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Maternal Influences over Offspring Allergic Responses

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Abstract

Asthma occurs as a result of complex interactions of environmental and genetic factors. Clinical studies and animal models of asthma indicate offspring of allergic mothers have increased risk of development of allergies. Environmental factors including stress-induced corticosterone and vitamin E isoforms during pregnancy regulate the risk for offspring development of allergy. In this review, we discuss mechanisms for the development of allergic disease early in life, environmental factors that may impact the development of risk for allergic disease early in life, and how the variation in global prevalence of asthma may be explained, at least in part, by some environmental components.

Keywords

Allergy; Neonate; Fetus; Dendritic cells; Corticosterone; α-Tocopherol

Introduction

Asthma is a heterogeneous disease resulting from complex interactions of environmental and genetic factors [1, 2]. The World Health Organization reported that the prevalence of asthma from 1950 to the present has increased in countries regardless of whether they had high, intermediate, or low rates of asthma [3–6]. The rise in rates of asthma over a few decades [4–6] and the differences in rates among countries and in migrating populations suggest an important role of the local environment in the development of asthma. Therefore, it is critical to determine mechanisms for the development of allergy/asthma and identify environmental mediators that regulate the development of allergy in order to identify novel targets for intervention. Allergic disease often starts early in life in humans and animal models [7–15]. In this review, we discuss mechanisms for the development of allergic

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Compliance with Ethics Guidelines

Conflict of Interest Dr. Cook-Mills has a patent pre-application, Compositions and Methods for the Treatment of Natal and Prenatal Conditions with Alpha-Tocopherol Pending.

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disease early in life and discuss environmental factors that impact the development of risk for allergic disease early in life.

Maternal Transfer of Risk of Allergy to Offspring

Some studies suggest that the development of allergen responsiveness may occur prenatally [16–18]. In reports examining human maternal and paternal asthma associations with the development of allergies in offspring, most associations are with maternal allergy/asthma [7, 19–26], suggesting that sensitization can occur prenatally or early postnatally. It is suggested that in utero and early exposures to environmental factors are critical for increased risk of allergic disease [27]. There is an association of higher risk of eczema, wheezing, and lower respiratory tract infections in early life with increases in human maternal and cord blood C-reactive protein, which is an acute phase protein produced during inflammation [28, 29]. A mouse model for maternal transfer of risk of allergy to offspring has been established [7–14]. This model reflects many of the parameters of development of allergic disease in humans including increased risk for development of allergies in offspring of allergic mothers. Moreover, as in humans, in this mouse model, the allergic responses of the offspring are not specific to the allergen of the mother.

In the mouse model of maternal transfer of risk of allergy to offspring, allergy is induced in female mice by sensitizing with chicken egg ovalbumin (OVA)/alum on weeks 1 and 2 and then challenging with OVA three times on weeks 4, 8, and 12 [7–14]. After the last OVA challenge in week 12, these female mice are mated [7–14]. Therefore, the female mice have allergic lung inflammation during the first half of the pregnancy because it takes about 2 weeks for resolution of allergic lung inflammation, which is the majority of the 3 weeks of mouse gestation. Additional challenge with OVA during pregnancy is not necessary for induction of risk of allergy in the offspring [30]. To determine allergen responsiveness in the offspring, the offspring are treated with a suboptimal OVA protocol, such that the neonates receive only one instead of two OVA/alum treatments at postnatal day 3–5 and then starting 7 days later; the neonates are challenged with aerosolized OVA for three consecutive days [7–14]. Alternatively, the offspring are challenged with casein [30]. The offspring of these allergic mothers develop allergic lung inflammation and airway responsiveness whereas pups from non-allergic mothers do not develop inflammation in response to the allergen challenge [7–14] (Fig. 1a, b). Moreover, this ability of the offspring of allergic mothers to respond to allergen is sustained for up to 8 weeks of age in the mouse [9]. The magnitude of the offspring response to an initial allergen challenge declines in the offspring after 8 weeks [9]. Allergic responses are inhibited in the mother by anti- IL-4 antibody administration to the mothers at preconception and this maternal anti-IL-4 treatment blocks the development of responsiveness of offspring to suboptimal allergen [30]. These data suggest that an IL-4-dependent allergic response in the mother is involved in the transmission of risk to the offspring. However, IL-4 and IgE do not pass to the fetus from the mother [18, 31–33]. It was reported that antibody depletion of T cells in allergic mothers modulates the development of responsiveness of offspring to allergen [10]. In other studies, adoptive transfer of allergen-specific T cells from OVA TCR transgenic mice DO11.10 mice to females prior to mating results in offspring with responsiveness to suboptimal challenge of antigen [11]. These data suggest that maternal Th2 responses induce maternal signals that

