Idiopathic pulmonary fibrosis: unmasking cryptogenic environmental factors

Coralynn Sack[1,2,3] and Ganesh Raghu[1,2]

Affiliations:
[1]Dept of Medicine, University of Washington, Seattle, WA, USA.
[2]Center for Interstitial Lung Disease, University of Washington, Seattle, WA, USA.
[3]Dept of Environmental and Occupational Health, University of Washington, Seattle, WA, USA.

Correspondence:
Ganesh Raghu, Center for Interstitial Lung Disease, University of Washington, Seattle, WA 98195, USA.
E-mail: graghu@uw.edu

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Occult environmental exposures are important factors in the pathogenesis of idiopathic pulmonary fibrosis. Research is needed to determine if eliminating these exposures prevents onset and/or disease progression in genetically susceptible persons. http://ow.ly/agd830mNGVU

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ABSTRACT Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic lung disease of unknown origin that is associated with high morbidity and mortality. In this perspective, we briefly review the current understanding of the pathophysiology of IPF and the importance of environmental triggers as a precipitant of disease. We discuss occult intrinsic and extrinsic environmental factors that affect the lung microenvironment and may contribute to the development and progression of disease. The clinical implications of this framework need to be further elucidated, because prompt identification and elimination of occult exposures may represent a novel treatment modality.

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Introduction

Among the large, heterogeneous and complex family of interstitial lung diseases (ILD), idiopathic pulmonary fibrosis (IPF) has emerged as a clinically distinct entity associated with progressive fibrosis and a relatively poor prognosis. IPF is usually diagnosed in older adults, in their sixth or seventh decade, who present with insidious onset of dyspnoea, with or without cough, and bibasilar crackles. Disease is limited to the lungs without extra-pulmonary manifestations. High resolution computed tomography (HRCT) imaging of the chest characteristically shows subpleural fibrosis with honeycombing; histopathology demonstrates usual interstitial pneumonia (UIP) with fibroblastic foci interspersed with normal lung tissue. The treatment of IPF has recently focused on targeting the fibrotic pathway, an aftermath of onset of the disease pathway. The two available anti-fibrotic agents, pirfenidone and nintedanib, have only a modest effect on slowing the decline of forced vital capacity (FVC), a marker of disease progression, and on overall mortality.

One of the distinctive features of IPF is the lack of an apparent aetiology. Current diagnostic criteria require the exclusion of secondary causes of ILD, including domestic and occupational exposures, connective tissue disease and drug toxicity [1–3]. However, numerous studies have shown that environmental risk factors, including viral infections, microaspiration, tobacco smoke, air pollution and occupational exposures, are associated with disease pathogenesis (table 1). It is apparent that exposure to environmental factors alone is not sufficient to cause disease, but such factors may increase the probability of developing IPF in a genetically susceptible individual [4].

Many of the risk factors that are associated with IPF are also implicated in the pathogenesis of other ILDs. This observation has several possible explanations. First, many cases of IPF may be misdiagnosed as such and may simply represent manifestations of advanced stage ILDs with defined environmental causes. Second, similar environmental exposures may fuel ongoing inflammation and fibrosis in the lung, regardless of disease subtype. Third, IPF may represent an overlapping spectrum of ILDs that share a final common pathway of fibrosis [5].

TABLE 1 Overt or occult environmental risk factors for idiopathic pulmonary fibrosis

	Risk factor
Intrinsic factors	Gastro-oesophageal reflux
	Microaspiration
	Microbiome
	Viral infection
Extrinsic factors	
Domestic/environmental	Tobacco smoke
	Wood fires
	Birds (including poultry, bird droppings, birdfeeders)
	Feather products (including feather duvets, comforter, pillows, jackets)
	Moulds (visible or unseen)
	Organic dusts
	Ventilation
	Hairspray
	Air pollution
Occupational[#]	Welding
	Farming/agriculture
	Hairdressing
	Dentists/dental technicians
	Metal dust
	Wood dust/paper mill factory workers
	Livestock, particularly birds
	Nuclear waste/radiation hazards
	Chemicals
	Aluminium, Corion®
	Stone cutting/sand/granite/silica
	Talc

[#]: these and other occupational exposures may be the cause of "occupational lung diseases" and thus not truly risk factors for patients diagnosed with idiopathic pulmonary fibrosis (IPF). Nevertheless, these may be occult if the patient otherwise diagnosed with IPF is not gainfully engaged with such environmental factors/exposures.

