Current Pulmonology Reports (2018) 7:118–125
https://doi.org/10.1007/s13665-018-0210-7

INTERSTITIAL LUNG DISEASE (A. HAJARI CASE, SECTION EDITOR)

Risk Factors for the Development of Idiopathic Pulmonary Fibrosis: a Review

Tanzira Zaman[1] · Joyce S. Lee[1]

Published online: 16 October 2018

Abstract

Purpose of Review Idiopathic pulmonary fibrosis (IPF) is an invariably progressive disease. Current treatment options simply slow disease progression, and better therapeutic options are needed. We aimed to review an emerging literature on risk factors associated with the development of IPF.

Recent Findings There is increasing data to support the role of intrinsic risk factors (e.g., genetics, aging, sex, lung microbiome), comorbidities (e.g., gastroesophageal reflux, obstructive sleep apnea, diabetes mellitus, herpes virus infection), and extrinsic risk factors (e.g., cigarette smoking, environmental exposures, air pollution) in IPF development. These risk factors may independently increase susceptibility for IPF or act in a synergistic fashion to contribute to increased risk for disease development.

Summary Various risk factors have been identified in IPF development that fit within the current paradigm of disease pathogenesis. Further investigation of these risk factors may help us better understand the pathophysiology of IPF and may guide future therapeutic interventions.

Keywords Aging · Gastroesophageal reflux · Obstructive sleep apnea · Cigarette smoking · Genetics

Introduction

Idiopathic pulmonary fibrosis (IPF) is a disease of progressive scarring of the lung associated with high morbidity and mortality [1]. IPF is a heterogeneous disease with a variable clinical course [2]. The leading conceptual model of the pathogenesis of IPF suggests recurrent insults or microinjuries to the alveolar epithelium resulting in aberrant activation of both epithelial cells and fibroblasts and, ultimately, dysregulated collagen deposition, leading to the irreversible fibrosis associated with the disease [3].

The treatment options available in IPF have demonstrated modest clinical gains [4•, 5, 6•]. Consequently, there is an ongoing need for additional therapeutic options. Identification of risk factors for IPF can serve as starting points for understanding the complex and varied pathophysiology of this disease, as well as serve to better phenotype this disease and identify novel targets for therapy. In this review, we summarize several risk factors associated with IPF based on their hypothesized role in the pathogenesis of IPF (Fig. 1).

This article is part of the Topical Collection on *Interstitial Lung Disease*

✉ Joyce S. Lee
Joyce.lee@ucdenver.edu

[1] Department of Medicine, University of Colorado Denver, Aurora, CO, USA

Intrinsic Risk Factors

Genetics of IPF

Studies of familial clustering of pulmonary fibrosis provided the first clue toward a genetic susceptibility to IPF [7]. Kaur et al. grouped the genetic variants associated with predisposition to IPF into four broad categories based on their suspected role in the pathogenesis of IPF: There are genes that can affect alveolar stability, most importantly genes encoding surfactant proteins A and C—*SFTPC*, *SFTPA1*, *SFTPA2*; genes associated with accelerated cell senescence via disrupted telomerase function, most importantly *TERT*, *TERC*, but also *DKC1*, *PARN*, and *RTEL1*; genes affecting host defense, which include the human airway mucin *MUC5B* and the immune regulator *TOLLIP*; and a gene that impairs integrity of the epithelial barrier, variants of *DSK*, a gene that encodes a mutant desmosomal protein [8].

