severe asthma. In their study, not surprisingly, high-dose ICS and systemic corticosteroids were significantly associated with severe asthma and low CC16 expression levels in BECs. Critically, adjusting for ICS dose eliminated the association between CC16 concentrations and asthma severity. The authors propose that this may be because of overadjustment. However, it is difficult to untangle the influence of ICS use in this study, which represents a major challenge in translational asthma research in general. Studies of the effect of ICS on BEC CC16 expression in normal individuals and *in vitro* BEC studies would clarify and contextualize the findings of this publication. Finally, the authors present CC16 as a nontraditional Th2 biomarker rather than a negative T2 biomarker. If this is truly the case, then a better understanding of its mechanistic contribution to asthma will be crucial.

Although Li and colleagues from SARP present a promising airway biomarker, there are still important questions that need to be addressed, including identifying the molecular mechanism of CC16 in asthma and the influence of corticosteroids on its utility as a biomarker. However, the approach itself is an important illustration of the path toward refined asthma endotypes. ■

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

Brinda Desai, M.D.
Praveen Akuthota, M.D.
Division of Pulmonary, Critical Care, Sleep Medicine & Physiology
University of California San Diego
La Jolla, California

References

1. Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. *Lancet* 2018;391: 783–800.
2. Wan XC, Woodruff PG. Biomarkers in severe asthma. *Immunol Allergy Clin North Am* 2016;36:547–557.
3. Denton E, Price DB, Tran TN, Canonica GW, Menzies-Gow A, FitzGerald JM, *et al.* Cluster analysis of inflammatory biomarker expression in the international severe asthma registry. *J Allergy Clin Immunol Pract* 2021; 9:2680–2688.e7.
4. Menzies-Gow A, Corren J, Bourdin A, Chupp G, Israel E, Wechsler ME, *et al.* Tezepelumab in adults and adolescents with severe, uncontrolled asthma. *N Engl J Med* 2021;384:1800–1809.
5. Bernard AM, Roels HA, Buchet JP, Lauwerys RR. Serum clara cell protein: an indicator of bronchial cell dysfunction caused by tobacco smoking. *Environ Res* 1994;66:96–104.
6. Guerra S, Halonen M, Vasquez MM, Spangenberg A, Stern DA, Morgan WJ, *et al.* Relation between circulating CC16 concentrations, lung function, and development of chronic obstructive pulmonary disease across the lifespan: a prospective study. *Lancet Respir Med* 2015;3: 613–620.
7. Li X, Guerra S, Ledford JG, Kraft M, Li H, Hastie AT, *et al.*; NHLBI Severe Asthma Research Program (SARP). Low CC16 mRNA expression levels in bronchial epithelial cells are associated with asthma severity. *Am J Respir Crit Care Med* 2023;207:438–451.
8. Peters MC, McGrath KW, Hawkins GA, Hastie AT, Levy BD, Israel E, *et al.*; National Heart, Lung, and Blood Institute Severe Asthma Research Program. Plasma interleukin-6 concentrations, metabolic dysfunction, and asthma severity: a cross-sectional analysis of two cohorts. *Lancet Respir Med* 2016;4:574–584.
9. Yao Y, Welp T, Liu Q, Niu N, Wang X, Britto CJ, *et al.* Multiparameter single cell profiling of airway inflammatory cells. *Cytometry B Clin Cytom* 2017;92:12–20.

A Few Bad Airways Can Wreak Havoc: Recognizing Asthma as a Local Disorder

Stimulating airway smooth muscle (ASM) in an individual with asthma can cause some airways to hyperconstrict in ways healthy airways would not. Although several reasons could contribute to this, there is unequivocal experimental evidence that the ASM surrounding many asthmatic airways is thicker, and more so with severe asthma (1). Starting with Lambert and colleagues (2) and continued with increasing more morphometrically and three-dimensionally consistent airway trees (3–5), computational models consistently show that if one assumes maximum ASM force generation scales proportionately with its thickness, the thickened ASM found in asthmatic airways can lead to hyperresponsiveness. The above, however, is inadequate to fully understand how lung function degrades during an asthma attack in a specific patient or to guide optimal treatment strategies in a patient-specific fashion. The percentage of ASM thickening is not the same everywhere, either in large versus small airways or across airways of similar original diameter throughout the lung or across subjects with a similar clinical classification of asthma severity (6, 7).

