Toward Precision Medicine of Symptom Control in Asthma

Despite significant advances in asthma therapeutics, the optimization of symptom control is often an unmet need in asthma. Symptom control is the aggregate result of a complex interplay between an individual's genetic makeup, immune response, environment, behavioral aspects, and the therapy itself. Guideline-based asthma care emphasizes interventions aimed at optimizing several of these modifiable elements (1). Despite these strategies, poorly controlled asthma continues to drive a substantial fraction of disease burden and healthcare costs. Data from the Behavioral Risk Factors Surveillance System-Child and Adult Asthma Callback survey identified high rates of uncontrolled asthma in children (38%) and adults (50%) in the United States between 2006 and 2010 (https://www.cdc.gov/asthma/asthma_stats/uncontrolled_asthma.htm), and significant differences in asthma control are seen around the world (2).

The ideal way to optimize symptom control in asthma is to identify molecular pathways active in a unique individual and target these pathways with specific therapies, an approach commonly defined as precision medicine (3). High-throughput profiling studies of well-characterized patients aim to identify such disease-driving molecular pathways and stratify patients based on their underlying endotypes with the goal of guiding therapy. Perhaps the most notable example of this approach has been the identification of periostin, an IL-13–responsive biomarker that uses gene expression microarrays of bronchial epithelial cells obtained from patients with asthma (4). In a trial of lebrikizumab, an anti–IL-13 monoclonal antibody, high levels of blood periostin identified responders (5). Additional studies have aimed to determine disease endotypes by exploring the transcriptome of the airway compartment, including the airway epithelium (6) and sputum (7), to identify molecular pathways associated with clinical features of asthma. Despite the innovation and potential clinical relevance of these findings, the adoption of transcriptomic readouts in the classification of asthma has not been widespread, in part because of the lack of studies replicating these observations in larger populations of individuals with asthma.

In this issue of the *Journal*, Croteau-Chonka and colleagues (pp. 179–188) identified molecular pathways associated with a modified version of the asthma control test using transcriptomic profiles of whole blood (WB) or $CD4^+$ T lymphocytes (CD4) (8). This analysis of samples from the Asthma BioRepository for Integrative Genomic Exploration and the Childhood Asthma Management Program cohorts is among the most comprehensive transcriptomic signature studies in the pulmonary literature, encompassing 1,170 subjects from four independent cohorts in two blood compartments. The authors explored how self-reported measures of acute and chronic asthma control were associated with transcriptomic changes in WB and CD4 compartments. Rather than applying a single gene identification strategy, they applied state-of-the-art network- and pathway-based analytical approaches and thus leveraged the modular nature of biologic processes to glean pathobiologic insights from these individuals. They performed gene set enrichment analyses of asthma control using the chemical and genetic perturbations and the immunologic signatures gene set collections from the Molecular Signatures Database, and determined that optimal control signatures were enriched for immature lymphocytic gene expression patterns, whereas suboptimal control was associated with signatures of eosinophilic and granulocytic inflammatory signals. The authors identified specific pathways associated with each.

One of the most novel and intriguing findings in this article is the suggestion that the triggering receptor expressed on myeloid cells 1 (*TREM1*) pathway, a relatively understudied pathway in respiratory research, is involved in asthma control. *TREM1* (also designated as CD354) is a cell surface receptor expressed on activated monocytes, neutrophils, granulocytes, dendritic cells, and natural killer cells. *TREM1* amplifies Toll-like receptor activation and is involved in the response to infectious pathogens, including fungus and bacteria (9), and as discovered more recently, viruses and parasites (10). Lipopolysaccharide pathways, which are similarly involved in the response to components of the bacterial cell wall (11), were also enriched in the patients who exhibited suboptimal control. Taken together, these findings suggest that individuals with suboptimal control of asthma exhibit signs of persistent innate immune activation, potentially reflecting a unique interaction of environmental factors, host susceptibility, and asthma control, a finding not unlike that recently described in Hutterite children (12). These novel observations in a relatively large cohort should encourage future studies to explore the potential role of *TREM1*-based interventions in poorly controlled asthma.

The use of WB in this study can be considered both a disadvantage and an advantage. It is a disadvantage because it is very difficult to obtain specific answers or mechanistic conclusions from the study of cellular admixtures. The signature in the blood is a complex aggregate of multiple, common, and rare cell types, and even the CD4 signature is an aggregate of the signatures of several $CD4^+$ lymphocyte subpopulation signatures. To overcome this limitation, the authors performed advanced computational adjustments to cell differentials, but these did not account for rare cell types, shifting profiles in known cell populations, or the averaging out of signal by opposite direction changes in gene expression among cellular subpopulations. However, the use of cellular admixtures is also a strength; had the authors only studied a highly selected cell population they would not have been able to generate novel hypotheses. In addition, the potential relevance of the novel signatures as easily accessible biomarkers for future precision medicine interventions would have probably gone unnoticed. Novel technologies that allow analysis of single cell genome scale transcript profiling or large numbers of proteins per cell do address some of these concerns (13). However, they are still limited by throughput, significant costs, and the risk of introducing bias through sample manipulation. It can be easily perceived that follow-up studies will be divided into three

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types: large prospective clinical studies that test the usefulness of the *TREM1* signature in predicting suboptimal asthma control over time; small size translational studies that identify the specific cell populations and regulatory events that underlie this persistent signature using state-of-the-art methods for immunophenotyping (e.g., mass cytometry and single-cell transcript profiling); and preclinical studies that determine whether targeted interventions on the *TREM1* pathway can be used for enhanced asthma control. Together, these studies would lay the ground work for implementing precision medicine approaches in optimization of asthma symptom control.

