Update in Interstitial Lung Disease 2019

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The year 2019 brought advances in our understanding of pulmonary fibrosis, including disease burden, elucidation of pathogenic drivers of fibrogenesis and potential therapeutic targets, identification of outcome predictors, application of molecular imaging to fibrosis, and demonstration of efficacy of antifibrotic therapy in progressive non–idiopathic pulmonary fibrosis (IPF) interstitial lung diseases (ILDs). Here, we review critical research in the field of pulmonary fibrosis published over the past year in the *American Journal of Respiratory and Critical Care Medicine*, the *American Journal of Respiratory Cell and Molecular Biology*, and *AnnalsATS* and highlight notable findings published in other major journals. We acknowledge that not every major advancement could be captured in this update.

Morbidity and Mortality

Pulmonary fibrosis remains a highly morbid and fatal pathological response. Mortality rates for IPF are increasing as demonstrated using data from the United States National Vital Statistics System from 2000 to 2017 (1). During this time, age-adjusted mortality related to IPF increased by 9.85% (from 18.81 per 100,000 persons in 2000 to 20.66 in 2017). Mortality rates were higher in men and increased with age. Similarly, data from the Office of National Statistics were used to quantify the number of IPF deaths in the United Kingdom from 1979 to 2016 (2). The age-standardized mortality rates attributed to what the authors define as "IPF clinical syndrome" increased substantially from 1.66 per 100,000 person-years in 1979 to 8.29 in 2016. Again, mortality rates were highest in males and those with advanced age. Using data from the National Center of Health Statistics, the number of deaths attributed to hypersensitivity pneumonitis (HP) in the United States, including deaths in which HP was designated as a contributor to the cause of death, increased significantly from 1988 to 2016, reaching an age-adjusted mortality rate of 0.68 per 1,000,000 persons in 2016 from 0.12 in 1988 (3). Despite limitations in using population-level data for ILD-attributable mortality, these results demonstrate a concerning rise in mortality rates associated with pulmonary fibrosis.

The impact of ILD in patients with systemic sclerosis (SSc) was assessed in a nationwide cohort of 815 patients in Norway (4). Of the 650 patients with SSc with a baseline high-resolution computed tomography (HRCT) exam, half had evidence of ILD. The presence of ILD at baseline was associated with decreased survival even in patients with normal pulmonary function tests. These data suggest a potential role for HRCT imaging as an adjunct to pulmonary function tests performed at the time of SSc diagnosis given that the presence of ILD on HRCT imaging confers additional prognostic information.

Pathogenesis

Genetics

IPF likely develops from a multifaceted interaction of genetic and environmental risk factors, aging-related mechanisms, and epigenetic profibrotic reprogramming (5, 6). In a large study of IPF that evaluated 3,624 patients and 4,442 control subjects by using deep targeted resequencing, the strongest common risk variant was the presence of the *MUC5B* promoter polymorphism rs35705950 (7). In addition, several rare gene variations that increase the risk for IPF were identified for the first time, including in *FAM13A*. Variants in *FAM13A* have been demonstrated in chronic obstructive pulmonary disease (8), and, notably, the C allele at rs2609260 has been shown to confer protection for chronic obstructive pulmonary disease (9) but increased risk for IPF (7), highlighting the differences in gene-associated risk between both diseases (10). A homozygous *PARN* mutation that cosegregates with familial IPF was described, furthering the connection between pulmonary fibrosis and abnormal telomere shortening (11). A subset of patients with chronic HP were

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found to harbor rare protein-altering variants in certain telomere-related genes (such as *TERT*, *RTEL1*, and *PARN*), the presence of which was associated with decreased transplant-free survival and short telomere length (12). Thus, heterozygous mutations related to telomere biology and abnormal shortening of telomeres are not exclusive to IPF and occur in several ILDs (13, 14).

In a genome-wide association study, interstitial lung abnormalities (ILAs) were associated with gene variants linked with IPF in prior studies, including *MUC5B*, *DPP9*, *DSP*, *FAM13A*, and *IVD* (15). Hermansky-Pudlak syndrome (HPS) is an autosomal-recessive disease with a high prevalence of pulmonary fibrosis in patients with 3 of the 10 identified HPS genes (16). Interestingly, rare missense mutations in *HPS1* or *HPS4* and a novel *HPS4* mutation with a frameshift were identified in several patients with familial pulmonary fibrosis (17).

