaturated fatty acids in cell membranes, and inactivation of enzymes. Results from several studies have indicated a severe lung redox imbalance in IPF, probably caused by an increase in oxidants associated with extracellular glutathione deficiency.115 Excessive oxidative stress has various deleterious effects that might contribute to the pathogenesis of IPF, including activation of redox-sensitive signalling pathways, changes in cytokine or chemokine expression, modification of protease or antiprotease balance, induction of apoptosis, and activation of fibroblasts.116

Epigenetic processes involve transmissible alterations in gene expression caused by mechanisms other than changes in DNA sequence, and these processes are essential for normal development and maintenance of tissue-specific gene expression patterns. The most common epigenetic mechanisms include DNA methylation, post-translational modifications of histones, and transcriptional effects of non-coding RNA molecules, including microRNAs.

In the elderly (>65 years of age), there is a progressive loss of DNA methylation in repetitive elements dispersed throughout the genome, which seems to be proportional to life expectancy.117 An aberrant reprogramming of the epigenome is involved in cancer initiation and progression.118 Epigenetic changes contribute to the aggressive behaviour of IPF fibroblasts. Thy1, a receptor that inhibits the differentiation of fibroblasts to myofibroblasts and that decreases fibrogenic activity, is not expressed in fibroblastic foci in vivo.119 The loss of this receptor occurs by epigenetic silencing through the hypermethylation of cytokine–guanine islands in the gene promoter.

Compared with normal fibroblasts, IPF fibroblasts express less cyclooxygenase 2 and synthesise less prostaglandin E2, a potent downregulator of fibroblast activation.120 The reduced expression of cyclooxygenase 2 in IPF fibroblasts seems to be caused by epigenetic abnormalities of histone acetylation that prevents activated transcription factors from binding to the cyclooxygenase-2 promoter.121 MicroRNAs are post-transcriptional regulators that bind to specific sequences, blocking translation or causing degradation of the target messenger RNA, which results in gene silencing. microRNAs probably control most biological pathways and networks. During ageing, dysregulated expression of microRNAs generally occurs in groups, suggesting that their actions might be functionally coordinated together by common transcriptional regulators.122 Age-dependent disruption of these vital partnerships might contribute to the development of diseases in elderly individuals. For example, downregulation of some microRNAs (eg, miR1, mirR30) coupled with the upregulation of others (eg, miR20a, miR21) are commonly reported in patients with cardiac hypertrophy and coronary arteriosclerosis.123 46 microRNAs were recently reported to be differentially expressed in IPF compared with normal lungs, with a significant decrease of microRNA let-7d.124 Inhibition of let-7d in vitro induced EMT, whereas inhibition in vivo caused alveolar septal fibrosis. Similarly, lungs affected by IPF have an upregulation of miR21 and a downregulation of miR29, mainly localised to myofibroblasts.125,126 Increasing miR21 levels promoted the profibrogenic activity of TGFβ1 in fibroblasts, whereas downregulating miR-21 attenuated this activity.127 By contrast, miR29 levels inversely correlated with the expression of several profibrotic target genes and with the severity of fibrosis.128
Therefore, epigenetic deregulation that contributes to the ageing phenotype might increase the risk in developing IPF if a crucial threshold of epimutations is reached.

**Treatment approaches**

In clinical trials of novel drugs (etanercept, IFNy, bosentan, imatinib mesilate) in patients with IPF who have mild-to-moderate functional impairment, no significant benefit was reported with these interventions. In general, patients with IPF who have moderate-to-severe functional impairment and associated comorbidities (eg, pulmonary hypertension) have been excluded from trials. Consequently, many patients seen in clinical practice have not been studied. Several clinical trials are ongoing (table).

For several new therapies, there is evidence to suggest clinical benefit in patients with IPF. N-Acetylcysteine, an antioxidant, used in combination with prednisone and azathioprine, reduces the rate of decline in forced vital capacity and diffusing capacity for carbon monoxide after 12 months of treatment. However, the observed changes in clinical practice have not been studied. Several clinical trials are ongoing (table).

