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The Potential of Maternal Dietary Modification for Prevention of Food Allergy

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Abstract

Effective primary preventions strategies aimed at reducing the onset of IgE sensitization are urgently needed as the incidence of childhood food allergy keeps increasing.

Studies eliminating food allergens during pregnancy have failed to show reduction in the prevalence of long-term IgE-mediated food allergy in children, and recent data provides direct evidence supporting early oral exposure as a means of preventing development of allergy. Since effects on early immune programming may be more significant in utero, there has been increasing interest in the potential protective role of maternal dietary modifications on the development of FA in offspring.

In this article, we will review the current knowledge from animal and clinical studies on the role of maternal dietary modification, mainly through supplementation with vitamins, polyunsaturated fatty acids and probiotics, for the prevention of food allergy. Besides, the potential role of some promising FA treatments like Chinese herbal formula FAHF-2 for the primary prevention of FA in offspring will be reviewed.

Keywords: Food allergy; Prevention; Pregnancy; Maternal diet

Introduction

The rates of childhood food allergy (FA) and eczema are continuing to increase as part of what appears to be a "second wave" of the allergy epidemic [1]. In this context, primary prevention strategies aimed at reducing the onset of IgE sensitization are urgently needed.

Because progressively earlier presentations of food allergy implicate early environmental influences, there is intense interest in the prenatal factors inducing tolerogenic immune responses. Studies eliminating food allergens during pregnancy have failed to show reduction in the prevalence of long-term IgE-mediated food allergy in children, and recent data provides direct evidence supporting early oral exposure as a means of preventing development of allergy.

The parallel between the increase in food allergies and changes in dietary components during the last decades has also led researchers to investigate preventive strategies aiming at restoring the dietary and gut microbial balance, mainly through supplementation with vitamins, polyunsaturated fatty acids and probiotics. Other dietary factors currently under investigation in animal studies to prevent food allergy include polyphenols and isoflavones. Furthermore, there are also new data on Chinese herbal formula FAHF-2, proved to be effective in induction of long term tolerance in peanut allergic mice, which was associated with skewing Th2 immune responses to Th1 (and regulatory) response. Because maternal allergies increase the risk of peanut allergy in offspring, restoration of maternal food allergy points to the potential role to FAHF-2 for prevention of offspring food allergy.

In this article we will review current knowledge from previous publications, published abstracts and newly generated data from animal and clinical studies on the role of maternal dietary modification for the prevention of food allergy.

Exposure to Food Allergens

Studies of food allergen avoidance during pregnancy, lactation, and infancy have consistently failed to reduce long-term IgE-mediated food allergen in children [2].

Clinical studies

Approximately 74% of peanut (PN) anaphylactic reactions occur at first known exposure in infants [3,4] suggesting a critical window for early life prevention [5]. The recommendation for mothers to implement a PN restrictive diet during pregnancy/lactation was abandoned in 2008 [6] due to the lack of conclusive evidence of benefit [7], and early evidence that it might even be harmful [8,9]. The theory behind the early life PN restriction diet is mainly based on the conception of "in utero or early life sensitization" based on the findings of allergens/antibodies presented in amniotic fluid and cord blood [10], and placenta [11,12] and peanut antigen in breast milk of lactation women after ingestion of PN [13], although studies providing a direct association of offspring sensitization were lacking. Recently, an alternative hypothesis that early life introduction of PN or other allergenic foods may be beneficial because oral tolerance induction is an active process that requires antigen has been put forward [14,15]. This is based on several observational studies. For example, a recent cross-sectional study of Jewish children in Israel and the UK, found that the prevalence of peanut allergy (PNA) was 10-fold higher in the UK (1.85%) than in Israel (0.17%, $p<0.001$), and that peanut is introduced earlier and is eaten more frequently and in larger quantities in Israel than in the UK by 8-14 month infants [16,17]. However, the evidence of benefit of early life exposure is no consistent. Recent studies showed that maternal consumption of peanut during pregnancy is associated with peanut sensitization in atopic infants [18,19]. Conflicting findings may

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be due to uncontrolled environmental factors, timing of introduction to PN and different study protocols and populations, as well as undefined co-factors in maternal diet such as microbes [18-20]. In addition, retrospective maternal recall of dietary intake during pregnancy (and or lactation), sometimes months or years later, may contain recall bias. At present, the standard practice for PNA and other food allergies is strict allergen avoidance. There is no clinical study reporting whether peanut allergic mother consumption of controlled low doses of peanut that do not trigger clinical reactions would prevent offspring peanut or other food allergies.

Maternal allergenic food consumption for preventing food allergy in offspring: Animal studies

In recent years several studies in animal models have provided direct evidence supporting early oral exposure as a means of preventing development of allergy.

Melkild et al. [21] showed that intraperitoneal immunization of naïve mice with ovalbumin and adjuvant ($Al(OH)_3$) during pregnancy and lactation significantly reduced the specific IgE response and increased the IgG2a response in their offspring. Moreover, the IgE suppression was stronger if maternal allergen exposure was during early pregnancy (3 days into pregnancy) compared to a late pregnancy exposure (17 days into pregnancy). The same group reported that the protective effect of maternal immunization was affected by the type of adjuvant used: while offspring from mothers immunized with OVA and either pertussis toxin (PT) or $Al(OH)_3$ showed reduced levels of OVA-specific IgE and IgG1 and increased levels of OVA-specific IgG2a antibodies, maternal immunization with CpG and OVA did not affect antibody responses in offspring [22]. However, whether this effect is dependent on the specific adjuvant and/or the route of exposure employed has to be further investigated.

