

Dietary Immunomodulatory Factors in the Development of Immune Tolerance

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Abstract Emerging evidence suggests that exposures during pregnancy and the early postnatal period can modify gene expression and disease propensity. Diet is a major environmental exposure, and dietary factors, including polyunsaturated fatty acids, probiotics, oligosaccharides, antioxidants, folate, and other vitamins, have effects on immune function. Some also have been implicated in reduced risk of allergy in observational studies. Intervention trials with polyunsaturated fatty acids, probiotics, and oligosaccharides suggest preliminary but as-of-yet-unconfirmed benefits. Food allergen avoidance during pregnancy, lactation, or infancy has provided no consistent evidence in allergy prevention and is no longer recommended. Rather, there is now a focus on food allergens in tolerance induction. Specific nutrients can induce changes in gene expression during early development and have been implicated in potentially heritable “epigenetic” changes in disease predisposition. Collectively, these observations emphasize that early exposures may modify tolerance development and that further research on these exposures should remain a priority.

Keywords Allergy prevention · Immune tolerance · Dietary immunomodulatory factors · Antioxidants · Complementary feeding · Folate · Vitamin D · Polyunsaturated fatty acids · Prebiotics · Probiotics

Introduction

Growing evidence indicates that early environmental exposures may influence susceptibility to development of immune-mediated disorders such as allergic disease. Recognized effects of several dietary components on immune function support the hypothesis that dietary change is one of the key factors implicated in the steep increase in immune disease [1–3]. Compared with traditional diets, modern diets contain more complex, processed, and synthetic foods and less fresh fish, fruits, and vegetables. This has resulted in substantial changes in the amounts and patterns of a wide range of dietary components. Complex interactions make it difficult to separate the specific role of individual dietary factors. Consequently, any observed relationships with disease need to be interpreted in the wider context of the composite diet. Moreover, additional interactions with other modern environmental changes add to this complexity. This may at least partly explain some of the inconsistencies in the associations between dietary factors and disease in previous reports.

The Critical Role of Maternal Diet During Pregnancy

Predisposing patterns of immune dysfunction are manifest already at birth [4•], and increasing evidence suggests that maternal diet [2] and other antenatal exposures [5] can modify these neonatal immune responses. This together with the rising rate of allergic disease in early infancy implies that

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the effects of modern environmental changes commence in utero. Epigenetic paradigms provide new mechanisms by which these early environmental exposures lead to heritable changes in gene expression and disease susceptibility [6]. Notably, dietary change is one of the leading factors currently implicated in these “epigenetic modifications.” Some evidence from animal models suggests that specific maternal dietary changes (below) can have epigenetic effects on immune function and predisposition to an allergic phenotype [3], also suggesting that pregnancy is an important window of opportunity for disease prevention. During pregnancy and lactation, maternal diet can influence various aspects of developing structures and functions (Fig. 1). Collectively, antenatal and postnatal events may influence susceptibility to immune dysregulation.

While several dietary factors have documented effects on immune function, as discussed separately below, it remains unclear how this may be contributing to the perinatal differ-

ences in immune function that are associated with subsequent allergic disease. These well-documented presymptomatic differences in neonatal immune function include immaturity in effector T-cell function [7–9], regulatory T cells [10], and differences in innate cell function [4, 11]. Notably, we recently observed abnormalities in neonatal T-cell signaling in children who developed subsequent allergic disease, and this could be modified by a dietary intervention (namely fish oil) in pregnancy [9]. Ongoing research seeks to unravel this important issue with the hope of developing more definitive prevention strategies.

Significance of Postnatal Diet and Early Events in the Gastrointestinal Tract

The culminating events of immune tolerance occur in the postnatal period, and the gastrointestinal tract is the central