Table: Ongoing clinical trials in IPF

<table>
<thead>
<tr>
<th>Study compounds</th>
<th>ACE-IPF</th>
<th>PANTHER-IPF</th>
<th>TOMORROW</th>
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<th>Thalidomide</th>
<th>CNTO 888</th>
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<tr>
<td>Warfarin vs placebo</td>
<td>Prednisone plus azathioprine plus N-acetylcysteine vs N-acetylcysteine vs placebo</td>
<td>Prednisone vs placebo</td>
<td>BIBF 1120 (oral dose escalation: 50 mg once daily, 50 mg twice daily, 100 mg twice daily, and 150 mg twice daily)</td>
<td>10 mg, once daily</td>
<td>Thalidomide vs placebo</td>
<td>CNTO 888 (anti CC-chemokine ligand 2) 1 mg/kg or 5 mg/kg or 15 mg/kg vs placebo</td>
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<td>Patients enrolled (n)</td>
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<tr>
<td>Target population</td>
<td>Advanced disease</td>
<td>Treatment naive (&lt;12 weeks of IPF therapy)</td>
<td>Mild-to-moderate disease</td>
<td>Mild-to-moderate disease (limited HC on HRCT ≤5%)</td>
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<td>Mild-to-moderate disease with evidence of progression before enrolment</td>
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<td>Primary endpoint</td>
<td>All-cause mortality; non-elective admission to hospital; decrease in the absolute FVC ≥10% from baseline</td>
<td>Change in FVC at 60 weeks</td>
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IPF=idiopathic pulmonary fibrosis. FVC=forced vital capacity. HC=honeycombing. PH=pulmonary hypertension. HRCT=high-resolution CT. PFT=pulmonary function tests. NIH=National Institutes of Health.
organs, including the lungs. The main problem after injury is to re-establish the integrity and functional organisation of the epithelial layer and of the alveolar-capillary units. This process probably occurs during normal repair by the migration and spreading of nearby and newly recruited circulating progenitor cells that proliferate and undergo phenotypic differentiation to cover the denuded surfaces. Mesenchymal stem cells are a promising prospect for tissue regeneration. These cells migrate to the lung, adopt an epithelium-like phenotype, and reduce fibrosis in bleomycin-injured lungs from mice. Additionally, after intratracheal injection of bleomycin, prominin 1–CD133-positive epithelial progenitor cells, co-expressing stem and haematopoietic cell markers engraft in the lungs, differentiate into type II pneumocytes and protect against bleomycin-induced fibrosis. More recently, the therapeutic potential of AEC type II derived from human embryonic stem cells was studied in the mouse model of bleomycin-induced injury. These cells differentiated into type I pneumocytes, and abrogated the inflammatory and fibrotic response. Unfortunately, almost all the experiments have been done in the bleomycin-lung model, which is a modest inflammatory and fibrotic model, spontaneously reversible, and does not represent the progressive and lethal nature of IPF.

Another growing area of investigation is lung bioengineering using decellularised lung tissue repopulated with neonatal lung epithelial cells and microvascular lung endothelial cells. When transplanted, these engineered lungs were effective in exchanging oxygen and carbon dioxide. Although far from human lung bioengineering, this approach is encouraging.

Additional management factors

Patients with acute exacerbations are usually treated with broad-spectrum antibiotics and corticosteroids. Mechanical ventilation is often needed but is usually unsuccessful, with a high hospital mortality rate. For patients who survive and are discharged from hospital, recurrence is common and is usually fatal.

Patients with IPF who have pulmonary arterial hypertension have increased mortality. Consequently, therapy directed against pulmonary arterial hypertension might be beneficial. Sildenafil, an oral drug that preferentially blocks phosphodiesterase 5 in well ventilated areas of the lung, reduces pulmonary vascular resistance and improves gas exchange in patients with severe pulmonary fibrosis. Sildenafil can cause important improvements in dyspnoea and quality of life in patients with advanced disease.

Although the potential pathogenic association between chronic microaspiration and IPF remains unclear, some evidence supports attempts at management of gastroesophageal reflux disease. However, further studies are needed to see if aggressive, chronic treatment of this disease is able to improve or halt further progression of IPF.

Given the link between ageing and IPF, physicians should pay attention to geriatric comorbidities and increase focus on symptom-based management to complement emerging disease-modifying therapies to improve quality of life. Pulmonary rehabilitation, education programmes, and joining support groups can help patients to breathe more efficiently and to perform their activities of daily living with less breathlessness. Supplemental oxygen therapy is commonly needed to treat the hypoxaemia that usually worsens with exercise.

Conclusions

IPF is a devastating lung disease whose incidence and prevalence increases markedly with ageing. The disease course is heterogeneous; however, the median survival is about 3 years after diagnosis. The cause of IPF is unknown, but it appears to be a disorder likely arising from the interplay between environmental and genetic factors. Cigarette smoking is the most consistent environmental risk factor. Gene mutations and polymorphisms have been shown in both sporadic IPF and familial pulmonary fibrosis. Although the pathogenic mechanisms are unknown, a growing body of evidence suggests that the disease process is initiated through alveolar epithelial cell microinjuries and apoptosis, which results in the aberrant activation of neighbouring epithelial cells, the arrival of stem or progenitor cells, or both that in turn produce the factors responsible for the expansion of the fibroblasts and myofibroblasts population in the IPF lungs. These peculiar fibroblastic foci secrete exaggerated amounts of extracellular matrix components that destroy the lung parenchyma. No effective treatment exists. Lung transplant is the only treatment that prolongs the life of patients with IPF. Thus, the fundamental challenge for the future is to find appropriate therapeutic approaches that will reverse or stop the progression of the disease. Combination of drugs that target epithelial cells and fibroblasts, and, crucial signalling pathways could, at least theoretically, open new therapeutic opportunities. Another new strategy includes the use of stem cells (eg, embryonic or induced-pluripotent, or mesenchymal stem cells) to rebuild the fibrotic lungs. Finally, the absence of a fitting animal model (or an in-vitro system) that would allow preclinical testing of potential drugs is a crucial missing link.

Contributors

All authors contributed equally to the design, literature search, figures, and writing of this manuscript.

Conflicts of interest

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