Air Pollution and Interstitial Lung Diseases: Defining Epigenomic Effects

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Air pollution is a massive global health problem, with over 90% of the world's population living in areas where daily exposures exceed the World Health Organization's air quality recommendations (1). Outdoor sources of particulate matter with a diameter $\leq 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$) caused between 4.2 and 8.9 million premature deaths in 2015 alone (2, 3). The burden of disability and mortality from air pollution exposure is disproportionately experienced by vulnerable populations and patients with chronic respiratory diseases (2, 4). The adverse effects of air pollution exposure are well established in patients with chronic obstructive pulmonary disease (COPD) and asthma (5, 6), whereas the impact on patients with interstitial lung disease (ILD) remains poorly characterized.

Occupational and environmental exposures contribute to the development and progression of ILD through mechanisms that are not yet fully understood (7). Several previous single-center studies have demonstrated that air pollution exposure is associated with

increased incidence and adverse outcomes in idiopathic pulmonary fibrosis (IPF), the most common form of ILD (8–12). Airborne pollutants have multiple deleterious physiologic effects in the lungs, such as triggering alterations to mucosal surfaces by overwhelming ciliary and macrophage clearance mechanisms, which induces oxidative stress, and by transiting toxic metals into the bloodstream (13). One other mechanism whereby air pollution likely mediates adverse impacts in ILD and other diseases is through epigenetic modifications (14), referring to molecular mechanisms that regulate gene expression without changing nucleotide base sequences.

In this Pulmonary Perspective, we review the associations between air pollution exposure and adverse clinical outcomes in patients with ILD. Subsequently, we present an overview of the current understanding of the role of epigenetics in ILD. Lastly, we summarize how epigenetic methods can be adapted to explore how changes to the epigenome may mediate the adverse impacts of air pollution

in ILD. Given the increasing global burden of ILD (15) and recent increases in air pollution-related mortality across the United States (16), it is more important than ever to understand the molecular mechanisms relating air pollution exposure to ILD development and progression. Air pollution may play an important role in lung remodeling and fibrogenesis, such that targeting this environmental risk factor may help to reduce the development and progression of ILD. Research in this area will inform pathophysiology, identify opportunities to reduce adverse impacts in at-risk individuals, and may guide policymakers who institute regulations on emissions standards and pollution mitigation strategies.

Air Pollution and Clinical Impacts in ILD

Preclinical Disease and ILD Incidence

Air pollution exposure is increasingly recognized as a risk factor for the development and progression of ILD (Table 1). Patients at risk for the

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Table 1. Summary of Selected Clinical Outcomes from Air Pollution Exposure in Patients with ILD and Preclinical Disease

Population	Sample Size	Exposure Evaluated	Outcome Measured	Effect Size	Confidence Interval	P Value	Reference
Healthy U.S. subjects from the MESA	2,671 5,495	40 ppb increase in 10-yr mean NO _x exposure	Odds of ILA Percentage increase in HAA per year	1.77 0.45%	1.06 to 2.95 −0.02% to 0.92%	0.03 0.06	Sack and colleagues, 2017 (19)
Healthy U.S. subjects from the Framingham Heart Study	1,344 709	5-yr EC exposure of 0.14 μg/m ³	Odds of ILA Odds of ILA progression	1.27 1.33	1.04 to 1.55 1.00 to 1.77	NR NR	Rice and colleagues, 2019 (20)
Incident cases of IPF in Northern Italy based on ICD-9-CM code 516.3	2,093	10 μg/m ³ increase in 5-yr mean NO ₂ exposure during cold season	Incidence rate of IPF	7.93%*	0.36% to 16.08%	NR	Conti and colleagues, 2018 (8)
Patients with newly diagnosed ILD enrolled in the ILD-India Registry	842	1 μg/m ³ increase in mean annual PM _{2.5}	Odds HP diagnosis rather than other forms of ILD	1.007	1.001 to 1.013	0.017	Singh and colleagues, 2019 (21)
Patients with IPF enrolled in French ILD Cohort Fibrose (COFI)	192	10 μg/m ³ increase in preceding 6-wk mean O ₃	Hazard ratio for AE event	1.47	1.13 to 1.92	0.005	Sesé and colleagues, 2018 (12)
		10 μg/m ³ increase in mean PM ₁₀ from inclusion to death, transplant, or censoring	Hazard ratio for mortality	2.01	1.07 to 3.77	0.03	
		10 μg/m ³ increase in mean PM _{2.5} from inclusion to death, transplant, or censoring	Hazard ratio for mortality	7.93	2.93 to 21.33	<0.001	
Patients with IPF enrolled in the longitudinal ILD cohort in Seoul, South Korea	436	Increased mean O ₃ over 6-wk exposure period	Hazard ratio for AE event	1.57	1.09 to 2.24	0.01	Johannson and colleagues, 2014 (9)
		Increased maximum O ₃ over 6-wk exposure period		1.42	1.11 to 1.82	0.01	
		Increased number of exceedances above air quality standards for O ₃ over 6-wk exposure period		1.51	1.17 to 1.94	0.002	
		Increased mean NO ₂ over 6-wk exposure period		1.41	1.04 to 1.91	0.03	
		Increased maximum NO ₂ over 6-wk exposure period		1.27	1.01 to 1.59	0.04	
		Increased number of exceedances above air quality standards for NO ₂ over 6-wk exposure period		1.20	1.10 to 1.31	<0.001	
		Increased number of exceedances above air quality standards for NO ₂ over 6-wk exposure period					
Patients with IPF seen at single U.S. center	135	5 μg/m ³ increase in mean PM ₁₀ from enrollment to death, transplant, or censoring	Rate of decline in FVC	46 ml/yr increased FVC decline	12 ml/yr to 81 ml/yr	NR	Winterbottom and colleagues, 2018 (10)

