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Nature versus Nurture: Does Genetic Ancestry Alter the Effect of Air Pollution in Children with Asthma?

As one of the most common respiratory illnesses, asthma is also a disease characterized by striking ethnic disparities. The prevalence of asthma among black and Latino individuals is almost double that seen among white individuals. The differences in morbidity and mortality are even more significant: Child mortality rates in non-Hispanic black individuals are eightfold higher than in non-Hispanic white individuals (1, 2). Unpacking the etiology of these differences is difficult, given the complex intersection between social, environmental, and heritable factors that modulate disease susceptibility and manifestations. Understanding the role of ethnicity is even harder, particularly in an admixed society where interracial marriage and multiethnic groups are increasingly common.

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In this issue of the *Journal*, Neophytou and colleagues (pp. 1271–1280) tackle this issue by exploring the interaction between environmental exposure and genetic variation in a study of minority adolescents with asthma (3). The authors focus their analysis on air pollution, a risk factor that has been repeatedly linked with adverse asthma-related outcomes. Because minorities tend to cluster in neighborhoods with poor air quality, they are expected to be particularly vulnerable to exposure. Although many epidemiologic studies have shown an association between incident asthma and poor symptom control, asthma-related hospitalizations, and reduced lung function, few of these studies have been performed in populations with a significant proportion of minorities (4–6).

While minorities are likely exposed to higher levels of pollution, they may also be more susceptible to the adverse health effects. There is mounting evidence that certain gene polymorphisms, particularly within the oxidative stress pathway, modify the effects of air pollution and can increase the risk for asthma (7). Although variation in these polymorphisms is greater between individuals of the same ethnicity than between individuals of different ethnicities, it is possible that other important genetic variations or

epigenetic effects cluster with ancestral background (8). Genome-wide association studies have identified single nucleotide polymorphisms with substantial differences in allele frequency between different ancestor populations and previous studies have shown that percentage of African ancestry is associated with reduced lung function (9, 10). By using these markers of genetic ancestry instead of self-identified ethnicity, epidemiologic studies can better distinguish between shared socioenvironmental exposures and genetic differences.

Neophytou and colleagues use this approach in a cross-sectional analysis to assess whether exposure to air pollution was associated with lung function in minorities with asthma and whether this effect was modified by genetic ancestry. The study population was composed of children and adolescents (aged 8–21 yr) with a physician diagnosis of asthma from two large case-control studies. This includes 1,449 participants who self-identify as Latino from the GALA (Genes–Environments and Admixture in Latino Americans) II study and 519 participants who self-identify as African American from SAGE (Study of African Americans, Asthma, Genes, and Environment) II. All participants were genotyped to determine the proportion of African, European, and Native American global genetic ancestry. The authors measured air quality through short- and long-term estimates of nitrogen dioxide, sulfur dioxide, ozone, particulate matter less than 2.5 μm, and particulate matter less than 10 μm, according to residential address, including weighted residential histories. Lung function was measured through spirometry, without bronchodilator testing. All analyses were adjusted for potential confounders, including African ancestry and a surrogate marker of socioeconomic status, composed of maternal education, income, and insurance.

Specifically, the study found that each 5 $\mu g/m^3$ increase in lifetime particulate matter less than 2.5 μm is associated with a 7.7% decrease in FEV_1. In addition, there was a trend toward reduced lung function with both 24-hour and early-lifetime exposure to particulate matter less than 10 μm, although this did not reach statistical significance. There was no evidence of effect modification by genetic ancestry based on interaction terms with pollutant concentration. The study did not contain a comparison group of non-minority children, so we are unable to quantitatively compare whether the effect size is larger in minorities.

The adverse health consequences of prolonged environmental exposures make randomized control trials unethical, with the exception of some ecological studies aimed at policy reform. As a result, epidemiologic studies of long-term exposure to pollution are limited to observational research, with all the accompanying limitations of exposure misclassification, residual confounding, and the inability to infer causation. The authors mitigate these weaknesses by defining ethnicity through genetic ancestry and self-identification, using sophisticated modeling of pollutants with different time periods of exposure, careful selection of confounding, including variables representative of socioeconomic status and robust measurements of lung function. They increase power by selecting a large, geographically diverse population. Although their overall effect size was small, the results documenting a clear effect of air pollutants in minority adolescents are compelling, as the associations are consistent in stratified analysis and reach statistical significance after adjustment for multiple comparisons. Importantly, these results show that air pollution is a potentially modifiable risk factor that leads to reduced lung function in minorities.

The conclusions that can be drawn from the analysis of effect modification by genetic ancestry are less clear. Superficially, this suggests that other psychosocial constructs of ethnicity may alter susceptibility to air pollution rather than genetic background. But modeling the effect of genetic ancestry by using an interaction term with pollutant concentration may be a statistical simplification of a complex biologic relationship. Interaction terms assume there is a multiplicative effect on the outcome, whereas in reality, the effect could be additive, synergistic, or effected by additional environmental factors. Moreover, defining genetic ancestry through the identification of single nucleotide polymorphisms is a crude estimation of the genetic diversity between different populations that may not capture significant biologic effects. If a rare polymorphism that confers increased susceptibility is found within a subset of an ancestral population, then the heterogeneity within the larger population can increase the likelihood of a false negative association. This is particularly true in African populations that tend to have complex geographical histories and a higher level of genetic diversity. An alternative approach would be to genotype the single nucleotide polymorphisms in individuals with low lung function, instead of relying on population-level genetics as a surrogate (11).

