Smoking and interstitial lung diseases

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ABSTRACT For many years has been well known that smoking could cause lung damage. Chronic obstructive pulmonary disease and lung cancer have been the two most common smoking-related lung diseases. In the recent years, attention has also focused on the role of smoking in the development of interstitial lung diseases (ILDs). Indeed, there are three diseases, namely respiratory bronchiolitis-associated ILD, desquamative interstitial pneumonia and pulmonary Langerhans cell histiocytosis, that are currently considered aetiologically linked to smoking and a few others which are more likely to develop in smokers. Here, we aim to focus on the most recent findings regarding the role of smoking in the pathogenesis and clinical behaviour of ILDs.

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Introduction

Cigarette smoking is a very common and addictive habit and is well known for its harmful effects because of the high number of chemicals contained. The role of smoking in many human diseases, such as chronic obstructive pulmonary disease (COPD), lung cancer and atherosclerosis, has already been defined [1–3]. Interestingly, the link between cigarette smoking and interstitial lung diseases (ILDs) is not yet well established.

Recently, Vassallo *et al.* [4] proposed four groups of smoking-related ILDs based on associations with cigarette smoking (table 1). The first group includes respiratory bronchiolitis-associated ILD (RB-ILD), desquamative interstitial pneumonia (DIP) and pulmonary Langerhans cell histiocytosis (PLCH), three chronic diffuse lung diseases that are strongly aetiologically linked to smoking (fig. 1) [5, 6]. The second group consists of two acute ILDs, acute eosinophilic pneumonia and pulmonary haemorrhage syndrome, in which smoking seems to have an important pathogenetic role, although to a lesser extent than in the first group. The third group contains idiopathic pulmonary fibrosis (IPF) and rheumatoid arthritis-related ILD (RA-ILD), diseases in which smoking is increased in prevalence. Finally, the fourth group includes sarcoidosis and hypersensitivity pneumonitis, two diseases that are actually less likely to develop in smokers [4]. The protective effect of smoking in these diseases may result from suppression of T-helper cell (Th)1 immunity by cigarette smoking, but at a price in terms of other forms of damage and functional impairment of the immune system, potentially leading to alternative lung diseases. Nonetheless, even in sarcoidosis it has been demonstrated that when smokers develop the disease the outcome is worse than in nonsmokers [7].

Plainly, identifying the exact role of smoking in ILDs is extremely important as understanding the relevant pathogenetic pathways may allow the development of new drugs targeting pathways activated by smoking as well as the inclusion of ILDs in the campaigns against smoking, as is already happening with great

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TABLE 1 Classification of smoking related-interstitial lung diseases (ILDs)

1) Chronic ILDs strongly associated with cigarette smoking	Respiratory bronchiolitis-associated ILD
	Desquamative interstitial pneumonia
	Adult pulmonary Langerhans cell histiocytosis
2) Acute ILDs related to smoking	Acute eosinophilic pneumonia
	Pulmonary haemorrhage syndromes
3) ILDs that are more prevalent in smokers	Idiopathic pulmonary fibrosis
	Rheumatoid arthritis-associated ILD
4) ILDs that may be less prevalent in smokers	Hypersensitivity pneumonitis
	Sarcoidosis

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success for non-ILDs including COPD and lung cancer. It is also important from a clinical point of view as recognition of a smoking-related phenotype would facilitate early diagnosis and treatment, especially with regard to IPF, the most common and progressive form of ILD.

Is smoking related to the pathogenesis of ILDs?

There has been a lot of progress regarding the understanding of the role of smoking in the pathogenesis of ILDs, but many pieces of the jigsaw are still missing. The lungs of smokers are continuously exposed to insults, such as the cytotoxic, mutagenic and proinflammatory substances contained in cigarettes, leading to an increasing risk of the development of lung disorders. Respiratory bronchiolitis, which is present histologically in all active smokers, is characterised by the accumulation of pigmented "smoker's macrophages" in respiratory bronchioles and neighbouring alveoli, containing granular, yellow-brown cytoplasmic pigments [8]. Therefore, respiratory bronchiolitis may be considered a "normal" physiological response to cigarette smoking unless it is sufficiently severe to have the features of a clinically overt ILD, based on clinical symptoms or lung function impairment [4, 9–13]. Thus, the definition of a healthy smoker refers to an asymptomatic smoker with normal lung function values, even if respiratory bronchiolitis is present. Oxidative stress, increased epithelial apoptosis and deregulated immune responses represent well known smoking induced mechanisms [14–21]. It is known that cigarette smoking causes inflammatory cell recruitment, mostly macrophages, which have reduced apoptosis and increased survival. Lung macrophages are also functionally affected and recent evidence suggests an induction of the M2 phenotype upon smoking stimulation [22–25]. The M2 phenotype of macrophages is known to enhance resolution of inflammation and tissue remodelling.