Surely all airways do not constrict identically during an asthma attack; ergo, heterogeneous constriction is a fundamental feature of asthma (8, 9). In fact, this feature is the most important contributor to the degradation of lung function that occurs during an attack (3–5). Models predict that ASM thickening enhances the heterogeneity of the resulting constriction (4). Hence, it would seem useful to identify the precise locations of abnormal ASM thickening. Stated another way, understanding the average constriction across all airways is of limited value when conceptualizing more effective future treatment methods. Rather, it is all about the anatomic origins of heterogeneity. This last statement speaks to the heart of insights from the new study by James and colleagues (pp. 452–460) in this issue of the *Journal* (10).

Originally Published in Press as DOI: 10.1164/rccm.202212-2231ED on December 14, 2022

James and colleagues (10) meticulously measured the thickness of the ASM for nine consecutive airway generations along three distinct airway pathways in the lungs of subjects without asthma, subjects with nonfatal asthma (NFA), and subjects with fatal asthma. Each pathway progresses from larger (~9 mm diameter) to smaller (~1 mm diameter) airways. The data allowed them to assess two forms of heterogeneity in ASM thickening: longitudinal (e.g., large vs. small) and spatially distributed heterogeneity (airways of similar generations but distinctly different lung areas). They classified any airway as having abnormal ASM thickness if the thickness was 2 Standard Deviation above the mean from a corresponding normal airway. They found that subjects without asthma had little evidence of thickening of their ASM on average or even in any individual airway along any of the pathways. In contrast, subjects with NFA were far more likely to possess at least one airway, and in many cases a few airways, with highly thickened ASM along one or more pathways, even though the mean ASM across all airways was often within the normal range. Interestingly, they also found that about 20% of subjects with NFA had abnormal thickening only in their small airways. Most of the subjects with fatal asthma showed abnormal thickening in the ASM of both one or more large and one or more small airways and across all three pathways in almost all such subjects. But, even here, averaging across all airways often dampened evidence that there were always at least some individual airways along a pathway with highly abnormal ASM thickness. They conclude that using mean data to compare cases of asthma underestimates the potential severity of disease due to ASM remodeling. This conclusion inherently appreciates that it is the capacity to create heterogeneous constriction that drives asthma severity for subjects with NFA and that only a few airways along a pathway need to possess abnormally thick ASM to accomplish this (i.e., many airways can be within the normal range).

They also report that although there was no correlation of abnormal ASM across airways of the same generation, along different pathways there was some degree of correlation along adjacent airways, suggesting that if an airway in each path had abnormal ASM thickening it was more likely to find another airway close by with the same.

James and colleagues did not report any functional data to support their notion that assessing mean data only might depress one's sense of asthma clinical severity. But there are ample studies that are consistent with this notion. Computational models have shown that when a few airways hyperconstrict heterogeneously the result is a dramatic degradation of lung mechanical function and ventilation distribution in ways that may not at all be evident by simply measuring the overall increase in airway resistance, which reflects mean diameter reduction (3–5). To match measured degradation in mechanics and ventilation distribution simultaneously, Tgavalekos and colleagues (5) only had to hyperconstrict a small percentage of small airways heterogeneously. Constriction of only large airways could not replicate these measurements. Imaging studies (9, 11) have shown that many ventilation defects occur in similar anatomic locations in the same subjects with asthma when imaged longitudinally in time, suggesting elevated ASM thickness might be a local pathology.

Taken together, the study by James and colleagues convincingly supports that asthma is more likely a consequence of local airway abnormalities. James and colleagues showed that more often than not subjects with moderate asthma have abnormal thickening in only a few airways, even while the mean change in ASM thickness is not abnormal. Moreover, the most abnormal airways were in different places from subject to subject.