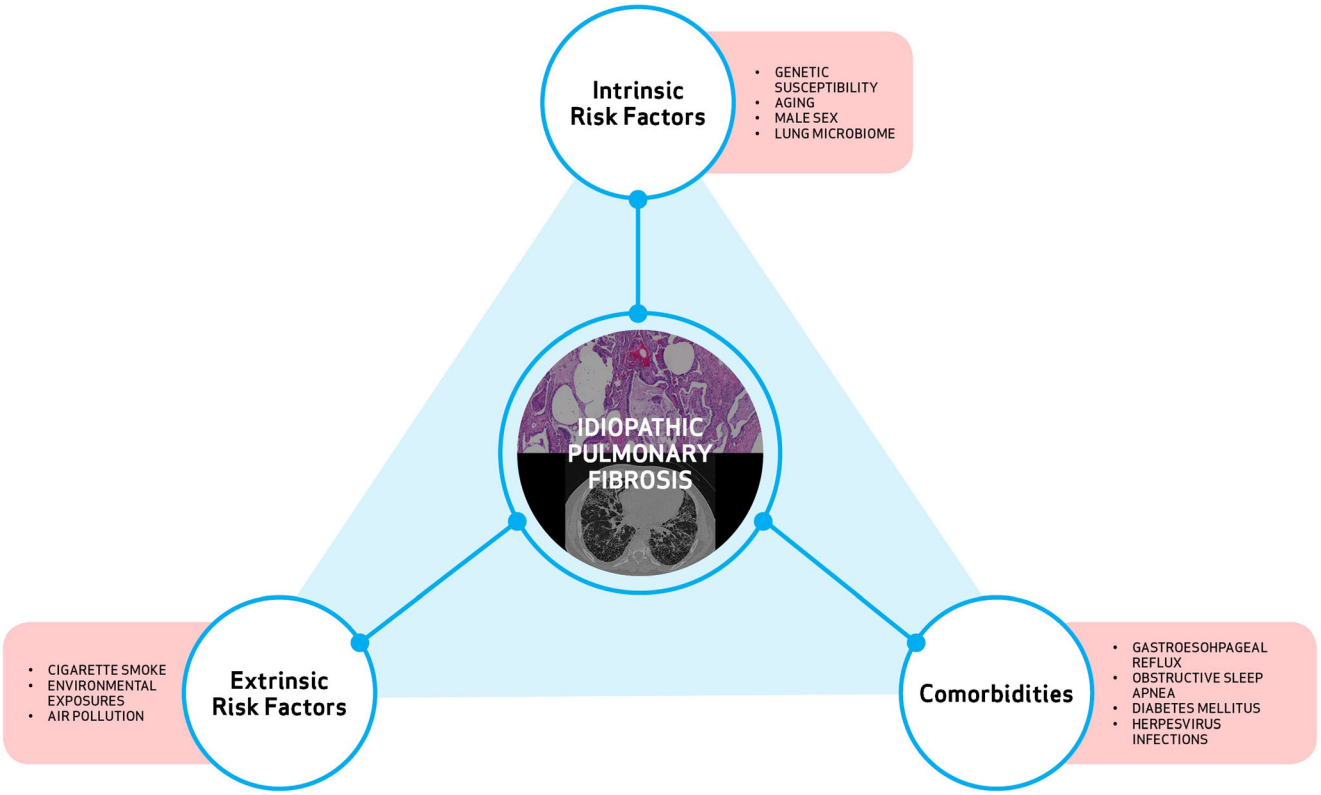

Fig. 1 The various described risk factors may independently increase susceptibility for idiopathic pulmonary fibrosis or act in an additive or synergistic fashion with each other to contribute to increased risk for the development of disease. Histopathology image courtesy of Dr. Carlyne Cool

Results from two genome-wide association studies (GWAS) have identified multiple loci associated with risk for IPF (Table 1). While most of these are rare, the GWAS studies found that the variants of *MUC5B* and *TOLLIP* are common, which is defined as minor allele frequency > 5% [16, 27]. In control subjects, the minor allele is associated with higher expression of the *MUC5B* in lung tissue, whereas in established IPF, MUC5B levels are uniformly elevated regardless of genotype [28]. While the minor allele of *MUC5B* has been postulated to account for approximately 30% of the risk for developing IPF, it is also associated with better survival than the wild-type genotype in established IPF [29]. Similarly, while the *TOLLIP* minor allele is protective against the development of IPF, it is associated with worse survival in established IPF [27]. Further work is required to elucidate the role of these genes in the pathobiology of IPF; however, the variable outcomes associated with specific genotypes has implications on heterogeneity within the disease and should be accounted for in future IPF research in which mortality is an outcome.

Table 1 Genetic associations in idiopathic pulmonary fibrosis and their proposed role in pathogenesis

Proposed mechanism	Pathologic effects	Associated genes
Alveolar instability	Increased endoplasmic reticulum stress Activation of the unfolded protein response Apoptotic signaling	*SFTPC* [9–11], *SFTPA1* [12], *SFTPA2* [13] *ABCA3* [14, 15]
Early cell senescence	Telomere shortening Impaired telomere stabilization	*TERT* [7, 11, 16, 17], *TERC* [18–20] *DKC1* [21], *TINF2* [21, 22], *PARN* [23, 24] *RTEL1* [23, 25, 26]
Altered host defense	Increased mucous accumulation Proinflammatory milieu Reduced pathogen recognition	*MUC5B* [16, 27–29], *MUC2* [16] *TOLLIP* [27], *TLR3* [22], *HLA-DRB1* [30], *IL1RN* [31], *IL8* [32, 33]
Cell-cell adhesion	Loss of epithelial integrity	*DSP* [16], *DPP9* [16]

Adapted from Kaur et al. [8]

Aging

As IPF is most commonly diagnosed in the elderly, senescence on both the organismal and cellular levels are of relevance. Population studies have demonstrated an increased incidence and prevalence of IPF with older age [34], with the majority of cases diagnosed in the fifth through seventh decades of life. Indeed, premature presentation with pulmonary fibrosis in patients with dyskeratosis congenita, a disease of accelerated aging, led to the sequencing of the telomerase genes that have been associated with IPF [35, 36]. However, shortened telomeres in peripheral blood leukocytes [17] and lung tissue [18, 37] of IPF patients relative to controls have been reported even in those IPF patients without mutations in the telomerase genes. Beyond abnormal telomere shortening, the molecular basis underlying the susceptibility of the aging lung to a dysregulated response to lung microinjury includes a senescent phenotype in IPF lung fibroblasts that alters the ratio of proliferation to apoptosis [38]. Other mechanisms include the accumulation of genetic and epigenetic variability [16, 39], decreased alveolar stability, and loss of the capacity for differentiation (and thus repair) among bone marrow-derived mesenchymal stem cells [40], all of which promote fibrosis.

Male Sex

Across the world, IPF is more prevalent in men, who account for approximately 70% of all cases globally, based on data derived from national registries and international trials of IPF [41]. The exact basis behind the sex bias is unclear. Initially, the increased risk among men was attributed to inhaled exposures, such as tobacco smoking or occupational exposures, which historically have been more common among men. However, sex-stratified analyses have demonstrated that specifically men with inhalational exposures are more likely to develop IPF than women [42–44], indicating an interaction between sex and exposure.

Sex hormones have been hypothesized as one rationale for the sex difference, especially in the bleomycin mouse model of pulmonary fibrosis. This animal model of pulmonary fibrosis demonstrates a similar sexual dimorphism as observed in humans with male mice being more susceptible to disease [45]. Animal models suggest that male sex hormones are associated with accelerated fibrosis [46], whereas female sex hormones may be protective against pulmonary fibrosis [47]. The effects of sex hormones are organ- and species-specific, though, so it is imperative to study sex hormones in human samples to determine their role in IPF.