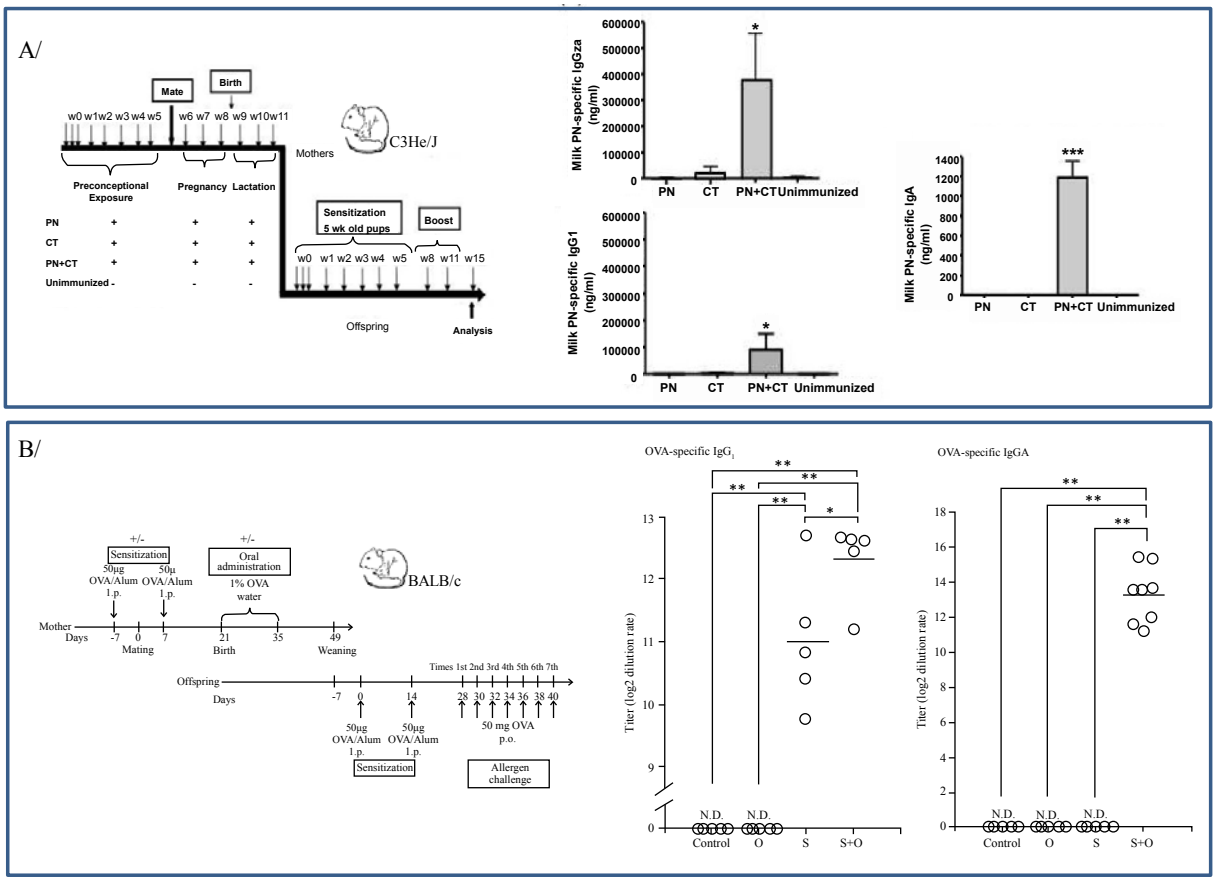

Figure 1: Maternal allergenic food consumption for preventing food allergy in offspring.Transmission of maternal specific immunoglobulins by breast milk in two murine models of FA

A: Maternal peanut consumption provides protection in offspring against peanut sensitization [23]

Left: Experimental protocol of mothers' and offsprings' peanut (PN) sensitization. Female C3He/J mice were fed either with peanut and cholera toxin ig (PN+CT), peanut ig (PN) or cholera toxin alone (CT) for five weeks and, after mating with naïve males, during pregnancy and lactation. An unimmunized group was employed as a control. 5-week old offspring from all the 4 groups were sensitized with PN+CT i.g. weekly for 5 weeks followed by 2 boosting doses. Mothers were sacrificed at weaning and offspring at week 15 for analysis.

Right: Peanut-specific immunoglobulin levels in mouse milk: peanut-specific IgG2a (ng/mL), peanut-specific IgG1 (ng/mL) and peanut-specific IgA (ng/mL) measuredby antigen-specific ELISA. Data are expressed as means ± SEM of duplicates for each group (n=3–4) *P<0.05, ***P<0.001 vs Unimmunized.

B: Transfer of specific immunoglobulin by breast milk leads to antigen-specific offspring protection from food allergy [26]

Left: Experimental protocol. Sensitized mice were exposed to 1% OVA in drinking water for 2 weeks immediately after delivery. Offspring were weaned at 4 weeks and 5-week-old offspring were used for the FA model.

Right: OVA-specific IgG1 and IgA levels in breast milk. OVA-specific IgG1 is only found in the breast milk from OVA-sensitized mothers, which implies that mother micesecrete IgG1 into their breastmilk. OVA-specific IgA is only found in the breastmilk from OVA-sensitized and OVA-exposed mothers. Data are shown as the means and individual data points. N.D.: not detectable. *P<0.05, **P < 0.01, n=5–9.

