Published in final edited form as:

Pulm Pharmacol Ther. 2008 ; 21(3): 474–484. doi:10.1016/j.pupt.2007.06.005.

Maternal Influence in the Transmission of Asthma Susceptibility

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Abstract

Asthma is one of the most common chronic diseases in children, with increasing morbidity and mortality. A genetic predisposition and exposure to allergens have been implicated as major risk factors for the development of asthma. However, increasing evidence indicates that the mother plays a crucial role in mediating the development of fetal-infant immune responses to inhaled allergens. The exact nature and mechanism of this maternal influence and how it might be associated with the development of allergic sensitization and asthma are not clear. Under normal conditions, the maternal environment during pregnancy promotes an initial Th2 skewed immune response in the offspring which transitions to a nonallergic Th1 type response after birth. However, the allergic mother's influence may delay the normal transition to a nonallergic immune response to inhaled allergens in her children, thus increasing the risk for the development of allergic sensitization and/or asthma. Understanding the underlying mechanisms by which the maternal immune environment can influence the development of the fetal-infant immune response to inhaled allergens may lead to identifying new targets for the prevention of allergic sensitization and asthma.

Keywords

in utero; postnatal; immune; development; allergy; lung

1. Introduction

A growing body of evidence suggests that the immunological changes leading to allergic diseases, such as asthma, start very early in childhood or even during pregnancy. Several lines of evidence further suggest that maternal exposure to allergens and/or the immune status of the mother, independent of a genetic contribution, may play a crucial role in the development-response of the fetal-infant immune system to inhaled allergens. Various studies have reported that children from allergic mothers are more likely to develop allergies/asthma than children from allergic fathers [1–8]. Infants of atopic mothers have an almost 5-fold higher probability of developing atopic dermatitis in comparison with children from atopic fathers [9]. Further, atopy in children is more closely associated with maternal asthma and IgE levels rather than paternal asthma and IgE [10–12]. This suggests that children from allergic mothers are exposed to a unique biological environment that may increase their risk for the development of asthma/allergies. However, the exact nature and mechanisms of this maternal influence and how it might be associated with the development of allergic sensitization and asthma are not clear.

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2. Prevalence of asthma during pregnancy

In concert with the increasing incidence of asthma in the general population, the number of females with asthma during pregnancy is also increasing. Recent estimates from a review of U.S. health surveys covering the years 1997 – 2001 indicate that between 3.7% – 8.4% of pregnant females had asthma [13]. That is an increase from 3.2% for the years 1988 – 1994 [13]. Even higher rates of asthma, 12.4%, have been reported in pregnant woman from Western Australia, with 8.8% reporting exacerbation of symptoms or the use of asthma medication during pregnancy [14]. Asthma is the most common respiratory disorder that may complicate pregnancy and potentially impact fetal/infant immune development.

3. Effects of maternal asthma on pregnancy

Asthma can have serious effects on the outcome of a pregnancy, and conversely, pregnancy can alter the clinical status of the pregnant female with asthma (reviewed [15,16]). While there are conflicting results amongst the many studies examining the relationship between asthma and pregnancy outcomes, the general consensus is that asthmatic females are at greater risk of low birth weight neonates, preterm neonates, cesarean delivery, and complications such as preeclampsia. Further, the poorest outcomes appear to be associated with females with uncontrolled asthma [16,17]. Changes in asthma symptoms brought about by pregnancy are unpredictable on an individual basis; but a general paradigm that asthma will worsen in one-third, remain the same in one-third, and improve in one-third of the women has been accepted for years. Whether these effects additionally alter long-term outcomes in offspring is not clear, but they likely share some common mechanisms.

