Published in final edited form as:

J Leukoc Biol. 2020 July ; 108(1): 113–121. doi:10.1002/JLB.3MR1219-338R.

Inflammatory mechanisms linking maternal and childhood asthma

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Abstract

Asthma is a chronic inflammatory airway disease characterized by airway hyperresponsiveness, inflammation, and remodeling. Asthma often develops during childhood and causes lifelong decrements in lung function and quality of life. Risk factors for childhood asthma are numerous and include genetic, epigenetic, developmental, and environmental factors. Uncontrolled maternal asthma during pregnancy exposes the developing fetus to inflammatory insults, which further increase the risk of childhood asthma independent of genetic predisposition. This review focuses on the role of maternal asthma in the development of asthma in offspring. We will present maternal asthma as a targetable and modifiable risk factor for childhood asthma and discuss the mechanisms by which maternal inflammation increases childhood asthma risk. Topics include how exposure to maternal asthma in utero shapes structural lung development with a special emphasis on airway nerves, how maternal type-2 cytokines such as IL-5 activate the fetal immune system, and how changes in lung and immune cell development inform responses to aero-allergens later in life. Finally, we highlight emerging evidence that maternal asthma establishes a unique “asthma signature” in the airways of children, leading to novel mechanisms of airway hyperreactivity and inflammatory cell responses.

Keywords

asthma; childhood; developmental origins; eosinophil; inflammation; maternal; nerves

1 | INTRODUCTION

Asthma is a chronic inflammatory airway disease characterized by excessive bronchoconstriction and airway hyperresponsiveness.¹ The resulting airflow obstruction manifests with wheezing, shortness of breath, chest tightness, and cough that significantly affects quality of life.² Over 300 million people worldwide suffer from asthma,³ which often begins in childhood and can lead to lifelong reductions in pulmonary function.^{4–10} Parental asthma and atopy are clearly linked to development of asthma in children^{11,12};

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AUTHORSHIP

All authors wrote original draft, reviewed and edited the manuscript.

DISCLOSURE

The authors have nothing to disclose.

however genetic inheritance and environmental exposures explain only part of this risk. Maternal asthma confers more risk than paternal asthma¹³ and improved asthma control during pregnancy reduces asthma in offspring,¹⁴ suggesting exposure to maternal factors in utero uniquely impacts fetal development and asthma risk. This review focuses on the role of maternal asthma in the development of asthma in offspring, with an emphasis on maternal cytokines and effects of eosinophils on airway development and function.

2 | DEVELOPMENTAL ORIGINS OF CHILDHOOD ASTHMA

Asthma that develops in childhood has a profound impact on lifelong lung health.¹⁰ Reduced lung function in childhood strongly predicts reduced lung function in adulthood^{4,5} and is associated with lifelong asthma risk.⁵⁻⁹ Risk factors for development of childhood asthma are numerous and include genetic, developmental, and environmental factors. For example, parental atopy,^{11,12} smoking,¹⁵ maternal obesity,¹⁶ and lower socioeconomic status¹⁵ are parental factors that increase childhood asthma risk, whereas male sex,¹⁵ low birth weight,¹⁷ and prematurity¹⁸ are fetal factors that increase disease risk. Furthermore, airway hyperreactivity at birth predicts persistent wheezing during childhood and childhood asthma,^{19,20} suggesting in utero programming of airway responses has a central role in childhood asthma risk. Children with risk factors for asthma are particularly susceptible to early life environmental exposures to respiratory virus infections from respiratory syncytial virus²¹ and rhinovirus,²² and early allergen sensitization to house dust mites,²³ which trigger wheezing that often persists.²⁴ These risk factors are representative of the complex interactions between genetics and environmental exposures that influence fetal lung development and immunologic responses, which lead to asthma later in life.