In this perspective, we briefly review the current understanding of the pathophysiology of IPF and suggest that IPF should be regarded as an "environmental" disorder manifesting in genetically susceptible individuals. We discuss intrinsic and extrinsic environmental factors that affect the lung microenvironment and may contribute to the development and progression of disease. We also explore the potential clinical implications of this framework, and propose a new treatment strategy for IPF that attempts to prevent the onset or abort ongoing fibrosis by identifying and eliminating occult environmental exposures.

Diagnosing idiopathic pulmonary fibrosis is not straightforward

The diagnosis of IPF is inherently challenging, particularly in the setting of evolving diagnostic criteria and diverse clinical practices. The classification scheme of the idiopathic ILDs has gone through revisions, and IPF did not emerge as a distinctive entity with specific clinical, radiographic and histopathological findings until consensus guidelines were published in 2000 [6]. Even with adherence to the 2011 diagnostic criteria, misdiagnosis of the disease is common [7]. Consequently, patients determined as having IPF both in the past and at present may be best interpreted as having a spectrum of overlapping ILDs.

Current recommendations for making an accurate diagnosis of IPF emphasise the importance of multidisciplinary discussions among experts, including experienced pulmonologists, radiologists and pathologists (and rheumatologists on a case-by-case basis) [3]. The key radiographic and histopathologic features of the pattern of UIP have recently been refined [3, 8]. In the appropriate clinical setting, the presence of UIP or probable UIP patterns on HRCT is sufficient to make a definitive diagnosis of IPF without surgical lung biopsy. Because some degree of uncertainty is often present, however, diagnosis frequently requires the integration of clinical, imaging and histologic information [3].

Many of the epidemiologic studies identifying risk factors for IPF were conducted in the 1990s and earlier, before current diagnostic criteria and advanced imaging technology were available. While UIP has been a recognised histologic pattern since the 1950s, the majority of patients involved in these studies did not undergo lung biopsy. Given the changing diagnostic criteria and likelihood of substantial disease misclassification, the results of epidemiologic studies must be interpreted cautiously.

The clinical history and exclusion of secondary causes of ILD are important, because a UIP pattern can be seen in many other fibrotic lung diseases, including connective tissue disease, asbestosis, hypersensitivity pneumonitis and sarcoidosis [9]. Identifying relevant pulmonary exposures requires a high index of suspicion, and failure to elicit the patient's history can lead to an incorrect presumption of IPF. A case series by Morell *et al.* [10] documented that 20 of 46 patients (43%) diagnosed with IPF based on the 2011 American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines actually had chronic hypersensitivity pneumonitis upon re-evaluation.

The restricted approval by regulatory agencies of pirfenidone and nintedanib as therapeutic anti-fibrotic agents for IPF may prompt off-label use for other fibrotic lung diseases. Physicians may be swayed to mislabel a diagnosis of IPF in an attempt to get prescription coverage for these drugs for non-IPF fibrotic lung diseases. Thus, diagnostic codes recorded by physicians may not reflect an accurate diagnosis of the fibrotic lung disease.

Environmental and genetic predisposing factors may be necessary for the development of the pulmonary fibrosis that we currently call "idiopathic" pulmonary fibrosis

The lungs are constantly exposed to the ambient environment, which contains a variety of particulates, microbes, noxious fumes and pollutants. These exposures can occur in and outside homes, in the workplace, or elsewhere. This interaction creates a continuous cycle of lung injury, wound healing and tissue repair. The current understanding of IPF pathobiology highlights the importance of inhalational exposures as a precipitant of lung remodelling and fibrosis (figure 1). Support for this mechanistic pathway comes from comparisons to other environmental ILDs, which share similar genetic predispositions and histopathology.