Several mechanisms associated with the adverse effects of maternal asthma on pregnancy outcomes have been postulated and may include maternal hypoxia, inflammation, corticosteroid treatment, smoking, exacerbation of asthma, fetal sex, and altered placental function. Most direct evidence centers on the stimulation/control of inflammatory responses and placental factors. Reduced birth weight has been correlated with those asthmatics that have had at least one asthma attack during pregnancy (i.e., exacerbation of asthma) [18,19]. In a study by Murphy et al. [20] maternal asthma severity, inflammation, lung function, placental function, and treatment with inhaled corticosteroids (ICS) were examined in relation to fetal growth. Women with asthma who did not use ICS during pregnancy and were pregnant with a female fetus had significantly reduced birth weights, whereas male birth weights were unaffected. The presence of a female fetus was associated with increased maternal circulating monocytes, reduced placental 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2) activity and fetal estriol, and increased fetal plasma cortisol. Placental 11 β -HSD2 activity regulates the transmission of maternal glucocorticoids to the fetus. Additionally, the ratio of placental TH2/Th1 cytokines was increased in asthmatic women who did not use ICS during pregnancy and carried a female fetus [21]. The authors propose that the female fetus uniquely alters maternal asthma by upregulating maternal inflammatory pathways that subsequently alter placental function leading to increased fetal cortisol, reduced fetal growth, and reduced adrenal function.

A fetal sex-specific response in the maternal transmission of asthma susceptibility has not been identified. However, similar physiologic changes may be involved in modulating the development of fetal immune responses. Increased circulating monocytes could lead to altered placental function and or systemic cytokine production. Monocytes release numerous cytokines, including TNF- α , IL-1 β , IL-6, and granulocyte macrophage colony-stimulating factor. Further, co-culture of CD4⁺ T cells with monocytes from asthmatics leads to increased production of IL-4 and IL-5 [22,23]. Increased secretion of maternal cortisol may alter the developing immune system by affecting Th1/Th2 cell differentiation, resulting in an increased susceptibility for atopy and asthma [24]. The transmission of asthma risk from mother to child

likely involves both pre-and/or postnatal events that may be transmitted across the placenta or through breast milk

4. Insights from animal models of maternal influence

A canine model of maternal influence has been developed in which offspring from ragweed (RW)-sensitized female beagle dogs develop serum RW-specific IgE and IgG, increased pulmonary resistance to inhaled RW or histamine challenge, increased lung eosinophilia, and increased mucus in the lung, whereas offspring from nonsensitized mothers do not [25,26]. Preliminary studies indicate that treatment of offspring from RW-sensitized mothers with a Th1 stimulus (30 µg inhaled CpG) within the first week after birth can prevent this maternal influence and the subsequent development of allergic sensitization and an asthmatic phenotype. Treatment with CpG oligodeoxynucleotides (gift from Sanofi-Aventis) prevented the development of serum RW-specific IgE (levels below limit of detection; results not shown), lung eosinophilia, and airway responsiveness to inhaled RW while inducing a RW-specific serum IgG₁ response (Fig. 1). CpG oligos contain unmethylated cytosine-phosphate-guanosine dinucleotides that mimic the immunostimulatory properties of bacterial DNA and are thought to act by creating a Th1 cytokine environment [27].

The concept of maternal influence is also supported by work utilizing rodent models. Offspring from ovalbumin (OVA)-sensitized and challenged female Balb/c mice develop an allergic airway response when treated with an intentionally “suboptimal” sensitization (intraperitoneal [i.p.] OVA-alum) and challenge (inhaled OVA) protocol that does not elicit a response in offspring from naïve mothers [28]. A similar response was observed when offspring from OVA-sensitized mothers were exposed to an unrelated allergen, casein, suggesting that the maternal influence is allergen independent and not dependent on allergen-specific antibodies. Additionally, treatment of the OVA-sensitized mother at the beginning of gestation with a neutralizing antibody against IL-4 significantly reduced the development of allergic responses in the offspring, suggesting that IL-4 plays a significant role in the maternal influence. Utilizing the same model, treatment of offspring with CpG prevents the maternal influence and development of allergic airway responses regardless of allergen specificity (e.g., OVA or casein) [29]. Either treatment with CpG (i.p. injection; day 3 after birth) prior to OVA sensitization or just prior to OVA inhalation challenge (i.p. injection; day 12 after birth) was successful in preventing the development of an allergic airway response. Interestingly, while treatment of the sensitized-mothers with CpG led to decreased airway hyperresponsiveness (AHR) in the offspring there was little effect on lung eosinophilia. Further, maternal CpG treatment led to decreased litter size in ~ 50% of treated mothers and premature deliveries or stillbirths. In contrast, lipopolysaccharide (LPS) exposure in nonsensitized mice during pregnancy leads to reduced antigen-specific IgG and IgE, lavaged eosinophils, Th2 cytokines (IL-5 and IL-13), and increased IFN-γ levels but has no effect on AHR in offspring subsequently sensitized with OVA [30].