induce development of allergen responsiveness in offspring. Thus, female mice that are allergic before conception and develop a Th2 response during pregnancy produce offspring that have augmented responsiveness to suboptimal allergen challenge.

The responses of the offspring from allergic mothers are not specific to the allergen to which the mother responds. Uthoff et al. [18] reported that allergens can cross the placenta but that offspring are responsive to BLG whereas mothers were stimulated with OVA, suggesting that the process is antigen-independent. The antigen-independent maternal transfer of risk of allergy to offspring was also demonstrated by Hamada et al. [30]. In their report, offspring are responsive to casein whereas the mothers were sensitized and challenged at preconception with OVA [30]. An antigen-independent effect of maternal allergy on allergen responsiveness in pups has also been demonstrated in canines [34]. Similarly, in humans, children respond to different allergens than the allergic mother [7]. Thus, the offspring responses are not specific to the allergen that the mother responds to but instead, the offspring have an increased responsiveness to sensitization to allergens.

Maternal Effect on Offspring Dendritic Cells

Offspring from allergic mothers have increased allergic responsiveness to suboptimal allergen challenge and we and others report that the maternal effect alters offspring dendritic cells [7, 8, 35•, 36, 37]. Fedulov et al. [37] reported that the increased responsiveness of the offspring occurs through changes in pup dendritic cells but not in pup macrophages. In their studies, the transfer of splenic dendritic cells from non-challenged neonates of allergic mothers into neonates from non-allergic mothers confers increased allergic susceptibility in recipient neonates (Fig. 1c) [37]. In contrast, the transfer of macrophages from non-challenged neonates of allergic mothers into neonates from non-allergic mothers does not confer increased allergic susceptibility in recipient neonates (Fig. 1d) [37]. This is suggestive of a functional change in neonatal dendritic cells in offspring from allergic mothers. Changes in dendritic cells are consistent with the antigen-independent transfer of risk from allergic mothers to offspring in humans [7] and in animal models [8–14].

We reported that offspring of allergic mothers have an increase in a distinct subset of dendritic cells. The fetal livers from allergic mothers and the OVA-challenged pup lungs from offspring of allergic mothers had increased numbers of CD11b+ subsets of CD11c+ dendrititc cells [35•], a dendritic cell subset that is critical for generation of allergic responses [38•]. In contrast, in these tissues, there were no changes in CD11b− regulatory dendritic cells subsets, including plasmacytoid dendritic cells and CD103+ dendritic cells [35•]. Furthermore, Mikhaylova et al. [39•] reported that before antigen challenge of the pups, the dendritic cells of pups from allergic mothers had little transcriptional changes but extensive DNA methylation changes. Then, after allergen challenge, there were many transcriptional changes in the dendritic cells [39•]. These studies suggest that mediators, which do not confer allergen specificity, may be transferred from the mother to the offspring and these mediators regulate offspring dendritic cells and heighten the responsiveness of offspring to challenge with suboptimal doses of allergens.

