

pollution causes asthma in children (3), but evidence that outdoor pollution causes adult-onset asthma is sparse and equivocal. A nationwide study of women from the United States found that each 3.6 $\mu\text{g}/\text{m}^3$ of long-term $\text{PM}_{2.5}$ exposure was associated with an odds ratio of 1.20 (95% confidence interval, 0.99–1.46) for adult-onset asthma, with similar findings for NO_2 (6). A large multicohort study in Europe (ESCAPE) reported numerous positive but insignificant associations between different traffic-related exposure metrics and adult asthma incidence (7). Perhaps the window of vulnerability for asthma onset due to air pollution has already passed by age 35. Unfortunately, the authors were limited in their ability to investigate exposures earlier than this 3-year window with a 1-year lag.

Sampling error is unlikely given that very large sample size, but bias is possible. The use of the health administrative databases precluded direct adjustment for potential individual-level confounders such as smoking, obesity, or family history of asthma. Unmeasured or residual confounding could bias results. Any negative confounding variables, however, would have to only (or more strongly) affect asthma over COPD to explain the null result for asthma only. Although outcome misclassification is possible, the asthma ascertainment method used here by Shin and colleagues is similar to methods commonly applied in epidemiologic studies and not likely a major source of bias. Finally, we would expect any severe exposure misclassification to bias both the COPD and asthma analyses, thus it is not likely a major factor to explain the null asthma findings.

Air pollution effect estimates are often relatively small (hazard ratio, 1.03–1.06 in this study), highlighting the need for large, well-conducted studies, such as the one by Shin and colleagues. Air pollution exposure is ubiquitous, and even a small effect estimate can have a large impact on the population's health, especially when it contributes to the incidence of a chronic disease that impairs quality of life and increases health care use. From a policy standpoint, an increase in the incidence of an irreversible chronic disease is even more costly to society than acute events, such as asthma or COPD hospitalizations. There is a great need for studies on long-term air pollution exposure from childhood into adulthood and the incidence of chronic respiratory disease in adults. Research such as this work that involves areas where pollution concentrations are mostly below current regulatory standards is especially informative for future policy decision-making to protect public health. ■

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

Erika Garcia, Ph.D., M.P.H.
Department of Preventive Medicine
University of Southern California
Los Angeles, California

Mary B. Rice, M.D., M.P.H.
Department of Medicine
Beth Israel Deaconess Medical Center
Boston, Massachusetts

ORCID IDs: 0000-0003-1540-9805 (E.G.); 0000-0003-2538-391X (M.B.R.).

References

- Shin S, Bai L, Burnett RT, Kwong JC, Hystad P, van Donkelaar A, *et al*. Air pollution as a risk factor for incident chronic obstructive pulmonary disease and asthma: 15-year population-based cohort study. *Am J Respir Crit Care Med* 2021;203:1138–1148.
- Di Q, Dai L, Wang Y, Zanobetti A, Choirat C, Schwartz JD, *et al*. Association of short-term exposure to air pollution with mortality in older adults. *JAMA* 2017;318:2446–2456.
- Thurston GD, Balmes JR, Garcia E, Gilliland FD, Rice MB, Schikowski T, *et al*. Outdoor air pollution and new-onset airway disease: an official American Thoracic Society workshop report. *Ann Am Thorac Soc* 2020;17:387–398.
- HEI Panel on the Health Effects of Traffic-Related Air Pollution. Traffic-related air pollution: a critical review of the literature on emissions, exposure, and health effects. Boston, MA: Health Effects Institute; 2010.
- Eisner MD, Anthonisen N, Coultas D, Kuenzli N, Perez-Padilla R, Postma D, *et al*. Committee on Nonsmoking COPD, Environmental and Occupational Health Assembly. An official American Thoracic Society public policy statement: novel risk factors and the global burden of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2010;182:693–718.
- Young MT, Sandler DP, DeRoo LA, Vedal S, Kaufman JD, London SJ. Ambient air pollution exposure and incident adult asthma in a nationwide cohort of U.S. women. *Am J Respir Crit Care Med* 2014;190:914–921.
- Jacquemin B, Siroux V, Sanchez M, Carsin AE, Schikowski T, Adam M, *et al*. Ambient air pollution and adult asthma incidence in six European cohorts (ESCAPE). *Environ Health Perspect* 2015;123:613–621.