More research is needed to determine the relative importance of the multiple socioeconomic and environmental risk factors that contribute to ethnic disparities in asthma, and to determine whether there may be certain heritable susceptibilities. Yet this article adds significantly to the literature and informs public policy by demonstrating a significant association between ambient air pollution and reduced lung function in minorities with asthma. By improving air quality, we could potentially reduce the burden of disease and improve asthma-related outcomes. ■

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Sarcoidosis and T-Helper Cells
Th1, Th17, or Th17.1?

It is widely accepted that sarcoidosis is a noninfectious disorder of the immune system characterized by an abnormal antigen-mediated adaptive immune response culminating in the formation of granulomas in affected tissues. The lungs are most commonly affected, incriminating inhaled environmental antigens as initiators of the disease process. There are clear gene-by-environment interactions that predispose to sarcoidosis, with several genetic association studies implicating $CD4^+$ T-cell immune response genes in disease pathogenesis (1). The prototypical adaptive immune response in sarcoidosis is characterized by the presence of IFN-γ–producing $CD4^+$ cells in inflamed tissues (2), which, taken together with the essential role played by IFN-γ during granuloma formation in animal models (3), supports the idea that sarcoidosis is a type 1 T-helper cell (Th1) disease.

Despite the Th1 bias in sarcoidosis, however, we now realize that the immunopathology of sarcoidosis is complex, with evidence for activation of the innate immune system, dysfunction of regulatory T cells, and expansion of IL-17–producing cells including $CD4^+$ Th17 cells (4–7). Th17 cells are prevalent in epithelial surfaces such as the lungs, skin, and gut, where they contribute to host immune responses against bacterial, fungal, and mycobacterial pathogens largely by orchestrating the recruitment of inflammatory cells (8). Interestingly, Th17 cells have been implicated in the development of Crohn's disease, another disease characterized by noninfectious granuloma formation (8). Several lines of evidence point to a role for Th17 cells in sarcoidosis. First, the frequency of IL-17–producing T cells is increased in peripheral blood and lungs of subjects with sarcoidosis compared with controls (9). Second, IL-17A was shown to be essential for mature granuloma formation in response to mycobacterial infections in mice (10). Third, a recent large case-control study confirmed an association between genetic variants near the IL-23 receptor (which promotes Th17 responses) in different cohorts of subjects with sarcoidosis (11).

In this issue of the *Journal*, Ramstein and colleagues (pp. 1281–1291) used multiparameter flow cytometry to analyze bronchoalveolar lavage (BAL) T cells and report that a subset of Th17 cells that coexpress IFN-γ is particularly enriched in the lung in sarcoidosis (12). IFN-γ–producing Th17 cells (termed Th17.1 or Th17/Th1 cells) were previously detected in mouse and man, including in human subjects with sarcoidosis or Crohn's disease (13–15). Ramstein and colleagues identified Th17.1 cells by their coexpression of the chemokine receptors CCR6 and CXCR3, which had been previously linked with Th17 and Th1 cells, respectively (12). IFN-γ production by these $CCR6^+CXCR3^+$ Th17.1 cells rivaled that of canonical $CCR6^-CXCR3^+$ Th1 cells, suggesting that Th17.1 cells are major producers of IFN-γ in the sarcoid lung. Interestingly, whereas traditional Th17 numbers were elevated in the blood of patients with sarcoidosis, Th17.1 cells were specifically elevated in BAL (and not blood). One possibility is that IFN-γ^- Th17 cells are recruited from the circulation into the lung, and differentiate into IFN-γ^+ Th17.1 cells under the influence of local inflammatory signals. This mechanism is supported by the differential expression of CXCR3 on Th17.1 cells in BAL (and not in blood), a chemokine receptor expressed on effector T cells that plays a role in cell trafficking and inflammation. The factors that control the development of Th17.1 cells *in vivo* are not known, but several cytokines have been implicated in this process, including IL-1β, IL-12, and IL-23 (16). Engagement of Th17 cells with IL-12 and IL-23 promotes the activation of transcription factor Tbet (Tbx21, T-box expressed in T cells), which in turn regulates the expression of *IFNγ* and related chemokine genes (*CXCL9*, *CXCL10*, and *CXCL11*), leading to the Th17.1 phenotype (17). Interestingly, human IFN-γ^+Th17.1 cells were preferentially induced *in vitro* by exposure to *Candida albicans* in an IL-1β–dependent manner (18). It remains to be seen what controls the preferential expansion of Th17.1 cells in the lung in sarcoidosis, and it will be informative in future studies to dissect the contributions of pathogen-encoded signals and inflammatory cytokines to this process. Future studies investigating how cellular metabolism and redox balance influence Th17 subset development in sarcoidosis also seem worthwhile, as these processes are likely perturbed in granulomatous inflammation.

The study by Ramstein and colleagues builds on growing evidence that "not all Th17 cells are created equal" (12). Major insights into Th17 subset differentiation have come from mouse

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