López-Expósito et al. [23] demonstrated that offspring of peanut allergic mothers exhibited significantly increased susceptibility to PN-induced IgE sensitization, and that low-dose consumption of peanut (beneath the threshold of triggering clinical reactions) with CT during pregnancy and lactation reduced the risk of peanut allergy in murine offspring. Further study by this group also showed that this effect persisted for at least 15 weeks. Importantly, administration of peanut extract alone was markedly less effective than peanut plus the mucosal adjuvant cholera toxin (CT) in the suppression of peanut-specific IgE or Th2 cytokine responses, and CT alone had no effect. Consistently, increased peanut specific-levels of IgG2a and/or IgA in milk were seen when peanut and cholera toxin were administered together, but not PN or CT alone, suggesting that transmission of maternal immunoglobulin may play a role in the observed protection (Figure 1) [24]. The important role of a mucosal adjuvant in providing protection against peanut sensitization was demonstrated in this study and we recently found that offspring protection also occurs when the non toxic to human mucosal adjuvant cholera toxin B is used.

Preventing allergy in offspring by maternal mucosal (intranasal) immunization has also been confirmed in another recent study in which maternal immunization with OVA reduced OVA-specific IgE and IgG1, and increased IgG2a and Th2 cytokine responses in offspring [25].

A recent study by Yamamoto et al. [26], showed that feeding OVA to lactating mice prevented offspring OVA allergy-induced diarrhea and suppressed the increases in plasma OVA-specific IgE levels and Th2 cytokine mRNA expression levels in the proximal colon, as well as the infiltration of mucosal mast cells into the colon. Detection of OVA in breast milk of from OVA-exposed nonallergic mothers during lactation, and increased titers of OVA-specific IgG1 and IgA in breast milk from allergic mothers, suggests that transfer of dietary antigens along with their specific immunoglobulin by breast milk leads to antigen-specific offspring protection from food allergy (Figure 1). How the breast milk antibodies provide protection against FA in the child has not been studied. However, in an asthma model Mosconi et al. [27] demonstrated that milk-borne OVA–IgG complexes were actively transferred from the mothers to the pups through the FcRn. Furthermore, FcRn-mediated transfer of OVA–IgG complexes resulted in the induction of FoxP3 regulatory T cells in mesenteric lymph nodes, and that FcRn-deficient mice breastfed by OVA-exposed sensitized mice were not protected against allergic airway inflammation.

Taken together, the results of these animal studies suggest that induction of oral tolerance by maternal ingestion of food antigens during lactation may be a strategy for prevention of FA in infants.

Maternal Dietary Supplement Interventions

In recent years, there is an active research focused on assessing whether the manipulation of nutritional factors, like vitamin D or polyunsaturated fatty acids (PUFA), in maternal diets may prevent the development of food allergy in their offspring.

Vitamin D

Vitamin D controls effector immune functions, promotes regulatory immune response and induces innate immune defenses [28,29]; all of which could be relevant to allergic disease.

Some studies have pointed towards an early induction of tolerogenic immune responses by maternal vitamin D intake. Chi et al. [30], have shown that higher vitamin D levels at birth may be associated with a lower number of T regulatory cells, and a relation between vitamin D supplementation during pregnancy and increased cord blood mRNA levels of the leucocyte receptors ILT3 and ILT4, both critical for the generation of T suppressor cells and induction of immunological tolerance, has been recently reported [31].

Clinical studies: Clinical studies on the effect of vitamin D in allergic diseases are mainly observational and have yielded very heterogeneous results, suggesting that either excessive or, conversely, vitamin D deficiency result in increased allergies (reviewed in [28]).

On one hand, allergies increased coinciding with vitamin D supplementation intervention programs to prevent rickets in childhood [32], and increased risk for asthma and food allergies has been reported among children receiving early vitamin supplementation [33]. In a recent German cohort study, it has been described that higher maternal $25(OH)D_3$ results in a higher risk of food allergy sensitization at 2 years of age [34]. On the other hand, the vitamin D deficiency (VDD) hypothesis argues that inadequate vitamin D is responsible for the increase in allergic diseases. Infantile vitamin D has been associated with higher rates of atopic disease at the age of 6 and 14 years [35] and enhanced eczema severity in children aged between 8 months and 12 years [36]. Several studies have reported higher rates of food allergy/anaphylaxis or proxy measures at higher absolute latitudes and in infants born in fall/winter compared with sunnier months in Europe, the United States, and Australia [37], and higher rates of food sensitization have been described in infants born to mothers with low vitamin D intake during pregnancy [38].

However, vitamin D insufficiency itself cannot be related to the increase of a topic diseases since allergy was nearly absent during rickets epidemics that occurred in the last centuries. It can also be argued that in northern developed countries like USA, where the use of dietary supplements is highly extended, VDD may be very unlikely and thus could not explain the increase of atopic disease in these countries. Nevertheless, an 8% of the US population is at risk of vitamin D deficiency [39] and a recent study on infants and their mothers in New England found that more than half of the infants and approximately one third of the mothers who gave birth were vitamin D deficient at the time of delivery even when prenatal vitamins were taken regularly [40].

Significant genetic variability of the response to dietary supplementation and metabolism of vitamin D, have been recently described [41] and could account for VDD even in people at low risk.

The apparent paradox of both vitamin D insufficiency and vitamin D supplementation having been linked to allergy and asthma may be explained by epigenetic programming in pregnancy by low vitamin D levels. Recent studies provide evidence for gene-vitamin D interaction effects on food sensitization. In a study on 649 children, vitamin D deficiency (VDD) increased the risk of food sensitization only among individuals with certain IL4 and MS4A2 (MS4A2 (Fc epsilon receptor 1 beta-chain) genotypes [42]. Later, Vimaleswaran et al. confirmed the association of VDD with higher total IgE levels in adults with IL4 and MS4A2 SNPs [43]. These data highlight the need to consider possible ethnic differences in the allergy-related responsiveness to VDD.