In both IPF and other ILDs, disease does not develop in everyone who is exposed to the same environmental factors. A genetic predisposition is evident from families with multiple members affected. Studies of both familial and sporadic cases of IPF have shown increased susceptibility with variation in genes associated with telomere length (*TERT*, *TERC*, *PARN*, *RTEL1*), cellular adhesion and integrity (*DSP*, *AKAP13*, *CTNNA*, *DPP9*), and the promoter region of the gene encoding mucin 5B (*MUC5B*) [4, 7, 11]. Recent observations suggest that some of these same genetic loci may be associated with an increased manifestation of chronic hypersensitivity pneumonitis [11]. Mice with silica-induced lung injury also display a transient increase in telomerase reverse transcriptase (TERT) [12]. The commonalities among these genetic pathways across a spectrum of fibrosing ILDs suggest that similar underlying pathobiologic pathways exist among different ILDs.

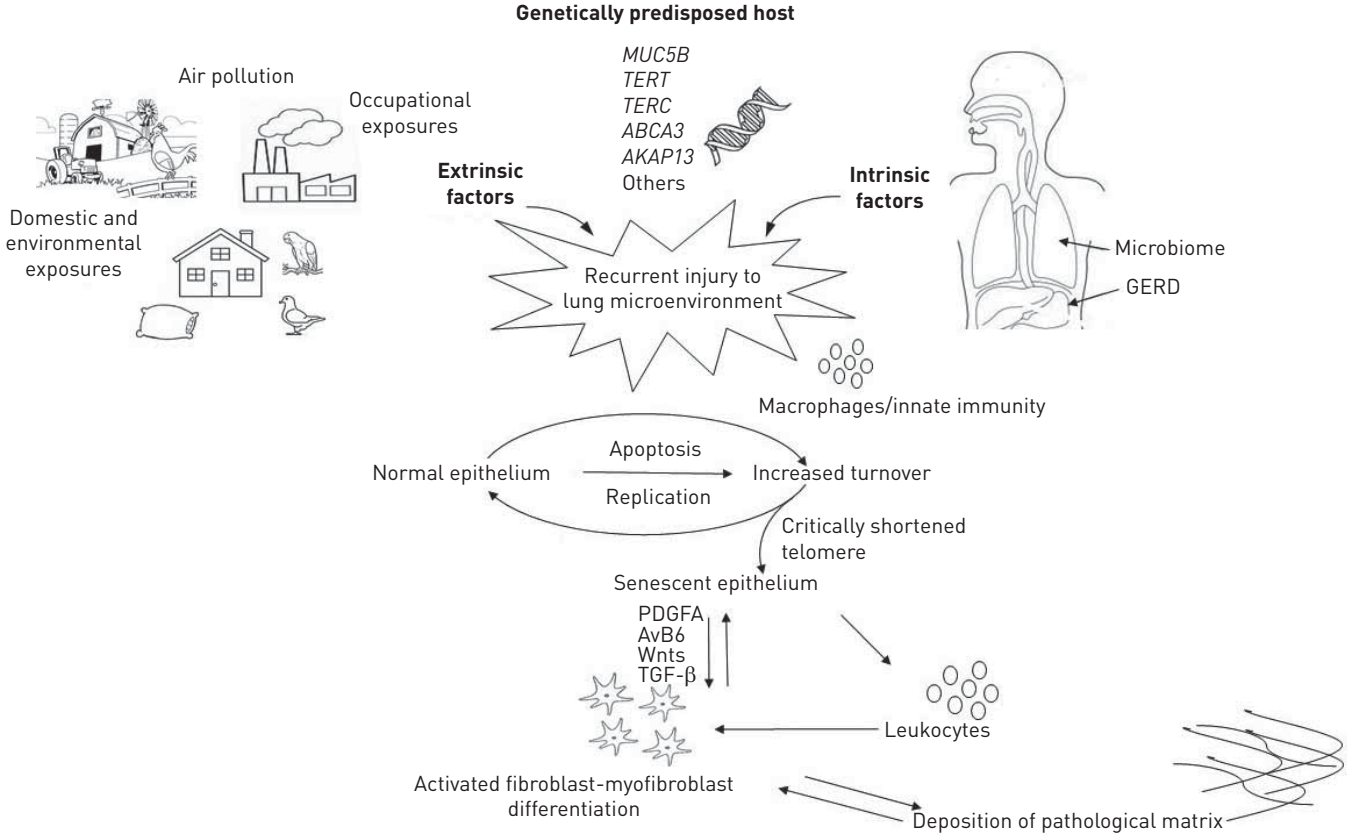

FIGURE 1 Proposed model for the pathogenesis of idiopathic pulmonary fibrosis. Extrinsic and intrinsic environmental exposures to the lung microenvironment cause recurrent airway injury. In the genetically predisposed host (mutations in mucin 5B (*MUC5B*), telomerase reverse transcriptase (*TERT*), telomerase RNA component (*TERC*), ATP binding cassette sub-family A3 (*ABCA3*), A-kinase anchor protein 13 (*AKAP13*), *etc*.), this cycle of increased epithelial turnover eventually leads to reprogramming to senescent epithelium. Fibroblasts are activated *via* pro-fibrotic mediators (platelet-derived growth factor subunit A (PDGFA), activating integrin B6 (avB6), Wnts, transforming growth factor-β (TGF-β)) that are released directly from abnormal epithelium, the activated innate immune system and leukocytes. Once activated, fibroblasts deposit pathological matrix, which leads to myofibroblast differentiation and progressive fibrosis. GERD: gastro-oesophageal reflux disease. Reproduced from [4] with permission.