Herz and colleagues found that T cells from the offspring of OVA-sensitized mothers have a reduced capacity to produce the Th1 cytokine, IFN-γ, when restimulated in vitro. Additionally, these offspring develop higher immunoglobulin (IgG and IgE) titers and higher frequencies of immediate-type skin test responses when immunized with a neoantigen, beta-lactoglobulin [31]. Interestingly, the same authors found that when offspring were sensitized with the same allergen (OVA) as the mother they did not develop an IgE response [32]. This effect was mediated by placental transfer of OVA-specific IgG₁ antibody. Similar results were observed in a model where maternal immunization with house dust mite (HDM) antigen negatively modulates the early allergic response in offspring, further suggesting that maternal pre-exposure to allergen before mating can be protective [33]. However, in both cases the inhibition

of allergic responses was transient, as offspring could be successfully immunized with allergen after the animals were 45 d old [33] or 90 d old [32].

The disparity between studies (e.g., maternal antibodies protective [32,33] vs. no effect [28]) may be related to differences in allergen exposure timing and methods. Mothers were either immunized or exposed to allergen during gestation and the offspring were only immunized once with alum-allergen in the protective models. In contrast, maternal allergen challenge occurred just prior to mating and the offspring received an injection of alum-allergen and inhalation exposure in the model that was not dependent on maternal antibodies. Thus, differing levels of maternal allergen-specific IgG, lack of in utero allergen exposure, and the combination of injected and inhaled allergen exposure in the offspring may have provided a more potent immunogenic environment for the offspring. This highlights the potential for a myriad of maternal and environmental factors that regulate the response of the infant to inhaled allergens.

Additional studies in the mouse model have explored the contribution of breast milk in mediating the maternal allergic influence [34]. Offspring from OVA-sensitized mothers when switched at birth (e.g., nursed by nonsensitized mother) still developed allergic airway responses, indicating that exposure to the breast milk of the allergic mother is not necessarily required for development of allergic responses. In contrast, offspring from nonsensitized mothers when nursed by OVA-sensitized mothers do develop allergic airway responses, suggesting that factors in the breast milk are sufficient to induce the development of allergic responses. Whether there is a defined set of factors that can both cross the placenta and be transmitted to the newborn via breast milk or each environment has its own set of unique factors that drive the maternal influence is unclear. The adoptive transfer of CD4⁺ T cells from OVA-sensitized mice or Th2 cells from OVA T cell receptor (TCR) transgenic mice to pregnant severe combined immunodeficiency (SCID) mice is sufficient to recapitulate the maternal allergic influence [32]. Transfer of these cells to the pregnant SCID mother was associated with lower frequency of IFN- γ , producing splenic mononuclear cells from the offspring collected at birth. Further, adoptive transfer of DO11.10 T cells to naive BALB/c females mice prior to breeding recapitulates the maternal allergic influence [35]. DO11.10 T cells (OVA responsive) could be identified in the spleen and placenta of the recipient females but were not found in fetal tissue; suggesting that factors produced by the transferred cells were mediating the response. Although recipient mothers did not exhibit allergic airway responses they did have elevated serum levels of IFN γ , IL-4, 10 and 13. This suggests that factors produced or interactions by maternal T cells are at least partly regulating the maternal influence.