Single-Cell Sequencing

Single-cell RNA sequencing has been recently used to examine the individual transcriptional heterogeneity in cell populations in normal and IPF lungs, revealing several abnormal epithelial cell phenotypes (6, 18). Interestingly, IPF and non–small cell lung cancer often occurring in the same individual share some common signatures of dysregulated genes associated with the lung epithelium (19, 20). After performing a gene set enrichment analysis of IPF and non–small cell lung cancer data sets, the oncogene *ECT2* (epithelial cell transforming sequence 2), was found to be strongly upregulated in both diseases (19). Increased expression of ECT2 was associated with increased proliferation of alveolar epithelial type II (ATII) cells from bleomycin-treated mice, and knockdown of *Ect2* decreased proliferation of ATII cells as well as collagen type I expression in ATII cells. These findings identify a novel and potential therapeutic target related to aberrant lung epithelium, a critical driver of IPF pathogenesis (5, 6). A single-cell atlas of human pulmonary fibrosis confirmed the heterogeneity of epithelial cells and, importantly, identified a novel profibrotic population of alveolar macrophages in patients with pulmonary fibrosis (21).

Cellular and Molecular Mechanisms

Recent studies suggest a potential role of macrophages in the progression of pulmonary fibrosis (21–26). Analysis of BAL from patients with IPF demonstrated an increase in alveolar macrophages that lacked the transferrin receptor 1 (CD71 [cluster of differentiation 71]) compared with healthy volunteers (22). Compared with $CD71^+$ macrophages, $CD71^-$ macrophages had a reduced phagocytic capacity and an upregulation of genes associated with fibrosis. Increased expansion of the $CD71^-$ macrophage population was associated with shorter survival in IPF. Likewise, TIM-3 (T-cell immunoglobulin domain and mucin domain-3), an important regulator of macrophage function, is upregulated in IPF (23). TIM-3 upregulation caused macrophages to increase secretion of TGF-β1 and IL-10 and resulted in increased bleomycin-induced lung fibrosis. Also, in IPF lungs, IL-9 was highly expressed in $CD68^+$ alveolar macrophages, with the IL-9 receptor being expressed by epithelial cells (24, 25). Interestingly, in a silica-induced lung fibrosis model, blocking IL-9 reduced the degree of lung inflammation and fibrosis (24). In a sarcoidosis mouse model, macrophage-specific PPARγ deficiency increased macrophage response and worsened pulmonary fibrosis (26).

Disease in any tissue may affect the bone marrow (BM), which may impact the behavior of the disease in the originally affected organ, and this concept was evaluated in context of experimental lung fibrosis (27). Bleomycin-induced lung injury caused significant alterations in BM cells, which enhanced the fibrotic response to a subsequent lung insult, central to which was the BM monocytic population. Mechanistically, the profibrotic effect was associated with the upregulation of B7H3, IL-33/ST2 signaling activation, and a Th2-skewed phenotype.

IPF occurs more commonly in men, although the reasons are unclear. The ratio of the estrogen receptors ERα:ERβ is critical for epithelial cell function, and studies have shown that the estrogen-mediated protection against certain conditions is mediated through ERβ (28). Recently, it was shown that the receptor ERα is increased in male IPF lungs and in aged male mice injured with bleomycin, resulting in enhanced estrogen receptor activity and upregulation of profibrotic pathways (29). Mechanistically, let-7a and -7d microRNAs, which target this estrogen receptor, were decreased in IPF lungs, as previously demonstrated (30). Recent evidence indicates that long noncoding RNAs may also regulate protein-coding gene expression. In this context, a long noncoding RNA named DNM3OS was found to be a fibroblast-specific downstream effector of TGF-β signaling, and it promoted the development of fibrosis in bleomycin-injured mice (31). This effect was associated with profibrotic microRNAs, which enhanced fibrogenesis via a caveolin-dependent mechanism. P311, an RNA-binding protein involved in TGF-β1, -β2, and -β3 translation, was expressed in hyperplastic ATII cells and activated fibroblasts from IPF lungs (32, 33). P311 was also expressed in experimental lung fibrosis, and importantly, P311-knockout mice showed an attenuated fibrotic response to bleomycin injury (32). More studies related to noncoding RNA are necessary to understand the role of these post-transcriptional regulators in pulmonary fibrosis.