Breast Milk and Offspring Allergy

There is a role of breast milk of allergic mice on the development of allergic responses in offspring in the model in Fig. 1b. However, the milk of allergic mothers is not necessary for the offspring allergic responses because the in utero maternal effects are sufficient for allergic responses by offspring of allergic mothers. This was demonstrated by cross-fostering the offspring. Briefly, pups from allergic mothers that are nursed by non-allergic mothers still have an allergic response to suboptimal challenge with OVA [32]. Therefore, maternal effects in utero mediate development of allergen responsiveness in offspring of allergic mothers [32]. Breast milk is sufficient, but not necessary, for maternal transmission of asthma risk in the offspring because when pups from non-allergic mothers are nursed by allergic mothers, the pups exhibit a response to suboptimal allergen challenge [32]. In this study, the breast milk from allergic and non-allergic mothers contained no detectable IFNγ, IL-2, IL-4, IL-5, IL-13, or TNFα, suggesting that other mediators increase the risk of offspring allergy through breast milk [32]. In clinical studies, it is reported that the mediators, omega-3 and omega-6 polyunsaturated fatty acids, in human milk associate with asthma and atopy but the mechanism is not known [40, 41]. Miyake et al. [42] reported that omega-3 fatty acids during pregnancy associate with lower infantile wheeze.

In other mouse models, the function of breast milk has been studied in female mothers that were not allergic at preconception. In these models, the non-allergic mother mice were exposed during pregnancy or lactation to allergen or an antigen tolerance protocol. This is in contrast to the clinical reports demonstrating that the risk for allergy in children has been associated with mothers with existing allergic disease before conception [7, 19–26]. Nevertheless, in mouse models where the mother was not allergic at preconception, but then exposed during pregnancy or lactation to allergen or an antigen tolerance protocol, there was protection of offspring responses to allergen sensitization/challenge. Briefly, it is reported that exposure of normal female mice during lactation to OVA results in transfer of antigen and TGFβ in milk, and this inhibited allergic inflammation in offspring treated later as adults (6–8 weeks old) with two sensitizations with OVA/alum and five OVA challenges [43]. These adult offspring also had elevated regulatory CD4+ T cells and the increase in T regulatory cells was dependent on milk TGFβ but not milk immunoglobulins [43]. In another approach, it was demonstrated that sensitization of females before mating and then extensive antigen challenges (10 OVA challenges) during lactation resulted in transfer of IgG immune complexes in the milk and induction of regulatory T cells and tolerance in the offspring when offspring were challenged with OVA at 6–8 weeks old; in this model, immune complexes but not TGFβ in the milk was required for tolerance [44]. Similar data were reported for allergic mothers and an offspring 60-day treatment protocol with subcutaneous OVA/alum, intraperitoneal OVA, and then five OVA challenges [45]. In summary, depending on timing, doses, and number of antigen challenges, factors in breast milk can contribute mediators that either increase or decrease offspring responses to allergen.

Maternal Exposure to Th2-Inducing Environmental Irritants Also Enhances Offspring Allergic Responses, Whereas Th1 Stimuli Reduce Offspring Allergic Responses

A maternal effect on offspring allergic responses has also been demonstrated for maternal exposure to environmental irritants. Maternal inhalation of titanium oxide or diesel exhaust particles during pregnancy increased responses of offspring to allergen challenge [46]. Also, skin sensitization to toluene diisocyanate (TDI) induces a Th2 response in the mother, and when the mother was mated after second dose of TDI, the offspring had increased allergic responses to suboptimal OVA [36].

It is also reported that a Th1 response in the mother may protect the offspring from developing allergic responses. When females are sensitized to dinitrochlorobenzene (DNCB), which induces a Th1 response, and then mated, the offspring do not develop an allergic response to suboptimal OVA [36]. Also, offspring are protected from the development of asthma by prenatal challenge of the mother with LPS, which induces a Th1 inflammation, an increase in IFNγ, and a decrease in IL-5 and IL-13 [47–50]. In addition, injection of non-allergic mothers with IFNγ on gestational day 6.5 protects against the development of allergic responses in offspring [51]. Fedolov et al. [52] demonstrated that treatment of the offspring from allergic mothers on postnatal day 4 with CpG oligonucleotides, a TLR9 agonist and Th1-type stimulant [53], protected the offspring from the development of allergic responses to suboptimal OVA using the model in Fig. 1a, b. Therefore, exposure of mothers, allergic mothers, or offspring from allergic mothers to Th1 stimuli inhibited the offspring response to allergen challenge.