The paper by Croteau-Chonka and colleagues (8) is also an opportunity to reflect on the impact of a unique NHLBI initiative. In 2009, as part of the American Recovery and Reinvestment Act, NHLBI participated in the Research and Research Infrastructure "Grand Opportunities" projects. Eight of these large projects focused on lung disease, and six focused on high-throughput genomic and transcriptomic profiling of well-characterized populations of patients with lung disease (RePORT—the NIH Portfolio online reporting tool, https://projectreporter.nih.gov/reporter_SearchResults.cfm?icde=30591578). Seven years later, four years after most of the projects have been completed, it is important to recognize the impact of these projects on respiratory research. American Recovery and Reinvestment Act–funded lung disease projects have resulted in more than 120 publications, including 10 in the *Journal* and many in other high-impact journals, multiple follow-up projects, careers, and publically available data sets. The results of these projects are still driving patient relevant insights and discoveries, and the paper by Croteau-Chonka and colleagues (8) is a great example of an important step in generating the information required for implementing precision medicine in asthma. ■

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References

1. National Asthma Education and Prevention Program. Expert panel report 3 (EPR-3): guidelines for the diagnosis and management of asthma-summary report 2007. *J Allergy Clin Immunol* 2007;120(5, Suppl): S94–S138.
2. To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, Boulet LP. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health* 2012; 12:204.
3. Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med* 2015;372:793–795.
4. Woodruff PG, Boushey HA, Dolganov GM, Barker CS, Yang YH, Donnelly S, Ellwanger A, Sidhu SS, Dao-Pick TP, Pantoja C, *et al*. Genome-wide profiling identifies epithelial cell genes associated with asthma and with treatment response to corticosteroids. *Proc Natl Acad Sci USA* 2007;104:15858–15863.
5. Corren J, Lemanske RF, Hanania NA, Korenblat PE, Parsey MV, Arron JR, Harris JM, Scheerens H, Wu LC, Su Z, *et al*. Lebrikizumab treatment in adults with asthma. *N Engl J Med* 2011;365: 1088–1098.
6. Modena BD, Tedrow JR, Milosevic J, Bleecker ER, Meyers DA, Wu W, Bar-Joseph Z, Erzurum SC, Gaston BM, Busse WW, *et al*. Gene expression in relation to exhaled nitric oxide identifies novel asthma phenotypes with unique biomolecular pathways. *Am J Respir Crit Care Med* 2014;190:1363–1372.
7. Yan X, Chu JH, Gomez J, Koenigs M, Holm C, He X, Perez MF, Zhao H, Mane S, Martinez FD, *et al*. Noninvasive analysis of the sputum transcriptome discriminates clinical phenotypes of asthma. *Am J Respir Crit Care Med* 2015;191:1116–1125.
8. Croteau-Chonka DC, Qiu W, Martinez FD, Strunk RC, Lemanske RF, Liu AH, Gilliland FD, Millstein J, Gauderman WJ, Ober C, *et al*.; Asthma BioRepository for Integrative Genomic Exploration (Asthma BRIDGE) Consortium. Gene expression profiling in blood provides reproducible molecular insights into asthma control. *Am J Respir Crit Care Med* 2017; 195:179–188.
9. Colonna M, Facchetti F. TREM-1 (triggering receptor expressed on myeloid cells): a new player in acute inflammatory responses. *J Infect Dis* 2003;187:S397–S401.
10. Weber B, Schuster S, Zysset D, Rihs S, Dickgreber N, Schürch C, Riether C, Siegrist M, Schneider C, Pawelski H, *et al*. TREM-1 deficiency can attenuate disease severity without affecting pathogen clearance. *PLoS Pathog* 2014;10:e1003900.
11. Schwechheimer C, Kuehn MJ. Outer-membrane vesicles from Gram-negative bacteria: biogenesis and functions. *Nat Rev Microbiol* 2015; 13:605–619.
12. Stein MM, Hrusch CL, Gozdz J, Igartua C, Pivniouk V, Murray SE, Ledford JG, dos Santos MM, Anderson RL, Metwali N, *et al*. Innate immunity and asthma risk in Amish and Hutterite farm children. *N Engl J Med* 2016;375:411–421.
13. Darmanis S, Gallant CJ, Marinescu VD, Niklasson M, Segerman A, Flamourakis G, Fredriksson S, Assarsson E, Lundberg M, Nelander S, *et al*. Simultaneous multiplexed measurement of RNA and proteins in single cells. *Cell Reports* 2016;14:380–389.

Peripheral Artery Disease in Patients with Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is a highly prevalent chronic pulmonary disease defined by persistent airflow limitation, but is frequently associated with extrapulmonary manifestations and comorbidities. Because of common risk factors such as smoking and aging, COPD often coexists with cardiovascular diseases that have an important impact on prognosis. Atherosclerosis is the main driver in the pathogenesis of vascular diseases and can occur in various arterial vascular beds. In smokers, a strong association has been demonstrated between COPD and coronary artery disease, causing ischemic heart disease (encompassing angina pectoris and myocardial