Maternal Allergen Exposures and Development of Asthma: Kids Are Airways Nervy

Asthma is a chronic inflammatory lung disease that is influenced by both genetic and environmental factors (1). Studies show that both not only contribute to the development of asthma but also may influence severity (1, 2). For the fetus, exposures within the maternal environment are believed to have a long-lasting impact on lung immune responses and airway function in the offspring. Several maternal factors, including atopy, asthma, smoking, obesity, stress, and environmental exposures, are among the immunological and physiological factors that influence asthma development (3–6). The underlying mechanisms by which maternal asthma contributes to the development of asthma in offspring remain poorly defined. One reason is the lack of established animal models to interrogate the likely complex immunological responses and interactions between mother and fetus.

In this issue of the *Journal*, Lebold and colleagues (pp. 89–98) report on their investigations of allergic airway inflammation and airway hyperresponsiveness (AHR) in mouse pups born from allergen-challenged dams (7). In the model, female mice were chronically challenged with PBS or a common household allergen, house dust mite (HDM), before and during pregnancy. Subsequently, newborn pups were sensitized and challenged with PBS or HDM, allowing an opportunity to understand how established maternal asthma affects the development of allergic airway inflammation in the offspring. The authors found that maternal HDM before, during, and after pregnancy resulted in enhanced immune cell infiltration and AHR in offspring. Although it is not clear which period is most important for these augmented responses, the authors do provide a model that can be used to determine the potential underlying mechanisms involved.

Interestingly, HDM-challenged pups from HDM-challenged dams exhibited increased T-helper cell type 1 (Th1) and Th17 signatures with less robust type 2 inflammation. This complex immune environment has increased Th1 and/or Th17 cells and neutrophil infiltration, which are associated with more severe asthma endotypes (8). Given the known effects of HDM challenge on type 2 inflammation, it is interesting that the offspring develop a skewed Th1/Th17 inflammatory profile (9). However, these interpretations are largely based on gene expression; thus, the immune cell composition within the lung remains to be confirmed. Nonetheless, these data suggest that maternal allergen exposure may contribute to a predisposition to increased asthma severity in offspring. Because Th1/Th17 inflammation is associated with corticosteroid insensitivity, maternal asthma may also have implications for managing asthma symptoms in children born to mothers with asthma. These findings also raise the question whether new biological therapies targeting type 2 inflammation in maternal asthma could have an impact on the development of asthma in children (10).

In addition to airway inflammation, maternal and postnatal HDM exposure induced greater airway sensory nerve innervation, which is important for airway inflammation and AHR. Increases in airway nerve density promote eosinophil recruitment and airway smooth muscle hypercontractility, impacting airway tone (11, 12). The contributions of type 2 inflammation to airway nerve innervation are highlighted by studies showing increased airway nerve density in mice overexpressing IL-5 (13). Furthermore, increased maternal IL-5 expression also increases airway nerve density, which results in sustained AHR in mouse pups (14). In the study by Lebold and colleagues, the PBS-challenged pups born to HDM-challenged dams also exhibited increased airway innervation. This suggests that maternal asthma can influence airway nerve plasticity and potentially predispose to asthma in the absence of allergen sensitization and/or atopy.

Neurotrophins, neuropeptides, and other nerve growth–related signaling pathways play key roles in nerve innervation in the developing lung (11). To understand mechanisms associated with increased airway innervation, the gene expression of NGFs (nerve growth factors) and related signaling pathways was measured. Expression of several genes involved in nerve development, neuronal proliferation, and sensory axon growth was found to be increased in pup lungs exposed to maternal and postnatal HDM. Among neurotrophins, NGF and its receptor, TrkA (tropomyosin-related kinase A), were also increased. NGF has previously been shown to affect neuronal plasticity, increase AHR, and reduce eosinophil apoptosis (11). It remains unclear whether Th1 and/or Th17 inflammatory responses contribute to NGF production or other mechanisms associated with airway innervation. Collectively, maternal asthma may impact nerve plasticity and airway innervation through multiple signaling pathways associated with airway nerve growth.

This study also raises important questions regarding maternal allergen sensitization, asthma, and their influence on allergen sensitivity in the offspring. In other words, is the same allergen responsible for maternal allergic responses necessary for the hypersensitization in the offspring? Here, the authors show that exposure to the same allergen, HDM, exacerbates allergic airway responses, indicating that the same allergen can induce a heightened allergic response in the offspring. Previous studies showed that pups born to mothers exposed to other environmental insults, such as secondhand smoke or diesel exhaust particles, exhibit enhanced allergic airway inflammation and AHR when challenged with different allergens (15, 16). Taken together, the type of maternal allergen or insult may not be the most important determinant of altered nerve plasticity and asthma development. Perhaps it is the altered maternal immune environment that affects the allergic

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immune responses in the fetus that contributes to asthma development and severity in the offspring. This novel approach provides a template for exploring these intriguing questions and others in future studies.

Overall, the novel work by Lebold and colleagues highlights the impact that maternal asthma may have on asthma development. Certainly, there are more questions raised than answered. As asthma prevalence continues to increase, particularly in children, there remains an urgent need to understand the complex maternal–fetal–infant interactions that predispose to childhood asthma. The contributions of maternal allergen exposure to immune cell infiltration, AHR, and airway nerve density are striking and could possibly drive a more severe asthma phenotype. These critical studies will allow elucidation of immunological and physiological mechanisms associated with the effects of maternal asthma on offspring and may create opportunities to identify therapeutic interventions for mother and child. ■

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