The Lung Microbiome

The role of constituent micro-organisms in the development and progression of IPF has been recently investigated. Within the current paradigm of IPF pathogenesis, microbes might serve as a stimulus for microinjury. In a prospective study, Molyneaux et al. reported that subjects with IPF had greater bacterial burden in bronchoalveolar lavage (BAL) fluid compared to controls and subjects with moderate COPD. Among IPF subjects, greater bacterial burden predicted worse survival. Lower bacterial burden was independently associated with the *MUC5B* minor risk allele but not lung function [48]. As such, studies of bacteria may shed greater light on the mechanism by which common genetic variants affect risk for and outcomes in IPF.

Specific bacterial genera may be associated with both disease development and prognosis: In a prospective, but uncontrolled study of subjects with IPF, Han et al. found that *Streptococcus* and *Staphylococcus* were associated with disease progression [49]. While the prognostic value of these specific organisms was not validated in a subsequent study, *Streptococcus* also was found to be more abundant in the BAL of subjects with IPF compared to healthy controls and COPD [48], suggesting a role for bacteria in the pathogenesis of IPF. Prospective, controlled studies with greater follow-up time and larger populations are necessary to continue the evaluation of these preliminary findings.

Last, trials of antimicrobials in IPF may provide new insight into the relationship between the lung microbiome and disease outcomes in IPF. There are currently two active trials of co-trimoxazole in IPF (NCT02759120 and EudraCT number 2014-004058-32) to follow-up on an initial study that showed no change in pulmonary function, but a possible trend toward reduced mortality [50]. It will be important to discern whether outcomes in these trials are driven by differences in acute exacerbations or infection-related deaths versus slowed progression of disease. This will help determine whether bacteria contribute to pathogenesis of IPF or if they simply cause secondary complications.

Comorbidities

Gastroesophageal Reflux

Gastroesophageal reflux (GER) with subsequent secondary and chronic microaspiration has been hypothesized as a contributor to the pathogenesis of IPF due to a repetitive injury to the lung [51]. Several studies have reported a high prevalence of GER in patients with IPF. A single-center retrospective analysis of CT scans found that hiatal hernia, which is associated with GER, was significantly more prevalent in patients with IPF compared to those with COPD or asthma [52]. In a prospective study, Raghu et al. found that 80% of patients with well-characterized IPF had GER as determined by 24-h ambulatory pH monitoring. In those patients who were not being treated with PPI at the time of pH monitoring, the prevalence

was greater at 87% [53]. However, these prevalence studies do not answer the question of causation: does GER contribute to the pathophysiology of IPF, or does IPF cause GER?

While there are few biologic studies investigating the directionality of this relationship, there are some emerging treatment data to support the impact of GER and secondary microaspiration in patients with IPF (Table 2). In retrospective analyses, the use of anti-acid therapy has been associated with longer survival time [54, 56]. However, data on the effect of anti-acid therapy on lung function changes have been mixed [55, 57]. More recently, the results of a randomized controlled trial of laparoscopic anti-reflux surgery in IPF suggest a possible benefit on lung function [58]. These findings provide compelling (if indirect) support for a pathogenic role for GER in IPF.

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is common in IPF, with prevalence estimates from 59 to 88% [59–62]. Screening questionnaires have poor specificity in the IPF population and are thus of limited clinical utility in ruling out those with OSA [59].

OSA is characterized by periodic apneas and/or hypopneas caused by partial or complete collapse of the upper airway. As the respiratory muscles continue to make efforts toward inspiration despite proximal obstruction, there are consequently large swings in pleural pressure that may result in tractional microinjury to the alveoli [63]. These recurrent alveolar microinjuries leading to aberrant epithelial cell activation and fibroblast recruitment have been proposed as mechanisms involved in the pathogenesis of IPF [3].

The areas of the lung that are most susceptible to physiologic alveolar collapse, as well as recurrent stretch injury given their proximity to the pleura, are the subpleural and basilar portions of the lung [64], which is the characteristic distribution of fibrosis in IPF. The hypothesis that OSA can cause this type of microinjury is supported by an association between OSA and biomarkers of extracellular matrix remodeling, surfactant protein A (SP-A), and matrix metalloprotein-7 (MMP-7), as well as with subclinical interstitial lung disease, as reported from data derived from a large cohort of community-dwelling adults without lung disease [65]. Similarly, serum levels of the glycoprotein KL-6, which is associated with both lung injury and survival in IPF [66], are elevated in OSA [67].

Table 2 Summary of studies evaluating the relationship between medical and/or surgical therapy for gastroesophageal reflux and outcomes in IPF