Maternal Vitamins Regulate Offspring Allergic Responses

The prevalence of allergies has increased in just a few decades [4–6], suggesting that environmental factors likely impact allergies and asthma. Environmental factors that regulate allergy and asthma in the mother could then affect the risk of development of allergy and asthma in offspring. Exposure to environmental factors, such as chemical irritants or nutrients, during pregnancy has been associated with allergic disease in offspring [54, 55]. The data for vitamin D association with asthma and allergy is controversial in adults [56, 57] and in offspring [55–60]. Supplementation with higher levels of vitamin D during pregnancy or in cord blood has been associated with both a higher risk of allergy and with a lower risk of allergy in early infancy, but adequate vitamin D levels during pregnancy support fetal maturation [56, 57]. An environmental change over the past 40 years, which may contribute to elevating allergic responses, has been an increase in the d-γ-tocopherol isoform of vitamin E in the diet and in infant formulas [61–65].

Most clinical studies on vitamin E include mixed forms of natural and synthetic tocopherols from supplementation or diet. Vitamin E consists of eight natural isomers, d-α-tocopherol; d-β-tocopherol; d-γ-tocopherol; d-δ-tocopherol; and d-α-, d-β-, d-γ-, and d-δ-tocotrienol. In addition, there are synthetic racemic forms of tocopherols. Of these forms, the two most abundant natural forms are d-α-tocopherol and d-γ-tocopherol. Plants synthesize the natural

isoforms from tyrosine and chlorophyll [66]. Then, these tocols are consumed in the diet from plant lipids. Mammals do not interconvert the tocopherol isoforms. In the liver, d-α-tocopherol is preferentially transferred to lipoproteins by the liver α-tocopherol transfer protein, resulting in 10-fold higher tissue concentrations of α-tocopherol than γ-tocopherol [67–71]. In mechanistic studies, we demonstrated that α-tocopherol is an antagonist and γ-tocopherol is an agonist of endothelial cell PKCα during signals that mediate eosinophil recruitment [72]. In a mouse model of adult allergic lung inflammation to OVA that is characterized by high eosinophils and low neutrophils, we demonstrated that α-tocopherol and γ-tocopherol have opposing regulatory functions during inflammation [64, 65, 73]. Briefly, supplementing with γ-tocopherol elevated allergic responses in adult mice [65, 74]. Moreover, even at the 10-fold lower concentrations of γ-tocopherol than α-tocopherol, γ-tocopherol opposed the anti-inflammatory benefit of α-tocopherol in adult mouse allergic responses [65, 74]. The opposing functions of these two tocopherol isoforms have implications on interpretation of studies with mixed tocopherols as discussed in other reviews [57, 64, 75, 76]. Importantly, tocopherol isoform regulation of maternal allergy may influence the risk for development of allergy in offspring.

Consistent with animal models demonstrating opposing functions of α-tocopherol and γ-tocopherol with allergic inflammation and airway responsiveness, we reported that in a study with 4500 adult participants, increasing plasma concentrations of α-tocopherol associate with better lung function and increasing plasma concentrations of γ-tocopherol associate with lower lung function [77•]. Interestingly, countries with higher plasma levels of γ-tocopherol tend to have the highest prevalence rate of asthma [65, 78–83]. In the USA, the average plasma γ-tocopherol levels are two to five times higher than those of European and Asian countries whereas the average plasma α-tocopherol levels are about the same among these countries [83]. The plasma γ-tocopherol levels are high in the USA where the diet is rich in γ-tocopherol found in soy oil, corn oil, and canola oil [61–65]. In contrast, γ-tocopherol is low in olive oil and sunflower oil used in European countries [65, 83, 84]. The differences in outcomes from clinical reports on vitamin E and asthma in Europe and the USA may, in part, reflect the opposing functions of α-tocopherol and γ-tocopherol.