Studies examining the effect of maternal vitamin D status on food allergy on offspring, summarized in table 1, are mainly observational [44-48]. Randomized control trials are ultimately required to determine any potential role of vitamin D supplementation in preventing allergic disease. Until then, no clear recommendation on the use of vitamin D in pregnancy for the prevention of allergies can be formulated.

Publication	Study design	Outcome
Nwaru et al. (2010) [38]	Prospective birth cohort study. Food intake questionnaire 8m pregnancy sIgE serum samples children 5y	Increased vitamin D intake during pregnancy is negatively associated with the risk of food allergies at 5y age.
Vasallo et al. (2010) [44]	Medical record review of all patients presenting to emergency departments for food-related acute allergic reactions between 2001-2006.	Seasonal fluctuations in UV-B irradiation and perhaps vitamin D are involved in involved in the pathogenesis of food allergy in children
Mullins et al. (2011) [45]	Comparison of food allergy rates by season of birth between children with FA diagnosis in a specialist referral clinic and population births controls.	Reduced UV exposure/vitamin D status might be responsible for higher rates of food allergy of children born in autumn/winter
Keet et al. (2012) [46]	Logistic regression comparison of fall or non fall birth between (i) food allergic and nonallergic subjects in NHANES, and (ii) food allergic children from Johns Hopkins and the general Maryland population	Fall birth is associated with increased risk of food allergy, and this risk is greatest among those most likely to have seasonal variation in vitamin D during infancy and those at risk for skin barrier dysfunction, suggesting that vitamin D and the skin barrier may be implicated in seasonal associations with food allergy.
Mullins et al. (2012) [47]	Neonatal serum 25(OH)D_3 levels were compared between children with IgE-mediated peanut allergy and matched population births.	Nonlinear relationship between neonatal 25(OH)D level and childhood peanut allergy: slightly higher levels were associated with lower risk than those in the reference group.
Jones et al. (2012) [48]	Prospective birth cohort study. Food intake questionnaire last trimester pregnancy. Cord blood 25 (OH)D_3 levels at delivery	No association between vitD status and allergen sensitization or presence of IgE-mediated food allergy. Lower cord blood vitamin D status risk factor for the development of eczema in the 1st y.
Weisse et al. (2013) [34]	LINA cohort study Maternal and cord blood 25 (OH)D_3 levels during pregnancy & at birth. Total IgE, sIgE for inhalants and food allergens at birth 1 & 2 years. Atopic outcomes (AD, FA) recorded as parental report of a doctor diagnosis	Higher maternal 25 (OH)D_3 levels associated with a higher risk of sensitization to food allergens at 2y. Cord blood 25 (OH)D_3 levels were negatively associated with regulatory T cell numbers.

Table 1: Clinical studies on the role of vitamin D during pregnancy in food allergy [28].

Polyunsaturated Fatty Acids (PUFA)

Lower consumption of n–3 PUFA is a key characteristic of modern 'western' diets, which are typically rich in more pro-inflammatory n–6 PUFA. This has raised interest in the use of fish oil as a preventative strategy to 'restore the balance' of n–3/n–6 PUFA, supported by the recognized anti-inflammatory effects of n–3 PUFA and evidence that metabolic products of n–6 PUFA are more inflammatory.

Animal studies: The dietary ratio of n-6/n-3 fatty acids during gestation and throughout lactation has been found to influence the induction of immunological tolerance to OVA in neonatal rats [49]. Moreover, dietary supplementation with n-3 PUFA (fish oil source) of OVA-sensitized mice reduces serum specific OVA-antiIgE and IgG1, small intestine edema and eosinophil infiltration, mucus production, and Paneth cell degranulation [50]. These results are consistent with the findings of Watanabe et al. [51] that the IgE antibody response to egg albumin was significantly lower in mice fed with safflower seed oil. On the other hand, Johansson et al. [52] found, in a murine model of airway hypersensitivity (Th2), that mice fed fish oil produced higher levels of OVA- specific IgE and exhibited greater lung eosinophil infiltration. As far, there has been no report in animal model how maternal PUFA intake influences offspring food allergy outcomes.

Clinical studies: There is interest in the potential protective role of maternal n–3 PUFA supplementation during pregnancy, particularly as effects on early immune programming may be more significant in utero.

A systematic review conducted in 2009 [53] concluded that "supplementation with omega3 and omega6 oils is unlikely to play a role in the strategy for the primary prevention of sensitization or allergic disease". The few studies specifically addressing the preventive effect of n-3 PUFA supplementation of pregnant women on children at risk of food allergies, summarized in table 2, have not yet confirmed their beneficial role as a strategy for the primary prevention of food allergy [54-58].

Antioxidants

The available epidemiological, animal, molecular and immunological data suggest potentially beneficial associations between maternal intake of some antioxidants during pregnancy and childhood asthma and to a much lesser extent, atopic dermatitis and allergic rhinitis (reviewed in [59]). To date, no such data are available for food allergy.

Fruit polyphenols and soybean isoflavones effect on FA in animal models

Dietary polyphenols are a class of bioactive compounds found in abundance in plant (tea, cocoa, coffee, etc.) and fruit (apple, grapes, pomegranate, etc.) sources. Their effects on allergic disorders are just beginning to be unraveled and future research is required to substantiate their role as anti-allergy agents. Certain classes of polyphenols can influence the development of allergic immune responses at two critical stages, during allergic sensitization and following re-exposure to the allergen. Polyphenols can form insoluble complexes with allergenic proteins and render them hypoallergenic, which leads to inefficient antigen presentation by specialized cells such as dendritic cells (DC) [60].