Study	Design	Methods and specified outcomes	Results
Lee et al. [54]	Multicenter retrospective study	Association between survival time and several GER-related variables	Use of anti-acid medication was independently associated with improved survival on multivariate analysis ($p = 0.03$).
Lee et al. [55]	Pooled analysis from three multinational randomized controlled trials in IPFnet (PANTHER-IPF, STEP-IPF, ACE-IPF)	Analysis of FVC decline in subjects in the placebo arm of IPFnet trials using anti-acid therapy ($n = 124$) versus no anti-acid therapy ($n = 188$). Primary outcome was the estimated change in FVC at 30 weeks.	Subjects taking anti-acid therapy had a smaller decline in FVC ($p = 0.05$).
Ghebremariam et al. [56]	Multicenter retrospective study	Association between use of anti-acid medication and survival	Use of anti-acid medication for at least 12 months was associated with improved survival ($p = 0.006$) over 5 years.
Kreuter et al. [57]	Pooled analysis from three multinational, prospective drug trials in IPF (CAPACITY 004 and 006) and ASCEND 016	Analysis of disease outcomes in subjects from the placebo arm of IPF drug trials stratified by use of anti-acid therapy ($n = 291$) versus no anti-acid therapy ($n = 333$) Primary outcome was disease progression (all-cause death, absolute FVC decrease by 10%, or 6MWD decrease by $\geq$ 50 m)	There was no change in disease progression by any of the prespecified criteria between the two groups.
Raghu et al. [58]	Multicenter randomized controlled trial	Patients with IPF ($n = 58$) and abnormal GER were randomized 1:1 to laparoscopic fundoplication or no surgery. Primary outcome was change in FVC from baseline to 48 weeks.	There was a nonsignificant benefit in the adjusted rate of FVC change in the fundoplication arm.

GER gastroesophageal reflux, *FVC* forced vital capacity, *DLCO* diffusion capacity of the lung for carbon monoxide

While these findings lend plausibility to a link between OSA and IPF, directionality has not been established; in other words, whether OSA precedes IPF or vice versa has not been determined. Further research is needed to clarify the antecedent process, as well as to determine whether therapy for OSA can be of benefit in the management of IPF.

Diabetes Mellitus

Diabetes mellitus (DM) is a systemic disease that commonly causes end-organ damage to the kidneys, nerves, and the cardiovascular system. Less well-established is a definitive effect on the lung, although several lines of research have established a link between DM and pulmonary fibrosis.

In a systematic review, Klein et al. identified seven cross-sectional studies between 1975 and 2009 that reported an association between DM and indices of restriction (forced vital capacity (FVC) and diffusion capacity of the lung for carbon monoxide (DLCO)) on pulmonary function testing [68]. Several autopsy studies have reported increased thickening of the basal lamina of alveoli in DM relative to controls.

Further, case-control studies from Japan and Mexico have reported a fourfold greater adjusted odds for DM among those with IPF [69, 70]. A large retrospective cohort study using data from the Kaiser Permanente Medical Care Program in northern California reported a 50% increase in the risk for pulmonary fibrosis among patients with DM, adjusting for age, sex, race, education, obesity, and smoking history [71]. It is important to note that pulmonary fibrosis cases were identified by listing as the primary discharge diagnosis from a hospitalization or the underlying cause of death, so the definition of pulmonary fibrosis was not strictly restricted to IPF in this study.

The main theory regarding the mechanism by which DM may be a risk factor for IPF relates to hyperglycemia-mediated overproduction of advanced glycosylation end products leading to oxidative injury and subsequent overexpression of profibrotic cytokines, fibroblast proliferation, and extracellular matrix deposition [72].

Metformin, the most commonly prescribed oral drug for DM, has been demonstrated in vitro to attenuate epithelial-to-mesenchymal transition mediated by transforming growth factor-beta (TGF-β). In vivo studies of metformin in the bleomycin mouse model of pulmonary fibrosis have demonstrated attenuation [73] and, more recently, reversal of lung fibrosis [74]. Further study is required in human subjects.

Herpesvirus Infection

Chronic viral infection, particularly by members of the Herpesviridae family, has been proposed as a mechanism by which alveolar epithelial cells may undergo repetitive injury leading to a dysregulated repair response in IPF. Evaluation of lung tissue and serum from IPF subjects have found these viruses to be common in IPF: 97% of IPF subjects tested positive for at least one of the following herpesviruses compared to 35% of controls: Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpesvirus-7 (HHV-7), and human herpesvirus-8 (HHV-8) [75]. The more frequent finding of EBV and CMV, specifically, in the lung tissue of subjects with IPF over controls has been demonstrated in multiple studies [76, 77]. Mechanisms by which latent viral infection may contribute to the pathogenesis of IPF include activation of the epithelial-to-mesenchymal transition pathway [78], as well as the pro-fibrotic mediator TGF-β [79].

Extrinsic Risk Factors

Cigarette Smoke

A history of cigarette smoking, whether current or former, is overrepresented in IPF, with prevalence ranging from 41 to 83% [80]. In a multicenter US case-control study, Baumgartner et al. explored the odds for smoking in IPF cases versus age- and sex-matched controls. These investigators found that IPF cases reported significantly greater odds for smoking exposure compared to controls [42]. A study of families with IPF also found that a history of smoking cigarettes was associated with the development of familial interstitial pneumonia [81].

Cigarette smoke exposure has a myriad of effects in the lung that are associated with the development of IPF. Alveolar epithelial cells exposed to cigarette smoke in vitro overexpress genes associated with epithelial-to-mesenchymal transition and acquire a fibroblast-like phenotype [82]. Nicotine itself can induce the production of TGF-β [83], an important mediator of fibrosis in IPF. Cigarette smoking is also associated with both acceleration of telomere shortening [84] and endoplasmic reticulum stress [85, 86]. Aside from these various molecular effects, the act of smoking involves repetitive mechanical stretch, which has been linked to microinjury to the lung by increasing epithelial permeability, promoting the production of reactive oxidative species, and impairing tissue regeneration [87].