Strong evidence supports the notion that IPF is an epithelial-driven disease involving both alveolar and airway epithelial cells (5, 6, 18). Gene and protein expression analyses of IPF tissue and BAL demonstrated increased airway basal cells (34). A BAL transcriptional signature, containing many airway basal cell–derived genes, predicted mortality in IPF across three cohorts. Differentiation of fibroblasts to myofibroblasts is critical for excessive extracellular matrix accumulation. Recently, it was demonstrated that sustained phosphorylation of Smad2 in response to TGF-β is crucial for myofibroblast differentiation (35). Though rare, ILD can affect children. Aptamer-based proteomics was performed on BAL from patients with children's interstitial and diffuse lung disease (36). This demonstrated distinct aptamer signatures in subtypes of children's interstitial and diffuse lung disease compared with control subjects, providing potentially important information on the mechanisms underlying these rare diseases.

Therapeutic Targeting of Fibrosis

Although prostaglandin E2 (PGE2) is known to have antifibrotic effects, fibroblasts from patients with pulmonary fibrosis have demonstrated resistance to PGE2 administration; however, targeting the prostacyclin receptor may be a potential therapeutic alternative (37, 38). ACT-333679, a prostacyclin receptor selective

agonist, inhibited fibroblast differentiation and reduced fibroblast proliferation, collagen synthesis, and the secretion of several profibrotic mediators, and central to its effect was inhibition of YAP/TAZ, transcriptional regulators crucial for the expression of many profibrotic genes (39). Fibroblasts were discovered to secrete PGE2 in extracellular vesicles (EVs), which can inhibit their differentiation to myofibroblasts (40, 41). PGD2 also plays a role in the resolution of lung inflammation and suppression of fibrosis during bleomycin-induced lung injury, likely through cells (especially γδT lymphocytes) expressing the receptor CRTH2 (chemoattractant receptor homologous with T-helper cell type 2 cells) (42). Migration of fibroblasts is critical for the expansion of the fibroblast/myofibroblast population. Recently, it was demonstrated that EVs derived from fibroblasts increased the invasiveness of fibroblasts, essential to which was the presence of fibronectin on the EV surface (43). Targeting a ligand of fibronectin, α5β1 integrin, by using an α5β1 monoclonal antibody inhibited fibroblast invasion (43, 44).

Likewise, MMI-0100, a synthetic small peptide that inhibits the activity of MK2 (mitogen-activated protein kinase-activated protein kinase 2) reduced invasion of IPF-derived lung fibroblasts and the degree of bleomycin-induced lung fibrosis (45). TAS-115 inhibits multiple tyrosine kinases and was shown to suppress PDGFR phosphorylation, thereby decreasing proliferation and migration of human fibroblasts, more effectively than nintedanib and to mitigate the degree of fibrosis in the bleomycin-model (46, 47). An open-label, phase II trial (JapicCTI-183898) is ongoing to test the safety and efficacy of TAS-115 in patients with IPF. IL-15 deficiency in mice resulted in increased accumulation of collagen in the lungs (48). In a mouse model of allergen-induced bronchial fibrosis, administration of recombinant IL-15 or the use of an IL-15 agonist (ALT-803) resulted in decreased IL-13, TGF-β1, α-SMA, and collagen in the lung, suggesting a potent antifibrotic effect of IL-15.

Cellular senescence is a key pathogenic mechanism in IPF epithelial cells and fibroblasts (49, 50). Administration of quercetin, a senolytic drug, to human lung fibroblasts rendered the fibroblasts more susceptible to death ligand-mediated apoptosis through decreased AKT activation as well as increased expression of FasL and caveolin-1 receptors (51, 52). In aged mice treated with bleomycin, administration of quercetin starting at 7 days attenuated the development of pulmonary fibrosis (51). A phase 1 study of administration of dasatinib and quercetin as senolytic therapy in IPF has been completed (53). Undoubtedly, additional translational studies are needed before potentially reaching the clinical arena.

