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A Role for the Rho-GTPase Pathway in Pediatric Obese Asthma

Asthma and obesity are two of the most common chronic disorders in the pediatric population. Asthma is a heterogeneous disease characterized by chronic airway inflammation affecting approximately 5.5 million children in the United States (1). Childhood obesity, a growing public health problem, has been shown to disproportionately impact minority populations including African American and Hispanic children (2). Obesity is both a risk factor and an important disease modifier of childhood asthma (3–5). Subjects with obesity and early-onset asthma include a large proportion of African American individuals and those with increased airflow obstruction (6). In addition, subjects with obesity and asthma have increased respiratory symptoms and disease exacerbations (6). Pediatric obese asthma is associated with increased T-helper cell type 1 (Th1) cell polarization (7), which has been postulated as a mechanism underlying the association of this subgroup of patients with decreased responsiveness to inhaled corticosteroids (8). These observations highlight the need to better elucidate the biologic mechanisms that result in the pediatric obese asthma endotype.

Asthma and obesity are complex disorders that are influenced by both genetic and environmental factors. The parallel rise in the prevalence of both disorders worldwide suggests that they may be linked (9). Previous studies have established the importance of numerous environmental exposures, including dietary and nutritional risk factors, on the subsequent development of childhood asthma and obesity (10, 11). But studies investigating shared genetic determinants have been inconsistent with some studies suggesting shared genetics (12, 13) and others failing to demonstrate convincing evidence for shared genetic determinants of obesity and childhood asthma (14, 15). Therefore, epigenetic studies, including DNA methylation changes that result from environmental exposures, may help to elucidate additional relevant biological pathways that influence the susceptibility to pediatric obese asthma. Furthermore, integrative genomics approaches may illuminate novel biologic pathways involved in pediatric obese asthma and may help to identify novel therapeutic targets for this population (8).

In this issue of the *Journal*, Rastogi and colleagues (pp. 259–274) report the results of their genomics and epigenomic analyses of the pediatric obese asthma phenotype in minority populations (16). Using a multiomics approach including differential gene expression from $CD4^+$ Th cells, expression quantitative trait loci (eQTL) mapping, differential methylation, and methylation quantitative trait loci, the authors demonstrate enrichment of genes in the Rho-GTPase pathway in the obese asthma phenotype in African American and Hispanic children. Using deconvolution methods to address differences in Th cell subpopulations that exist between subjects with asthma with and without obesity, the authors also demonstrate that both Rho-GTPase gene expression and methylation changes are robust to differences in Th cell subtype proportion. Although the authors did not identify an enrichment of Rho-GTPase genes in the eQTL analysis, they did demonstrate that genes proximal to the cytosine targets for the methylation quantitative trait loci were enriched with genes in this pathway. The authors also demonstrate the clinical impact of Rho-GTPase genes by demonstrating an association with increased airflow obstruction (reduced FEV_1/FVC) and obesity-related deficits in lung function (reduced expiratory reserve volume). Moreover, the authors demonstrate the functional relevance of Rho-GTPase pathways in Th1 polarization, by transfecting primary human Th cells with siRNA to silence the *CDC42* gene, one of the Rho-GTPase genes identified in their analyses. Silencing *CDC42* resulted in decreased gene expression of IFN-γ, but no change in IL-4 expression, confirming a role for the Rho-GTPase pathway in Th1 polarization.

Although the focus of their integrative genomics analysis was on the Rho-GTPase pathway, the authors also identified a role for the *RPS27L* (ribosomal protein s27-like) gene in pediatric obese asthma. The authors demonstrate that *RPS27L* was downregulated in subjects with obesity. This gene also includes an eQTL that is found with increased frequency in Latino and Afro-Caribbean populations, is associated with lower expression of *RPS27L*, and is associated with obese asthma. These results highlight the impact of the use of integrative genomic approaches on identifying novel biology in populations not often represented in genomic studies.

Previous studies have demonstrated genetic associations with Rho-GTPase polymorphisms with obesity-related metabolic traits (17), and genes in this pathway have been shown to impact adipocyte lipolysis in obesity (18). Although genetic

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polymorphisms in the Rho-GTPase pathway have not been previously associated with asthma susceptibility, their impact on metabolic traits suggests a plausible link with the obese asthma phenotype.

This study is a significant addition to the growing literature demonstrating the impact of the use of integrative genomics approaches to identify novel biologic pathways in complex diseases. Notably, this study provides a comprehensive investigation of the genomic determinants of the obese asthma phenotype in admixed populations, who are disproportionately impacted by disease severity yet are often not represented in genomic analyses.

Several limitations of the study are also worthy of mention. First, the sample size is small. Although the limited power does not diminish the importance of their findings, a larger sample size may have been able to identify additional molecular pathways of interest. Furthermore, the authors performed their genomic analyses in $CD4^+$ Th cells, which is a cell type known to play an integral role in asthma pathobiology. However, there are myriad other tissue types including adipose tissue, which may provide additional biologic insights into the obese asthma phenotype. Thus, similar investigations in other disease-relevant tissues may be warranted. Although the authors use a novel integrative genomics approach that incorporates genetics, gene expression, and methylation, their statistical approach may not have fully captured the wealth of the "omics" data types that were generated for each subject. Network-based approaches that incorporate genetics, gene expression, and methylation into the same model may capture additional disease-relevant biology and should be considered in this population in the future.

The results of this study provide evidence for the importance of integrative genomic approaches in $CD4^+$ Th cells to further our understanding of the biologic mechanisms underlying pediatric obese asthma. These findings motivate additional investigation of the Rho-GTPase pathway to fully understand the biologic basis of the genomic determinants of pediatric obese asthma and how this pathway may inform novel therapeutic targets in this population. ■

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