Environmental Exposures

Certain occupational and environmental exposures have also been associated with IPF. In a meta-analysis of six case-control studies, wood dust, metal dust, stone/sand, agricultural/farming, and livestock were all significantly more likely in IPF cases versus controls [88]. Analysis of autopsy results from the UK [89] and Japan [90] has reported higher odds of death from IPF among metal workers. A single study in Northern Italy has suggested an increased risk of incident IPF

in association with air pollution, although the findings did not achieve statistical significance [91].

Conclusion

Various risk factors have been identified in the development of IPF that fit within the current paradigm of disease pathogenesis. As IPF is a heterogeneous disease, the presence of specific risk factors may help define and refine phenotypes and endotypes of this disease to better develop personalized care for individual patients with IPF. Additionally, a better understanding of how risk translates into disease can aid in earlier recognition of disease in those at risk and shed insight into the development of adjunct or novel therapeutic options in this invariably progressive disease.

Funding This study was financially supported by the NIH/NHLBI K23 HL138131 and T32 HL007085.

Compliance with Ethical Standards

Conflict of Interest Joyce Lee reports grants from NIH and personal fees from Celgene, Genetech, and Boehringer Ingelheim for serving on advisory boards, outside the submitted work.

Tanzira Zaman declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. Lederer DJ, Martinez FJ. Idiopathic pulmonary fibrosis. N Engl J Med. 2018;378(19):1811–23.
2. Fell CD. Idiopathic pulmonary fibrosis: phenotypes and comorbidities. Clin Chest Med. 2012;33(1):51–7.
3. King TE Jr, Pardo A, Selman M. Idiopathic pulmonary fibrosis. Lancet. 2011;378(9807):1949–61.
4.• King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2083–92 **This study led to the approval of the first pharmacologic therapy in idiopathic pulmonary fibrosis.**
5. Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet. 2011;377(9779):1760–9.
6.• Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2071–82 **This study led to the approval of the first pharmacologic therapy in idiopathic pulmonary fibrosis.**
7. Kropski JA, Blackwell TS, Loyd JE. The genetic basis of idiopathic pulmonary fibrosis. Eur Respir J. 2015;45(6):1717–27.
8. Kaur A, Mathai SK, Schwartz DA. Genetics in idiopathic pulmonary fibrosis pathogenesis, prognosis, and treatment. Front Med (Lausanne). 2017;4:154.
9. Whitsett JA, Wert SE, Weaver TE. Alveolar surfactant homeostasis and the pathogenesis of pulmonary disease. Annu Rev Med. 2010;61:105–19.
10. Mulugeta S, Nguyen V, Russo SJ, Muniswamy M, Beers MF. A surfactant protein C precursor protein BRICHOS domain mutation causes endoplasmic reticulum stress, proteasome dysfunction, and caspase 3 activation. Am J Respir Cell Mol Biol. 2005;32(6):521–30.
11. van Moorsel CH, Hoffman TW, van Batenburg AA, Klay D, van der Vis JJ, Grutters JC. Understanding idiopathic interstitial pneumonia: a gene-based review of stressed lungs. Biomed Res Int. 2015;2015:304186.
12. Nathan N, Giraud V, Picard C, Nunes H, Dastot-Le Moal F, Copin B, et al. Germline SFTPA1 mutation in familial idiopathic interstitial pneumonia and lung cancer. Hum Mol Genet. 2016;25(8):1457–67.
13. Wang Y, Kuan PJ, Xing C, Cronkhite JT, Torres F, Rosenblatt RL, et al. Genetic defects in surfactant protein A2 are associated with pulmonary fibrosis and lung cancer. Am J Hum Genet. 2009;84(1):52–9.
14. Yamano G, Funahashi H, Kawanami O, Zhao LX, Ban N, Uchida Y, et al. ABCA3 is a lamellar body membrane protein in human lung alveolar type II cells. FEBS Lett. 2001;508(2):221–5.
15. Weichert N, Kaltenborn E, Hector A, Woischnik M, Schams A, Holzinger A, et al. Some ABCA3 mutations elevate ER stress and initiate apoptosis of lung epithelial cells. Respir Res. 2011;12:4.
16. Fingerlin TE, Murphy E, Zhang W, Peljto AL, Brown KK, Steele MP, et al. Genome-wide association study identifies multiple susceptibility loci for pulmonary fibrosis. Nat Genet. 2013;45(6):613–20.
17. Stuart BD, Lee JS, Kozlitina J, Noth I, Devine MS, Glazer CS, et al. Effect of telomere length on survival in patients with idiopathic pulmonary fibrosis: an observational cohort study with independent validation. Lancet Respir Med. 2014;2(7):557–65.
18. Alder JK, Chen JJ, Lancaster L, Danoff S, Su SC, Cogan JD, et al. Short telomeres are a risk factor for idiopathic pulmonary fibrosis. Proc Natl Acad Sci U S A. 2008;105(35):13051–6.
19. Armanios MY, Chen JJ, Cogan JD, Alder JK, Ingersoll RG, Markin C, et al. Telomerase mutations in families with idiopathic pulmonary fibrosis. N Engl J Med. 2007;356(13):1317–26.
20. Cronkhite JT, Xing C, Raghu G, Chin KM, Torres F, Rosenblatt RL, et al. Telomere shortening in familial and sporadic pulmonary fibrosis. Am J Respir Crit Care Med. 2008;178(7):729–37.
21. Kim SH, Kaminker P, Campisi J. TIN2, a new regulator of telomere length in human cells. Nat Genet. 1999;23(4):405–12.
22. O'Dwyer DN, Armstrong ME, Trujillo G, Cooke G, Keane MP, Fallon PG, et al. The Toll-like receptor 3 L412F polymorphism and disease progression in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2013;188(12):1442–50.
23. Stuart BD, Choi J, Zaidi S, Xing C, Holohan B, Chen R, et al. Exome sequencing links mutations in PARN and RTEL1 with familial pulmonary fibrosis and telomere shortening. Nat Genet. 2015;47(5):512–7.
24. Tummala H, Walne A, Collopy L, Cardoso S, de la Fuente J, Lawson S, et al. Poly(A)-specific ribonuclease deficiency impacts telomere biology and causes dyskeratosis congenita. J Clin Invest. 2015;125(5):2151–60.
25. Vannier JB, Sarek G, Boulton SJ. RTEL1: functions of a disease-associated helicase. Trends Cell Biol. 2014;24(7):416–25.