Endoplasmic Reticulum Stress, Proteostasis, and Metabolic Dysfunction

Silicosis is an important fibrotic and usually progressive occupational lung disease. PPP1R13B, a member of the apoptosis-stimulating protein of the p53 family, is upregulated in lung tissues of patients with silicosis and in fibroblasts after silicon dioxide (SiO_2) stimulation (54). Mechanistically, upregulation of PPP1R13B in SiO_2-stimulated cells seemed to associate with the downregulation of a circular RNA, circ-012091, a noncoding RNA. Fibroblasts stimulated by SiO_2 and transfected with PPP1R13B clustered regularly interspaced short palindromic repeats (CRISPR) ACT plasmid displayed increased cell migration and proliferation, likely mediated by endoplasmic reticulum (ER) stress and autophagy. Administration of a high-fat diet rich in saturated fatty acids, including palmitic acid, resulted in increased epithelial cell apoptosis and ER stress and increased fibrosis in lungs of bleomycin-treated mice compared with mice receiving a standard diet (55, 56). Expression of mutant proteins, viral infections, reactive oxygen species, and cigarette smoke cause ER stress and have been linked to fibrosis through apoptotic cell death, activation and differentiation of fibroblasts, and epithelial–mesenchymal transition (57). Thus, targeting ER stress is a potential therapeutic avenue for pulmonary fibrosis (58, 59).

Given the contribution of *MUC5B* promoter variant (rs35705950) to the risk of developing different ILDs, elucidating the pathways causing increased MUC5B production and its effect on lung architecture is critical (60). In this context, it was revealed that injury causes ER stress and activation of the stress sensor ERN2 (ER-to-nucleus signaling 2), and then, the spliced XBP1 (X-box–binding protein 1) increases transcription of both unfolded protein response genes and *MUC5B* (61). Supporting the pathogenic role of dysfunctional proteostasis, expression of HSP 70 (heat shock protein 70) was decreased in lung tissue and fibroblasts from patients with pulmonary fibrosis compared with donors without fibrosis (62, 63). Mice that had a deletion of the inducible form of HSP 70 (Hsp 72) developed increased lung fibrosis in response to bleomycin administration compared with wild-type mice (62).

Glutaminolysis is the conversion of glutamine to glutamate by GLS (glutaminase). Recently, several studies investigated the putative role of this critical metabolic process in lung fibrosis. Glutaminolysis contributed to the resistance of IPF lung fibroblasts to apoptosis though upregulation of *XIAP* and *survivin*, and central to this process is the role of demethylase JMJD3 (64, 65). Gls1 was upregulated in fibroblasts from the lungs of fibrotic mice, and conditional knockout of *Gls1* within fibroblasts decreased the degree of fibrosis resultant from bleomycin injury (66). Administration of CB-839, an inhibitor of Gls1, attenuated the development of pulmonary fibrosis in two mouse models. Finally, it was demonstrated that glutamine metabolism in fibroblasts is essential for amino acid synthesis, including glycine and proline, which is necessary for myofibroblast differentiation and the production of collagen protein (67, 68). These investigations open the window for further investigations testing novel therapeutic approaches related to metabolism dysfunction to inhibit the development or progression of pulmonary fibrosis (64–69).

Lung Organoids

Recently developed three-dimensional organoids have arisen as important tools to understand cell–cell interactions and self-organization and for modeling healthy and disease processes. A nascent organoid model that contained epithelial and mesenchymal cells from mouse and human lungs revealed that normal lung epithelium can suppress key functions of lung fibroblasts through the bone morphogenetic protein pathway (70). The three-dimensional organoid model allowed for important discoveries not available from two-dimensional culture, such as the inhibitory effect of epithelial cells on mesenchymal activation (71), a process that is likely lost during the development of IPF.

Microbiome

There has been increasing interest in the role of the microbiome in IPF; however, questions remain as to whether lung dysbiosis in IPF is in itself pathogenic or a consequence of disease and the resultant structural alterations. In BAL samples from patients with IPF enrolled in the COMET (Correlating Outcomes with Biochemical Markers to Estimate Time-Progression in Idiopathic Pulmonary Fibrosis) study, the degree of bacterial burden was associated with disease progression, with the greatest bacterial burden having the highest risk for IPF progression (72). Decreased bacterial diversity was associated with higher levels of BAL-measured growth factors and cytokines, such as G-CSF, VEGF, IL-1Ra, IL-1β, and CXCL8. Alterations in the lung microbiome were seen with bleomycin-induced lung injury and subsequent fibrosis. Notably, bleomycin-treated germ-free mice had improved mortality but no reduction in the degree of pulmonary fibrosis compared with non–germ-free bleomycin-treated mice. BAL samples from patients with IPF enrolled in the COMET study were also used to assess differences in lung microbiota between patients with IPF based on the presence and absence of honeycombing on HRCT imaging (73). Despite similarities in the lung microbiota between the two groups, differences were detected in community composition; however, significance was lost when adjusting for potential confounders. Notably, the bacterial burden did not differ between groups.

