Air Pollution Exposure

A Novel Environmental Risk Factor for Interstitial Lung Disease?

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Air pollution exposure is a well-established risk factor for several adverse respiratory outcomes, including airways diseases and lung cancer. Few studies have investigated the relationship between air pollution and interstitial lung disease (ILD) despite many forms of ILD arising from environmental exposures. There are potential mechanisms by which air pollution could cause, exacerbate, or accelerate the progression of certain forms of ILD via pulmonary and systemic inflammation as well as oxidative stress. This article will review the current epidemiologic and translational data supporting the plausibility of this relationship and propose a new conceptual framework for characterizing novel environmental risk factors for these forms of lung disease.

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ABBREVIATIONS: ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; NO₂ = nitrogen dioxide; NO_x = nitrogen oxides; O₃ = ozone; PM = particulate matter; ROS = reactive oxygen species; TGF-β = transforming growth factor-β

The interstitial lung diseases (ILDs) comprise a diverse group of entities primarily characterized by the proliferation and thickening of the pulmonary interstitium. Despite a wide range of etiologic processes, many share a common phenotype of irreversible lung fibrosis that, in some patients, leads to progressive hypoxemia, respiratory failure, and death. Inhaled environmental causes have been identified in several well-described forms of ILD, including hypersensitivity pneumonitis, asbestosis, and silicosis.

Ambient air pollution has received relatively little attention in the field of ILD but is known to contribute to a range of pulmo-

nary and systemic diseases. Air pollution exposure is increasingly implicated in adverse health outcomes, including asthma, COPD, cardiovascular disease, and, most recently, lung cancer. We believe that a plausible argument can be made for a relationship between ambient air pollution and ILD. This article reviews the current clinical and biologic evidence linking air pollution exposure to the development and progression of ILD and proposes a new way of conceptualizing cumulative environmental risk factors in this patient population.

Air Pollution Overview

Ambient air pollution includes chemical, biologic, and particulate materials released

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into the atmosphere. Of the six criteria air pollutants regulated by the US Environmental Protection Agency (particulate matter [PM], ozone [O₃], nitrogen dioxide [NO₂], sulfur dioxide, carbon monoxide, and lead), PM, ground-level O₃, and NO₂ have been most strongly associated with adverse respiratory outcomes.

PM is a uniquely complex mixture that may include solid particles, liquids, and vapors. Sources of PM include geologic sources (eg, sand, salt), metals, and fossil fuel combustion (eg, diesel exhaust particles, black carbon). PM is typically defined by size, such as PM_{≤10}, PM_{≤2.5}, or PM_{≤0.1} in aerodynamic diameter (PM₁₀, PM_{2.5}, and PM_{0.1}, respectively), or more qualitatively as coarse, fine, and ultrafine. However, its toxicity varies depending on factors like particle weight and composition, as well as host factors determining the location and density of deposition in the respiratory tract.¹ PM toxicity can be further enhanced by exposure to other pollutants like NO₂ and O₃, with which it is frequently accompanied. PM exerts its effects directly from deposition in the respiratory tract and indirectly from triggering a local inflammatory response that can spread to the systemic circulation.

NO₂ is emitted whenever fossil fuels are combusted. It is a good marker of traffic-related air pollution and is an indicator for the larger group of nitrogen oxides (NOx). NOx combine with other compounds such as ammonia and moisture to form small particles capable of penetrating deep into the lung. Exposure to NO₂ induces a proinflammatory response in bronchial epithelial cells and can alter the distribution of leukocyte subsets in both blood and bronchoalveolar fluid.²⁻⁴ NO₂ also reacts with volatile organic compounds, heat, and ultraviolet radiation to produce ground-level O₃.

Tropospheric O₃ exists within 10 km of the Earth's surface and is photochemically produced through the reactions of sunlight with other pollutants like volatile organic compounds and NOx. In both human and animal studies, O₃ has been found to induce airway hyperactivity and airway inflammation, as well as to modify the cell-surface phenotypic expression of immunoregulatory proteins.⁵⁻⁸

Respiratory Health Effects of Air Pollution (Epidemiology)

Air pollution exposure has been linked extensively to respiratory-related morbidity, particularly with respect to airways disease. Increased exposure levels have been associated with poorly controlled asthma,^{9,10} asthma hospitalizations,¹¹ impaired lung function growth,¹²