26. Cogan JD, Kropski JA, Zhao M, Mitchell DB, Rives L, Markin C, et al. Rare variants in RTEL1 are associated with familial interstitial pneumonia. Am J Respir Crit Care Med. 2015;191(6):646–55.
27. Noth I, Zhang Y, Ma SF, Flores C, Barber M, Huang Y, et al. Genetic variants associated with idiopathic pulmonary fibrosis susceptibility and mortality: a genome-wide association study. Lancet Respir Med. 2013;1(4):309–17.
28. Seibold MA, Wise AL, Speer MC, Steele MP, Brown KK, Loyd JE, et al. A common MUC5B promoter polymorphism and pulmonary fibrosis. N Engl J Med. 2011;364(16):1503–12.
29. Peljto AL, Zhang Y, Fingerlin TE, Ma SF, Garcia JG, Richards TJ, et al. Association between the MUC5B promoter polymorphism and survival in patients with idiopathic pulmonary fibrosis. JAMA. 2013;309(21):2232–9.
30. Fingerlin TE, Zhang W, Yang IV, Ainsworth HC, Russell PH, Blumhagen RZ, et al. Genome-wide imputation study identifies novel HLA locus for pulmonary fibrosis and potential role for auto-immunity in fibrotic idiopathic interstitial pneumonia. BMC Genet. 2016;17(1):74.
31. Korthagen NM, van Moorsel CH, Kazemier KM, Ruven HJ, Grutters JC. IL1RN genetic variations and risk of IPF: a meta-analysis and mRNA expression study. Immunogenetics. 2012;64(5):371–7.
32. Ahn MH, Park BL, Lee SH, Park SW, Park JS, Kim DJ, et al. A promoter SNP rs4073T>A in the common allele of the interleukin 8 gene is associated with the development of idiopathic pulmonary fibrosis via the IL-8 protein enhancing mode. Respir Res. 2011;12:73.
33. Richards TJ, Kaminski N, Baribaud F, Flavin S, Brodmerkel C, Horowitz D, et al. Peripheral blood proteins predict mortality in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2012;185(1):67–76.
34. Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2006;174(7):810–6.
35. Utz JP, Ryu JH, Myers JL, Michels VV. Usual interstitial pneumonia complicating dyskeratosis congenita. Mayo Clin Proc. 2005;80(6):817–21.
36. Wolters PJ, Collard HR, Jones KD. Pathogenesis of idiopathic pulmonary fibrosis. Annu Rev Pathol. 2014;9:157–79.
37. Snetselaar R, van Batenburg AA, van Oosterhout MFM, Kazemier KM, Roothaan SM, Peeters T, et al. Short telomere length in IPF lung associates with fibrotic lesions and predicts survival. PLoS One. 2017;12(12):e0189467.
38. Alvarez D, Cardenes N, Sellares J, Bueno M, Corey C, Hanumanthu VS, et al. IPF lung fibroblasts have a senescent phenotype. Am J Physiol Lung Cell Mol Physiol. 2017;313(6):L1164–73.
39. Vassilakis DA, Sourvinos G, Spandidos DA, Siafakas NM, Bouros D. Frequent genetic alterations at the microsatellite level in cytologic sputum samples of patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2000;162(3 Pt 1):1115–9.
40. Leung J, Cho Y, Lockey RF, Kolliputi N. The role of aging in idiopathic pulmonary fibrosis. Lung. 2015;193(4):605–10.
41. Jo HE, Glaspole I, Grainge C, Goh N, Hopkins PM, Moodley Y, et al. Baseline characteristics of idiopathic pulmonary fibrosis: analysis from the Australian Idiopathic Pulmonary Fibrosis Registry. Eur Respir J. 2017;49(2).
42. Baumgartner KB, Samet JM, Stidley CA, Colby TV, Waldron JA. Cigarette smoking: a risk factor for idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 1997;155(1):242–8.
43. Ekstrom M, Gustafson T, Boman K, Nilsson K, Tornling G, Murgia N, et al. Effects of smoking, gender and occupational exposure on the risk of severe pulmonary fibrosis: a population-based case-control study. BMJ Open. 2014;4(1):e004018.