Diagnosis and Prognostication

Diagnosis

ILD diagnosis is an important area that continues to evolve. A modified Delphi process called convergence of opinion on recommendations and evidence (CORE) has been proposed as a method of producing guideline-type recommendations for certain clinical questions without necessitating a systematic review (74). When comparing the CORE process with the Institute of Medicine process for the 2018 IPF clinical practice guidelines (75), the CORE and Institute of Medicine processes resulted in concordant recommendations for 9 out of the 10 guideline questions and concordant strength of recommendation for 7 of the 8 (88%) graded recommendations; however, agreement regarding the quality of evidence was poor (76).

The current gold standard for ILD diagnosis is a multidisciplinary discussion (MDD) (77). However, access to such expertise is typically limited to large, specialized centers. In a retrospective cross-sectional study, remote access to an MDD frequently led to a change in ILD diagnosis and management (78). Though the routine use of a remote MDD requires further study and validation, this study supports its feasibility with the potential to address important gaps in patient access to specialized ILD care.

Diagnostic likelihood has been proposed as part of the framework for ILD diagnosis (79). Sixty ILD cases were evaluated independently by 404 physicians to determine how the degree of diagnostic likelihood for IPF diagnosis affected management decisions (80). For cases in which a provisional diagnosis of IPF was given with high confidence (consistent with a 70–89% likelihood of IPF), 63% of physicians would prescribe antifibrotic therapy without recommending surgical lung biopsy (SLB). SLB was most often requested for provisional low-confidence IPF diagnoses, but notable was the poor agreement among physicians in the decision to pursue biopsy.

Lung Biopsy

There has been growing interest in transbronchial lung cryobiopsy (TBLC) as a method of tissue sampling in ILD, yet few studies have addressed the accuracy of TBLC-obtained histology compared with the current histopathological gold standard, which includes SLB-obtained samples reviewed in an MDD. In a two-center prospective study of 21 patients with nondefinitive ILD pattern, all of whom underwent sequential TBLC and SLB with subsequent review in multidisciplinary assessment, TBLC and SLB histologic diagnoses were fully concordant in only 8 of 21 cases (38%) (81). Percentage agreement with final multidisciplinary assessment diagnosis was higher for SLB (62%) than TBLC (48%). The multicenter Australian COLDICE (Cryobiopsy versus Open Lung Biopsy in the Diagnosis of Interstitial Lung Disease Alliance) trial further addressed this issue of sampling accuracy in 65 patients with ILD undergoing concurrent TBLC and SLB (82). Samples were reviewed by three expert pathologists aiming to achieve consensus and then blindly reviewed within the context of an MDD to establish clinical diagnoses. Histological agreement between TBLC and SLB was high at 70.8%, and diagnostic agreement at MDD was 76.9%. These data suggest a potential role of TBLC in the pathologic evaluation of ILD.

A multicenter prospective study of 237 patients with ILD compared histological diagnoses to those obtained using histology plus a molecular classifier, developed through machine learning (83). The classifier identified a usual interstitial pneumonia (UIP) pattern, with 88% specificity, 70% sensitivity, and 86% agreement between classifier-based and histopathology-based clinical diagnoses, and increased diagnostic confidence for IPF. The molecular classifier is a potential diagnostic tool for ILD; however, further validation is needed before its widespread use.

Imaging

Molecular imaging enables noninvasive visualization and quantification of molecular processes and holds potential for imaging of fibrosis (84). The type I collagen–targeted positron emission technology probe, ^{68}Ga-CBP8 (85), was used in humans for the first time (86). When compared with the lungs of healthy volunteers, patients with IPF had an increased lung positron emission technology signal consistent with increased collagen deposition. Notably, areas of high signal were not limited to regions of known fibrosis but also occurred in lung areas that appeared "normal" on computed tomography (CT) imaging, suggesting that this probe may be sensitive to detecting active fibrosis not apparent on CT imaging.

Using three cohorts of individuals with ILAs and one cohort of patients with IPF, airway wall thickness (AWT) was measured by using chest CT imaging (87). AWT was increased in patients with ILAs and IPF compared with those without ILAs, across all cohorts, after adjusting for important confounders. These findings are intriguing, raising the possibility that increased AWT may be a marker of early ILD and lend support to the hypothesis that the pathogenic beginnings of ILD may involve the airways (88); however, more research is needed to determine the significance of these findings.

