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Risk factors for the development of idiopathic pulmonary fibrosis: A review

Tanzira Zaman, Joyce S. Lee

Department of Medicine, University of Colorado Denver, Aurora, CO

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 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), co-morbidities (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 in to 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.[4–6] Consequently, there is an ongoing need for additional therapeutic options. Identification of

Corresponding Author: Joyce S. Lee, MD, Joyce S. Lee, MD, 12631 E 17th Avenue, Aurora, CO 80045, Joyce.lee@ucdenver.edu.

Conflict of Interest

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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 (Figure 1).

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*, *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]

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%.[9, 10] 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.[11] 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.[12] Similarly, while the *TOLLIP* minor allele is protective against the development of IPF, it is associated with worse survival in established IPF.[10] 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.

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,[13] 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.[14, 15] However, shortened telomeres in peripheral blood leukocytes[16] and lung tissue[17, 18] 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 ageing lung to a dysregulated response to lung microinjury includes a senescent phenotype in IPF lung fibroblasts that alters the ratio of proliferation to apoptosis.

[19] Other mechanisms include the accumulation of genetic and epigenetic variability,[9, 20] decreased alveolar stability, and loss of the capacity for differentiation (and thus repair) among bone marrow-derived mesenchymal stem cells,[21] 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. [22] 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,[23–25] 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.[26] Animal models suggest that male sex hormones are associated with accelerated fibrosis,[27] whereas female sex hormones may be protective against pulmonary fibrosis.[28] The effect 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.[29] 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.[30] While the prognostic value of these specific organisms were 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,[29] 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)¹ to follow-up on an initial study that showed no change in pulmonary function, but a possible trend

toward reduced mortality.[31] 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 repetitive injury to the lung.[32] 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.[33] In a prospective study, Raghu, et al found that 80% of patients with well-characterized IPF had GER as determined by 24-hour 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%.[34] 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.[35, 36] However, data on the effect of anti-acid therapy on lung function changes have been mixed.[37, 38] More recently, the results of a randomized controlled trial of laparoscopic anti-reflux surgery in IPF suggest a possible benefit on lung function.[39] 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 – 88%. [40–43] Screening questionnaires have poor specificity in the IPF population and are thus of limited clinical utility in ruling out those with OSA.[40]

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.[44] 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,[45] 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.[46] Similarly, serum levels of the glycoprotein KL-6, which is associated with both lung injury and survival in IPF,[47] are elevated in OSA.[48] 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.[49] 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 four-fold greater adjusted odds for DM among those with IPF.[50, 51] 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.[52] 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 pro-fibrotic cytokines, fibroblast proliferation, and extracellular matrix deposition.[53]

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 has demonstrated attenuation[54] and more recently, reversal of lung fibrosis.[55] 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).[56] The more frequent finding of EBV and CMV, specifically, in lung tissue of subjects with IPF over controls has been demonstrated in multiple studies.[57, 58] Mechanisms by which latent viral infection may contribute to the pathogenesis of IPF include activation of the epithelial-to-mesenchymal transition pathway, [59] as well as the pro-fibrotic mediator TGF- β . [60]

EXTRINSIC RISK FACTORS

Cigarette Smoke

A history of cigarette smoking, whether current or former, is overrepresented in IPF, with prevalence ranging from 41–83%. [61] In a multicenter U.S. 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. [23] A study of families with IPF also found that a history of smoking cigarettes was associated with the development of familial interstitial pneumonia. [62]

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. [63] Nicotine itself can induce the production of TGF- β , [64] an important mediator of fibrosis in IPF. Cigarette smoking is also associated with both acceleration of telomere shortening [65] and endoplasmic reticulum stress. [66, 67] Aside from these various molecular effects, the act of smoking involves repetitive mechanical stretch, which has been linked to micro-injury to the lung by increasing epithelial permeability, promoting the production of reactive oxidative species, and impairing tissue regeneration. [68]

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. [69] Analysis of autopsy results from the United Kingdom [70] and Japan [71] have 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. [72]

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.

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Figure 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.

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	<i>SFTPC</i> [73–75], <i>SFTPA1</i> [76], <i>SFTPA2</i> [77] <i>ABCA3</i> [78, 79]
<i>Early Cell Senescence</i>	Telomere shortening Impaired telomere stabilization	<i>TERT</i> [7, 9, 16, 75], <i>TERC</i> [18, 80, 81] <i>DKC1</i> [82], <i>TINF2</i> [82, 83], <i>PARN</i> [84, 85] <i>RTEL1</i> [84, 86, 87]
<i>Altered Host Defense</i>	Increased mucous accumulation Proinflammatory milieu Reduced pathogen recognition	<i>MUC5B</i> [9–12], <i>MUC2</i> [9] <i>TOLLIP</i> [10], <i>TLR3</i> [83], <i>HLA-DRB1</i> [88], <i>IL1RN</i> [89], <i>IL8</i> [90, 91]
<i>Cell-cell Adhesion</i>	Loss of epithelial integrity	<i>DSP1</i> [9], <i>DPP4</i> [9]

Adapted from Kaur, et al. 2017.[8]

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
<i>Lee, et al.</i> 2011.[35]	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).
<i>Lee, et al.</i> 2013.[37]	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).
<i>Ghebremariam, et al.</i> 2015.[36]	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 five years.
<i>Kreuter, et al.</i> 2016. [38]	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 50 m).	There was no change in disease progression by any of the prespecified criteria between the two groups.
<i>Raghu, et al.</i> 2018. [39]	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.