Of particular importance to food allergy, polyphenols bind irreversibly to peanut allergens and reduce the allergenicity of peanut extracts [61]. Zuercher et al. [62] in an *in vivo* food allergy murine model showed that consumption of polyphenol enriched apple extract by OVA-sensitized mice attenuated clinical symptoms upon challenge, accompanied by reduced levels of intestinal mast cell protease, diminished cytokine secretion by lymph node (MLN) cells and reduced intestinal mRNA expression of various T-helper type-2 associated and pro-inflammatory genes. These data are in agreement with a previous study by Akiyama et al. [63], in which feeding of complex apple polyphenols reduced systemic anaphylaxis after allergen challenge in OVA-sensitized mice.

A word of caution to this approach must be mentioned, particularly in relation to allergen detection systems; the high polyphenol content within the food matrix can mask the detectable levels of allergen. Further research is needed in order to validate these findings and to generate hypoallergenic foods, by forming insoluble complexes with allergenic proteins, via polyphenol treatment.

Publication	Target	Omega 3 supplementation Intake (from/until)	Study	Findings & Summary
Dunstan et al. [54]	pregnant women with family history of allergic disease	Fish oil (3.7 g/d n-3 PUFA) 20 w gestation/ until birth	RDBPC	Infants were less likely to have a positive skin prick test to egg vs placebo (OR 0,34) at 1 y
Lauritzen et al. [55]	Pregnant women with a fish intake below the population median	Fish oil (1.5 g/d of n-3 PUFA) 4 mon of lactation	RDBPC	No difference in atopic disease and plasma IgE between active and placebo groups
Furuhjelm et al. (2009) [56] (2011) [57]	pregnant women with either personal or family history of allergic disease	1.6 g eicosapentaenoic ac.+1.1 g docosahexaenoic ac./daily. 25 w gestation/3-4 m postnatally	RDBPC	No effect on the prevalence of clinical symptoms of allergic disease, but a decrease in cumulative incidence of IgE-associated disease during the 1st y. Decrease in cumulative incidence of IgE-associated disease still remained until 2 y of age
Palmer et al. [58]	pregnant women with family history of allergic disease	fish oil (900 mg/d n-3 PUFA) 21 w gestation/ until birth	RDBPC	No differences in the overall percentage of infants with Ig E associated food allergy versus placebo.

Table 2: Clinical trials assessing the preventive effect of n-3 PUFA supplementation during pregnancy in food allergy in infants at high risk of atopy [53].

Resveratrol, a polyphenolic compound abundant in grapes and red wine, has a wide range of biological and pharmacological activities, including anti-inflammatory, anti-oxidative, and anticarcinogenic effects via multiple molecular mechanisms documented mainly in animal disease models (reviewed in [64]). In a recent study, Okada et al. [65] examined the effects of dietary resveratrol in a mouse model of food allergy induced by oral administration of OVA with the mucosal adjuvant cholera toxin (CT). The study demonstrated that ingestion of resveratrol prevented CT-driven mucosal sensitization to OVA in mice, and decreased OVA plus CT-induced splenocytes and bone marrow derived dendritic cell costimulatory molecule expression levels by as yet undetermined mechanism.

Soybeans are the most common source of isoflavones in the human diet, and some epidemiologic studies have linked soy intake with beneficial effects in patients with allergic diseases [66]. Masilamani et al. [67], showed that the dietary isoflavones genistein and daidzein suppressed allergic reactions to peanut in mice and regulated CT-activated human monocyte-derived DCs function *in vitro*. Recently, they extended this study by determining the effects of isoflavones on murine Th1 immune responses in vitro and *in vivo* [68], and found that they suppressed the expression of LPS-induced DC maturation markers, B7 costimulatory molecules and MHC molecules and selectively suppressed cytokine secretion (TNFα, IL-10, IL-6, IL-12) from LPS-activated DCs. Taken together, these data demonstrate immunoregulatory properties of isoflavones, which could have implications for future allergy prevention strategies. Since vegetables and fruits are the major sources of flavonoids, although there is no direct evidence that maternal consumption of flavonoid influences offspring food allergy outcomes, studies have shown that maternal consumption of vegetables and fruits are negatively associated with asthma risk in offspring [69]. Research into evaluation of the effect of maternal consumption of flavonoid on food allergy outcomes in offspring should be encouraged.

Possible mechanisms of dietary modification on offspring allergy outcomes

Although changes in dietary components during the last decades may have played a role in the increasing incidence of food allergy [1], they cannot explain the allergy epidemic all over the world. On the other hand, the rapid increase of allergic diseases in a short period of time makes it unlikely to be the result of genetic changes alone. It seems more likely that exposure to a combination of environmental factors may be producing, through epigenetic modifications, heritable change in gene expression that increase the risk of allergic disease.

DNA methylation is probably the best characterized inheritable epigenetic modification influenced by environmental factors [70]. DNA methylation status is heritable, but it is also plastic, thereby providing a potential opportunity to convert a Th2 predisposition to a tolerogenic Tregs status by manipulation of the maternal environment. A maternal gestational diet high in folic acid, a methyl donor in methylation reactions, has been shown to enhance the severity of offspring allergic airway disease [71] in mice. Exposing mothers to a farm environment and raw farm milk during pregnancy increased numbers of $CD4^+CD25^+$ T cells in cord blood, which was associated with significant DNA demethylation within the foxp3 locus [72]. However, this has not yet been shown to have an effect on their offspring.