3 | MATERNAL ASTHMA UNIQUELY INCREASES CHILDHOOD ASTHMA RISK

Parental asthma is a clear risk factor for childhood asthma^{11,12}; however, genetics and shared environments explain only part of this risk. Maternal asthma is a greater risk factor than paternal asthma for childhood asthma¹³ and children of mothers with uncontrolled asthma during pregnancy have greater risk of developing asthma than children of mothers with well-controlled asthma.^{25,26} Furthermore, mothers who had their asthma intensively managed during pregnancy had children with a lower risk of respiratory illnesses²⁷ and asthma¹⁴ compared to mothers with symptom-guided asthma care. Thus, maternal factors, which are potentially modifiable, influence childhood asthma risk by affecting fetal programming in utero. Fetal programming can have long-term consequences on airway function. Airway hyperreactivity can be detected at birth in newborn animals²⁸ and neonatal airway hyperreactivity in humans is associated with increased risk of asthma in adolescence^{19,20}. Maternal atopy and asthma are associated with impaired infant lung function²⁹ and airway hyperreactivity,³⁰ independent of allergen sensitization at birth. Postnatal allergen sensitization further augments airway hyperreactivity in children exposed to maternal asthma and allergen sensitization predicts the persistence of wheeze.²³

Augmented airway hyperreactivity in children exposed to maternal asthma in utero may occur secondary to structural changes in airways. Using a transgenic mouse model of

asthma, we found that dams with elevated eosinophils and IL-5, markers of type-2 high asthma (discussed in the following text) give birth to offspring with increased sensory nerve density in airway epithelium³¹ (Fig. 1). Airway sensory nerves respond to inhaled stimuli and provoke bronchoconstriction in response to a variety of chemical and mechanical stimuli.^{32,33} Correspondingly, offspring with increased airway epithelial innervation exhibited airway hyperreactivity at baseline and severe airway hyperreactivity after allergen sensitization and challenge.³¹ Innervation in these offspring did not increase further with postnatal exposure to house dust mite allergen or IL-5, demonstrating that in utero development of airway nerves and airway hyperreactivity is a uniquely sensitive time period to the influence of maternal asthma. These changes are reminiscent of changes in adults with asthma.³⁴ Bronchoscopic biopsies collected from adults with type 2-high asthma had increased sensory innervation, which correlated with worse lung function.³⁴ It is possible that hyperinnervation in adults with asthma occurred during prenatal development and predisposed to asthma development and worse disease later in life.

Airway nerves are not the only cell type that undergoes reprogramming when exposed to maternal asthma. Bronchial biopsies from children of asthmatics demonstrate epithelial basement membrane thickening.³⁵ Evidence of subepithelial remodeling precedes the clinical diagnosis of asthma in some children,³⁶ suggesting that tissue remodeling may be an inciting factor for asthma as opposed to simply a response to chronic airway inflammation. Airway epithelium also undergoes remodeling in response to maternal asthma. Mice born to dams sensitized to ovalbumin demonstrate increased goblet cell hyperplasia in response to allergen exposure compared to mice born to non-allergic dams.³⁷ Offspring born to allergic sheep have reduced type II alveolar cells³⁸ and surfactant B production,³⁹ which combined with potential goblet cell hyperplasia, would presumably increase airway narrowing and sputum production. These effects are not unique to maternal asthma, however, as maternal smoking can increase smooth muscle hypertrophy and subepithelial collagen deposition.⁴⁰

Maternal asthma also reprograms fetal immune cells. Murine offspring exposed to maternal asthma have potentiated inflammatory cell recruitment and cytokine secretion after allergen exposure later in life.⁴¹ We similarly found in a transgenic model of asthma that wild-type offspring born to IL-5 transgenic mice have potentiated inflammatory cell recruitment to lungs after allergen exposure.³¹ Inflammatory cell populations in the lungs of offspring born to IL-5 transgenic dams were not different before allergen exposure, suggesting fetal cells undergo reprogramming that may increase sensitivity to recruitment signals or enhance hematopoietic potential. In humans this is evidenced by infants born to parents with asthma who have potentiated immune proliferative responses to allergens without prior sensitization.⁴² Epigenetic changes may underlie these enhanced immune responses. Immune cells collected from children of asthmatic mothers harbor many differentially methylated regions compared to immune cells collected from children of nonasthmatic mothers.⁴³ Immune cell epigenetic profiles at birth also identify children who will later develop asthma, a trajectory that is modified by the presence of maternal asthma.⁴⁴ In mice, exposure to maternal asthma alters the epigenetic landscape in dendritic cells, which corresponds with enhanced antigen uptake and presentation.⁴⁵