In the current conception of IPF pathophysiology, the fibrogenic pathway is activated by recurrent airway injury leading to disordered repair of the epithelium. Oxidative stress or direct damage from air pollution exposure could potentially prime the epithelium to be more susceptible to injury from other exposures [13]. In genetically predisposed individuals, even minimal exposures to environmental agents, which include avian antigens and moulds, may be sufficient to cause disease.

Pathologic alteration of the epithelium is also more common with ageing, with telomere attrition contributing significantly to alveolar cell senescence [4]. Dead or dying epithelial cells stimulate the innate immune system, which plays a central role in wound healing. Whereas regulatory macrophages promote resolution of fibrosis through suppressive cytokines, M2 macrophages can secrete large amounts of pro-fibrotic cytokines and growth factors, such as fibroblast growth factor 2, platelet-derived growth factor, C-C motif chemokine ligand 18 and galectin-3 [14]. The abnormal epithelium activates mesenchymal cells either directly or through lymphocyte mediators, resulting in aberrant collagen production, extracellular matrix deposition, architectural distortion and the development of fibroblastic foci [4]. Once the cascade of fibrotic events has begun, it continues to self-perpetuate with progressive lung remodelling.

A similar process of airway injury, inflammation and fibrosis is observed in many of the other ILDs. In hypersensitivity pneumonitis, exposure to a range of exogenous inhaled particulates can cause an immunologic reaction with characteristic lymphocytic and granulomatous inflammation. In the setting of the pneumoconioses, such as asbestosis, the inhalation, deposition and retention of fibrogenic dusts is necessary for specific disease manifestation [15]. Disease does not develop in the majority of individuals who are exposed, but is dependent on multiple factors, including the dosage of particles inhaled, co-exposures and genetic susceptibility. Asbestosis and IPF share a similar distribution of disease as well as the characteristic UIP histologic pattern. Although asbestosis is distinguished by the appearance of the

causative asbestos bodies, the other pathological features are similar, including epithelial cell hyperplasia, basement membrane denudation, alveolar consolidation and fibrogenic foci that are spatially and temporally heterogeneous [16].