Osteopontin

Prasse *et al.* [26] showed that osteopontin (OPN), a glycoprotein with cytokine properties, is significantly increased in patients with smoking-related ILDs (fig. 2). This glycoprotein is found in the extracellular matrix of bone and has chemotactic properties for macrophages, monocytes, dendritic cells and Langerhans cells. Interestingly, this study demonstrated evidence of chronic nicotine stimulation in macrophages of patients with DIP and PLCH. The authors also proposed that nicotine is able to promote increased OPN and granulocyte-macrophage colony-stimulating factor production by alveolar macrophages, suggesting an association between nicotine and the accumulation of immune cells in smoking related-ILDs [26]. Nicotine is known to affect many organs in the human body and to alter the normal function of cells that express nicotine receptors.

Nicotine

Nicotine has pleiotropic effects which seem to be concentration-dependent; it has been hypothesised that it enhances fibrogenesis through several mechanisms [27] including endothelial and epithelial damage, production of proinflammatory cytokines, and activation of transforming growth factor (TGF)-β, macrophages and fibroblasts. An *in vivo* study, by Roomans *et al.* [28], reported that nicotine alters the homeostasis of epithelial cells in the lung, enhances inflammatory reactions and increases eosinophil numbers in the trachea. In the mouse kidney, nicotine increases the production of TGF-β and the expression of epithelial–mesenchymal transition markers [29]. While in human hepatic cells it also induces TGF-β and collagen expression, promoting fibrogenesis [30]. In addition, TGF-β release is induced by smoke exposure in rat tracheal explants, potentially promoting airway remodelling [31].