Our group recently found that maternal consumption of low doses of peanut plus the adjuvant cholera toxin subunit B in mice reduced peanut allergy risk in offspring that was accompanied by a significant reduction in DNA methylation at the Foxp3 promoter CpG site and increased IL-4 promoter methylation in the intestinal tissue, suggesting that epigenetic modifications may be involved in induction of tolerance to food allergen in this model.

Maternal Consumption of Probiotics for Prevention of Food Allergy in Offspring

With increasing evidence that allergic disease are associated with disruption of the microbial 'balance', including altered early colonization and reduced diversity of intestinal flora, attempts have been made to prevent allergic disease by restoring a more optimal pattern of microflora through probiotic supplements during pregnancy and/or infancy [73]. The Food and Agricultural Organization of the United Nations and the World Health Organization [74], defines probiotics as 'living microorganisms, which when administered in adequate amounts confer health benefits on the host. The major sources of probiotics are dairy products that contain Lactobacillus and Bifidobacterium species. The effects of probiotics have been attributed to restoration to normal of increased intestinal permeability and unbalanced gut micribiota, improvement of the intestine's immunologic barrier functions, and reduced generation of proinflammatory cytokines characteristic of local and systemic allergic inflammation [75].

Animal models

Schiavi et al. [76], in a murine model of shrimp-induced anaphylaxis, found that oral administration of a mixture of probiotics significantly reduced symptom scores and fecal histamine levels after challenge as well as serum shrimp-specific IgE levels. IL-4, IL-5, and IL-13 levels in the jejunum were significantly reduced, whereas FOXP3 and IL27 mRNA expression and IL-10, TGF-β, and IFN-β tissue content were increased. However, animal studies on the effect of maternal exposure to probiotics in the offspring are lacking, so further investigation is needed in this field.

Clinical studies

A recent meta-analysis on the impact of probiotics intake during pregnancy on development of eczema in children [77] concluded that administration of lactobacilli, but not a mixture of various bacterial strains, during pregnancy prevents atopic eczema in children aged 2 to 7 years. So far, studies on the preventive effect of probiotic intake during pregnancy/lactation on allergic diseases have not been designed to specifically asses their effect on FA. However, some of them have looked at surrogate markers of FA as secondary outcomes, and their results are summarized in table 3.

In 2009 Niers et al. [78], conducted a double-blind, randomized, placebo-controlled (RDBPC) trial aimed to study the primary prevention of allergic disease in high-risk children by pre- and postnatal supplementation with probiotics. A mixture of three probiotic bacteria (*Bifidobacteriumbifidum, B. lactis*, and *Lactococcuslactis*) was administered to pregnant mothers during the last 6 weeks of pregnancy and postnatally for 12 months to their offspring. No difference in food allergen sensitization (measured by serum specific IgE (sIgE)) was observed between active and placebo group at 1 and 2 years of age. This lack of effect on FA prevention was also observed by Kim et al. [79] in a RDBPC trial using a combination of three probiotics (*Bifidobacterium bifidum*, *B. lactis* and *Lactobacillus acidophilus*) starting at 4–8 weeks before delivery and continuing for 6 months. The same results were also reported with a probiotic mixture of three strains (*Lactobacillus rhamnosus GG*, *L. acidophilus* and *Bifidobacterium animalis*) given to a nonselected maternal population [80].

When administering only one strain of Lactobacillus (Lactobacillus GG) to pregnant women carrying infants at high risk of atopy, from 36 weeks of gestation until delivery, Boyle et al. [81] found no difference in sensitization to egg or peanut (assessed by positive SPT) in children at 1 year between active and placebo groups. Consistently, a recent RDBPC trial using the same Lactobacillus GG single strain starting at the second trimester of pregnancy did not find differences in the incidence of sensitization to food allergens (sIgE) in the offspring of actively treated mothers compared to the placebo group [82].

In a randomized trial of 1223 high-risk families, pregnant mothers ingested a probiotic mixture of 4 strains (LGG, *L. rhamnosus*, *Bifidobacterium breve* and *Propionibacterium freudenreichii*) from 36 weeks of gestation and their infants received the same probiotics for 6 months [83]. The children were followed until age 5 years and no difference in the cumulative incidence of food allergy sensitization (assessed by either a positive SPT or serum sIgE) could be found between active and placebo groups. Moreover, there were no differences on serum food-specific IgA, IgG1 or IgG4 concentrations among placebo and active groups at 2 years of age [84,85].

It is important to note that while studies on the potential effect of maternal dietary supplement interventions with either vitamin D or PUFA are mainly observational, the studies on the effect of maternal supplementation with probiotics are randomized controlled trials. Although data point towards a lack of effect of probiotic maternal supplementation on childhood FA, when interpreting these studies, it has to be considered that the microorganisms used, doses, and durations of therapy are different. A recent study also showed that time of probiotic exposure is critical to reducing eczema, and that although eczema incidence was decreased sensitization to food allergens was not [86]. This finding appeared to be contradictory to Lack et al. [5], indicating that eczema in children is highly associated with food allergy. The discrepancy might be due to the current study did not evaluate the food induced clinical reactions by double blind placebo controlled challenges, since sensitization to food allergens as determined by skin testing or IgE is not necessarily diagnostic for true food allergy. More studies specifically aimed at determining a potential preventive role of probiotics on FA sensitization as well as clinical reactions are needed.

