It All Begins *In Utero*: Cord Blood Bacterial DNA and T Cell Immunity

There is a well-established association between allergy and asthma. The prevalence of asthma is significantly higher among atopic individuals compared with nonatopic ones, and conversely, the prevalence of atopy is significantly higher among individuals with asthma compared with those without asthma (1). Multiple studies have supported the hygiene hypothesis, which states that early childhood exposure to infectious agents or their products influences susceptibility to allergic diseases by altering the natural development of the immune system, as originally proposed by Strachan in 1989 (2). Indeed, differential exposure to microbes and colonization of mucosal sites by microbes early in life have been linked to the subsequent development of asthma (3–5).

Neonatal mononuclear cells derived from umbilical cord blood respond by proliferating and releasing cytokines (e.g., IL-13 and interferon-γ [IFN-γ]) when cultured in the presence of common aeroallergens (6). Previous work by the Finn laboratory indicated independent contributions of neonatal and maternal influences, such as smoking and race/ethnicity, to umbilical cord blood lymphoproliferative responses to allergens (7). In this issue of the *Journal*, Turturice and colleagues (pp. 419–427) postulate a relationship between perinatal microbial exposure and T-helper cell type (Th)1/Th2 responses to specific aeroallergens (Der f1 and Bla g2) in cord blood (8). To test this hypothesis, they used high-throughput sequencing of cord blood bacterial 16S ribosomal DNA (rDNA) to assess bacterial diversity. They correlated the presence of specific bacterial taxa with lymphocyte proliferation and cytokine release in response to Bla g2 and Der f1, and with cord blood serum cytokine levels (IL-4, IL-5, IL-13, and IFN-γ). They found that the IL-13 cytokine response to these aeroallergens was related to the taxonomic structure and diversity of bacterial DNA. In particular, there was a strong association between the ratio of *Moraxellaceae* to *Proteobacteria* and IL-13 production after allergen exposure, and a significant correlation of serum IL-13 concentration with cord blood bacterial DNA diversity. Based on these results, they suggest a relationship between immune responses to aeroallergens and bacterial exposure during perinatal development. The study reinforces the concept of a relationship between an individual's microbiome and allergic responses, suggesting that assessment of cord blood bacterial diversity could be used as a predictor of asthma and allergy risk later in life.

This study has several important limitations. First, the small sample size (n = 27) limits analysis to the most abundant bacterial families and phyla, and results in reduced statistical power to detect potentially important associations between exposures and outcomes. Second, the study did not assess immune responses to the most common aeroallergens, including those derived from cat (Fel d1), dog (Can f1), and *Alternaria sp.* (9). Third, the authors only assessed cord blood IL-13 and IFN-γ cytokine responses, and did not examine other T cell responses, including Treg (IL-10), Th9 (IL-9), and Th17 (IL-17) responses. Fourth, it remains unclear whether 16S rDNA is simply a marker of bacterial exposure and other pathogen-associated molecular patterns or acts as the driver of the immune response. In addition, the source of the bacterial DNA remains enigmatic. Fifth, the cross-sectional nature of the analysis precludes a causal inference. Indeed, immune responses might influence exposure to bacteria rather than *vice versa* (10). Finally, the absence of clinical outcomes data in this cohort limits our ability to determine the contribution of cord blood bacterial 16S rDNA to the subsequent development of allergy and asthma.

The fact that bacterial rDNA diversity correlates with lymphoproliferative and cytokine responses in cord blood suggests that *in utero* exposures may influence the subsequent development of the immune system in the neonate. This study provides strong evidence for an association between perinatal bacterial exposure and T cell immunity. In addition to highlighting the value of cord blood microbial profiling for predicting the subsequent development of allergy and asthma, this study has important implications regarding the mechanisms by which perinatal bacterial exposures could influence T cell development and immune health. Furthermore, this information might facilitate the development of personalized interventional approaches. For example, the ability to manipulate the microbiome *in utero* or during the early perinatal period could be beneficial for the primary prevention of allergic diseases and asthma. Finally, the interindividual variability observed in the relationship between 16S rDNA exposure and the immune response suggests contributions from genetic and/or epigenetic factors. Future work performed in larger cohorts to examine long-term immunologic and clinical outcomes, and investigate other immune cell responses to the most common aeroallergens involved in allergy and asthma pathogenesis will lead to the development of novel preventative and therapeutic strategies to treat these conditions. In addition, future studies should focus on unraveling the precise molecular mechanisms underlying these associations, as well as the contributions of genetic and environmental factors. ■

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