the animal models are to the KRT8^{hi} cells in IPF should be assessed. We must also determine whether AECs permanently arrest or just pause in the early differentiation state, and whether a failure of KRT8 downregulation is causally related to this. Finally, although we propose that persistence of the early differentiation state may represent the ineffectual epithelial regeneration that is widely believed to promote fibrogenesis, whether KRT8/KRT18^{hi} AEC2s activate fibroblasts should also be examined. During the preparation of this work, an unpublished preprint reported the emergence of a transitional *Krt8/Krt18*^{hi}, TGF-β–activated state after lung injury induced by bleomycin (10), which is strikingly similar to the TGF-β–activated *Krt8/Krt18*^{hi} transitional cell state we previously identified in the LPS model (4). The upregulation of TNF, MYCN, and NRF2 target genes reported in the bleomycin model was also observed in the LPS model (4). Although bleomycin induces fibrosis, the fibrosis eventually resolves and late differentiation, with *Krt8/Krt18* downregulation and TGF-β deactivation, ensues (10).

The mechanisms underlying AEC2-to-AEC1 differentiation during physiologic regeneration and the manner in which alveolar regeneration may go awry during the pathogenesis of fibrosis have remained fundamental unanswered questions in the field. Here, we demonstrate that physiologic AEC2-to-AEC1 differentiation proceeds via an early differentiation state characterized by TGF-β–dependent KRT8/KRT18 upregulation and a late differentiation state characterized by TGF-β deactivation and KRT8/KRT18 downregulation. This regenerative lineage trajectory appears to be conserved in three injury models, which is a significant finding with therapeutic implications. However, in fibrosis, likely owing to persistent TGF-β activation, regenerating AEC2s persist in the KRT8/KRT18^{hi} early differentiation state. These findings may ultimately lead to novel therapies to promote physiologic regeneration and suppress fibrogenesis in IPF. ■

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

Acknowledgment: The authors thank Jay Hesselberth for thoughtful discussions, and Steven Huang, Eric White, Thomas Lanigan, Abigail Chinn, and Carol Wilke for technical assistance.

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References

1. Blackwell TS, Tager AM, Borok Z, Moore BB, Schwartz DA, Anstrom KJ, *et al*. Future directions in idiopathic pulmonary fibrosis research: an NHLBI workshop report. *Am J Respir Crit Care Med* 2014;189:214–222.
2. Katzenstein AL, Myers JL. Idiopathic pulmonary fibrosis: clinical relevance of pathologic classification. *Am J Respir Crit Care Med* 1998;157:1301–1315.
3. Xu Y, Mizuno T, Sridharan A, Du Y, Guo M, Tang J, *et al*. Single-cell RNA sequencing identifies diverse roles of epithelial cells in idiopathic pulmonary fibrosis. *JCI Insight* 2016;1:e90558.
4. Riemondy KA, Jansing NL, Jiang P, Redente EF, Gillen AE, Fu R, *et al*. Single cell RNA sequencing identifies TGFβ as a key regenerative cue following LPS-induced lung injury. *JCI Insight* 2019;5:123637.
5. Woodcock-Mitchell JL, Burkhardt AL, Mitchell JJ, Rannels SR, Rannels DE, Chiu JF, *et al*. Keratin species in type II pneumocytes in culture and during lung injury. *Am Rev Respir Dis* 1986;134:566–571.
6. Omary MB, Ku NO, Strnad P, Hanada S. Toward unraveling the complexity of simple epithelial keratins in human disease. *J Clin Invest* 2009;119:1794–1805.
7. Lähdeniemi IAK, Misiorek JO, Antila CJM, Landor SK, Stenvall CA, Fortelius LE, *et al*. Keratins regulate colonic epithelial cell differentiation through the Notch1 signalling pathway. *Cell Death Differ* 2017;24:984–996.
8. Paine R, Ben-Ze'ev A, Farmer SR, Brody JS. The pattern of cytokeratin synthesis is a marker of type 2 cell differentiation in adult and maturing fetal lung alveolar cells. *Dev Biol* 1988;129:505–515.
9. Reyfman PA, Walter JM, Joshi N, Anekalla KR, McQuattie-Pimentel AC, Chiu S, *et al*. Single-cell transcriptomic analysis of human lung provides insights into the pathobiology of pulmonary fibrosis. *Am J Respir Crit Care Med* 2019;199:1517–1536.
10. Strunz M, Simon LM, Ansari M, Mattner LF, Angelidis I, Mayr CH, *et al*. Longitudinal single cell transcriptomics reveals Krt8+ alveolar epithelial progenitors in lung regeneration [preprint]. *bioRxiv*; 2019 [accessed 2020 May 7]. Available from: https://www.biorxiv.org/content/10.1101/705244v1.full.
11. Seibold MA, Smith RW, Urbanek C, Groshong SD, Cosgrove GP, Brown KK, *et al*. The idiopathic pulmonary fibrosis honeycomb cyst contains a mucocilary pseudostratified epithelium. *PLoS One* 2013;8:e58658.