(Continued)

Table 1. (Continued)

Population	Sample Size	Exposure Evaluated	Outcome Measured	Effect Size	Confidence Interval	P Value	Reference
Patients with IPF at single U.S. center given home spirometers	25	1 ppb increase mean NO ₂ over study period (up to 40 wk)	Difference in mean FVC% predicted over study period (measured weekly)	−0.45%	−0.85% to −0.05%	0.03	Johannson and colleagues, 2018 (11)
		1 μg/m ³ increase mean PM _{2.5} over study period (up to 40 wk)		−0.45%	−0.84% to −0.07%	0.02	
		1 μg/m ³ increase mean PM ₁₀ over study period (up to 40 wk)		−0.57%	−0.92% to −0.21%	0.003	

Definition of abbreviations: AE = acute exacerbation; EC = elemental carbon; HAA = high-attenuation abnormalities; HP = hypersensitivity pneumonitis; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; ILA = interstitial lung abnormalities; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; MESA = Multi-Ethnic Study on Atherosclerosis; NO_x = nitrogen oxides; NR = not reported; PM_{2.5} = particulate matter with a diameter ≤2.5 μm; PM₁₀ = particulate matter with a diameter ≤10 μm.

Bold indicates significant *P* values.

*Unadjusted analysis. Results did not meet significance in multivariate analysis.

development of ILD may be incidentally identified by interstitial lung abnormalities (ILAs) or high-attenuation abnormalities on computed tomography scans of the chest. These subclinical features are associated with an increased likelihood of ILD diagnosis and mortality (17, 18). One study of healthy individuals from the MESA (Multi-Ethnic Study of Atherosclerosis) found that increased 10-year nitrogen oxide exposure was associated with higher odds of ILA incidence (19). Another study involving healthy individuals enrolled in the Framingham Heart Study found that increased 5-year elemental carbon exposure was associated with increased odds of ILA and ILA progression (20). This preliminary evidence suggests that cumulative air pollution exposures are linked to preclinical ILD. Further study is required to evaluate whether pollution modifies the risk of progression to ILD in patients with ILAs or high-attenuation abnormalities, how underlying genetics influence these risks, and whether imaging studies can be used for early identification of subclinical ILD in high-risk populations with significant environmental exposures.