Copyright © 2021 by the American Thoracic Society



⊗ Interstitial Lung Abnormalities and Aging Biomarkers: A Mediation

Benjamin Franklin famously wrote that “life’s tragedy is that we get old too soon and wise too late.” Although one may be faulted for getting wise too late, getting old too soon may be out of his or her

control. Molecular risk factors that predispose to accelerated aging have been identified across the genetic, epigenetic, transcriptomic, and proteomic landscape (1). Those with evidence of accelerated biologic aging are more likely to develop common age-related conditions such as heart disease and malignancy but also appear to be at increased risk of lung disease. Short telomere length and DNA methylation, both potential markers of accelerated biologic aging (1), predispose to the development of fibrosing interstitial lung disease (ILD), resulting in progressive lung function decline and high mortality (2–4). A number of biomarkers that reflect biologic aging processes are also key mediators of fibrogenesis (5–8),

⊗ This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0 (<https://creativecommons.org/licenses/by-nc-nd/4.0/>). For commercial usage and reprints, please contact Diane Gern (dgern@thoracic.org).

Supported by NHLBI (K23HL138190).

Originally Published in Press as DOI: 10.1164/rccm.202011-4046ED on November 23, 2020

suggesting a biologic link between fibrotic ILD and accelerated aging.

In this light, there exists high potential for the biologic processes of normal aging and pathologic accelerated aging to shed light on those contributing to the development of fibrosing ILD. Because the presence of pulmonary fibrosis suggest that the horse has already left the proverbial barn, studies aimed at elucidating the pathogenesis of fibrosing ILD could be particularly informative when performed in those with the earliest features of ILD, termed “interstitial lung abnormalities” (ILAs) (9). Most ILAs progress over time, increase in prevalence with age and smoking history, and likely have a negative impact on survival (10–13), supporting their classification as early ILD. Moreover, these associations appear to strengthen in those with fibrotic ILAs (11), suggesting that ILAs capture the entire continuum of ILD from early morphologic changes to clinically relevant disease.

In this issue of the *Journal*, Sanders and colleagues (pp. 1149–1157) seek to address the link between ILAs detected by chest computed tomography (CT) in participants from the Framingham Heart Study and plasma biomarkers of accelerated aging (14). These authors assessed 10 previously reported biomarkers of aging (8) and found that increasing plasma concentration of GDF15 (growth differentiation factor 15), TNFR (tumor necrosis factor α receptor II), IL-6, and CRP (C-reactive protein) was associated with increased odds of ILA presence. GDF15 and TNFR in particular were strongly associated ILA presence, with each unit increase in log transformed value increasing the odds of ILA presence by greater than threefold. Importantly, these results were robust to adjustment for other age-related conditions such as cancer, hypertension, and coronary artery disease, which was measured by coronary artery calcium score. To validate their GDF15 findings, Sanders and colleagues tested the association between this biomarker and ILAs in an independent cohort drawn from COPDgene study (NCT00608764). GDF15 was again associated with ILA presence, with each unit increase in log transformed value increasing the odds of ILA presence by greater than eightfold.

Sanders and colleagues then assessed the association between these aging biomarkers and mortality risk. Although no association reached statistical significance after adjustment for multiple testing, increased concentrations of GDF15, TNFR, and an insulin growth factor were associated with an increase in mortality risk. Among COPDgene participants, GDF15 was also associated with survival, with each unit increase in log transformed value increasing the hazard of death by 60%, supporting the findings in the Framingham cohort. Finally, given the shared associations between these biomarkers, aging, and the presence of ILAs, these authors conducted causal mediation analysis to determine the extent to which each biomarker mediated the association between ILAs and age. They found that TNFR and IL-6 mediated just under 10% of the association between ILAs and age, whereas GDF15 mediated 22% but failed to cross the statistical significance threshold after adjustment for multiple testing. GDF15 was again tested in COPDgene participants and was found to mediate 58% of the association between ILAs and age.

Taken together, these findings provide new and important insight into the shared pathobiology of ILA development and aging and support the work of others showing GDF15 to be an important mediator of fibrosing ILD (7). Validation of the observed

associations between ILA presence and IL-6, TNFR, and CRP concentrations would strengthen these findings even further, as these biomarkers were not available in the COPDgene cohort. Another limitation worth noting stems from the time interval between biomarker determination and chest CT acquisition. At least 1 year elapsed for all 10 biomarkers assessed, and more than 5 years elapsed for several of the key biomarkers identified in this study, including GDF15 (7 yr), IL-6 (5.1 yr), and TNFR (5.1 yr). These time intervals make the Framingham cohort results difficult to interpret in isolation, but GDF15 validation in COPDgene participants suggests true association and greatly strengthens the findings overall.