Prognostication

Identifying clinical predictors to reliably identify those patients with ILD at increased risk for mortality and disease progression remains a challenge. There is increased need for risk prediction models to identify patients at greatest risk for progressive fibrosing ILD given recent evidence supporting antifibrotic therapy in these patients (89). A multicenter observational cohort study of 1,330 patients with ILD evaluated the association between CT honeycombing and all-cause mortality (90), finding that patients with CT honeycombing had a shorter survival time compared with those without honeycombing. In a separate study, both a UIP pattern and a probable UIP pattern were associated with increased mortality as compared with an indeterminate for UIP pattern (91).

Interestingly, the presence of mediastinal lymph node enlargement ($\geq$10 mm) in patients with ILD was associated with worse transplant-free survival with findings replicated in three cohorts (92). Similarly, an elevated absolute peripheral monocyte count ($\geq$0.95 K/μl) was associated with reduced survival in IPF across several cohorts (93). Though both potential biomarkers need further study, they are examples of simple measurements that could easily be incorporated into clinical practice to provide individual prognostic information.

Treatment

Although nintedanib reduces the rate of disease progression in IPF (94), it was unknown whether it would show similar efficacy in other types of ILD. In the SENSCIS (Safety and Efficacy of Nintedanib in Systemic Sclerosis) trial, patients with SSc-associated ILD were randomized to receive nintedanib or placebo (95). Almost half of enrolled patients were concurrently receiving mycophenolate mofetil. Nintedanib reduced the rate of decline in FVC over 52 weeks compared with placebo ($-$52.4 ml vs. $-$93.3 ml; 95% confidence interval for the between-group difference, 2.9–79.0 ml; $P = 0.04$). The effect of nintedanib was also investigated in non-IPF progressive fibrosing ILD. Use of nintedanib reduced annual rate of decline in FVC by 107 ml ($-$80.8 ml with nintedanib vs. $-$187.8 ml with placebo; 95% confidence interval for the between-group difference, 65.4–148.5 ml; $P < 0.001$) (89), similar to the magnitude of difference seen in IPF (94). These data support the efficacy of nintedanib across several fibrotic ILD subtypes. Lastly, prespecified *post hoc* analyses of the INSTAGE trial (96) revealed no difference in the degree of change in FVC and St. George's Respiratory Questionnaire score with nintedanib plus sildenafil or nintedanib plus placebo based on the presence or absence of right heart dysfunction (97).

U.S. insurance database information was used to perform a retrospective matched cohort study comparing clinical outcomes of patients with IPF treated with pirfenidone or nintedanib with patients with IPF not receiving either therapy (98). Those receiving antifibrotic therapy had a lower risk of both all-cause mortality and all-cause hospitalizations. Of note, the difference in all-cause mortality between the treated and nontreated groups was lost at 2 years for reasons that are unclear and warrant further exploration.

The treatment landscape of IPF changed dramatically with the results of the PANTHER-IPF (Evaluating the Effectiveness of Prednisone, Azathioprine, and *N*-acetylcysteine in Patients with IPF) study, demonstrating that use of prednisone, azathioprine, and N-acetylcysteine in IPF resulted in increased mortality and hospitalizations compared with placebo (99) for reasons that have remained only speculative until now. Measurement of peripheral blood leukocyte telomere length was performed on DNA from patients enrolled in the PANTHER-IPF study (100). Leukocyte telomere length $<$10th percentile was associated with a lower composite endpoint-free survival with prednisone, azathioprine, and N-acetylcysteine exposure compared with placebo, with similar findings replicated in two additional IPF cohorts receiving immunosuppressive therapy. These results suggest a harmful interaction between the presence of short telomeres and immunosuppression use in IPF and may have treatment implications for patients with short telomeres and other forms of ILD.

Patient Education

YouTube is commonly used to disseminate health information targeted to patients; however, there has been little formal evaluation of content quality to date (101). The quality and content of 102 patient-directed YouTube videos were systematically evaluated as a source of information on IPF (102). The information provided was often incomplete and inaccurate, with almost one out of every five videos promoting nonrecommended and/or harmful therapies. Especially concerning was the higher viewership metrics seen for videos that endorsed nonrecommended treatments, highlighting the need for IPF stakeholders to take an active role in ensuring the reliability of health information disseminated by social media platforms.

These works from 2019 highlight the complex pathobiology of fibrosis, the value of interdisciplinary research, and the increasing clinical significance of pulmonary fibrosis. The advancements summarized herein are encouraging and reflect continued progress in characterizing the risk factors, pathogenesis, and outcomes associated with fibrotic lung disease. ■

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