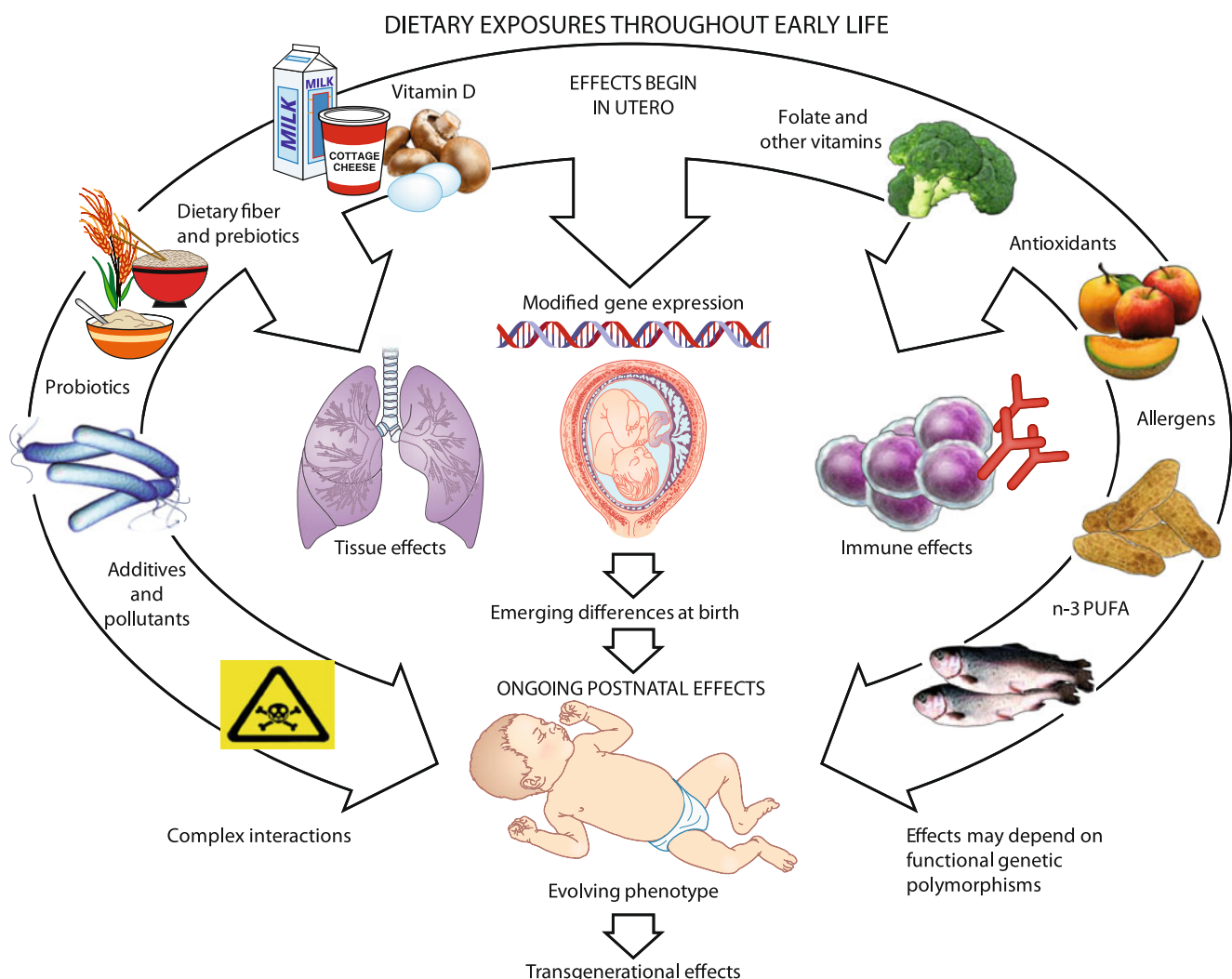


Fig 1 The potential of dietary factors to modify developing immune tolerance and disease risk in the prenatal and postnatal periods. PUFA—polyunsaturated fatty acid

site for this development. Within moments of birth, the infant gut is rapidly colonized by microorganisms, inducing the maturation of the associated mucosal network that comprises more than 70% of the total immune system. This dynamic process is modified by interactions between host-related factors, mucosal barrier mechanisms, local immune activation, and oral exposures. With an increasing array of new environmental antigens, mostly from dietary components and commensal microbiota, host survival depends on a strongly modulated immune “barrier” that prevents unnecessary inflammation to this vast array of generally harmless antigens while on the other hand quickly responding to infectious threats. The complex mechanisms that have evolved to promote tolerance as a default response are still not fully understood [12].

Breast milk, the most essential early nutritional source in the postnatal period, is rich in nutrients and growth factors with immunomodulatory properties, including immunoglobulins, lactoferrin, lysozymes, oligosaccharides, long-chain fatty acids, cytokines, nucleotides, hormones, and antioxidants [13]. It also contains maternal immune cells [13] and antigens derived from the maternal diet. Collectively, these factors appear to play a role in protection from infection and promotion of oral tolerance, although the underlying mechanisms need further study. Animal studies have shown that maternal milk is more tolerogenic than formula milks and that resulting immune tolerance is mediated by CD4⁺ regulatory T cells and dependent on transforming growth factor- β being in maternal milk [14]. Some evidence suggests that continued breastfeeding during introduction of complementary foods may promote tolerance [15], although specific allergy preventive effects have not been confirmed. Still, it remains important to promote breastfeeding for other nutritional and non-nutritional benefits to the mother and child. Because of the intrinsic difficulties in randomizing and double-blinding participants, it will remain challenging to definitively address the inconsistent relationships reported between breastfeeding and allergic disease. Future mechanistic studies of the immunomodulatory properties of breast milk may be helpful in optimizing the development of a tolerogenic environment in the gut.