Tocopherol isoforms may influence development of allergies early in life. We demonstrated in a 20-year prospective study in the USA that by age 21, human plasma α-tocopherol associates with better lung spirometry and human plasma γ-tocopherol associates with worse lung spirometry [77•]. This suggests that during human development prior to age 21, tocopherols may have regulatory functions on responsiveness to allergen. It is reported by Allan et al. [55] that low maternal α-tocopherol associates with increased risk for doctor-diagnosed asthma in first 10 years of life [55]. Thus, the balance of α-tocopherol and γ-tocopherol in women regulates adult allergic responses [77•] and the balance of tocopherol isoforms in pregnant females may influence the development of risk of allergies in her children.

In mice, α-tocopherol supplementation of allergic female mice during pregnancy/lactation decreased neonate development of allergic lung inflammation in response to suboptimal allergen challenge (Fig. 1e) [35•]. In these studies, allergic responses to OVA were induced in adult female mice and then the females were mated while receiving α-tocopherol-

supplemented diets (250 mg α-tocopherol/kg diet) or a basal α-tocopherol diet (45 mg α-tocopherol/kg diet) [35•]. A basal α-tocopherol diet is used as the control because adequate α-tocopherol levels are required for placental development [85, 86]. Then, the 3-day-old neonates received a suboptimal allergen sensitization with OVA/alum and OVA challenge on days 10–12 [35•]. α-Tocopherol is loaded in the liver onto lipoproteins that then enter circulation for delivery to peripheral tissues. The α-tocopherol-supplemented diet significantly increased liver α-tocopherol in the saline-treated mothers threefold as compared to basal diet controls The OVA treatment reduced the α-tocopherol tissue concentrations in the α-tocopherol-supplemented mothers, which is consistent with reduced α-tocopherol levels in asthmatics [87–90], suggesting that α-tocopherol supplementation may be especially necessary for asthmatic mothers. Maternal α-tocopherol supplementation increased pup liver α-tocopherol 2.5-fold [35•]. This α-tocopherol supplementation of allergic mothers during pregnancy/lactation resulted in a dose-dependent inhibition of lung eosinophils [35•] in the OVA-stimulated pups from allergic mothers as compared to OVA-challenged pups from non-allergic mothers (Fig. 1e) [35•]. There was no effect of treatments on pup weight, pup numbers, or pup gender distribution [35•]. OVA-treated pups from allergic mothers had increased serum IgE, but α-tocopherol supplementation did not alter the IgE [35•]. α-Tocopherol supplementation of allergic female mothers inhibited OVA-induced pup lung messenger RNA (mRNA) expression of cytokines that regulate allergic inflammation (IL-33 and IL-4) and chemokines for eosinophil recruitment (CCL11 and CCL24) [35•]. Therefore, α-tocopherol supplementation of allergic mothers inhibits allergic inflammation and cytokine/chemokine mediators of allergic inflammation in OVA-challenged pups from these allergic mothers. Studies are ongoing in our lab to determine mechanisms of γ-tocopherol regulation of maternal transfer of risk of allergy to offspring.

In studies to determine the regulatory effect of α-tocopherol in utero and in the milk, pups were cross-fostered at birth. Cross-fostering pups from allergic mothers with 250 mg α-tocopherol/kg diet to allergic mothers with basal diet (45 mg α-tocopherol/kg diet) indicated that α-tocopherol supplementation of the allergic mother during pregnancy was sufficient to inhibit the OVA-induced increase in neonate lung eosinophils [35•]. In addition, α-tocopherol supplementation during lactation reduced the allergic responses in the neonates [35•], suggesting a contribution of α-tocopherol after birth [35•]. In summary, α-tocopherol supplementation of allergic mothers during pregnancy was sufficient to reduce the development of allergic responses in the offspring.

α-Tocopherol supplementation starting at conception of a second pregnancy of allergic female mice also inhibits development of allergic lung inflammation in offspring. The offspring from allergic mothers that were supplemented with α-tocopherol at the time of the second mating had a >90 % inhibition of lung lavage eosinophils in the OVA-challenged pups [35•]. Moreover, in OVA-challenged pups from allergic mothers, α-tocopherol reduced lung mRNA expression of several mediators of allergic inflammation: the cytokines IL-4, IL-33, and TSLP and the chemokines CCL11 and CCL24 [35•]. This is consistent with α-tocopherol regulation of development of allergic inflammation. There were no effects of α-tocopherol on low levels of the Th1 cytokine IFNγ or the regulatory cytokine IL-10 [35•], indicating that α-tocopherol did not switch the response to OVA to a Th1 response.