Both the rodent and canine animal models suggest that a skewed Th2 immune environment exists in the allergic mother that significantly influences the development of allergic responses in her offspring (Fig. 2). Further, modulation of the maternal and/or infant immune response via a Th1 immune stimulus can prevent the development of subsequent allergen sensitization and asthmatic phenotype. The underlying mechanisms that regulate the maternal allergic influence likely include a complex interaction between maternal antibodies, maternal cytokine production (placenta and T cells), factors in breast milk, timing of allergen exposure (both in utero and postnatal), and exposure to environmental mediators (viral, bacterial, pollutants, etc.).

5. Maternal antibody

It is well known that maternal IgG crosses the placenta or is passed through breast milk to provide the fetus or infant with specific immunity at a stage when its own immune responses are still developing [36,37]. At birth there is a positive correlation between HDM-specific IgG subclass levels in cord blood, maternal atopy, and the magnitude of lymphoproliferative responses to HDM [38]. Passive sensitization of mice with antigen-specific IgG₁ but not IgG_{2a} or IgG₃ causes immediate cutaneous hypersensitivity and increased AHR after antigen

challenge [39]. In contrast, others suggest that maternal IgG may protect offspring from later development of allergic disease. Studies in rodents suggest that maternal IgG actually has a suppressive effect on IgE responses in the neonate [32,33,40]. The proposed mechanism of this inhibition involves antigen-induced cross-aggregation between IgG₁ antibodies bound to FcγRII and surface Ig expression by the B cell receptor. This induces a state of negative intracellular signals that prevent the cells from switching to IgE production. While other rodent studies indicate that the maternal allergic influence is allergen independent and not dependent on allergen-specific antibodies [28], proliferation responses to HDM by umbilical cord blood mononuclear cells (CBMCs) are inversely correlated with levels of cord blood HDM-specific IgG [36]. Additionally, elevated maternal anti-Bet v 1 IgG at birth is associated with a reduced prevalence of allergic disease at 18 months of age [41]. Serum IgA has also been associated with the passive protection of the infant immune system and decreased risk for atopy [42,43].

Jones et al. show that IgE is detectable in amniotic fluid at 16 – 17 weeks of gestation, as well as at term, in levels that correlate with maternal levels, suggesting that IgE passes from the vascularized decidua to amniotic fluid [44]. Thus, the fetus may be exposed to IgE throughout pregnancy by amniotic fluid absorption through the skin, respiratory tract, and gastrointestinal tract. This IgE may initiate antigen-specific responses via IgE-mediated antigen focusing as modulated by B cells and dendritic cells [45]. Jones et al. suggest that the IgE/IgG ratio of the mother may have the greatest consequence as to whether offspring are at a greater risk for the development of allergic disease [45]. Additionally, the presence of antigen-specific IgG₄, commonly elevated with IgE, may support an IgE response, whereas antigen-specific IgG₁ or IgG₃ may down regulate such a response in the fetus.

6. Th1-Th2 paradigm in pregnancy

Cytokine production by the mother/placenta/fetus at critical times during the development of the fetal-infant immune system could alter the final outcome in terms of whether the response to a particular antigen is of a Th1 or Th2 phenotype. Pregnancy is associated with a transient depression of specific maternal cell-mediated immunity [46], increased antibody production [47], and the predominance of Th2 cytokines at the materno-fetal interface [48,49]. It is unknown whether an allergic mother experiences an even greater shift to a Th2 environment and whether this influences fetal immune system development.