Regarding the origins of the abnormal ASM thickness, James and colleagues note that many individuals with asthma may already have abnormal ASM thickening at birth. But other factors throughout life can locally elevate ASM around an airway. Inflammatory mediators can upregulate both ASM and extracellular matrix (ECM) remodeling (12), and it seems reasonable that inflammation would not be identical throughout all airways. Similarly, elevated and repeated ASM and airway tension can induce remodeling because of mechanobiological factors upregulating growth factors (12). There is no reason to believe these factors will impact all airways identically. Finally, recent studies show that the ASM and ECM do not operate independently and that stiffening of the ECM can actually amplify the ability of the ASM to create an elevated and sustained force (13). Thickening of the ASM and ECM remodeling could work in tandem then to further create localized abnormalities causing heterogeneity and asthma.

The study by James and colleagues continues the recent trend of raising awareness that the pathological airway conditions in asthma are likely local rather than evenly spread. Consequently, optimal treatments might best target these local abnormalities. In principle, bronchial thermoplasty (BT) could address this, if the clinician knew in advance precisely which airways to target. But BT cannot yet get to all the small airways that are important. Nevertheless, we should focus on creative, perhaps hybrid (imaging plus delivery) methods to treat individuals with asthma on a personalized basis, targeting the specific locations in each individual subject that can create heterogeneity of constriction pattern (14, 15). In sum, preventing or minimizing the heterogeneity should be an explicit goal. ■

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

Kenneth Lutchen, Ph.D.
Department of Biomedical Engineering
Boston University
Boston, Massachusetts

References

1. Kuwano K, Bosken CH, Paré PD, Bai TR, Wiggs BR, Hogg JC. Small airways dimensions in asthma and in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1993;148:1220–1225.
2. Lambert RK, Wiggs BR, Kuwano K, Hogg JC, Paré PD. Functional significance of increased airway smooth muscle in asthma and COPD. *J Appl Physiol (1985)* 1993;74:2771–2781.
3. Lutchen KR, Gillis H. The relation between airway morphometry and lung resistance and elastance during constriction: a modeling study. *J Appl Physiol (1985)* 1997;83:1192–1201.
4. Gillis HL, Lutchen KR. Airway remodeling in asthma amplifies heterogeneities in smooth muscle shortening causing hyperresponsiveness. *J Appl Physiol (1985)* 1999;86:2001–2012.
5. Tgavalekos NT, Tawhai M, Harris RS, Musch G, Vidal-Melo M, Venegas JG, *et al.* Identifying airways responsible for heterogeneous ventilation and mechanical dysfunction in asthma: an image functional modeling approach. *J Appl Physiol (1985)* 2005;99:2388–2397.

6. Pascoe CD, Seow CY, Hackett TL, Paré PD, Donovan GM. Heterogeneity of airway wall dimensions in humans: a critical determinant of lung function in asthmatics and nonasthmatics. *Am J Physiol Lung Cell Mol Physiol* 2017;312:L425–L431.
7. Brown RH, Togias A. Measurement of intraindividual airway tone heterogeneity and its importance in asthma. *J Appl Physiol (1985)* 2016; 121:223–232.
8. Lutchen KR, Jensen A, Atileh H, Kaczka DW, Israel E, Suki B, *et al.* Airway constriction pattern is a central component of asthma severity: the role of deep inspirations. *Am J Respir Crit Care Med* 2001;164: 207–215.
9. Tzeng YS, Lutchen K, Albert M. The difference in ventilation heterogeneity between asthmatic and healthy subjects quantified using hyperpolarized 3He MRI. *J Appl Physiol (1985)* 2009;106:813–822.
10. James AL, Donovan GM, Green FHY, Mauad T, Abramson MJ, Cairncross A, *et al.* Heterogeneity of airway smooth muscle remodelling in asthma. *Am J Respir Crit Care Med* 2022;207:452–460.
11. de Lange EE, Altes TA, Patrie JT, Battiston JJ, Juersivich AP, Mugler JP III, *et al.* Changes in regional airflow obstruction over time in the lungs of patients with asthma: evaluation with 3He MR imaging. *Radiology* 2009; 250:567–575.
12. Joseph C, Tatler AL. Pathobiology of airway remodeling in asthma: the emerging role of integrins. *J Asthma Allergy* 2022;15: 595–610.
13. Jamieson RR, Stasiak SE, Polio SR, Augspurg RD, McCormick CA, Ruberti JW, *et al.* Stiffening of the extracellular matrix is a sufficient condition for airway hyperreactivity. *J Appl Physiol (1985)* 2021;130: 1635–1645.
14. Donovan GM, Elliot JG, Boser SR, Green FHY, James AL, Noble PB. Patient-specific targeted bronchial thermoplasty: predictions of improved outcomes with structure-guided treatment. *J Appl Physiol (1985)* 2019;126:599–606.
15. Hall CS, Quirk JD, Goss CW, Lew D, Kozlowski J, Thomen RP, *et al.* Single-session bronchial thermoplasty guided by ^{129}Xe magnetic resonance imaging: a pilot randomized controlled clinical trial. *Am J Respir Crit Care Med* 2020;202:524–534.