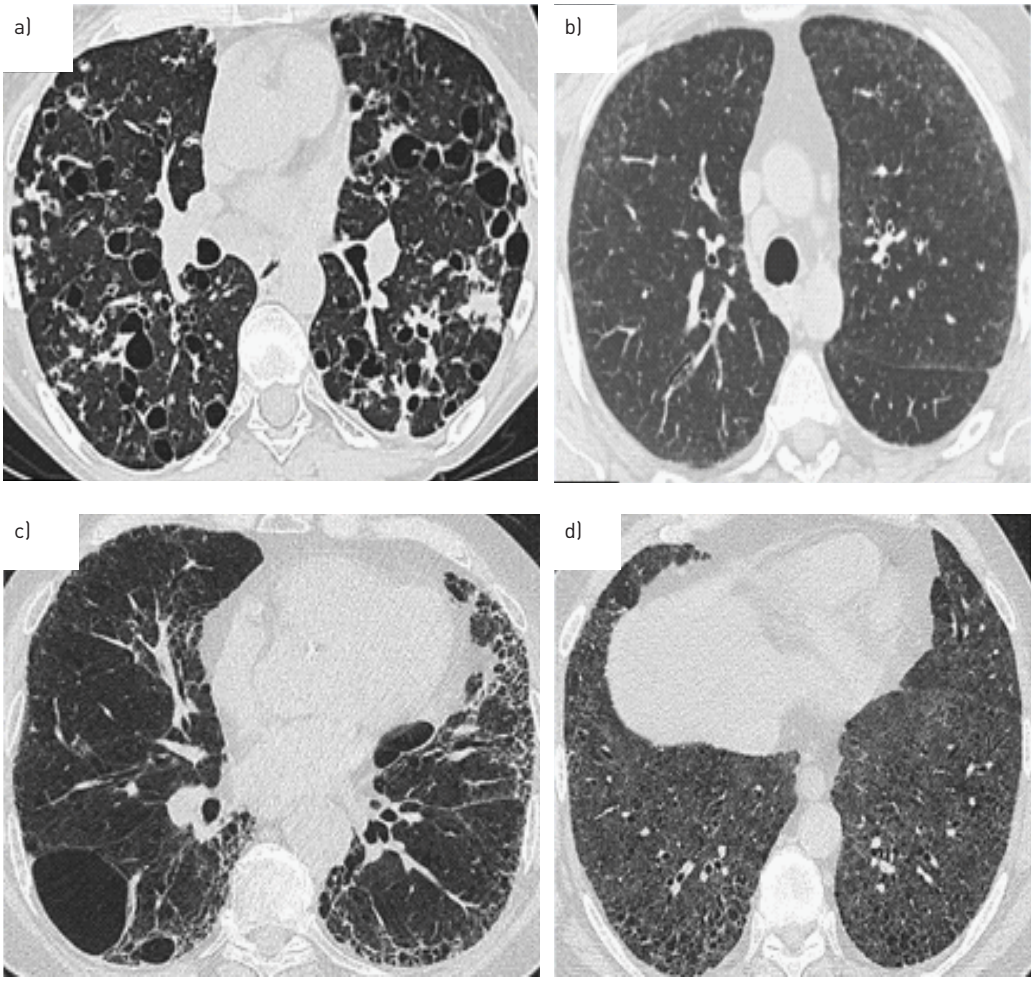

FIGURE 1 High-resolution computed tomography images of smoking-related interstitial lung diseases (ILDs). a) Pulmonary Langerhans cell histiocytosis, b) respiratory bronchiolitis-associated ILD, c) combined pulmonary fibrosis and emphysema, and d) desquamative interstitial pneumonia.

Smoking-related epigenetic alterations

Smoking promotes epigenetic alterations that persist for years even after smoking cessation. It has been detected that smokers display increased levels of promoter hypermethylation, and higher levels of DNA methyltransferase 1, resulting in decreased expression of several genes, mainly associated with the cell cycle [32]. Histone H4 acetylation, in parallel with reduced function of histone deacetylase-2, is also induced by smoking [33–35]. Two studies by Coward and colleagues suggested that defective histone acetylation and histone hypermethylation may have a role in the fibrogenic process in IPF [36, 37], highlighting the importance of epigenetic deregulation in the development of the disease.

Citrullination

Citrullination, a post-translational modification of proteins that alters their structure and has functional consequences regarding their immunogenicity, is triggered by smoking and appears to be characteristic of rheumatoid arthritis. Patients with anti-citrullinated protein antibodies (ACPAs) are more likely to have lung abnormalities [38, 39]. Interestingly, Fischer *et al.* [40] showed that, in some patients, ACPA positivity and lung abnormalities develop prior to joint disease. It is established that in smokers with rheumatoid arthritis there are citrullinated peptides in the bronchoalveolar lavage fluid cells, which are not present in nonsmokers [41]. Two recent studies revealed higher levels of specific ACPAs in RA-ILD patients than in patients with rheumatoid arthritis without ILD [42, 43], and there was also an association with a usual interstitial pneumonia (UIP) pattern on high-resolution computed tomography (HRCT) [43]. These findings may be indicative of an important role for smoking and citrullination in the development of ILD related to rheumatoid arthritis and provide new diagnostic tools concerning lung involvement [38, 44].

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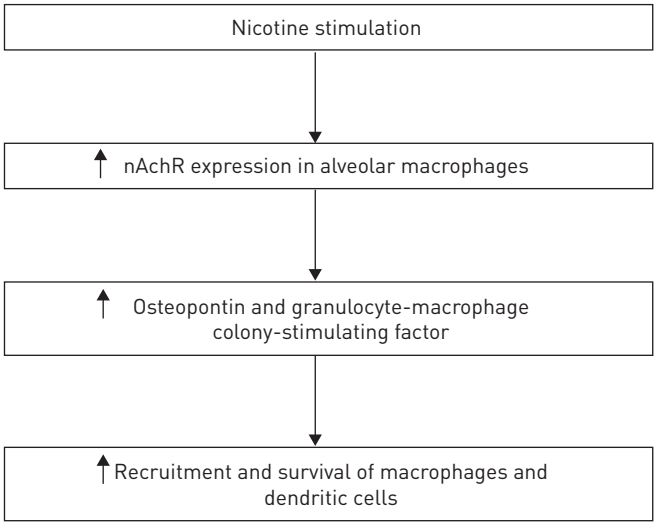

FIGURE 2 Chronic nicotine stimulation leads to recruitment of inflammatory cells. nAchR: nicotinic acetylcholine receptors.

Premature ageing

Premature ageing may be an important pathogenetic mechanism in lung diseases [45–48]. Cellular senescence, telomere shortening, oxidative stress and DNA damage are considered hallmarks of the ageing process [49]. Telomeres are special nucleotide repeats at the ends of chromosomes that provide chromosomal stability. Telomeres shorten progressively during replication, without losing coding information. When telomeres reach a critical length, however, the cell dies. Cigarette smoking is known to promote telomere shortening and this phenomenon has been described in alveolar epithelial cells and in peripheral blood cells in IPF [50–52]. Interestingly, circulating leukocytes in smokers have shorter telomeres in a dose-dependent manner [53, 54]. Additionally, DNA damage and oxidative stress have been found in higher levels in smokers [46, 55]. It has been demonstrated that tobacco, and other stimuli that cause DNA damage, result in an abnormal repair process and fibrosis, partially due to senescent bone marrow-derived stem cells [56]. These cells can migrate and make a major contribution to lung repair mechanisms. Cigarette smoke is also a known source of exogenous oxidants, resulting in an imbalance of pro-oxidant and antioxidant molecules, especially in the presence of a deficiency in the cellular control systems of reactive oxygen species (ROS) production [45, 57].