Lung tissue specimens from patients otherwise diagnosed as having IPF demonstrate a bioaccumulation of inorganic particles. Several studies have used polarised light microscopy, electron microscopy and X-ray fluoroscopy to examine the mineral content of lung parenchyma and mediastinal lymph nodes [17–21]. Even after excluding cases with potential occupational exposures, these studies showed higher levels of retained aluminium, silica and nickel in individuals with IPF compared to controls with other causes of ILD. While these data do not prove that the dust particles are involved in the pathophysiology of the disease, they do suggest that even occult exposures could be an important component of disease manifestation.

Intrinsic environmental factors

Gastro-oesophageal reflux

Gastro-oesophageal reflux, and consequent microaspiration, is a common comorbidity in individuals with IPF, with a suggested prevalence of >80% using oesophageal pH monitoring and manometry for diagnosis [22, 23]. Many patients have "silent reflux" and are asymptomatic, with no complaints of heartburn or with nonacidic reflux identified on oesophageal studies. While some controversy still exists, gastro-oesophageal reflux has been proposed as a cause of disease development and progression [24, 25]. It is unclear whether the acid or other constituents of gastric fluid, *e.g.* bile salts, pepsin, food particles or bacteria, are pathogenic [26].

The optimal strategy for diagnosing and treating abnormal gastro-oesophageal reflux in individuals with IPF is uncertain. Evidence from observational studies suggests that antacid therapy in individuals with IPF is associated with less lung function decline and improved survival [27, 28]. The 2015 ATS/ERS/Japanese Respiratory Society/Latin American Thoracic Society international guideline committee on the treatment of IPF made a conditional recommendation for antacid treatment in all patients with IPF [1]. Surgical treatment of hiatal hernia using Nissen fundoplication is also associated with the stabilisation of oxygenation levels and a decreased rate of FVC decline in patients with IPF [29, 30]. A recent phase 2 randomised clinical trial investigating the therapeutic benefits of surgical correction of gastro-oesophageal reflux disease (GERD) suggests potential benefits associated with laparoscopic Nissen fundoplication, and warrants further studies to determine safety and efficacy [31].

The lung microbiota

The lung microbiota, including bacteria, fungi, viruses and bacteriophages, has also become an area of recent scientific interest and a potential therapeutic target in IPF. Bacteria and viruses can cause direct injury to airway epithelial cells and indirect damage by activating the host immune response to infection [32]. The apparent importance of an intact host defence was suggested in the PANTHER-IPF (Prednisone, Azathioprine, and *N*-acetylcysteine: a Study that Evaluates Response in IPF) study, which showed worse outcomes in patients with IPF who were treated with immunosuppressants [33].

Viral infections, particularly human herpes virus and adenovirus, are thought to act as either exacerbating agents or initiators of disease. An increased incidence of human herpes viruses, such as cytomegalovirus, is seen in the lung samples of patients with IPF, acute IPF exacerbations and asymptomatic individuals who are at risk for familial IPF [34]. Many patients report a viral-type prodrome before the onset of disease symptoms [33]. These observations have led to the hypothesis that reactivation of latent viral infections may cause reprogramming of lung epithelial cells to produce fibrotic factors.

Studies demonstrate that individuals with IPF have a microbiome populated with a higher bacterial burden with more pathological strains. The aetiology of these changes to the microbial community is unknown, but may be due to recurrent gut microaspiration or a defective immune defence, or a consequence of the distorted parenchymal architecture from fibrosis [32]. Han *et al.* [35] found that *Prevotella*, *Veillonella* and *Cronobacter* species were the most prevalent species in a large cohort of individuals with IPF. After adjusting for confounders, they also found that the presence of *Streptococcus* and *Staphylococcus* species was associated with increased progression of disease. Although there was no group for comparison, the findings of this study are intriguing. Research is ongoing to determine whether chronic antibiotic administration can alter the lung microbiome and potentially affect disease progression [36].