COPD incidence,¹³ and COPD exacerbations.¹⁴ Proximity to a major road, as a proxy of traffic-related air pollution, was associated with elevated pulmonary and systemic markers of inflammation and an increased risk of bronchiolitis obliterans syndrome and death in a cohort of patients who had undergone lung transplantation.¹⁵ Additionally, air pollution has been identified as a risk factor for pulmonary exacerbations in cystic fibrosis.¹⁶⁻¹⁸ A large retrospective analysis identified an increased risk of respiratory-related mortality associated with elevations in chronic O₃ exposure.¹⁹ Using individualized exposure estimates, NO₂ exposure has been associated with an increased risk of death from lung cancer.²⁰ Other population-based studies have demonstrated improved health outcomes subsequent to reduced air pollution levels, ranging from incident COPD to greater life expectancy.^{21,22}

There has been a paucity of studies investigating air pollution and ILD despite many ILDs arising from inhalational exposures. Asbestosis and other pneumoconioses, hypersensitivity pneumonitis, chronic beryllium disease, and the smoking-related ILDs are all clearly linked to inhalational exposure to environmental agents. These agents range from toxic particulates and noxious gases to organic antigens, all of which are potentially modifiable in the patient's environment. Idiopathic pulmonary fibrosis (IPF) has been associated with industrial and production-based jobs as well as occupational metal and wood dust exposures, and it has been proposed that the male predominance of disease is attributable to the sex distribution in these occupations. The most well-established environmental risk factor for IPF is cigarette smoking, with smokers more likely to develop disease.²³ In a susceptible patient with underlying cumulative stress to the alveolar epithelium, cigarette smoking may accelerate fibrogenesis in the IPF lung via oxidative stress and other profibrotic signals inducing cellular senescence.²⁴⁻²⁶ Additionally, the age-related predominance of IPF suggests a cumulative, time-dependent risk, consistent with a dose-response relationship. The biologic and chemical agents discussed share similarities to the ambient air pollutants. Like the antigens known to cause hypersensitivity pneumonitis, organic components of PM may trigger abnormal immune responses leading to inflammation, epithelial damage, and over time, fibrosis. Cigarette smoking exposes the lung to particulates of varying size and to volatile organic compounds, both components of air pollution.

There is a small but growing body of evidence investigating the relationship between air pollution exposure

and the development or exacerbation of ILD. A study of asymptomatic children in Mexico found significantly higher rates of abnormal chest radiographic and spirometric findings in those with higher PM_{2.5} and O₃ exposures.²⁷ The abnormalities were mainly hyperinflation but also included reticular interstitial markings, with a subset of children demonstrating evidence of air trapping (suggestive of bronchiolitis) and subpleural nodularity on high-resolution CT scans of the chest. However, these data lack both accompanying pathology and longitudinal data describing the natural history of these radiographic changes. In a study of 325 patients with IPF, ambient air pollution was found to modify longitudinal changes in lung function, and the effect differed between pollutants. This suggests that pollutants may differentially alter the immunomodulatory pathways associated with this disease, but these data are preliminary and not peer reviewed.²⁸ One study of a well-defined cohort of patients with IPF found O₃ and NO₂ exposure to be associated with an increased risk of acute exacerbation, a clinically meaningful event associated with high mortality.²⁹ This is the first study to describe acute clinical outcomes in patients with ILD relative to air pollution exposure, and the findings warrant further prospective investigation. Studies of large, retrospective, epidemiologic populations are needed to identify variation in disease prevalence across different exposure levels. Prospective longitudinal cohort studies might best address this question but are limited by the relative rarity of ILD as well as the unknown potential latency period between exposure and incidence.

Potential Mechanisms

There are plausible mechanisms by which air pollution may cause or exacerbate ILD (Table 1). Early animal studies demonstrated that chronic and subchronic exposure to high O₃ levels in monkeys and rats was associated with irreversible increases in collagen deposition.^{30,31} Rats exposed to moderately high O₃ concentrations showed epithelial lesions with increased DNA synthesis in bronchiolar and type 2 epithelial cells shortly after exposure.³² The same study showed that coexposure to mixtures of urban dust and O₃ potentiates the effect of O₃ near the alveolar duct, leading to the accumulation of interstitial inflammatory cells. It has been proposed that particle deposition at a time of epithelial injury could allow particles or cytokines access to the pulmonary interstitium due to the loss of epithelial integrity.³³