Autophagy/mitophagy

During ageing, proteins and cellular debris are ineffectively cleared and accumulate in the cell. Such a defect in cellular housekeeping mechanisms leads to senescence or apoptosis [46, 58, 59]. Autophagy is a tightly regulated and selective process responsible for the degradation of cellular components *via* the lysosomal pathway. It is vital for cellular homeostasis, as it represents a quality control mechanism for the cell and participates in bioenergetic adaptation to starvation. It has several physiological and pathophysiological functions contributing to human disease pathogenesis [60–63]. Mitophagy is the selective autophagy of mitochondria, which are central to healthy cell metabolism but can also inflict cellular damage and trigger apoptosis by releasing toxic by-products of oxidative phosphorylation. Oxidative stress causes mitochondrial depolarisation and dysfunction and the accumulation of impaired mitochondria determinates cell fate and function [64]. Mitophagy is the major mechanism for efficient clearance of dysfunctional mitochondria, thereby having an important role in homeostasis [64–66]. Although recent studies have examined the contribution of autophagy and mitophagy to the development of lung disorders, its pathogenetic role is not well established. Smoke exposure enhances autophagy in mouse lungs leading to emphysema, perhaps by increasing epithelial cell apoptosis [67, 68]. However, autophagy is supposedly specific to cell type and, thus, in alveolar macrophages in COPD patients, there appears to be a selective defect in autophagy resulting in impaired clearance of damaged and dysfunctional mitochondria [69]. After treatment with cigarette smoke, recent studies have shown altered mitochondrial structure (elongation) and function in alveolar epithelial cells [70], and in primary bronchial epithelial cells [71]. By contrast, Hara *et al.* [72] demonstrated mitochondrial fragmentation in primary human bronchial epithelial cells upon stimulation with cigarette smoke extract for 48 h. It has been suggested that while mitochondria initially adapt to cigarette smoke and oxidative stress by altering their structure, this may be not beneficial in the long term due to a resultant decrease in mitophagy [70]. Recently, Ahmad *et al.* [73] proposed a pathway of smoke-induced cellular senescence due to impaired mitophagy. In 2012, Patel *et al.* [74] showed low levels of autophagy in IPF lungs. The suggested mechanism is TGF-β-induced activation of phosphatidylinositol-3 kinase and the mammalian target of rapamycin, which are known

inhibitors of autophagy. It has been suggested that autophagy protects against lung fibrosis and, thus, smoking may suppress autophagy by inducing TGF-β production. A more recent study by Patel *et al.* [75] demonstrated damaged mitochondria in IPF lungs and mitochondrial depolarisation in TGF-β treated lung epithelial cells. It had already been reported by Bueno *et al.* [76], in 2014, that a defect in mitophagy due to deficiency of a major regulatory molecule (PTEN-induced putative kinase (PINK)1) leads to mitochondrial damage and lung fibrosis.

Is smoking a risk factor and does it affect the progression of ILDs?

In IPF, smoking is now considered a risk factor, and probably interacts with genetic predisposition and other factors such as viral infections and gastro-oesophageal reflux [77]. Current or former smokers are almost 60% more likely than lifelong nonsmokers to develop IPF [78, 79]. In former smokers, the shorter the time interval from quitting smoking then the higher the likelihood of developing IPF is. Relatives of patients with familial IPF, which is either symptomatic or asymptomatic, with features of ILD on HRCT have a significantly higher prevalence of smoking compared with those without ILD features [80].