4 | EFFECTS OF MATERNAL INFLAMMATORY CYTOKINES ON FETAL LUNG DEVELOPMENT

Asthma is a heterogeneous disease with many underlying mechanisms. In order to group asthmatics who share a common mechanism, phenotypes have been developed that categorize asthmatics based on observable characteristics (e.g., severity, age of onset), environmental factors (e.g., allergen sensitivity), and airway inflammatory leukocytes profiles.⁴⁶ The most common phenotype, termed “type 2-high” asthma, accounts for two-thirds of asthmatics and is characterized by cytokines classically released from CD4⁺ Th2 T helper cells and type 2 innate lymphoid cells, such as IL-4, IL-5, and IL-13.⁴⁷ Type 2 cytokines stimulate eosinophil hematopoiesis, migration, and activation⁴⁸ and as a result, an abundance of airway and peripheral blood eosinophils is a hallmark of this phenotype.⁴⁹ Eosinophils contribute to pathogenic features of asthma such as airway remodeling⁵⁰ and hyperreactivity,⁵¹ and their levels in asthma correlate with disease severity,^{52,53} exacerbation frequency,^{54–56} and progressive decline in lung function.⁵⁷

Several human studies suggest maternal type 2 cytokines mediate increased childhood asthma risk. In pregnant mothers with asthma, higher maternal serum IL-5 levels correlates with increased infant asthma risk⁵⁸ whereas increased ratios of maternal IFN- γ to IL-13 or IL-4 were associated with lower rates of asthma in children.⁵⁹ Similarly, increased IFN- γ to IL-4 ratios in pregnant mothers were associated with reduced childhood atopy.⁶⁰ These studies suggest excessive maternal type-2 inflammation or an imbalance between type-2 and type-1 inflammation may increase childhood asthma risk.

The effects of maternal cytokines on fetal development are also observed in mice. Blocking maternal IL-4 in pregnant mice exposed to allergen throughout pregnancy reduces offspring airway hyperreactivity and inflammation,³⁷ as does exposing pregnant mice to type 1 IFNs⁶¹ or LPS.⁶² We recently demonstrated that maternal IL-5 crosses the murine placenta and affects fetal lung development in wild-type offspring born to IL-5 transgenic mice (IL-5tg) (31). IL-5tg mice express an IL-5 transgene in airway CC10 club cells, resulting in airway eosinophilia and elevated circulating IL-5⁶³ that expose the developing fetus to IL-5 in utero as well. Wild-type mice exposed to IL-5 in utero had significantly increased airway hyperreactivity and airway inflammation compared to wild-type offspring of wild-type dams.³¹

Whether maternal cytokines affect a developing fetus by passing through the placenta from maternal to fetal circulation or by modulating placental cytokine release is unclear. Cytokine passage across the placenta varies by species and by cytokine.^{64–67} In humans, IL-6, but not IL-8, TNF- α , or IL-1 crossed the placenta, whereas neither IL-4 or IL-13 cross the murine placenta.⁶⁸ We found elevated levels of IL-5 in amniotic fluid of wild-type offspring born to IL-5 transgenic dams, suggesting IL-5 crosses the placenta, albeit at highly variable rates.³¹ The placenta also secretes cytokines directly into fetal circulation^{69–72} and augments expression after maternal exposures, such as to LPS.⁷³ Furthermore, placentas from woman with asthma have increased expression of TNF- α , IL-1 β , IL-6, IL-8, and IL-5, particularly when the developing fetus was female,⁷⁴ and also have decreased vascularity⁷⁵ compared to

placentas from woman without asthma. Thus, the placenta may serve a key regulatory role in the transfer of maternal inflammation to the developing fetus.

5 | EFFECTS OF EOSINOPHILS ON AIRWAY NERVE FUNCTION

Whether cytokines pass from maternal circulation to the fetus or are derived from the placenta, the question remains as to how they change fetal development. We found that the effects of IL-5 on the developing lung were mediated by fetal eosinophils and fetuses with congenital eosinophil deficiency were protected from IL-5-induced nerve remodeling, airway hyperreactivity, and airway inflammation dams.³¹ These data suggest that activation of the fetal immune system by maternal cytokines is required for transmission of disease risk, as opposed to cytokines directly affecting lung cell development.