The findings presented here provide not only important pathobiologic information but also an exciting glimpse into the future of ILD screening. Like wisdom, fibrosing ILD is an evolution rather than discrete state of being and has early and late phases that bookend an intermediary phase of variable length. Detection of early-phase ILD remains a major challenge. Despite prior studies showing ILAs to be present in up to 10% of screened individuals (10–13), the proportion of these individuals who develop clinically significant ILD and the timeframe over which that happens remains unclear. Until these questions are answered, systematic ILD screening using chest CT is likely to remain unrealistic and cost ineffective. Consequently, the findings presented here may serve as a stepping-stone toward blood-based ILD screening. This will undoubtedly require the identification and validation of additional biomarkers beyond those presented here, but this study represents an exciting first step in the right direction. ■

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

Justin M. Oldham, M.D., M.S.
 Division of Pulmonary, Critical Care and Sleep Medicine
 University of California at Davis
 Sacramento, California

ORCID ID: 0000-0003-4957-8869 (J.M.O.).

References

1. Wagner KH, Cameron-Smith D, Wessner B, Franzke B. Biomarkers of aging: from function to molecular biology. *Nutrients* 2016;8:338.
2. Stuart BD, Lee JS, Kozlitina J, Noth I, Devine MS, Glazer CS, *et al.* Effect of telomere length on survival in patients with idiopathic pulmonary fibrosis: an observational cohort study with independent validation. *Lancet Respir Med* 2014;2:557–565.
3. Yang IV, Pedersen BS, Rabinovich E, Hennessy CE, Davidson EJ, Murphy E, *et al.* Relationship of DNA methylation and gene expression in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2014;190:1263–1272.
4. Ley B, Newton CA, Arnould I, Elicker BM, Henry TS, Vittinghoff E, *et al.* The MUC5B promoter polymorphism and telomere length in patients with chronic hypersensitivity pneumonitis: an observational cohort-control study. *Lancet Respir Med* 2017;5:639–647.
5. Kobayashi T, Tanaka K, Fujita T, Umezawa H, Amano H, Yoshioka K, *et al.* Bidirectional role of IL-6 signal in pathogenesis of lung fibrosis. *Respir Res* 2015;16:99.
6. Oikonomou N, Harokopos V, Zalevsky J, Valavanis C, Kotanidou A, Szymkowski DE, *et al.* Soluble TNF mediates the transition from pulmonary inflammation to fibrosis. *PLoS One* 2006;1:e108.

7. Zhang Y, Jiang M, Nouraei M, Roth MG, Tabib T, Winters S, *et al.* GDF15 is an epithelial-derived biomarker of idiopathic pulmonary fibrosis. *Am J Physiol Lung Cell Mol Physiol* 2019;317:L510–L521.
8. Justice JN, Ferrucci L, Newman AB, Aroda VR, Bahnson JL, Divers J, *et al.* A framework for selection of blood-based biomarkers for geroscience-guided clinical trials: report from the TAME Biomarkers Workgroup. *Geroscience* 2018;40:419–436.
9. Hatabu H, Hunninghake GM, Richeldi L, Brown KK, Wells AU, Remy-Jardin M, *et al.* Interstitial lung abnormalities detected incidentally on CT: a position paper from the Fleischner Society. *Lancet Respir Med* 2020;8:726–737.
10. Araki T, Putman RK, Hatabu H, Gao W, Dupuis J, Latourelle JC, *et al.* Development and progression of interstitial lung abnormalities in the Framingham Heart Study. *Am J Respir Crit Care Med* 2016;194:1514–1522.
11. Putman RK, Gudmundsson G, Axelsson GT, Hida T, Honda O, Araki T, *et al.* Imaging patterns are associated with interstitial lung abnormality progression and mortality. *Am J Respir Crit Care Med* 2019;200:175–183.
12. Putman RK, Hatabu H, Araki T, Gudmundsson G, Gao W, Nishino M, *et al.*; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators; COPDGene Investigators. Association between interstitial lung abnormalities and all-cause mortality. *JAMA* 2016;315:672–681.
13. Washko GR, Hunninghake GM, Fernandez IE, Nishino M, Okajima Y, Yamashiro T, *et al.*; COPDGene Investigators. Lung volumes and emphysema in smokers with interstitial lung abnormalities. *N Engl J Med* 2011;364:897–906.
14. Sanders JL, Putman RK, Dupuis J, Xu H, Murabito JM, Araki T, *et al.* The association of aging biomarkers, interstitial lung abnormalities, and mortality. *Am J Respir Crit Care Med* 2021;203:1149–1157.