It should be stressed that, ideally, the exact effect of smoking on the development and progression of ILDs would be explored through longitudinal studies, which are very unlikely to ever be undertaken due to the relative rarity of ILDs and the high number of the scans required. However, recent studies of lung cancer screening and COPD may shed some light on this matter. In the COPD Gene study, 8% of smokers had interstitial lung abnormalities (ILAs) on HRCT, which were subclassified as subpleural, centrilobular, subpleural and centilobular, and "radiographic evidence of ILD". The presence of ILD was associated with a significantly higher likelihood of a history of smoking and significantly greater exposure to tobacco smoke in smokers [81]. A follow-up HRCT trial for cancer screening has identified ILAs in 9.7% of participants who were current or former smokers with a smoking history >30 pack-years [82]. Non-fibrotic ILAs, defined as ground-glass opacities, consolidations and mosaic attenuation, were present in 5.9% of cases whereas fibrotic ILAs, defined as reticulation with or without ground-glass opacities and honeycombing, were present in 2.1% of cases. After a follow-up of 2 years, 49% of non-fibrotic ILAs had improved and 11% had progressed. In contrast, none of the patients with fibrotic ILAs (which may represent UIP or fibrotic nonspecific interstitial pneumonia) had improved and 37% had progressed [82]. However, the authors did not find any association between disease progression on HRCT and smoking status or smoking dose (pack-year smoking history). In another study, 25% of smokers with initial abnormalities defined as "other chronic interstitial pneumonia" had progressed after 3 years, with progression always linked to continuation of smoking [83]. The question of whether smoking is the only risk factor responsible for the development of ILD in smokers remains unanswered. A panel of clinicians, radiologists and pathologists with expertise in ILDs were unable to accurately specify smoking status in a group of patients with an unknown smoking history simply by applying characteristic HRCT ILD features identified in a group of known smokers. For example, in one patient considered to have truly classical features of smoking-related ILD, there was no history of either active or passive smoking, providing indirect support for the contribution of other pathogenetic factors [84].

Surprisingly, it was suggested in one study that smoking may confer a protective effect against IPF progression, based on the observation that currently smoking IPF patients had a better survival [85]. However, this finding is likely to be related to the fact that smokers with more severe disease usually quit smoking whereas smokers with less severe disease are less likely to. Therefore, current smoking is associated with lengthier survival by virtue of linkage to less severe disease. The existence of this apparent paradox, a form of the "healthy smoker effect", was confirmed in a subsequent IPF study, in which current smokers lived longer but had no survival advantage after adjustment for initial disease severity using the composite physiologic index (which captures the functional effects of ILD while excluding those of emphysema [86]). In this study, survival was significantly better in never-smokers compared with former smokers and also with the combined group of former and current smokers [87].

The coexistence of emphysema and IPF has drawn attention recently. The entity, known as combined pulmonary fibrosis and emphysema (CPFE), is characterised by the presence, on HRCT, of emphysema mainly in the upper lobes and fibrosis mainly in the lower lobes although the two patterns can be also admixed (fig. 1) [88]. This entity has some peculiarities. First, there is a spurious preservation of lung volumes in association with a disproportionate and sometimes devastating reduction in diffusing capacity of the lung for carbon monoxide and transfer coefficient of the lung for carbon monoxide. This means that serial forced vital capacity (FVC), the most reliable means of detecting disease progression in ILD, is likely to be less accurate in this context. This is especially important in IPF where even a minimal reduction in FVC (*i.e.* 5–10%) in 6 months has been associated with increased mortality [89]. These patients are more likely to develop pulmonary hypertension than IPF patients without emphysema with an important impact on survival [90], although it remains unclear whether a worse outcome merely reflects

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greater baseline disease severity when two separate disease processes are admixed. Importantly, it is sometimes difficult to discriminate between honeycombing and an admixture of emphysema and fibrosis on HRCT, a distinction that is pivotal in the diagnosis of IPF. CPFE can be also observed in the context of connective tissue disorders such as rheumatoid arthritis and systemic sclerosis [91, 92].

Clearly, smoking can indirectly affect the survival of patients with pulmonary fibrosis through the development of bronchogenic carcinoma. Certain intriguing similarities between lung cancer and IPF with regard to pathobiology and disease behaviour have been highlighted [93]. Conceivably, the development of lung cancer has a detrimental effect on survival of IPF patients. Recently, and in accordance with previous studies, it has been observed that patients with lung cancer have significantly lower median survival (38.7 months) than patients with IPF (63.9 months) [94]. This difference was mainly due to progression of lung cancer or to complications of IPF such as acute exacerbations after diagnostic or therapeutic procedures for lung cancer. Patients in the early stage of both diseases have better survival and a lower likelihood of complications than patients with severe disease. Therefore, early diagnosis and the accurate staging of severity in both diseases are equally important.

Conclusion

Our knowledge regarding the involvement of smoking in the pathogenesis of ILDs has evolved in the recent years. Smoking is now considered the principal pathogenetic factor for RB-ILD, DIP and PLCH, whereas it is an important cofactor, probably acting in synergy with genetic and environmental factors, for the development of other ILDs such as IPF and RA-ILD. It definitely has a significant impact on the survival of patients with either an isolated ILD or in cases of concurrent development of emphysema and lung cancer, two well established smoking-related lung diseases. Therefore, smoking cessation should be advised in all patients with ILDs.

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