How eosinophils function during development and cause increased airway innervation is less clear. Lung eosinophils are minimal at birth, increase rapidly during postnatal development, and then decline to adult levels.^{76,77} These lung resident eosinophils participate in immune homeostasis, generally exerting anti-inflammatory actions and suppressing Th2 sensitization.⁷⁸ Most studies have focused on eosinophils recruited in response to inflammatory stimuli and their effects in fully developed lungs, a population that is functionally and transcriptionally distinct from lung resident eosinophils.³¹ In animal models of asthma, inflammatory eosinophils are recruited and increase in the airways after exposure to allergen (e.g., house dust mite),⁷⁹ antigen (e.g., ovalbumin),^{80,81} and ozone.^{82,83} Once activated, eosinophils degranulate, releasing highly charged cationic proteins such as major basic protein and eosinophil peroxidase, as well as chemokines, cytokines, and growth factors^{84–86} that promote airway hyperreactivity and airway remodeling. Similarly, eosinophil accumulation and degranulation are provoked in transgenic mice that over-express eosinophil hematopoietic and chemotactic factors IL-5 and eotaxin.^{63,87} Eliminating eosinophils using eosinophil-specific cre-recombinase knockout technology (PHIL mice) protects against airway hyperreactivity and remodeling after allergen exposure,^{90,91} whereas adoptive transfer of eosinophils restores airway hyperreactivity in allergen-exposed IL-5^{-/-} knockout mice,⁸⁸ demonstrating that eosinophils contribute to airway hyperreactivity. At this time it is unclear whether fetal eosinophils mediating airway hyperinnervation after exposure to maternal IL-5 are “resident” or “inflammatory” in nature.

In developed lungs, eosinophils physically interact with nerves and affect nerve function. For example, eosinophils release the granule protein major basic protein, which blocks parasympathetic M2 muscarinic receptors, resulting in loss of M2's inhibitory feedback.⁸⁹ As a consequence, parasympathetic nerves release excessive amounts of acetylcholine, which potentiates bronchoconstriction in humans with asthma^{90,91} and in allergen-exposed animals.^{80,81,92–101} Eosinophil major basic protein and another granule protein eosinophil peroxidase also directly activate pulmonary sensory nerves¹⁰² and increase neuronal responsiveness capsaicin, ATP, and electrical stimulation.^{103,104} Similarly, these effects occur on sensory nerves in the skin in atopic dermatitis, where eosinophils increase sensory nerve density and exacerbate itch (a nerve-mediated reflex similar to reflex bronchoconstriction in the lung).^{105,106} How these individual eosinophil-derived mediators increase airway innervation is an active area of research and recent development of an

eosinophil-specific selective knockout mouse using cre-lox recombination will greatly aid future investigations.¹⁰⁷

Airway nerves actively recruit eosinophils by releasing chemotactic factors such as eotaxin-1. Parasympathetic and sensory nerves express eotaxin-1 and increase expression after antigen challenge.^{100,105} Eotaxin-1 then binds eosinophil CCR3 receptors to promote eosinophil migration to nerves. As a result, eosinophils are clustered around nerve axons and ganglia in humans who died of fatal asthma exacerbations and after antigen and ozone exposure in animals.^{80,97,98,101,108,109} Eosinophils' proximity to nerves is crucial to their effects on nerve function⁹⁶ and preventing eosinophil migration by blocking CCR3 specifically,¹⁰⁰ or by reducing eosinophils generally using corticosteroids,⁹⁹ prevents development of nerve-mediated airway hyperreactivity. Once eosinophils arrive at nerves, they physically adhere to neuronally expressed adhesion molecules VCAM-1 and ICAM-1.¹¹⁰ Binding triggers eosinophil degranulation and release of granule proteins that mediate eosinophils effects.^{111,112} Nerves up-regulate expression of adhesion molecules in response to antigen sensitization,¹¹³ TNF- α , IFN- γ ,¹¹⁴ and nerve growth factor.¹⁰⁵ In turn, blocking eosinophil binding to VCAM-1 or ICAM-1 prevents airway hyperreactivity in antigen challenged guinea pigs^{95,114} and monkeys in vivo.¹¹⁵