Copyright © 2021 by the American Thoracic Society



RNA Methylation: A New Regulator of Vascular Remodeling in Pulmonary Hypertension

Pulmonary hypertension (PH) is a chronic and progressive vascular disease characterized by a major constrictive remodeling of the distal pulmonary vasculature leading to increase in pulmonary artery pressure, resistance, and ultimately heart failure (1). Although there is a good understanding of the cellular processes occurring during the development of the disease, including endothelial cell dysfunction and apoptosis and smooth muscle cell (SMC) proliferation, the therapeutic options to limit or revert its progression are limited (2). This may be explained by a lack of understanding and knowledge of the intracellular mechanisms driving cellular dysfunction. Recent investigations have pointed out the contribution of nuclear, transcriptional, and epigenetic mechanisms in mediating PH-associated environmental changes into cell phenotypic and functional perturbations (1, 3). In this issue of the *Journal*, Hu and colleagues (pp. 1158–1172) identified a novel epigenetic mechanism, namely RNA methylation, as a driver of vascular remodeling and SMC proliferation in PH (4).

Epigenetics is an ensemble of mechanisms regulating genome organization, stability, and gene expression without modification of the DNA sequence. These mechanisms include DNA adenine and cytosine modifications, posttranslational modifications of histone residues, and expression of noncoding RNA. All these regulatory systems play a role in regulating gene expression by acting on chromatin conformation and gene accessibility to transcription machinery, transcription factor binding, and mRNA stability and degradation. More recently, mRNA base modifications have also been described, among them N^6 adenosine methylation or m^6A . Like other epigenetic systems, mRNA methylation dynamics and functions require the participation of three types of proteins: “writers” catalyzing N^6 adenosine methylation, “erasers” reverting

these modifications, and “readers” recognizing and utilizing methylated mRNA residues for the recruitment of translational complexes (5). Importantly, the role of methylation on mRNA highly depends on which “reader” is involved and may be diametrically different. Although m^6A “reader” YTHDF1 (YTH domain-containing family protein 1) promotes mRNA translation, YTHDF2 causes mRNA instability and degradation (6). This reflects the complexity and versatility of mRNA methylation on gene regulation and protein expression.

Hu and colleagues found a robust increase in mRNA methylation levels and m^6A “reader” YTHDF1 expression in the pulmonary vasculature of patients with PH as well as in animal and *in vitro* models of PH (Figure 1). By performing global genetic deletion of YTHDF1, they provide strong evidence that m^6A -mediated YTHDF1 recruitment on a subset of transcripts contributes to detrimental vascular remodeling in Sugen/hypoxia-treated mice. Mechanistically, m^6A and YTHDF1 exacerbate SMC proliferation, at least in part by increasing the translation of *MAGED1*. *MAGED1* transcript is methylated by the methyltransferase METTL3 and targeted by YTHDF1 in mice with PH. *MAGED1* knockout phenocopies YTHDF1 deletion and prevents PH development. These studies are compelling in demonstrating a causal role of this central epigenetic mechanism in the development of PH and draw an interesting parallel with recent discoveries in other proliferative disorders such as cancer, in which studies have already identified alteration of mRNA methylation homeostasis as a driver of tumoral cell proliferation. An elevated YTHDF1 expression has been reported in multiple cancers, and functional studies have demonstrated that YTHDF1 plays a detrimental role with respect to tumor growth, metastasis, and antitumor immunity (7, 8). These reports suggest a common YTHDF1-dependent pathway driving hyperproliferative processes in cancer and PH, thus reinforcing the cancer theory of PH (9). In contrast, *MAGED1* appears to display opposite roles in these diseases. In human and mouse models of PH, *MAGED1* is overexpressed due to an increase in translation mediated by YTHDF1. Knockout and knockdown experiments

©This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0 (<https://creativecommons.org/licenses/by-nc-nd/4.0/>). For commercial usage and reprints, please contact Diane Gern (dgern@thoracic.org).

Originally Published in Press as DOI: 10.1164/rccm.202011-4185ED on February 6, 2021