In humans, controlled exposure chamber studies have demonstrated that short-term air pollution exposure

TABLE 1] Air Pollution Exposures Associated With Mechanistic Pathways Involved in the Development of Interstitial Lung Disease

Air Pollutant	Mechanistic Pathway
PM _{2.5}	Oxidative stress
Black carbon	
Diesel exhaust	Oxidative stress
Urban particulate matter mixture	Transforming growth factor-β
PM _{2.5} organic extracts	
PM ₁₀	Shortened telomeres
Ozone	Oxidative stress
	Interstitial inflammatory cell accumulation
	IL-6
Diesel exhaust particle	Oxidative stress
	Epithelial mesenchymal transition
Organic carbon	Oxidative stress
	IL-6

PM_{2.5} = particulate matter < 2.5 μm in aerodynamic diameter; PM₁₀ = particulate matter < 10 μm in aerodynamic diameter.

(some at levels below current regulatory standards) induce both local pulmonary and systemic inflammation in healthy volunteers, based on BAL and serologic markers, respectively.^{3,4,34,35} Epidemiologic studies of short-term air pollution exposures have also consistently demonstrated relationships with both airway and systemic inflammation in healthy individuals.³⁶⁻³⁸ Whether longer-term exposures result in fibrosis in humans remains unknown.

Ambient air pollution causes oxidative stress via the production of excess reactive oxygen species (ROS) such as hydroxide radical and superoxide anion.³⁷⁻³⁹ Intrinsic antioxidants are generally capable of counterbalancing the effects of ROS, but when the production of ROS exceeds the body’s ability to remove them, cellular damage ensues. Patients with IPF have evidence of reduced antioxidant capacity, suggesting they may have increased vulnerability to excess ROS caused by exposure to air pollution.⁴⁰ Despite this, there is no evidence that antioxidant therapies such as N-acetylcysteine are beneficial in ILD. A randomized clinical trial in IPF failed to identify a benefit of N-acetylcysteine in halting disease progression.⁴¹ Whether there is benefit in other forms of ILD or whether antioxidant therapy could be preventive has yet to be determined.

Telomeres (noncoding regions of DNA that protect against the loss of genetic information during subsequent

cycles of replication) and telomerase are particularly vulnerable to the effects of oxidative stress.³⁹ Telomere length has been found to vary in response to the duration of air pollution exposures, with short-term exposures associated with longer telomeres and cumulative exposures associated with shortened telomeres.⁴² These data suggest that telomeres are capable of temporary adaptation in response to toxic environmental stimuli, but that eventually, they are exhausted by chronic exposures. Several studies have demonstrated abnormally shortened telomeres in certain forms of ILD, particularly IPF.^{43,44} In the majority of cases, no genetic explanation for shortened telomeres can be found, suggesting that an environmental mechanism may be responsible for telomere shortening.

A study of human bronchial epithelial cells exposed to diesel exhaust particles demonstrated the upregulation of proteins associated with epithelial-mesenchymal transition, one proposed mechanism of IPF.⁴⁵ Transforming growth factor- β (TGF- β) mediates fibrogenesis and is an important therapeutic target in IPF. In animal models, motorcycle exhaust induces cardiac fibrosis via upregulated TGF- β 1 protein, while urban PM and diesel exhaust upregulate TGF- β 1 and procollagen gene expression in rat tracheal explants.^{46,47} In human lung fibroblasts, the TGF- β signaling pathway is deregulated in a dose-dependent manner by exposure to extractable organic matter from ambient air pollution.⁴⁸ This occurs via both up- and downregulation of specific genes responsible for TGF- β signaling, highlighting the complex relationship between the exposure and downstream protein activity. Taken together, these data provide biologic plausibility that air pollution could be associated with the development, progression, or exacerbation of ILD via mechanisms of oxidative stress, dysregulated fibrogenesis, and/or inflammation (Fig 1).

It is important to note that ILD is an umbrella term for a diverse and heterogeneous group of disorders for which there are numerous pathophysiologic mechanisms. For convenience, they have been lumped together, as it is beyond the scope of this article to address the relationship of each disease with air pollution. The pleiotropic effects of air pollution may impact each disease differently at different stages of severity. Additionally, individual genetic or epigenetic factors may impact the phenotypic expression of ILD resulting from environmental exposures, and future research is necessary to delineate these pathobiologic mechanisms.