44. Gustafson T, Dahlman-Hoglund A, Nilsson K, Strom K, Tornling G, Toren K. Occupational exposure and severe pulmonary fibrosis. Respir Med. 2007;101(10):2207–12.
45. Redente EF, Jacobsen KM, Solomon JJ, Lara AR, Faubel S, Keith RC, et al. Age and sex dimorphisms contribute to the severity of bleomycin-induced lung injury and fibrosis. Am J Physiol Lung Cell Mol Physiol. 2011;301(4):L510–8.
46. Voltz JW, Card JW, Carey MA, Degraff LM, Ferguson CD, Flake GP, et al. Male sex hormones exacerbate lung function impairment after bleomycin-induced pulmonary fibrosis. Am J Respir Cell Mol Biol. 2008;39(1):45–52.
47. Lekgabe ED, Royce SG, Hewitson TD, Tang ML, Zhao C, Moore XL, et al. The effects of relaxin and estrogen deficiency on collagen deposition and hypertrophy of nonreproductive organs. Endocrinology. 2006;147(12):5575–83.
48. Molyneaux PL, Cox MJ, Willis-Owen SA, Mallia P, Russell KE, Russell AM, et al. The role of bacteria in the pathogenesis and progression of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2014;190(8):906–13.
49. Han MK, Zhou Y, Murray S, Tayob N, Noth I, Lama VN, et al. Lung microbiome and disease progression in idiopathic pulmonary fibrosis: an analysis of the COMET study. Lancet Respir Med. 2014;2(7):548–56.
50. Shulgina L, Cahn AP, Chilvers ER, Parfrey H, Clark AB, Wilson EC, et al. Treating idiopathic pulmonary fibrosis with the addition of co-trimoxazole: a randomised controlled trial. Thorax. 2013;68(2):155–62.
51. Lee JS, Collard HR, Raghu G, Sweet MP, Hays SR, Campos GM, et al. Does chronic microaspiration cause idiopathic pulmonary fibrosis? Am J Med. 2010;123(4):304–11.
52. Noth I, Zangan SM, Soares RV, Forsythe A, Demchuk C, Takahashi SM, et al. Prevalence of hiatal hernia by blinded multidetector CT in patients with idiopathic pulmonary fibrosis. Eur Respir J. 2012;39(2):344–51.
53. Raghu G, Freudenberger TD, Yang S, Curtis JR, Spada C, Hayes J, et al. High prevalence of abnormal acid gastro-oesophageal reflux in idiopathic pulmonary fibrosis. Eur Respir J. 2006;27(1):136–42.
54. Lee JS, Ryu JH, Elicker BM, Lydell CP, Jones KD, Wolters PJ, et al. Gastroesophageal reflux therapy is associated with longer survival in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2011;184(12):1390–4.
55. Lee JS, Collard HR, Anstrom KJ, Martinez FJ, Noth I, Roberts RS, et al. Anti-acid treatment and disease progression in idiopathic pulmonary fibrosis: an analysis of data from three randomised controlled trials. Lancet Respir Med. 2013;1(5):369–76.
56. Ghebremariam YT, Cooke JP, Gerhart W, Griego C, Brower JB, Doyle-Eisele M, et al. Pleiotropic effect of the proton pump inhibitor esomeprazole leading to suppression of lung inflammation and fibrosis. J Transl Med. 2015;13:249.
57. Kreuter M, Wuyts W, Renzoni E, Koschel D, Maher TM, Kolb M, et al. Antacid therapy and disease outcomes in idiopathic pulmonary fibrosis: a pooled analysis. Lancet Respir Med. 2016;4(5):381–9.
58. Raghu G, Pellegrini CA, Yow E, Flaherty KR, Meyer K, Noth I, et al. Laparoscopic anti-reflux surgery for the treatment of idiopathic pulmonary fibrosis (WRAP-IPF): a multicentre, randomised, controlled phase 2 trial. Lancet Resp Med. 2018;6(9):707–14.
59. Lancaster LH, Mason WR, Parnell JA, Rice TW, Loyd JE, Milstone AP, et al. Obstructive sleep apnea is common in idiopathic pulmonary fibrosis. Chest. 2009;136(3):772–8.
60. Mermigkis C, Stagaki E, Tryfon S, Schiza S, Amfilochiou A, Polychronopoulos V, et al. How common is sleep-disordered breathing in patients with idiopathic pulmonary fibrosis? Sleep Breath. 2010;14(4):387–90.