Exposure to airborne pollutants may be associated with ILD incidence. One study investigated the impact of average daily exposure to particulate matter with a diameter ≤10 μm (PM₁₀), nitrogen dioxide (NO₂), and ozone (O₃) on IPF incidence in Northern Italy (8). In unadjusted models, an increased NO₂ concentration was associated with IPF incidence during the cold season, although this was not statistically

significant on multivariable analysis. No significant association was found between PM₁₀ or O₃ exposure and IPF incidence. This was the first study to evaluate the impact of air pollution on ILD incidence, but it was limited by only evaluating a small geographic region with limited heterogeneity in air pollution exposures. This emphasizes the need to expand this type of methodology to larger and more heterogeneous populations and consider more comprehensive multipollutant models, including the criteria pollutants PM_{2.5}, PM₁₀, NO₂, sulfur dioxide (SO₂), carbon monoxide (CO), O₃, and lead, simultaneously.

Another recent study in India found a significant association between increased city-wide concentrations of PM_{2.5} and the percentage of cases of hypersensitivity pneumonitis enrolled in that center's ILD registry (21). The authors postulate that exposure to airborne pollutants may impair mucociliary clearance, leading to antigen retention and the initiation of the immunologic and fibrogenic pathways contributing to the development of hypersensitivity pneumonitis. Although not a formal incidence study, these findings suggest that the impact of airborne pollutants on the development of non-IPF ILD warrants further study.

Effects on Established ILD

High air pollution exposure is recognized as a risk factor for adverse clinical outcomes and lung function decline in patients with IPF, although evidence in other ILDs is lacking. One single-center U.S. study of

patients with IPF found that each 5 μg/m³ increase in 6-year cumulative exposure to PM₁₀ was associated with an additional 46 ml decline in FVC per year (10). Cumulative exposures to PM_{2.5} were not associated with the rate of decline in lung function. Another study using weekly spirometry in 25 patients with IPF demonstrated that higher weekly mean concentrations of NO₂, PM_{2.5}, and PM₁₀ were each associated with lower mean FVCs over the study period (11). There was no association between airborne pollutant exposure and the rate of decline in lung function, but this study was limited by small patient numbers and a finite follow-up duration. These physiological studies help to inform how air pollution contributes to disease progression and adverse clinical outcomes in ILD.

A French study of 192 patients with IPF is the only study to demonstrate a positive association between PM₁₀ or PM_{2.5} exposure and all-cause mortality (12). Increased average O₃ exposure was also associated with an increased number of acute exacerbations (AEs), although no association was found between NO₂, PM_{2.5}, or PM₁₀ and AEs. This positive association between air pollution exposure and AE rate was first described in a South Korean cohort of patients with IPF (9). The mean level, maximum level, and number of exceedances above accepted standards for O₃ and NO₂ over a 6-week period preceding the event were associated with increased incidence of AEs. Additional studies of these important clinical outcomes are needed to evaluate air pollution effects

on these outcomes in patients with non-IPF ILD and to explore the molecular mechanisms underlying these effects to identify mitigation strategies.

The Epigenome in ILDs

Despite the increasing body of literature linking exposure to multiple airborne pollutants with adverse outcomes in IPF, there remain critical knowledge gaps in the mechanisms underlying these relationships. Epigenetic mechanisms are prime candidates for evaluation given the known alterations to the epigenome in patients with ILD and the known epigenetic impacts of airborne pollutants in healthy individuals and in patients with other chronic respiratory diseases (14, 22, 23). The most commonly studied epigenetic mechanisms are DNA methylation (DNAm), histone modifications, and noncoding RNAs, especially microRNAs. Epigenomic patterns are inherited between cells, but environmental exposures throughout a lifetime can significantly change one's epigenetic landscape (24). Most epigenetic factors have been studied in IPF (23), but the role air pollution plays in altering these factors remains unknown. To understand the epigenetic impacts of air pollution in ILD, it is important to first understand how the epigenome is altered in these patients.

Widespread alterations in DNAm patterns occur in lung tissue from patients with IPF in comparison with that from control subjects (22). Some of these alterations occur near genes implicated in IPF pathogenesis, such as *TOLLIP*, *NOTCH1*, and *FBXO32*. Altered gene expression near these differentially methylated regions was found in these and other IPF-relevant genes, supporting the notion that changes in DNAm may mediate adverse mechanisms that contribute to IPF development and progression. Plasma cell-free DNAm patterns can be used with moderate specificity to distinguish between patients with fibrotic ILD and those with lung cancer or COPD (25), illustrating how DNAm patterns may represent novel diagnostic biomarkers in patients with ILD.