The presence of Th2 cytokines (IL-4, IL-5, IL-6, IL-10, and IL-13) during pregnancy is thought to suppress cell-mediated immunity (particularly natural killer [NK] cell activity) and to promote acceptance of the fetus in the womb by the mother [36]. In contrast, the Th1 cytokine, IFN-γ, is an abortifacient, whose effect may be mediated through the promotion of cytotoxic lymphocyte and NK cell development [50]. Adoptive transfer of Th1 skewed T cells into pregnant mice results in complete resorption of the fetus [32]. There are indications that the shift in the mother's immune response during pregnancy is mediated, in part, by factors produced by the placenta. In general, most findings support the view that once the placenta starts development during the first trimester, a local Th2-type bias within this tissue is perpetuated throughout pregnancy (reviewed [51,52]). The placenta produces high levels of a wide range of mediators, some of which are Th2-trophic and/or Th1 suppressive, including IL-4 and IL-10 [53]. The Th2 cytokines (IL-4, IL-10, IL-13) are expressed during the first trimester, third trimester, and in the term placenta [53–57]. Only IL-10 and IL-13 are expressed during the second trimester [54,57,58]. In contrast, of the key cytokines stimulating Th1 responses, IFN-γ has been detected only at relatively low levels in the placenta during the first three trimesters with an increase at term [49,59]. Cytokines or other proteins the mother and placenta produce could potentially cross placental membranes and interact with the fetus by amniotic fluid absorption through the skin, respiratory tract, and gastrointestinal tract [60]. Currently, there is no specific evidence that the in utero cytokine environment of an allergic

mother is different (e.g., greater Th2 bias) than a nonallergic mother. However, proteomic profiling has found 14 differences in the placenta and 10 differences in the umbilical cord plasma between asthmatic and nonasthmatic mothers [61]. Additionally, maternal leukocytes may cross the placenta and interact with the fetus (reviewed [62]). The transfer of maternal CD4⁺ Th2 skewed T cells across the placenta could potentially skew fetal immune development toward a Th2 bias.

The Th2 bias of the immature immune system is thought to be a result of antigen presentation by antigen-presenting cells (APC) with inadequate costimulation, different functioning of T cells upon antigen stimulation, lower efficiency of neonatal APC, and fewer T cells and APC [63,64]. The response of cord blood dendritic cells (DCs) to LPS is consistently attenuated, with almost complete failure to produce IL-12p70 [65]. After birth, there is a transition from the fetal Th2-polarized to the adult Th1-polarized cytokine phenotype [66]. Children with a high genetic risk for atopy have a reduced capacity to produce the Th1 cytokine IFN- γ [67, 68]. Thus, there is the potential that a reduced capacity to generate Th1 responses during infancy, in the form of IFN- γ and/or other Th1 polarizing mediators, such as IL-12, may compromise or delay the transition to a Th1-competent immune response to inhaled allergens. Kopp et al. have reported that maternal sensitization to allergens is associated with the reduced maternal production of IFN- γ from stimulated peripheral blood mononuclear cells (PBMCs) and elevated production of IL-13 in CBMCs from the offspring [69]. Results from the dog and mouse models indicate that stimulation of a Th1 environment after birth can prevent the maternal influence in subsequent development of allergic sensitization in the offspring.

7. In utero sensitization

Several studies showed that CBMCs proliferate when stimulated with inhaled allergens [70–77]. Many investigators have interpreted this proliferative response to indicate that in utero exposure of the fetus to allergens has led to the priming of infant T cells (e.g., in utero sensitization) [70–77]. Mature CD4⁺ and CD8⁺ T cells are present at 17 weeks of gestation in humans and thus, potentially capable of generating antigen specific T cell responses in utero [71]. Jones et al. found that infants of mothers who were exposed to birch pollen at 22 weeks of gestation or beyond have significantly higher CBMC-proliferative responses to birch pollen at the time of birth than infants of mothers who had either not been exposed at all during their pregnancy or whose exposure had been prior to 22 weeks [71]. The findings of these studies suggest that inhaled allergens might have crossed the placenta during a critical period during fetal development and primed the infant T cells.