Extrinsic environmental factors/exposures

Tobacco smoke

Tobacco exposure was one of the earliest and most consistently identified risk factors for IPF, with disease occurring more frequently in smokers. The association is particularly robust in individuals with familial IPF,

with smokers (former or current) having an odds ratio of 3.6 (95% CI 1.3–9.8) of developing disease [37]. Non-smokers have also been shown to have slower disease progression than either current or former smokers [38]. One cohort study suggested that current smokers may have a better prognosis than former smokers, but this was likely attributable to lead time bias from an earlier diagnosis rather than a true biologic mechanism [39].

Exposures at the workplace (occult occupational exposures)

The first epidemiologic evidence of the association between occupational exposures and IPF came from a case series that documented disease in certain professions with high amounts of dust and fume exposure, including industrial car cleaners, dairy farmers and welders [40]. Subsequent studies in the UK showed a higher incidence of IPF in industrialised areas and among men, who are more likely to have occupational exposures then women [41]. Subsequently there have been numerous case–control and cohort studies from diverse geographic areas, including the USA, Japan, Egypt and Korea, which have demonstrated similar associations. The most consistent data are for metal and wood dust exposure, with several studies also finding a dose–response relationship. Other occupational exposures and job activities that have been implicated include raising birds, hairdressing, stone cutting/polishing and exposure to livestock and vegetable dusts [42–46].

Occult domestic and environmental exposures

Many of the occupational exposures implicated above can also be present in domestic or recreational exposures of individuals with IPF. In particular, careful attention to both overt and occult exposure to organic dusts, unkempt ventilation, heating and cooling systems, moulds and avian antigens is warranted. A recent, provocative single-centre cohort study of individuals diagnosed with IPF at multidisciplinary discussion showed that individuals with pre-specified exposure to birds or moulds had a better survival rate compared to individuals without these pre-specified exposures [47]. In this study, a diagnosis of chronic hypersensitivity pneumonitis was excluded based on imaging features, bronchoalveolar lavage and presence of a specific IgG against exposed inhalants. This observation needs to be replicated and further explored. It is unclear whether patients with IPF and identifiable environmental exposures have a different natural history compared to individuals without these risk factors, or whether exposure remediation slowed the disease course.

Air pollution

Several recent studies highlight the importance of ambient air pollution in both the incidence and progression of IPF. Pollutants are a well-established cause of epithelial damage, oxidative stress and airway inflammation. There is also evidence that air pollution can precipitate epigenetic changes in the lung that enhance the pathogenicity of co-exposure to other antigens [13]. Through these mechanisms, air pollutants may initiate or contribute to alveolar damage and disordered repair. Three cohort studies in New Zealand, USA and France have shown that short-term exposure to pollutants is associated with accelerated decline in lung function and IPF exacerbations, while another recent study found that higher pollution exposure was associated with lower lung function [48–51]. A multi-city, population-based cohort study demonstrated that higher chronic exposure to air pollutants was associated with progression of subclinical ILD measurements on serial computed tomography scans [52]. In another multi-centre prospective study, an increase in the level of particles with a 50% cut-off aerodynamic diameter of 2.5 μm was associated with an increased risk of developing hypersensitivity pneumonitis in urban cities in India [53].

Clinical implications

While evidence supports the hypothesis that environmental exposures contribute to the manifestation and progression of IPF, the implications for clinical practice need to be further delineated. Research is needed to determine effective means of identifying pertinent exposures and how this can help refine our definition of IPF, and to investigate whether there are any therapeutic benefits to the elimination of these exposures. While the distortion in lung architecture that results from fibrosis may be irreversible, removing precipitants of ongoing airway injury may help to prevent further damage.

Determining the relevant exposures in pulmonary fibrosis is challenging. In part, this is due to the presumed long latency period before disease manifestation. IPF is usually diagnosed in older adults after a lifetime of chronic and mixed exposures, making it difficult for both physicians and researchers to isolate potentially relevant causes. Most epidemiologic studies have used participant questionnaires, which raises the concern that recall bias could increase the likelihood of finding a positive association. In the clinical realm, appointment time constraints, patient unawareness and complex exposure histories are all barriers to obtaining a comprehensive environmental and occupational history.