Histone modifications also have pathophysiologic relevance in pulmonary fibrosis. In bleomycin mouse models of pulmonary fibrosis and in IPF-derived fibroblasts, histone modifications are associated with alterations in apoptotic

pathways (26). Inhibiting histone deacetylase, which leads to alterations in histone modification and DNAm patterns, results in increased fibroblast apoptosis and prolonged survival in bleomycin-injured mice (27). These data support the notion that resistance to apoptosis, which is believed to represent a major pathophysiologic mechanism in fibroproliferative diseases like IPF, is mediated in part by epigenetic changes (28). Histone modifications in circulating nucleosomes have also been used to distinguish between serum from healthy subjects and patients with IPF (29), emphasizing its potential utility as a biomarker of disease.

Multiple studies, which are reviewed elsewhere (23), have previously demonstrated that noncoding RNAs play an important role in ILD through the regulation of fibroblast proliferation, through profibrotic and antifibrotic pathways, and as potential disease biomarkers and therapeutic targets.

Investigating the Epigenetic Effects of Air Pollution in ILD

Air pollution may contribute to ILD development and progression by altering the epigenome in ways that lead to upregulation of aberrant inflammatory or profibrotic responses. Air pollution has been shown to impact each of the three main types of epigenetic mechanisms *in vitro*, *in vivo*, in healthy individuals, and in people with chronic diseases. The known mechanisms by which air pollution modifies the epigenome are illustrated in the Figure 1 (14). Little is known about the impact of air pollution on the epigenome of patients with ILD, and a systematic approach is required to gain a comprehensive understanding of these relationships. DNAm is the most frequently evaluated epigenetic marker and would be a natural starting point, followed by studies evaluating histone modifications, noncoding RNA patterns, and gene–environment interactions. Research approaches range from *in vitro* studies of ILD-relevant cell types to *in vivo* models of pulmonary fibrosis and to observational and experimental studies in patients with ILD.

In Vitro Methods

In vitro methods can be used to investigate how airborne pollutants contribute to

epigenetic changes and disease mechanisms on a cellular level. A study using human bronchial epithelial cells found that PM_{2.5} exposure resulted in globally reduced DNAm, site-specific histone modifications, shortened telomere length, and altered telomerase activity in a concentration- and exposure-dependent manner, especially in cells derived from patients with COPD (30). These telomere findings have been validated in human studies, with a recent meta-analysis finding that each 5 µg/m³ increase in PM_{2.5} exposure is associated with −0.03 (relative units) shorter telomeres (31). This may have important implications given the pathophysiologic relevance of short telomeres in multiple forms of ILD (32). Recent studies in nasal mucociliary epithelial cells have demonstrated changes in gene expression profiles in response to treatment with PM_{2.5} organic extract (33). Similar studies should be performed to delineate the transcriptomic and epigenomic responses to airborne pollutants in alveolar epithelial cells, fibroblasts, and immune cells derived from normal control subjects and patients with ILD. This will help to clarify on a molecular level how air pollution triggers immune dysregulation and fibrogenesis.

In Vivo Methods

Model organisms, for example bleomycin lung-injured mice, can be used to evaluate how exposure to airborne pollutants affects disease pathophysiology *in vivo*. One study exposed rats to traffic-related air pollutants and demonstrated a dose- and time-responsive change in DNAm and histone modifications at multiple specific regions across the genome in both blood and lung tissue in molecular pathways relevant to chronic respiratory diseases (34). The *in vivo* evaluation of air pollution impacts on fibrosis is limited by the lack of existing animal models of pollutant-induced fibrosis. Aged or genetically modified model organisms could be used to better simulate patient characteristics of ILD.

Observational Genomic and Epigenomic Methods

Genomic and epigenomic patterns can be investigated at specific loci of known pathogenic relevance to ILD. For example, DNAm has been investigated at one key transcription factor locus in regulatory T cells that is important in both IPF and asthma, *FOXP3* (Forkhead box