It is reported that transfer of dendritic cells but not macrophages from pups from allergic mothers are sufficient for the development of the allergic responses in pups in response to suboptimal OVA challenge [37]. We reported that offspring from allergic mothers with a suboptimal OVA challenge have elevated numbers of distinct subsets of lung dendritic cells (CD11b+CD11c+ resident and alveolar dendritic cells) but there are no changes in numbers of CD11b−CD11c+ dendritic cells (plasmacytoid dendritic cells and CD103+ dendritic cells) in the pup lung [35•]. During development of gestational day 18 fetal livers of allergic mothers, there is an increase in dendritic cells of the phenotype of CD11b+CD11c+ resident dendritic cells [35•]. Therefore, there is an effect of maternal allergy on the development of dendritic cells in the fetus.

The increase in the numbers of dendritic cell subsets in offspring of allergic mothers is regulated by α-tocopherol. Maternal supplementation with α-tocopherol significantly reduces the OVA-stimulated pup lung numbers of CD11b+ subsets of CD11c+ dendritic cells, including resident dendritic cells, myeloid dendritic cells, and CD11b+ alveolar dendritic cells, without altering CD11b− subsets of CD11c+ dendritic cells, including plasmacytoid dendritic cells, CD103+ dendritic cells, CD11b− alveolar dendritic cells, and alveolar macrophages [35•]. Interestingly, α-tocopherol supplementation does not completely deplete CD11b+ dendritic cells, but instead, α-tocopherol supplementation of allergic mothers reduces the numbers of pup CD11b+ dendritic cells to the numbers of these dendritic cells in pups from non-allergic mothers [35•]. For all dendritic cell subsets, the mean fluorescence intensity (MFI) for MHCII, CD80, and CD86 was not different among the groups [35•]. In the fetus on gestational day 18, α-tocopherol supplementation of allergic mothers reduces the number of fetal liver CD11b+ subsets of CD11c+ dendritic cells, including those of the phenotype of myeloid dendritic cells and phenotype of resident DCs without altering MFI for MHCII, CD80, or CD86 [35•]. The fetal liver CD11b− subsets of CD11c+ dendritic cells are not altered by maternal supplementation of α-tocopherol [35•]. We also demonstrated a direct effect of tocopherols on bone marrow dendritic cell differentiation in vitro. Bone marrow from 10-day-old mouse neonates from non-allergic mothers with basal diet was incubated with GM-CSF for 8 days in vitro in the presence of α-tocopherol. In these cultures, α-tocopherol reduces the number of CD45+CD11b+CD11c+ dendritic cells and the number of cells with resident dendritic cell phenotype (CD45+CD11b +CD11c+Ly6c-MHC- dendritic cells) without affecting the percent of viable cells in the culture [35•], indicating that α-tocopherol regulates differentiation of bone marrow cells to dendritic cells. Whether the inhibition of offspring risk for allergic responsiveness by maternal supplementation with α-tocopherol is through regulation by a maternal transplacental mediator or by the offspring response to the maternal mediator is not known and is under investigation in our laboratory. These studies of tocopherol isoform regulation impacts our understanding of mechanisms of regulation of dendritic cells by environmental factors during the development of allergies, the design of clinical studies with tocopherol isforms, and, perhaps, risk for allergic disease in future generations.

Transplacental Mediators and Development of Allergic Disease

It is not known whether transplacental cytokines influence the maternal effect on the offspring development of allergic responses. Th2 cytokines (IL-4, IL-5, and IL-13) are

elevated in the placenta but transplacental crossing of these cytokines has not been demonstrated [91–93]. It is reported that only 2 % of maternal GM-CSF crosses the human placenta in ex vivo perfusate studies [94]. Whether maternal GM-CSF increases risk of offspring for allergic responses is not known. Understanding mechanisms of maternal transfer of risk for allergy to offspring and mechanisms for regulation of this risk will have an impact on limiting the development of allergic disease early in life.