Figure 1 – Proposed relationship between air pollution exposure and interstitial lung disease. Proposed mechanisms by which air pollution exposure could trigger the development of ILD in a genetically susceptible individual. Via oxidative stress, inflammation, and telomere shortening, air pollution may also result in acute exacerbation and/or disease progression in an individual with established ILD. ILD = interstitial lung disease.

Integrating Environmental Exposures Into Disease Models: The Exposome

We believe a comprehensive assessment of environmental risk factors (termed the “exposome”) must be undertaken to fully delineate the contribution of ambient air pollution (and other exposures) to the complex pathobiology of pulmonary fibrosis. This global approach has been pioneered in cancer research and could be applied to the study of ILD.

The concept of the exposome was initially proposed as a framework to complement the genome, accounting for an individual’s nongenetic/environmental risk factors for malignancy.⁴⁹ It has since been refined and applied more broadly to environmental epidemiology and exposure assessment in the context of other disease processes, including type 2 diabetes, inflammatory bowel disease, and addiction.^{50–54} The exposome characterizes all cellular processes in a framework where the “environment” can be conceptualized as the individual’s internal environment and “exposures” include all biologically active chemicals within this internal environment.⁵⁴ Such processes range from toxic ingestions to epigenetic methylation to the physiologic effects of neighborhood socioeconomic status, all of which are relevant to an individual’s health status. In its ideal form, the exposome accounts for a lifetime of exposures

from the prenatal period through to death. Since actual measurement of exposures over a lifetime is impossible, constructing an exposome relies primarily upon the use of validated biomarkers of cumulative exposure to specific agents. Defining the exposome in patients with pulmonary fibrosis would require the identification and repeated measurement of exposure biomarkers in large population-based prospective cohorts. Several exposure-related biomarkers have been identified, paving the way for further characterization of the exposome in this population. Though not specific for air pollution exposure, biomarkers with the potential for future clinical application include exhaled nitric oxide, micronuclei frequency in buccal mucosa cells, microRNA in induced sputum samples, malondialdehyde in exhaled breath condensate, and serum IL-6 levels.^{37,55-58}

Of the ILDs, IPF, in particular, is age-related, raising the possibility that lifetime cumulative environmental exposures may relate to the advanced cellular senescence seen in this disease.^{23,59} Comprehensively characterizing the environmental contributors to fibrogenesis (either directly or through gene and environment interactions) may be an essential step in understanding the complex pathobiology of IPF. While the potential environmental risk factors for ILD are many, air pollution exposure assessment provides a logical starting point for scientific investigation. Whether it is causally involved in the pathogenesis or exacerbates or accelerates already established disease, this ubiquitous exposure is readily quantifiable and will be useful in establishing a framework for environmental risk assessment in future studies of ILD. Identifying a potentially modifiable risk factor for IPF and other ILDs could result in significant public health and individual patient benefits.

Clinical and Public Health Implications

There are potential clinical and public health implications of identifying a relationship between air pollution exposure and ILD. In many regions of the world, air quality guidelines or standards have been established to protect the public health, particularly those at highest risk of adverse health impacts of exposure. At-risk populations typically include people with asthma, children, the elderly, and those with other chronic lung and heart conditions.⁶⁰ Evidence-based management approaches for such patients include recommendations to minimize exposures and avoid strenuous activity during bad-air-quality days.⁶¹ No such recommendations currently exist for patients living with chronic ILD, although arguments presented herein suggest potential benefit. Additionally, for diseases with few effective

treatments, environmental mitigation is a relatively cost-effective, easily implemented management strategy. General recommendations, such as avoiding strenuous activity during bad-air-quality days or wearing face masks to protect against particulates, would be prudent, though not evidence based at this point. Further research should be conducted before uniformly recommending air filters or purifiers or even residential relocation, as these may introduce undue cost to the patient in the absence of supportive data.

Conclusions

Ambient air pollution is a well-established risk factor for the development and worsening of many forms of pulmonary disease, and based on our evidence, we propose it may have an important role in the ILDs, particularly IPF. While definitive evidence is lacking, translational and epidemiologic data support the plausibility of a contributory relationship. The exposome may be a useful research concept, promoting characterization of the cumulative environmental exposures and their contribution to disease etiology and progression. Once identified, these environmental risk factors can be mitigated, leading to improved health outcomes in patients with interstitial lung disease.

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