The concept of in utero sensitization and its relationship to the subsequent development of allergic sensitization and/or asthma is not without controversy. Smillie et al. reported no relationship between maternal HDM exposure during pregnancy and CBMC- or PBMC-proliferative responses at birth and 1 year, respectively [78]. Additionally, Chan-Yeung et al. showed that there is no association between maternal exposure to HDM, CBMC proliferation, and the incidence of asthma phenotype and rhinitis at 12 and 24 months after birth [79]. Others hypothesized that based on estimated daily maternal exposure levels of allergen (10 to 100 ng) it is unlikely that sufficient allergen can be absorbed and cross the placenta to stimulate an immune response in the fetus [80,81]. Studies utilizing both dog and mouse models of maternal influence indicate that allergen exposure during pregnancy is not required for the subsequent development of allergic sensitization and asthma in offspring from allergic mothers [25,28].

8. Natriuretic peptides in maternal influence

Natriuretic peptide hormones (NP), which have received wide attention for their cardiovascular effects, may contribute to the development of immunity or tolerance in the mucosa of the respiratory tract. Immune cells including macrophages, DCs, and T lymphocytes, express

receptors for atrial natriuretic factor. The NPs appear to influence cross-talk between epithelial cells and DCs followed by presentation of antigen to T cells, which together forms a link between innate and adaptive immunity [82]. Atrial natriuretic peptides (ANP) are produced by a number of tissues, central nervous system, lung, cardiovascular, and placental, with the potential to increase local and systemic levels, thus impacting the allergic status of the mother and potentially the development of the fetal-infant immune system. ANP is present in the fetoplacental circulation in humans and ANP concentrations are elevated during fetal distress [83–85]. Maternal plasma ANP concentrations are significantly higher in women with preeclampsia than in normal control subjects [86,87]. Whether ANP levels are higher in pregnant asthmatic women is unknown; however, ANP levels are increased in severe asthma [88], and severe exacerbations of asthma during pregnancy are associated with preeclampsia [15,16]. There are conflicting reports as to whether ANP crosses the placenta [89,90].

The co-expression of receptors for NPs in various immune cells, such as macrophages, DCs, and T lymphocytes, suggests a potential role for ANP in modulating immune responses. NP receptor-deficient mice exhibit significantly reduced lung eosinophilia when sensitized and challenged with OVA [82]. Mohapatra et al. hypothesize that ANPs may augment allergic sensitization and inflammation by acting on a number of cells in the lung (reviewed [82]). Briefly, ANP acts as an immunostimulant that augments immune response to allergens by affecting the innate immune cells such as DCs, modulating their function and by promoting their function and differentiation toward a phenotype that promotes a Th2-like phenotype. On the other hand, the kaliuretic peptide of pro-ANP hormone, which antagonizes with the ANP action, possesses not only bronchoprotective effects but also an anti-Th2 and pro-Treg effect [82]. Inhibition of the ANP/NP-receptor pathway through the promotion of tolerogenic DCs and augmenting Treg cells via kaliuretic peptides may be a means of regulating the maternal influence. Thus, in the context of the allergic mother, activation of the ANP/NP-receptor pathway may lead to enhanced allergic inflammation and subsequent release of pro Th2 cytokines that may modulate fetal and infant immune response to inhaled allergens. Regulation of the ANP pathway either during pregnancy or early infancy may prevent the maternal transmission of asthma susceptibility and subsequent development of an asthmatic phenotype in the infant.

9. Breast-feeding

Breast-feeding is the preferred method of infant nutrition in most cases; however, controversy remains as to whether it is protective against or a risk factor for the development of allergic disease in the infant. There are numerous studies showing that breast-feeding protects against the development of atopy while others indicate a neutral effect or that breast-feeding may induce the development of atopy (reviewed [91]). Even in the case of breast-feeding by mothers with asthma there are conflicting reports. Results from the Tucson Children's Respiratory Study indicate that while exclusive breast-feeding was associated with a lower rate of wheezing in the first 2 years of life irrespective of maternal asthma, beginning at 6 years of age, breast-feeding was related to a higher rate of asthma in children of mothers with asthma [92]. Specifically, atopic children of mothers with asthma that never breast-fed, breast-fed for less than 4 months, or breast-fed for greater than 4 months developed asthma at a rate of 9, 24, and 48%, respectively. However, an Australian study found that there was no statistical correlation between maternal asthma and the development of subsequent asthma in the breast-fed child, regardless of the duration of breast-feeding [93]. The previously described mouse model of maternal influence supports the idea that breast milk is sufficient, but not necessary, to mediate allergen-independent transmission of asthma risk to offspring.