61. Pihtili A, Bingol Z, Kiyan E, Cuhadaroglu C, Issever H, Gulbaran Z. Obstructive sleep apnea is common in patients with interstitial lung disease. Sleep Breath. 2013;17(4):1281–8.
62. Gille T, Didier M, Boubaya M, Moya L, Sutton A, Carton Z, et al. Obstructive sleep apnoea and related comorbidities in incident idiopathic pulmonary fibrosis. Eur Respir J. 2017;49(6).
63. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. Physiol Rev. 2010;90(1):47–112.
64. Leslie KO. Idiopathic pulmonary fibrosis may be a disease of recurrent, tractional injury to the periphery of the aging lung: a unifying hypothesis regarding etiology and pathogenesis. Arch Pathol Lab Med. 2012;136(6):591–600.
65. Kim JS, Podolanczuk AJ, Borker P, Kawut SM, Raghu G, Kaufman JD, et al. Obstructive sleep apnea and subclinical interstitial lung disease in the Multi-Ethnic Study of Atherosclerosis (MESA). Ann Am Thorac Soc. 2017;14(12):1786–95.
66. Yokoyama A, Kondo K, Nakajima M, Matsushima T, Takahashi T, Nishimura M, et al. Prognostic value of circulating KL-6 in idiopathic pulmonary fibrosis. Respirology. 2006;11(2):164–8.
67. Lederer DJ, Jelic S, Basner RC, Ishizaka A, Bhattacharya J. Circulating KL-6, a biomarker of lung injury, in obstructive sleep apnoea. Eur Respir J. 2009;33(4):793–6.
68. Klein OL, Krishnan JA, Glick S, Smith LJ. Systematic review of the association between lung function and type 2 diabetes mellitus. Diabet Med. 2010;27(9):977–87.
69. Enomoto T, Usuki J, Azuma A, Nakagawa T, Kudoh S. Diabetes mellitus may increase risk for idiopathic pulmonary fibrosis. Chest. 2003;123(6):2007–11.
70. Garcia-Sancho Figueroa MC, Carrillo G, Perez-Padilla R, Fernandez-Plata MR, Buendia-Roldan I, Vargas MH, et al. Risk factors for idiopathic pulmonary fibrosis in a Mexican population. A case-control study. Respir Med. 2010;104(2):305–9.
71. Ehrlich SF, Quesenberry CP Jr, Van Den Eeden SK, Shan J, Ferrara A. Patients diagnosed with diabetes are at increased risk for asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, and pneumonia but not lung cancer. Diabetes Care. 2010;33(1):55–60.
72. Yang J, Xue Q, Miao L, Cai L. Pulmonary fibrosis: a possible diabetic complication. Diabetes Metab Res Rev. 2011;27(4):311–7.
73. Sato N, Takasaka N, Yoshida M, Tsubouchi K, Minagawa S, Araya J, et al. Metformin attenuates lung fibrosis development via NOX4 suppression. Respir Res. 2016;17(1):107.
74. Rangarajan S, Bone NB, Zmijewska AA, Jiang S, Park DW, Bernard K, et al. Metformin reverses established lung fibrosis in a bleomycin model. Nat Med. 2018;24(8):1121–7.
75. Tang YW, Johnson JE, Browning PJ, Cruz-Gervis RA, Davis A, Graham BS, et al. Herpesvirus DNA is consistently detected in lungs of patients with idiopathic pulmonary fibrosis. J Clin Microbiol. 2003;41(6):2633–40.
76. Stewart JP, Egan JJ, Ross AJ, Kelly BG, Lok SS, Hasleton PS, et al. The detection of Epstein-Barr virus DNA in lung tissue from patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 1999;159(4 Pt 1):1336–41.
77. Yonemaru M, Kasuga I, Kusumoto H, Kunisawa A, Kiyokawa H, Kuwabara S, et al. Elevation of antibodies to cytomegalovirus and other herpes viruses in pulmonary fibrosis. Eur Respir J. 1997;10(9):2040–5.
78. Sides MD, Klingsberg RC, Shan B, Gordon KA, Nguyen HT, Lin Z, et al. The Epstein-Barr virus latent membrane protein 1 and transforming growth factor–beta1 synergistically induce epithelial–mesenchymal transition in lung epithelial cells. Am J Respir Cell Mol Biol. 2011;44(6):852–62.
79. Malizia AP, Keating DT, Smith SM, Walls D, Doran PP, Egan JJ. Alveolar epithelial cell injury with Epstein-Barr virus upregulates TGFbeta1 expression. Am J Physiol Lung Cell Mol Physiol. 2008;295(3):L451–60.
80. Oh CK, Murray LA, Molfino NA. Smoking and idiopathic pulmonary fibrosis. Pulm Med. 2012;2012:808260.
81. Steele MP, Speer MC, Loyd JE, Brown KK, Herron A, Slifer SH, et al. Clinical and pathologic features of familial interstitial pneumonia. Am J Respir Crit Care Med. 2005;172(9):1146–52.
82. Checa M, Hagood JS, Velazquez-Cruz R, Ruiz V, Garcia-De-Alba C, Rangel-Escareno C, et al. Cigarette smoke enhances the expression of profibrotic molecules in alveolar epithelial cells. PLoS One. 2016;11(3):e0150383.
83. Jensen K, Nizamutdinov D, Guerrier M, Afroze S, Dostal D, Glaser S. General mechanisms of nicotine-induced fibrogenesis. FASEB J. 2012;26(12):4778–87.
84. Huzen J, Wong LS, van Veldhuisen DJ, Samani NJ, Zwinderman AH, Codd V, et al. Telomere length loss due to smoking and metabolic traits. J Intern Med. 2014;275(2):155–63.
85. Jorgensen E, Stinson A, Shan L, Yang J, Gietl D, Albino AP. Cigarette smoke induces endoplasmic reticulum stress and the unfolded protein response in normal and malignant human lung cells. BMC Cancer. 2008;8:229.
86. Tanjore H, Blackwell TS, Lawson WE. Emerging evidence for endoplasmic reticulum stress in the pathogenesis of idiopathic pulmonary fibrosis. Am J Physiol Lung Cell Mol Physiol. 2012;302(8):L721–9.
87. Camelo A, Dunmore R, Sleeman MA, Clarke DL. The epithelium in idiopathic pulmonary fibrosis: breaking the barrier. Front Pharmacol. 2014;4:173.
88. Taskar VS, Coultas DB. Is idiopathic pulmonary fibrosis an environmental disease? Proc Am Thorac Soc. 2006;3(4):293–8.
89. Hubbard R, Cooper M, Antoniak M, Venn A, Khan S, Johnston I, et al. Risk of cryptogenic fibrosing alveolitis in metal workers. Lancet. 2000;355(9202):466–7.
90. Iwai K, Mori T, Yamada N, Yamaguchi M, Hosoda Y. Idiopathic pulmonary fibrosis. Epidemiologic approaches to occupational exposure. Am J Respir Crit Care Med. 1994;150(3):670–5.
91. Conti S, Harari S, Caminati A, Zanobetti A, Schwartz JD, Bertazzi PA, et al. The association between air pollution and the incidence of idiopathic pulmonary fibrosis in Northern Italy. Eur Respir J. 2018;51(1).