Interplay between Immune and Airway Smooth Muscle Cells in Obese Asthma

Increasing rates of obesity in children and adults have been associated with the development of severe, difficult-to-control asthma (1). Although some people with asthma and comorbid obesity have type 2–high disease, others experience airway disease associated with insulin resistance and metabolic dysfunction, with little in the way of type 2 inflammation. Asthma in obese people likely consists of many different endotypes of disease, and earlier work by Rastogi and colleagues identified a type of asthma in children with obesity characterized by insulin resistance, augmented T-helper cell type 1 (Th1) function, and upregulation of a pathway related to the Rho-family GTPase cell division cycle 42 (CDC42) in Th1 cells (2). CDC42 is critical in actin cytoskeleton assembly and mediates functions such as vesicle trafficking, orientation of receptors on the cell surface, chemotaxis, and cell adhesion (3). Although the observation of induction in this CDC42 pathway is fascinating, it provides limited insights into how changes in Th1 cell function might be linked to airway disease.

Clearly, airway reactivity is not simply mediated by T cells in isolation; many other cell types are involved. In this context, earlier work by Hakonarson and colleagues is relevant: Cooperative signaling between human airway smooth muscle (ASM) cells and T lymphocytes mediated induction of proasthmatic changes in ASM (4). Furthermore, Orfanos and colleagues identified hypercontractility of ASM cells isolated from individuals with obesity (5), suggesting that ASM changes could be involved in the asthma of obesity. However, the reasons for ASM dysfunction in obesity are not known. In this issue of the *Journal*, Yon and colleagues (pp. 461–474) set out to determine if perhaps there could be a link between Th1 cell dysfunction and ASM dysfunction that might provide insights into the pathogenesis of asthma in children with obesity (6).

Yon and colleagues first studied Th1 cells, then the ASM cells, and finally the interaction between these two cell types. The team used Th1 cells from obese children with asthma that expressed high levels of CDC42 and those from lean children that expressed very low levels of CDC42. The Th1 cells were first stimulated *in vitro* with CD3-CD28. The Th1 cells from obese children tended to have higher levels of the integrin LFA-1 (lymphocyte function–associated antigen 1), and migration in response to the ligand SDF-1 (stromal differentiation factor 1) was independent of CDC42. Although CDC42 is a biomarker identifying these cells, inhibition of this pathway did not affect migration. The investigators also included Th1 cells from three obese and three healthy-weight children without asthma as a control. A higher proportion of T-helper cells from obese children with asthma than from obese children without asthma migrated in response to SDF-1. These data suggest there may be altered expression of cell surface integrins and differences in chemotaxis responses between Th1 cells isolated from lean and obese children that are specific to obese asthma rather than just obesity.

The investigators then studied ASM from obese individuals and lean individuals without asthma obtained from lungs not suitable for transplant. The investigators found that cells from obese individuals expressed higher levels of ICAM-1 (intercellular adhesion molecule 1), the ligand for LFA-1 that mediates adherence of immune cells to smooth muscle. This suggests that ASM from obese individuals is more primed for adherence of immune cells than ASM from lean individuals. Indeed, in coculture experiments, Th1 cells from obese individuals with asthma adhered in greater number to ASM isolated from obese individuals than Th1 cells from

Supported by National Institutes of Health (R01 HL133920).

Originally Published in Press as DOI: 10.1164/rccm.202210-1870ED on October 11, 2022