Like mother, like child: The maternal microbiome impacts offspring asthma

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The link between the maternal microbiome and offspring allergy is poorly defined. McCauley and colleagues now demonstrate that heritable bacteria are associated with infant asthma susceptibility and induce immunosuppression of allergic inflammation, suggesting significant implications for asthma-preventative interventions.

Type 2 asthma is characterized by enhanced activation of T helper 2 (Th2) cells in response to allergens, resulting in lung eosinophil accumulation, immunoglobulin E (IgE) production, and subsequent airway inflammation. Early-life microbiome composition is found to alter Th1/Th2 balance, thus influencing allergy risk. Accordingly, Boutin et al. identified several bacteria associated with increased asthma susceptibility at one year of age, and supplementation of “asthma-protective” microbes is found to reduce airway inflammation in mice, indicating a key role of the infant microbiome in asthma development. However, the link between the maternal microbiome and offspring asthma remains unexplored. Recent literature indicates the importance of the maternal microbiome on infant microbiota colonization and subsequent disease. For instance, both caesarean delivery and maternal antibiotic exposure are associated with microbial dysbiosis and allergy in offspring.

Despite this, little research has established whether increased asthma prevalence in infants with asthmatic mothers is in part explained by vertical transmission of bacteria. Furthermore, maternal bacterial species that mediate offspring asthma risk have not been identified. Addressing this gap, McCauley et al. demonstrate a heritable component of asthma, whereby maternal vaginal bacteria are vertically transmitted and associated with infant IgE and allergic immunomodulation.

Using paired maternal vaginal microbiome and infant stool samples, McCauley et al. identified four compositionally and functionally distinct Lactobacillus-dominated vaginal microbiota clusters that differentially correlated with prenatal maternal exposures (farm exposure, diet, stress) and infant IgE at one year of age, suggesting that the maternal microbiome and prenatal factors influence vertical transmission of microbes functionally associated with asthma susceptibility in offspring.

Regarding prenatal exposures, McCauley et al. found mothers with reduced farm exposure had vaginal clusters dominated by L.fornicalis or G.vaginalis, which were associated with increased allergic sensitizations in offspring. It is known that residing on a farm is correlated with reduced childhood allergy due to exposure to a microbiotically rich environment, which promotes microbiota maturation, thus influencing early-life immune programming. Of note, G.vaginalis is a pathogen involved in bacterial vaginosis, and infection with G.Vaginalis stimulates microbial production of inflammatory endotoxin lipopolysaccharide (LPS), resulting in microbiota dysbiosis and inflammation in mice. Taken together, McCauley et al.’s findings suggest that reduced exposure to asthma-protective farming environments during pregnancy increases susceptibility to microbial dysbiosis and pathogen domination in the vaginal microbiome, which is linked to offspring allergy via vertical transmission. Future research should investigate whether farm-like microbial environments can be replicated in interventions for urban-dwelling infants.

To assess the immunomodulatory capacity of heritable bacteria associated with low infant IgE, McCauley et al. incubated fetal antigen-presenting cells with L.jensenii isolated from meconium. The authors found L.jensenii reduced expression of activation markers CD83 and CD86, exhibiting an immunosuppressive effect. This suggests that vertically transmitted Lactobacillus are capable of directly modulating fetal immune function in utero, which may promote immunotolerance against allergy in infancy. Until recently, it was thought that the fetal environment was sterile and that microbiome colonization began during and after birth. However, McCauley et al.’s findings discredit this long-standing hypothesis, demonstrating that maternal microbes not only exist in fetal meconium, but impact fetal immune development, as Figure 1 illustrates. These findings have major implications for understanding maternal factors that alter infant microbiome colonization in utero and developing prenatal interventions to reduce childhood allergy.

Following this, McCauley et al. assessed the impact of L.jensenii on asthma in a murine model, revealing that L.jensenii supplementation significantly reduced the proportion of inflammatory interleukin (IL)-4+ T cells, eosinophils, and neutrophil expansion in the lungs, alongside Th1, Th2, and T17 cells in the lymph nodes. Thus, the vertically transmitted species had a global dampening effect on asthmatic inflammation, suggesting valuable implications for asthma-preventative probiotic interventions.

However, the mechanisms by which maternally transmitted lactobacilli influences immune response in asthma remain
unknown. One possible mechanism is through the production of microbial-derived metabolites, short-chain fatty acids (SCFAs). SCFAs have asthma-protective and immunomodulatory effects through the generation of regulatory T cells (Tregs) from dendritic and naive T cells via G protein-coupled receptor (GPR) activation and histone-deacetylase
Recent findings reveal that the placenta contains SCFAs and their receptors, indicating microbial-derived metabolite interactions in utero, which may influence fetal immune programming. Notably, lactobacilli are key SCFA producers. Thus, vertically transmitted lactobacilli may offer asthma protection through the production of SCFAs, which can cross the placenta and potentially influence fetal immune development. Future research should determine the functional mechanisms of these bacteria and their metabolites on fetal immune development. For instance, administration of identified bacteria to pregnant G protein-coupled receptor 41/43 (GPR41/43) knockout mice could establish whether their anti-inflammatory effects in offspring result from SCFAs via GPR activation.

Although our understanding of the importance of the maternal and infant microbiome in allergy is advancing, work is needed to translate findings into applicable interventions to reduce asthma prevalence. To date, several trials have assessed the efficacy of probiotic interventions on allergy outcomes, yet findings are inconsistent. McCauley et al. reveal administration of L. jensenii, a vertically transmitted species, has powerful immunosuppressive effects in an asthma murine model. This has clear implications for developing probiotic interventions to reduce asthma prevalence. Notably, previous literature has defined a critical window of opportunity in infancy—the first 100 days of life—whereby microbiome colonization is most influential on immune development, and thus microbiota interventions are most effective. However, McCauley et al. demonstrated that bacteria present in fetal meconium have immunomodulatory capacity on fetal immune cells, indicating the window of opportunity should in fact extend into pregnancy, whereby the maternal microbiome can influence offspring allergy risk via both transplacental transfer in utero and vaginal transmission during birth. As asthma is driven by Th2 skewing, microbiota-targeted interventions should be considered early in the second trimester, when fetal T cell development occurs, for optimal efficacy. Consequently, future research should develop interventions that target the maternal and fetal microbiome during pregnancy to promote healthy fetal immune programming, with the aim of preventing allergy even before birth.

Overall, McCauley et al.’s work significantly advances the field, demonstrating that vertical transmission of maternal bacteria influences fetal immune programming and subsequent allergy risk. The authors highlight the importance of prenatal factors on offspring allergy susceptibility and demonstrate the potential for probiotic interventions of heritable bacteria. To gain an integrated perspective on the complex relationship between maternal and infant microbiota, microbial interactions in utero, and fetal immune programming, further longitudinal multi-omics studies assessing microbiome composition, metabolomics, proteomics, immune biomarkers, and maternal factors are needed. Future research should further establish the mechanistic role of heritable bacteria in infant immune priming and develop prenatal microbiota-targeted interventions to prevent allergy as early as in the womb.

DECLARATION OF INTERESTS
The authors declare no competing interests.

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