One endogenous transplacental maternal mediator in mice has been reported to be sufficient to induce the increased responsiveness in the offspring to suboptimal OVA challenge [95•]. This mediator is low-level maternal corticosterone [95•]. In adult mice and rats, OVA sensitization and challenge increases stress [96–101] and increases endogenous serum corticosterone [102, 103]. Moreover, it is reported that symptoms of stress/anxiety are commonly associated with allergy/asthma in adult mice and in humans [104–108]. In addition, it is reported that stress in adult 4-week-old mice exacerbates OVA-induced allergic responses and this stress-induced effect is blocked by pretreatment with a glucocorticoid receptor antagonist [103]. When maternal corticosterone is elevated during pregnancy, the maternal cortisol can cross the placenta and affect fetal cortisol levels [109, 110]. Others reported that maternal corticosterone crosses the placenta to the fetus and is a strong inducer of Th2 responses [111, 112]. Cortisol is also present in human breast milk [113] and has the potential to affect allergic responses in neonates. Consistent with the mechanistic studies in mouse models, in pregnant asthmatic women without treatment for asthma, a deficiency in the placenta of a cortisol-metabolizing enzyme 11 beta-hydroxysteroid dehydrogenase 2 leads to increased fetal cortisol and low birth weight which is predictive of lower lung function later in life [114, 115].

In mice, it has been demonstrated that subjecting pregnant female mice to stress increases endogenous corticosterone, increases offspring allergic responses to suboptimal allergen, and increases airway responsiveness after suboptimal allergen challenge [95•, 109]. Furthermore, glucocorticoid during pregnancy is sufficient for allergic responses in offspring because administration of a low dose of glucocorticoid to non-allergic mothers on day 15 of gestation increases off-spring allergic responsiveness to suboptimal allergen challenge [95•]. In addition, when these mothers are subjected to stress and treated during pregnancy with an inhibitor of endogenous corticosterone synthesis, there is a reduction in the allergic response by the offspring [95•]. Therefore, elevated corticosterone in allergic pregnant mice may be a mediator that is transferred from the mother to the fetus or in the breast milk to the neonate, resulting in enhanced responses of off-spring to suboptimal allergen challenge. This mechanism is consistent with the antigen-independent transfer of risk from mother to offspring [30, 34].

Conclusion

The development of allergic disease often begins in utero or early in life and environmental factors impact the development of risk for allergic disease. Animal models and clinical studies indicate that the development of increased risk for allergies in offspring of allergic mothers may occur in utero. In animal models, this occurs by in utero regulation of distinct dendritic cell subsets that are able to transfer risk to naïve offspring. One maternal factor

transferred from allergic or Th2 stressed mothers to the fetus or transferred to the offspring in breast milk is low levels of corticosterone. The development of allergic responses and distinct dendritic cell subsets in offspring from allergic mothers is blocked by maternal supplementation with the α-tocopherol isoform of vitamin E. Understanding the epidemiology, biology, and regulation of asthma inception by environmental factors will lead to approaches to reduce the development of allergy and asthma. The marked differences in rates of disease across the world, changes over short periods, and changes with migrating populations mean that asthma and allergic diseases are not inevitable consequences of a genetic predisposition. This is important, as the ability to modify diet and lifestyle means that lower rates of these diseases can be attained without medications or sophisticated medical infrastructures and can be achieved worldwide.