The complexity of the interactions between breast milk and the infant's intestinal environment and developing immune system likely contribute to the disparity amongst associations between

breast milk and allergy. Some components of breast milk are thought to protect the infant from developing allergies whereas others components promote an allergic response. Allergic mothers have higher concentrations of the cytokines and chemokines IL-4, IL-5, IL-8, IL-13, and RANTES (regulated on activation, normal T cell expressed and secreted) in their breast milk [94,95]. Although the role of such cytokines and chemokines in breast milk is unknown, they could possibly increase IgE production and/or stimulate a Th2 immune bias in infants. Interestingly, as described earlier, significant levels of IL-2, IL-4, IL-5, IL-13, IFN- γ , and TNF- α were not detected in the breast milk of either OVA-sensitized or nonsensitized mothers in a mouse model of maternal influence [34]. Higher levels of eosinophilic cationic protein in breast milk, regardless of maternal allergic status, has been associated with a higher incidence of cow's milk allergy and atopic dermatitis in infant recipients [96]. In contrast, higher levels of the cytokine TGF β increases the ability of the newborn to produce IgA against potential food allergens such as OVA, where serum IgA is thought to confer passive protection to the infants immune system [42]. While lower levels of serum IgA have been measured in the allergic mother, these levels do not correlate with increased allergies in their infants [43].

The composition of polyunsaturated fatty acids in breast milk has been associated with a higher risk for the development of atopy in children. Lower levels of eicosapentaenoic acid, docosapentaenoic acid, and docosatetraenoic acid are found in mature milk from mothers of allergic children as compared to milk from mothers of non-allergic children [43]. More specifically, a high arachidonic acid to eicosapentaenoic acid ratio is associated with a greater risk of atopy in children [43]. In contrast, an Australian study found that higher levels of docosapentaenoic acid and docosahexaenoic acid in breast milk are associated with greater sensitization to food and aero-allergens in children [97]. It remains unclear which and/or how the immunomodulatory components of breast milk specifically interact with the infant and effect the development of allergies in a given child.

10. Relationship between exposure and immune response

Persistence of an allergic-Th2 immune phenotype in response to inhaled allergens throughout childhood and beyond likely involves complex interactions with genotype, early ex utero exposure to allergen and/or other environmental exposures (respiratory syncytial virus, rhinovirus, bacteria, air pollution, etc.). Understanding the relationship between the timing of the allergen exposure and the development of the immune response in the context of the maternal influence is important in that it defines when avoidance measures or other interventions would be needed to influence these responses. Several studies suggest that exposure to HDM allergen during the first year of life can influence immune responses [98–101]. However, since definitive evidence about immune responses (e.g., skin test or allergen-specific IgE or IgG) is not reliably detectable until after 3 years of age in children, it is currently not possible to determine whether exposure in the first 6 months or whether the cumulative exposure over 3 years is important. Animal models, in particular those that allow a longitudinal study design such as the dog model, will play a critical role in identifying the temporal pattern of exposures that solidifies or modifies the maternal allergic influence in the development of childhood asthma.