Whether these mechanisms of eosinophil-nerve interactions in fully developed lungs after allergen exposures translate to prenatal development remain to be tested. However, it is clear that the effects of eosinophils during lung development have particularly severe consequences for airway function later in life. For example, mice with increased sensory innervation that are subsequently sensitized to house dust mite allergen in adulthood, develop fatal bronchoconstriction in response to inhaled serotonin.⁹¹ Airway hyperreactivity in these animals was far worse than airway hyperreactivity due to either increased airway sensory innervation or house dust mite sensitization alone. Animals that lacked eosinophils were protected from these effects, underscoring the significance of eosinophil-nerve interactions when airway nerve development is dysregulated. Vagotomy prevented lethal bronchoconstriction after house dust mite, further reinforcing the central role of nerve reflexes in severe bronchoconstriction. In a separate study, maternal house dust mite exposure similarly potentiated offspring airway responses after offspring were exposed to house dust mite.⁴¹ This study did not specifically address the role of eosinophils, but did show that maternal immunoglobulins were not required for vertical transmission of asthma risk. Thus, humans with type 2-high asthma and increased airway innervation may suffer more severe outcomes after concurrent sensitization to aero-allergens.

6 | TARGETING MATERNAL CYTOKINES TO MODIFY CHILDHOOD ASTHMA RISK

The advent of tailored treatments based on asthma phenotype holds great promise for maternal transmission of asthma risk, both for the mother and child. Efforts to target type 2-high asthma by depleting airway eosinophils recently led to the development of anti-IL-5 monoclonal antibodies mepolizumab and reslizumab,^{116–120} followed more recently by the anti-IL-5 receptor antibody benralizumab.^{121,122} Animal studies demonstrated

that pharmacologic neutralization of IL-5 reduced airway eosinophilia, remodeling, and hyperreactivity.^{123–128} Subsequent human trials with patients selected for type 2-high asthma based on elevated peripheral blood eosinophil counts showed improvements in exacerbations, lung function, and quality of life.^{116–122} Because IL-5 is a key mediator in the transmission of asthma risk, both mothers with type 2-high asthma and their children may benefit from these targeted therapies. However, this must be balanced with the duality of eosinophil functions in the lung. Like other immune cells, subsets of eosinophils exist in the lungs. In healthy fully developed lungs, “resident” eosinophils are present, which are IL-5 independent, don’t expand after allergen exposure, and express genes involved in tissue homeostasis and suppression of inflammation.⁷⁸ In contrast, IL-5 dependent “inflammatory” eosinophils are recruited to lungs after exposure to environmental allergens.^{78,129,130} Inflammatory eosinophils express proinflammatory genes⁷⁸ and are suppressed by steroids¹³¹ and by blocking IL-5.¹³² The discovery of tissue resident eosinophils coupled the recently identified immune regulatory roles of eosinophils (reviewed in Lee et al., 2010¹³³) suggests eosinophils play important roles in maintaining tissue homeostasis and healthy immune responses. Whether blocking IL-5 during development could selectively prevent the harmful effector functions of eosinophils while preserving beneficial regulatory functions remains to be tested.

Approximately one-third of asthmatics do not have eosinophilia in blood or lungs and perhaps unsurprisingly, these patients respond poorly to type 2 cytokine targeted therapies. This group is classified as a type 2-low asthma phenotype⁴⁶ and its inflammatory mechanisms are not well understood, which has hampered discovery of biomarkers and effective treatments for this phenotype. In type 2 low asthma, elevated levels of IL-17A, IL-17F, IL-21, and IL-22 are present and neutrophilic inflammation is common.¹³⁴ Whether children born to woman with type 2-low asthma have the same asthma risk as children born to woman with type 2-high asthma remains to be tested. Furthermore, how cytokines identified in type 2 low asthma contribute to asthma pathogenesis remains to be fully clarified. For example, data are conflicting as to whether IL-17A is beneficial or harmful in asthma. Airway IL-17A increases in animals after allergen exposure, and in children, serum levels correlate with disease severity.¹³⁵ Neutralizing IL-17A reduces airway inflammation and airway remodeling in allergic animals,¹³⁶ whereas exogenous IL-17A potentiates airway smooth muscle proliferation,¹³⁷ secretion of proinflammatory cytokines,^{137,138} and methacholine-induced smooth muscle contraction.¹³⁹ Conversely, others have found that neutralizing IL-17A in allergen-sensitized animals increases allergic inflammation¹⁴⁰ and blocking IL-17 receptor alpha in humans with moderate to severe asthma showed no improvement in asthma control or pulmonary function.¹⁴¹