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Asthma and Obstructive Sleep Apnea: Taking It to Heart

To the Editor:

In a recent article, Prasad and colleagues eloquently consolidated the current evidence regarding the bidirectional interaction

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Originally Published in Press as DOI: 10.1164/rccm.201912-2537LE on February 6, 2020

between asthma and obstructive sleep apnea (OSA) (1). However, to develop a personalized approach toward the treatment of comorbid pulmonary diseases with systemic spillover of inflammation (1), we have to appreciate their cardiovascular interactions (2). Because the cardiovascular impact of OSA and chronic obstructive pulmonary disease is relatively well described (2), a brief discussion with regard to asthma and cardiovascular disease (CVD) is warranted.

A recent large retrospective cohort of patients admitted to National Health Service hospitals in the United Kingdom reported a strong and independent association of asthma, chronic obstructive pulmonary disease, and interstitial lung disease with CVD (3). Asthma was independently associated with ischemic heart disease, and heart failure (hazard ratio, 1.81; 95% confidence interval, 1.75–1.87) and ischemic heart disease (hazard ratio, 1.04; 95% confidence interval, 1.01–1.07) were among the variables that were independently associated with mortality in patients with asthma (3). In another large study, late-onset asthma, diagnosed at age ⩾18 years, was associated with an increased risk of incident CVD events after adjustment for age, sex, and CVD risk factors (4). In a biracial, community-based, long-term investigation of risk factors and natural history of CVD, young adults with a history of asthma were found to have a significantly greater risk of increased left ventricular mass index independently of other major cardiovascular risk factors (5).

Many similarities exist between the biochemical and cellular pathways of cardiac and pulmonary fibrosis (6). As we read the article by Prasad and colleagues and appreciate the multifaceted overlap between asthma and OSA, we have to remind ourselves of the current evidence and knowledge gaps regarding cardiopulmonary interactions in asthma to help improve risk stratification, devise precise management strategies, and identify novel therapeutic targets. ■

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

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References

1. Prasad B, Nyenhuis SM, Imayama I, Siddiqi A, Teodorescu M. Asthma and obstructive sleep apnea overlap: what has the evidence taught us? *Am J Respir Crit Care Med* [online ahead of print] 16 Dec 2019; DOI: 10.1164/rccm.201810-1838TR.
2. Mehmood M. Obstructive sleep apnea, chronic obstructive pulmonary disease, and heart failure with preserved ejection fraction: a cardiopulmonary perspective. *Am J Respir Crit Care Med* 2020;201: 500.
3. Carter P, Lagan J, Fortune C, Deepak L. Association of cardiovascular disease with respiratory disease. *J Am Coll Cardiol* 2019;73: 2166–2177.
4. Tattersall MC, Barnet JH, Korcarz CE, Hagen EW, Peppard PE, Stein JH. Late-onset asthma predicts cardiovascular disease events: the Wisconsin sleep cohort. *J Am Heart Assoc* 2016;5:e003448.
5. Sun D, Wang T, Heianza Y, Lv J, Han L, Rabito F, *et al*. A history of asthma from childhood and left ventricular mass in asymptomatic young adults: the Bogalusa heart study. *JACC Heart Fail* 2017;5:497–504.
6. Murtha LA, Schuliga MJ, Mabotuwana NS, Hardy SA, Waters DW, Burgess JK, *et al*. The processes and mechanisms of cardiac and pulmonary fibrosis. *Front Physiol* 2017;8:777.

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Reply to Mehmood

From the Authors:

We appreciate the point made by Dr. Mehmood in his letter with regard to our review of the evidence supporting the overlap between asthma and obstructive sleep apnea (OSA) (1). Several reviews on this topic have been published over time, presenting multiple putative pathways whereby asthma and OSA could interact (2–5). Among them, the role of cardiopulmonary interactions in this relationship was brought forward more than a decade ago (2, 4). Since then, much of the evidence has remained at the epidemiologic, database level, as referenced in the letter, with a lack of evidence from well-characterized patients or experimental studies. Furthermore, none of the cited epidemiologic studies that focused on individuals with asthma included OSA in their analyses (6–8), even though objective, standard laboratory-based sleep data were readily available (8). This raises several questions: *1*) does OSA independently modulate the interaction of asthma with cardiovascular disease, *2*) is there any bidirectionality in the relationship of asthma with cardiovascular disease, and *3*) what are the underlying pathways?

The *a priori* set goal of our review was to focus on mechanisms for which *multiple lines of evidence* (epidemiologic, clinical, and experimental) have amassed, as detailed for each direction of the relationship (1). Although many other mechanisms (3, 4), including cardiopulmonary interactions, may play a role in the asthma–OSA relationship, in our opinion, the underlying mechanism (or mechanisms) remains to be identified by testing in clinical and experimental studies. ■

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

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Originally Published in Press as DOI: 10.1164/rccm.202001-0151LE on February 6, 2020