11. Conclusion

Asthma is one of the most common chronic diseases in children, with increasing morbidity and mortality [102]. A genetic predisposition and exposure to allergens have been implicated as major risk factors for the development of asthma. However, increasing evidence indicates that the mother plays a crucial role in mediating the development of fetal-infant immune responses to inhaled allergens (Fig. 3). Under normal conditions, the maternal environment during pregnancy promotes an initial Th2 skewed immune response in the offspring which

transitions to a nonallergic Th1 type response after birth [66]. However, little work has focused on whether the allergic mother's influence prevents or delays the normal transition to a nonallergic immune response to inhaled allergens in her children, thus increasing the risk for the development of allergic sensitization and/or asthma. Various animal models support the idea that the allergic mother can impart a greater risk for the development of an asthmatic phenotype in her offspring; however, many unanswered questions still exist with regard to the mechanisms of this influence.

The maternal CD4+ T-cell likely plays a central role; however, the exact nature of its regulatory influence is not clear. There is the potential for the T-cell to release regulatory cytokines (IL-4, IL-13, IL-10) that may cross the placenta and interact with the fetus or maternal cells themselves may cross the placenta. Cells within the placenta itself may be stimulated to release various cytokines. Further, factors within the breast milk, which remain to be fully elucidated, contribute to the shaping of the newborn's immune response to inhaled allergens. How long these maternal factors or influences may persist in the newborn is unclear. Further complicating the picture is the fact that children do not grow up in a bubble and are constantly being exposed to environmental stimuli (e.g., pollutants, bacteria, viruses, food, etc.) that may solidify or antagonize the maternal influence. Ultimately, understanding the maternal component of the risk for developing childhood asthma and how it relates more broadly to the maturation of the fetus or infant could lead to new treatment and prevention strategies for asthma and other diseases. In fact, studies in mice and dogs indicate that treatment (e.g., immune modulation) of newborns may be a realistic approach to preventing the development of allergic disease. This approach, however, dictates that we must expand further our understanding of infant development and the potential benefits and/or risk of early interventions.

ACKNOWLEDGMENTS

Work utilizing canine model (Dr. Barrett) was supported by National Institutes of Health AI061787-02 and P30 ES-012072.

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Figure 1.

Treatment of canine offspring from allergic mothers with inhaled CpG prevents the development allergic airway responses. Offspring from allergic mothers were exposed to ragweed (RW) or air and their responses characterized as previously described [25]. Some offspring were exposed by inhalation to CpG (30 μ g estimated deposited in the lung) ~ 30 minutes prior to the first RW challenge (7 days after birth). CpG treatment prevented the development of lung eosinophilia as measured in bronchoalveolar lavage cells (A) taken at 24 and 28 weeks of age and day 1 and 4 following inhaled RW challenge at 29 weeks of age. At 40 weeks of age RW-induced increases in airway resistance (B) were prevented by the previous CpG treatment. Serum levels of RW-specific IgG₁ (C) were significantly increased following CpG treatment. Maternal = levels in maternal serum during nursing at weeks 4, 6, and 8 after birth. *p < 0.05 vs. all treatment groups.

Figure 2.

Potential maternal influences that may skew the development of the fetal-infant immune response to inhaled allergens toward a Th2 (e.g., asthmatic phenotype) bias. Allergen, allergen-specific antibodies, and/or allergen-antibody complexes may cross the placenta and interact with the fetus. During pregnancy, the placenta produces predominantly Th2-type cytokines (IL-4, IL-6, IL-10, IL-13) and very little Th1 (IFN- γ) cytokines. After birth, offspring from allergic mothers may be exposed to higher levels of allergen-specific antibodies and Th2 promoting cytokines and chemokines in breast milk. Additionally, maternal lymphocytes may cross the placenta or be passed via the breast milk. Allergen exposure early after birth during this strong Th2 and/or weak Th1 maternal influence may solidify a Th2 immune bias to inhaled allergens in the infant.

Figure 3.

The maternal allergic influence and the persistence of an allergic-Th2 immune phenotype in response to inhaled allergens throughout childhood and beyond likely involves complex interactions with genotype, maternal factors, early ex utero exposure to allergen and/or other environmental exposures (respiratory syncytial virus, bacteria, air pollution, etc.).