Maternal asthma may also change the underlying mechanism(s) of asthma in children and thus the efficacy of different treatment modalities. Immune cells collected from neonates born to mothers with asthma contain hundreds of differentially methylated regions compared to neonates born to mother without asthma.⁴⁴ Monitoring these neonates for development of asthma later in life identified SMAD3 hypermethylation and secretion of IL-1 β as a unique signature in children born to asthmatic mothers who would then go on to develop asthma themselves.⁴⁴ In mice, we found that airway hyperreactivity in wild-type offspring born to IL-5 transgenic dams could be blocked with an antagonist of neurokinin-1 receptors,

which are the target of the sensory neuropeptide substance P (unpublished observation). In contrast, neurokinin-1 antagonists worsened airway hyperreactivity in wild-type offspring born to wild-type dams. How exposure to maternal IL-5 during development changed the therapeutic efficacy of neurokinin-1 antagonists is currently unclear, but it suggests fetal programming from maternal asthma influences response to neurokinin antagonists or other therapeutics may be selectively beneficial in children born to mothers with asthma.

7 | FUTURE DIRECTIONS

Maternal asthma represents a unique and potentially modifiable risk factor for childhood asthma. Crucial next steps need to focus on treatment modalities that reduce maternal inflammation and improve disease control during pregnancy, while testing whether targeted therapies against type-2 cytokines like IL-5 are superior to indiscriminate suppression of inflammation (i.e., steroids). It is unknown whether all children born to mothers with asthma have an increased risk of developing asthma themselves via the mechanisms discussed in this review or whether these findings are restricted to children born to mothers with allergic or type 2-high phenotypes. If maternal inflammatory phenotypes during pregnancy inform those in the developing fetus, and targeted therapies are either not available or without proven efficacy in controlling maternal disease, alternative strategies could focus on reversing lung changes in offspring after birth. Investigating reversibility of hyperinnervation and immune signatures in the early postnatal period could be highly valuable as results may apply to both adults and children with asthma. Finally, several fundamental questions remain regarding eosinophil biology. Specifically, how and which eosinophil-derived products increase airway innervation, and whether this occurs in all tissues with resident eosinophil populations or is somehow restricted to developing lungs, is of interest. Although there is scant knowledge on how eosinophils function during in utero development, recent studies indicate they have an active role in shaping airway physiology and immune responses that impact lung function throughout life.

ACKNOWLEDGMENTS

Funded by the National Institutes of Health: F30HL132414, K08HL121254, R01HL124165, R01HL144008.

Abbreviations:

IL-5tg IL-5 transgenic mice

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FIGURE 1. Mechanisms of increased childhood asthma risk in offspring born to mothers with asthma.

(A) Under homeostatic conditions, afferent sensory nerves detect external stimuli and activate efferent parasympathetic nerves through a central nerve-reflex pathway. Parasympathetic nerves release acetylcholine (ACh) onto airway smooth muscle M3-muscarinic receptors (M3) to induce airway contraction. M2-muscarinic receptors (M2) located on presynaptic postganglionic nerves inhibit further acetylcholine release. (B) Maternal asthma increases airway hyperreactivity and bronchoconstriction in offspring by inducing airway sensory hyperinnervation, basement membrane thickening, and smooth muscle hypertrophy. In mice, developmental reprogramming is mediated by maternal IL-5 and fetal eosinophils. Eosinophils also increase bronchoconstriction by releasing cationic proteins that inhibit M2-muscarinic receptor function and potentiate acetylcholine release