Chinese Herbs

Food allergy herbal formula-2

The Chinese herbal medicine FAHF-2 has attracted attention as an allergen non-specific therapy for food allergy [87] FAHF-2, a tablet form of a 9-herb extract (*Prunus mume, Zanthoxylum schinifolium, Angelica sinensis, Zingiber officinalis, Cinnamomum cassiae, Phellodendron chinense, Coptis chinensis, Panax ginseng* and *Ganoderma Lucidum*) has been shown to completely eliminate PN-induced anaphylaxis in murine food allergy models and has an excellent safety profile in humans [88,89]. Protection persists for up to 6 months following therapy in mice (half of the murine life span) and is associated with sustained reduction of serum PN-IgE levels. It also reduces the numbers of peripheral blood basophils and peritoneal mast cells and FcεRI, FcεRI γ mRNA subunit expression by mast cells and basophils, and T-cell proliferation as well as histamine release following food allergen challenge in a murine model of food allergies [90]. FAHF-2 treatment protection is also associated with immunomodulatory effect on T and B cells [91]. To increase the potency and ease of clinical use,

Publication	Target	Probiotic Intake (from/until)	Study	Findings and Summary
Kim et al. [79]	pregnant women with family history of allergic disease	Mixture of 2 strains 32 w.gestation/3m postnatally	RDBPC	No difference in food sensitization or probable food allergy in treatment versus placebo groups after 1 year
Niers et al. [78]	pregnant women with family history of allergic disease	Mixure of 3 strains 34 w.gestation/ 12m postnatally	RDBPC	No difference in food sensitization in treatment versus placebo after 1 & 2y.
Boyle et al. [81]	pregnant women with family history of allergic disease	Lactobacillus GG 36 w.gestation/until delivery	RDBPC	No difference in food sensitization in treatment versus placebo after 1 year
Dotterud et al. [80]	Nonselected maternal population	Mixure of 3 strains 36th w.gestation/3m postnatally	RDPPC	Reduced cumulative incidence of atopic dermatitis, but no effect on atopic sensitization
Kuitunen et al. (2009) [83] Kukkonen et al. (2011) [84] Kuitunen et al. (2012) [85]	pregnant women with family history of allergic disease same cohort same cohort	Mixure of 4 strains 36 w.gestation/6m postnatally	RDPPC	No difference in cumulative incidence of allergic diseases and IgE sensitization versus placebo at 5 y. No difference on serum food-specific IgA, IgG1 or IgG4 concentrations versus placebo at age 2y Increased IL-10 and decreased casein IgA Abs in breast milk from mothers treated with probiotic vs placebo.
Ou et al. [82]	pregnant women with personal history of allergic disease	Lactobacillus GG 24 w.gestation/until delivery	RDPPC	Reduced severity of maternal allergic disease but not the incidence of childhood allergic disease.

Table 3: Clinical studies assessing the preventive effect of probiotic intake during pregnany/lactation in children's food allergy [95].

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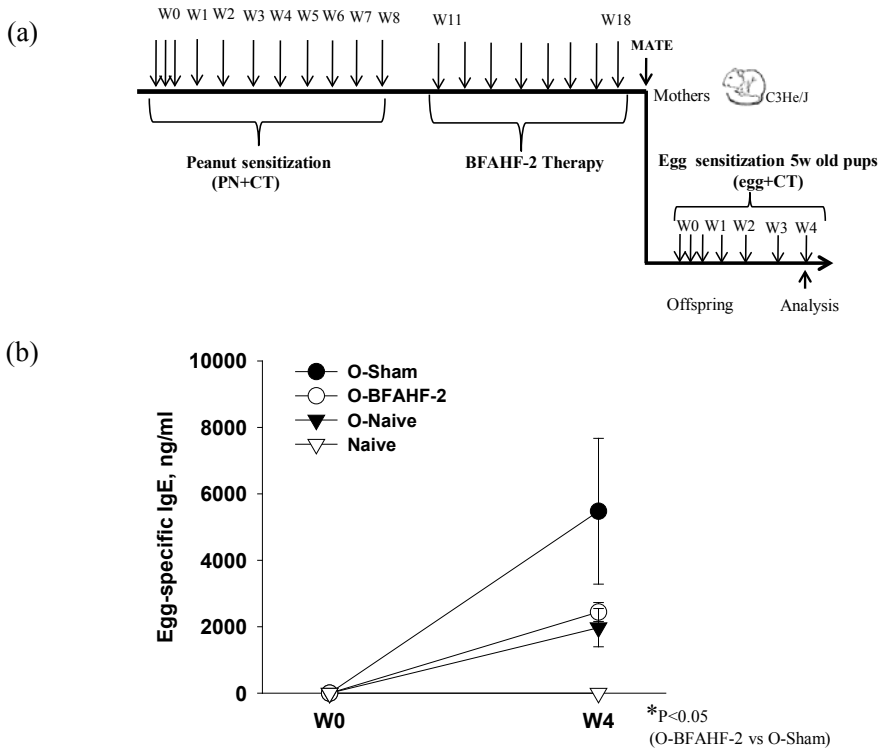

Figure 2: Maternal allergenic food consumption for preventing food allergy in offspring.Transmission of maternal specific immunoglobulins by breast milk in two murine models of FA

A: Maternal peanut consumption provides protection in offspring against peanut sensitization [23]

Left: Experimental protocol of mothers' and offsprings' peanut (PN) sensitization. Female C3He/J mice were fed either with peanut and cholera toxin ig (PN+CT), peanut ig (PN) or cholera toxin alone (CT) for five weeks and, after mating with naïve males, during pregnancy and lactation. An unimmunized group was employed as a control. 5-week old offspring from all the 4 groups were sensitized with PN+CT i.g. weekly for 5 weeks followed by 2 boosting doses. Mothers were sacrificed at weaning and offspring at week 15 for analysis.