Figure 1. Major air pollution sources and criteria air pollutants (ozone, carbon monoxide, sulfur dioxide, nitrogen dioxide, particulate matter, and lead) and how these affect the three primary epigenetic mechanisms (23). (A) Histone modifications (methylation and acetylation) regulate whether chromatin is open or closed and thus whether it is accessible to transcriptional machinery. (B) DNA methylation at CpG (cytosine-guanine dinucleotide) sites generally reduces nearby gene expression. Alterations to DNA methylation have been shown to mediate the association between nitrogen dioxide exposure and reduced pulmonary function (39). (C) The most studied noncoding RNA is microRNA, which influences gene expression posttranscriptionally by impairing mRNA translation. 5mC = 5-methyl cytosine; AC = acetylation; DNAm = DNA methylation; DNMT = methyltransferase; Me = methylation; miRNA = microRNA; PM_{2.5} = particulate matter with a diameter $\leq 2.5 \mu\text{m}$; PM₁₀ = particulate matter with a diameter $\leq 10 \mu\text{m}$; TET = ten-eleven translocation. Biorender.com was used for creation of this figure.

transcription factor 3) (35). Two studies have demonstrated altered DNAm at regulatory CpG (cytosine-guanine dinucleotide) sites of the *FOXP3* locus in relation to ambient exposures to polycyclic aromatic hydrocarbons, NO₂, CO, and PM_{2.5} in subjects with asthma (36, 37). Altered DNAm in these and other related pathways may play an important role in immune dysregulation that contributes to the development of ILD.

Genome-wide DNAm studies can incorporate an assessment of air pollution exposures and permit mediation analyses to deduce whether adverse outcomes are mediated by epigenetic changes. Mediation analysis considers the effect of a mediator

variable that more clearly explains the relationship between exposure and outcome (38). A similar analysis was performed in healthy subjects, in whom alterations in DNAm patterns were found to mediate NO₂-induced reductions in lung function (39). Other studies have evaluated genome-wide histone acetylation profiles in healthy individuals and noted alterations in the histone landscape in individuals with higher PM_{2.5} exposure (40). This approach could be adapted by performing global DNAm or histone modification analyses on patients with ILD and a high-risk of air pollution exposures, thereby identifying modifiable epigenetic regions that may lead

to fibrogenesis or immune dysregulation. Previously performed genome-wide association studies can also be reevaluated to investigate the presence of any interactions between significant SNPs and exposure to specific airborne pollutants, as was previously done for childhood asthma (41). These approaches represent feasible extensions of prior research that can be performed using biologic samples collected from large ILD patient registries and biobanks.

Experimental Methods

Experimental approaches may provide evidence of causal associations between air pollution exposure, epigenetic changes, and outcomes in ILD. One approach is to evaluate how individual-level interventions, such as personal air quality monitors or air purifiers, modulate epigenomic responses and clinical outcomes in response to air pollution exposure (42, 43). One case-control study in Beijing provided healthy subjects with personal air pollution monitors and found that increased PM₁₀ exposure was associated with decreased histone H3 methylation (44). A randomized, double-blind, crossover trial provided 36 healthy adults in Shanghai with air purifiers to lower personal indoor PM_{2.5} exposure (45). Peripheral blood genome-wide DNAm was analyzed before and after the air purifier intervention, and significant alterations were noted at 49 CpG loci, with involvement of inflammatory, oxidative stress, cell survival, and apoptosis pathways. Similar analyses could be performed in patients with ILD, with repeated blood sampling during high and low pollution periods to assess for altered epigenomic patterns as a consequence of exposure. A novel systematic review is currently underway, exploring the role of individual interventions aimed at reducing the adverse impacts of air pollution exposure in patients with chronic respiratory diseases (43). It is essential that healthcare providers remain apprised of interventions that can help protect vulnerable patient populations from the harmful impacts of air pollution exposure.

Experimental approaches have also been undertaken in which patients with asthma are exposed to diesel exhaust followed by a bronchoscopy to investigate the impact on epigenetic patterns (46–48). A double-blind, randomized, crossover study exposed 13 subjects with asthma to diesel

exhaust and found alterations in the expression of multiple microRNAs and subsequent downregulation of antioxidant pathways (49). These effects were attenuated by the addition of N-acetylcysteine, suggesting a potential role for this antioxidant in mitigating the effects of traffic-related air pollution in people with asthma. Similar evaluations of the impact of N-acetylcysteine on pollution-induced epigenetic changes in ILD would be useful given the potential efficacy of this drug in some patients with ILD (50). The role of other antioxidant therapies, such as B vitamins, is also worth further study given their beneficial effect on air pollution-induced DNAm changes in CD4⁺ T cells (51).