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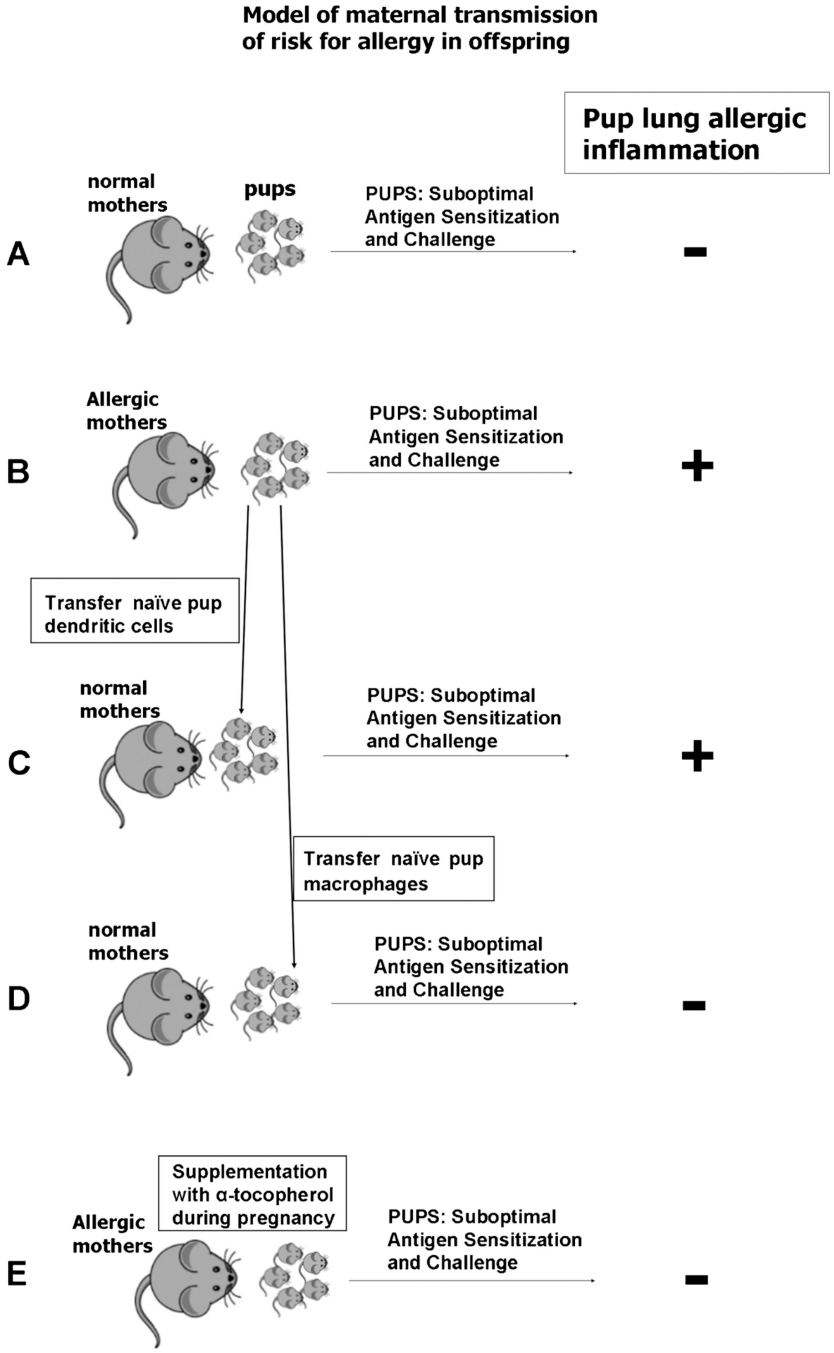

Fig. 1.

Model of maternal transmission of risk for allergy in offspring. Female mice are sensitized with chicken egg ovalbumin (OVA)/alum on weeks 1 and 2 and then challenging with OVA three times on weeks 4, 8, and 12 [7–14]. After the last OVA challenge in week 12, these female mice are mated [7–14]. To determine allergen responsiveness in the offspring, the offspring are treated with a suboptimal OVA protocol, such that the neonates receive only one instead of two OVA/alum treatments at postnatal day 3–5, and then starting 7 days later, the neonates are challenged with aerosolized OVA for three consecutive days [7–14]. **a**

Normal mothers. **b** Allergic mothers. **c** Dendritic cells are isolated from the spleens of pups from allergic mothers before pup treatment with allergen. These dendritic cells are transferred to pups from non-allergic mothers. **d** Macrophages are isolated from the spleens of pups from allergic mothers before pup treatment with allergen. Macrophages are transferred to pups from non-allergic mothers. **e** Allergic mothers are supplemented with α-tocopherol at the time of mating