Right: Peanut-specific immunoglobulin levels in mouse milk: peanut-specific IgG2a (ng/mL), peanut-specific IgG1 (ng/mL) and peanut-specific IgA (ng/mL) measuredby antigen-specific ELISA. Data are expressed as means ± SEM of duplicates for each group (n=3–4) *P<0.05, ***P<0.001 vs Unimmunized.

B: Transfer of specific immunoglobulin by breast milk leads to antigen-specific offspring protection from food allergy [26]

Left: Experimental protocol. Sensitized mice were exposed to 1% OVA in drinking water for 2 weeks immediately after delivery. Offspring were weaned at 4 weeks and 5-week-old offspring were used for the FA model.

Right: OVA-specific IgG1 and IgA levels in breast milk. OVA-specific IgG1 is only found in the breast milk from OVA-sensitized mothers, which implies that mother micesecrete IgG1 into their breastmilk. OVA-specific IgA is only found in the breastmilk from OVA-sensitized and OVA-exposed mothers. Data are shown as the means and individual data points. N.D.: not detectable. *P<0.05, **P<0.01, n=5–9.

we recently developed a more concentrated version of FAHF-2 by butanol purification, named B-FAHF-2, which reduced daily doses by 80% [92]. Given that concomitant egg and peanut sensitization is high (>70%) in infants [16] and we previously found in murine model that maternal peanut allergy significantly increased offspring susceptibility to PN sensitization [23], we asked whether maternal peanut allergy also increase susceptibility to egg sensitization and whether B-FAHF-2 can reduce this risk. To this end, female C3H/HeJ mice were sensitized with peanut and then treated with FAHF-2 or PBS (Sham). They were then mated with naive male mice. 5-week-old offspring were sensitized with egg white plus CT epicutaneously 3 times at weekly intervals. It was shown that offspring of PN allergic mothers receiving preconception sham treatment showed significantly higher egg specific IgE levels than in offspring of naïve mothers ($p<0.05$; Figure 2). Interestingly, offspring of B-FAHF-2 treated mothers showed marked and significant suppression of egg-specific IgE ($p<0.05$) than offspring of Sham treated mothers, and were essentially the same as in naïve offspring (Figure 2). These data suggested that in addition to the potential of B-FAHF-2 as a therapeutic botanical drug, it may also have a potential approach by preconception treatment to prevent maternal allergy mediated food allergy risk in offspring. More research is required to develop maternal preconception B-FAHF-2 treatment as safe and effective interventions to prevent offspring food allergy high risk.

That such an approach is worth pursuing is shown by the finding in a murine model of asthma that treatment of asthmatic mothers with ASHMI (Anti-Asthma Herbal Medicine Intervention) prevent early onset of allergic airway inflammation and mucus cell development in offspring [93].

Clinical studies

Our recent phase-1 safety trial in 19 food-allergic subjects (12-45 years old) demonstrated the safety and tolerability of FAHF-2, also showed that FAHF-2 increased IFN-γ and IL-10 and reduces IL-5 and IL-13 production by peripheral blood mononuclear cells from adults and children with food allergy *in vitro* [91]. In an extended phase 1 study, 6 months of FAHF-2 was safe, well tolerated and associated with a significant reduction in basophil CD63 expression upon *ex vivo* stimulation and a trend for reduced numbers of basophils.

A multicenter double-blind placebo controlled phase II trial on

safety and efficacy of the treatment with FAHF-2 in patients (age 12-45 y) allergic to peanut, tree nuts, sesame, fish, and/or shellfish, is currently ongoing (clinicaltrials.gov identifier: NCT00602160). As yet no clinical study of FAHF-2 or B-FAHF-2 as preventive approach for high-risk children has been conducted, and such studies should be encouraged given its high safety profile and immunomodulatory effects.

Methodological Limitations

Before concluding, the reader has to bear in mind that the results of the studies reviewed in the present article should be interpreted with caution due to their inherent limitations.

On one hand, animal models results cannot be directly extrapolated to humans but they are important to establish the mechanistic basis of interventions and to generate hypothesis that have to be validated in human clinical studies. On the other hand, designs of clinical studies on pregnant women are constraint by logical ethical limitations. Another major limitation of these studies is the phenotypic description of food allergy, most commonly diagnosed through a surrogate marker (such as skin prick test or serum sIgE) rather than using the gold standard food challenge method. In addition, dietary intake is usually determined by food frequency questionnaires that are subject to recall bias. Other limitations of these studies include selection bias and reverse causality [94]. For this reason, potential strategies to prevent food allergy in infants need to be tested in randomized controlled interventional studies.

Conclusion

The prevalence of food allergy has increased over the past 10-15 years and there is no indication that this trend will decrease. It is important to develop primary preventive approaches for prevention. The suggestion that there is a critical window for early life prevention has raised interest in the potential of dietary interventions for mothers of infants at high risk of atopy as an early food allergy prevention strategy. Several studies have provided evidence supporting early oral exposure as means of preventing development of food allergy, but the data are not consistent. There are limited intervention- based clinical studies of the relationship between maternal diet and offspring food allergy. Continued effort is required to overcome the many methodological challenges of maternal preventive studies and to make safe and effective dietary interventions an early preventive strategy for FA. Epigenetic alterations appear to cause, and may possibly prevent food allergy. Future strategies should focus on the creation of favorable epigenetic modifications in offspring of atopic and non-atopic mothers by dietary modification. Animal models that mimic IgE mediated food allergies with a fixed genetic background and controlled exposures are likely to remain a crucial component of future studies in this field by provide a rational for human clinical study design.

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