One crossover study aimed to determine whether interactions exist between exposure to diesel exhaust and allergens (48). Similar interaction analyses could be performed in patients with ILD, looking at the interaction between smoking, sociodemographic factors, or occupational exposures and air pollution exposures on epigenetic patterns in these patients. These approaches will be essential in helping to elucidate the complex network of interactions that occur between the exposome and the epigenome in patients with ILD (52).

Limitations and Future Directions

Although our knowledge of the impact of air pollution and other environmental factors on the epigenome is rapidly expanding, there exist significant methodological and knowledge limitations. Previous studies have demonstrated low reproducibility of DNAm and other epigenetic patterns between different groups of patients with respiratory diseases (23, 53). This is likely due to different analysis methods, cell types, patient populations, and environmental exposures. Consistency in methods and correlation of epigenetic modifications with expression profiles and clinical outcomes in patients with ILD will be required. It is also imperative that we clarify the relationship between epigenetic patterns in peripheral blood and lung tissue so that we may then explore how these patterns vary with air pollution exposure. Single-cell DNAm

sequencing and other single-cell epigenetic techniques promise to address, in part, the impact of airborne pollutants on epigenetic patterns in ILD-relevant cell types.

Further research is needed to investigate the impact of air pollution on other forms of ILD, potentially considering fibrotic ILDs together given their shared disease pathophysiology (54). Future studies should also consider using more complex multipollutant analyses, such as Bayesian Kernel Regression models, to evaluate the effects of simultaneous exposures to multiple airborne pollutants (55). This should include analyses of the major criteria pollutants (PM_{2.5}, PM₁₀, NO₂, SO₂, CO, O₃, and lead), atmospheric heavy metals, and polychlorinated or polybrominated pollutants, because these have all been associated with adverse impacts on lung function and respiratory disease development (56, 57).

Recent U.S. evidence suggests that PM_{2.5}-associated deaths most affect individuals living in neighborhoods with greater socioeconomic deprivation and non-Hispanic Black or African American populations (4). This demonstrates the concept of environmental justice and emphasizes the need to consider potential interactions or confounding by sociodemographic factors in air pollution research. The investigation of interaction effects between multiple airborne pollutants, other environmental exposures (e.g., cigarette smoke, allergens, and socioeconomic factors), and genetic or epigenetic factors will paint a more detailed picture of how the “miasma” of airborne pollutants contribute to disease pathophysiology (55, 58, 59).

Future directions will also involve validating epigenetic modifications as biomarkers of air pollution exposure in patients with ILD. Given the potentially reversible nature of epigenetic modifications, these mechanisms have potential as prognostic and therapeutic targets to mitigate the adverse impacts of air pollution in ILD. Large ILD patient registries and biobanks should be further developed, with plans for multinational collaborative efforts aimed at elucidating the multiomic effects of air pollution on patients with ILD. These cooperative efforts will facilitate novel avenues for diagnosis,

monitoring progression, and disease prevention. These approaches need to be undertaken in conjunction with public health policies aimed at reducing global air pollution exposures.

Conclusions

The burden of ILD is increasing worldwide (2), yet there remain substantial knowledge gaps in our understanding of the environmental risk factors contributing to the development and progression of this condition. Recent research indicates that exposure to airborne pollutants is associated with increased incidence and adverse clinical outcomes in IPF. These data are still sparse and need to be validated in larger multicenter cohorts, using multipollutant models and longer time periods of assessment. In addition, we need to investigate the role that air pollution and other environmental exposures play in non-IPF ILDs and the potential interactions between different exposures that contribute to disease development.

Given recent findings that air pollution concentrations have been increasing across the United States since 2016, resulting in an additional 9,700 premature deaths attributable to air pollution in 2018 alone (16), it is imperative that researchers understand the biologic mechanisms through which airborne pollutants contribute to disease. Epigenetic modifications are a likely mechanism through which air pollution can interfere with normal physiologic functions. Exploring the impact of air pollution on the epigenome of patients with ILDs will provide critical insights into how environmental factors contribute to the development and progression of these highly morbid conditions. Increased understanding of the genome–epigenome–environment interactions in patients with ILD and other chronic diseases may enable prevention and mitigation strategies aimed at reducing the disease burden associated with environmental pollution (60). ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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