Standardised and detailed questionnaires designed according to local customs, cultural and geographical lifestyle and occupations could potentially address this gap. For example, a recent prospective cohort study of individuals with ILD in India identified relevant domestic exposures in >40% of the participants. Interestingly, 47% of these were attributed to home air coolers, which are believed to be a source of mould and pigeon antigen exposure. Most of these individuals were diagnosed with hypersensitivity pneumonitis rather than IPF; this was predominantly based on imaging characteristics (which can mimic UIP) and the exposure history [54].

In addition to detailed questionnaires, there is a need for better objective measurements of exposure. Having a trained professional, *e.g.* an industrial hygienist, assess the home and work environment could better identify and quantify exposures. Individual circulating or other biomarkers of exposure can help determine the internalised dose and sensitisation. Because many of these exposures are ubiquitous in the environment, it will be important to determine whether there is individualised susceptibility to certain exposures.

Better questionnaires and objective assessments of environmental exposures may also help to distinguish individuals with other fibrotic lung diseases. In particular, chronic exposure to occult environmental factors can cause chronic hypersensitivity pneumonitis with UIP features. Such patients could easily be diagnosed with IPF if a careful and thorough exposure history is not obtained. Based on experience within our own institution and on observations by Morell *et al.* [10], ⩾25% of patients referred for management of IPF may actually have chronic hypersensitivity pneumonitis or other fibrotic lung diseases.

The benefits of eliminating exposures need to be explored as a therapeutic approach. As outlined above, treatment of GERD may slow progression and perhaps improve survival in IPF. However, there is a paucity of data investigating similar outcomes for other environmental exposures. Measurements made during home and workplace assessments by a trained professional could lead to environmental remediation and potential health improvement. The efficacy of such interventions in reducing respiratory symptoms has been demonstrated in asthma [55]. No studies have been performed in individuals with IPF. We believe that avoiding intrinsic and extrinsic exposures that are known to cause lung injury, inflammation and fibrosis may minimise further insults to the fibrotic lung and could slow down disease progression. Hence, eliminating these environmental exposures in a patient with IPF could be an adjunct, cost-effective "treatment strategy" to approved pharmacologic modalities and the current standard of care.

Conclusions

We suggest that it is time to incorporate accumulating scientific evidence of the interaction between environmental exposures and genetic susceptibility into clinical practice. Research should focus on "environmental factors", *i.e.* those "intrinsic" and "extrinsic" factors that may play important roles in the pathogenesis of IPF, especially in genetically predisposed individuals living in polluted urban areas. There is a critical need for more research to characterise relevant exposures in IPF patients through the development of standardised questionnaires, identification and validation of circulating biomarkers, and investigations by industrial hygienists. Work is needed to understand the ecogenetics of disease pathobiology and how gene–environment interactions impact disease development and progression. Finally, there is an absolute need for clinical studies to determine whether the elimination of both intrinsic and extrinsic environmental factors can have an impact on the prognosis of patients diagnosed with IPF based on current understanding, guidelines and standard of care.

In essence, we hope that our perspective will increase awareness of occult intrinsic and extrinsic environmental factors that may be contributing to the pathogenesis of "idiopathic" pulmonary fibrosis and prompt well-designed investigations of these factors in future studies. We believe that such studies will 1) demonstrate that the vast majority of patients with "IPF" have occult exposures known to induce lung injury and/or perpetuate progression of pulmonary fibrosis; 2) provide evidence that avoiding these exposures can help prevent further injury to the lung microenvironment, particularly in genetically susceptible individuals and in patients with "early UIP/IPF"; and 3) eventually reduce the incidence of true IPF over time.

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Conflict of interest: C. Sack has nothing to disclose. G. Raghu reports research grants for IPF studies from National Institutes of Health during the conduct of the study; has acted as a consultant on IPF studies for Biogen, BMS, Fibrogen, Gilead Sciences, Promedior, Roche-Genentech, Bellerophan and Nitto, has received personal fees, non-financial support and has acted as a consultant for Boehringer-Ingelheim and Sanofi, and has received personal fees and has acted as a consultant for Patara and Veracyte, outside the submitted work.

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