Specific Dietary Factors and Dietary Patterns

The epidemic rise in allergic disease provides the clearest evidence that the modern environment is not optimal for tolerance development, with gut microbial colonization patterns and early dietary factors clearly implicated in this rising predisposition. This has fueled interest in the role of specific factors and how they may therefore be modified to prevent allergic disease. There is conjecture that a range of dietary immunomodulatory factors (Fig. 1) can promote

tolerogenic conditions in the gut, including polyunsaturated fatty acids (PUFAs), for their effects on T-cell [2, 16] and dendritic cell function [17]; prebiotic oligosaccharides [18–20] and probiotics [21–23], for their effects on both colonization and immune function; and vitamin A (retinoic acid for promoting regulatory T-cell differentiation) [24]. As discussed below, some of these also have been investigated as prenatal and/or postnatal interventions for promotion of oral tolerance and allergy prevention.

Although this discussion focuses on specific nutrients, we emphasize that it is ultimately more meaningful to take a more integrated approach and examine the effects of shifting composite patterns of specific nutrient intakes [25]. Some studies have suggested “dietary patterns” such as the Mediterranean diet to be protective in the development of atopy and wheeze [26–28]. One study suggested dietary effects in pregnancy [28], while another study found no effect of maternal dietary patterns on childhood wheeze [29]. Thus, although we evaluate the effects of dietary factors below, a more holistic approach ultimately will be required.

Polyunsaturated Fatty Acids

One of the most significant modern dietary changes includes an altered balance of PUFAs, particularly long-chain PUFAs. There has been a reduction in anti-inflammatory omega (n)-3 PUFA intakes in favor of increased consumption of relatively inflammatory n-6 PUFAs. Based on the more proinflammatory properties of the n-6 PUFAs (and contrasting anti-inflammatory n-3 PUFAs), this changing PUFA balance is plausibly implicated in the increasing rates of many inflammatory diseases. The immunologic effects of PUFAs are manifold and include the strongly differential effects of n-3 and n-6 PUFAs on eicosanoid metabolites, which mediate or control inflammation, and molecular effects on cell signaling and cytokine production, which may underlie the observed differences in T-cell and monocyte function [30]. More recently, PUFA-mediated differences in the production of resolvins—critical factors in terminating inflammation—also have been described [31]. These observations suggest a likely role of n-3/n-6 PUFA composition in immune development and disease predisposition.

While several observational studies suggest that favorable n-3 PUFA intake or status in childhood protects against the development of allergic disease, others are inconclusive or contradictory [32]. Furthermore, postnatal supplementation with n-3-rich fish oil [33, 34, 35•] as early as birth (D’Vaz et al., unpublished data) has not been effective in reducing allergy development. In pregnancy, when developmental effects are potentially greater, observational studies have generally suggested that n-3 PUFA intake

may reduce the allergy risk in the offspring [36]. Intervention trials using fish oil in pregnancy have also shown some early promise in reducing infant allergies [2, 37, 38]. Although more studies in the area are needed, it remains possible that pregnancy provides a window of opportunity for a role of n-3 PUFAs in beneficially influencing the fetal immune system and increasing the likelihood of infants developing tolerogenic phenotypes. Several large, ongoing studies are anticipated to clarify this more definitively.

Probiotics

The critical role of gut microbiota in the development of immune tolerance [39] has led to huge interest in dietary supplements that promote “favorable” early colonization. The most common approach has been to use probiotics, health-promoting nonpathogenic bacteria that have been shown to exert immune-stimulating effects [40]. At least 14 published trials have assessed the effects of probiotics in primary prevention of allergic disease [41•]. At this stage, slightly more than half of the reported studies have shown a reduction in eczema, while the remaining studies have not. Some evidence also suggests that a probiotic or synbiotic containing *Lactobacillus rhamnosus* may reduce the incidence of eczema in infants at high risk of allergic disease, but no reproducible evidence exists for other probiotics [41•], and the effects of *L. rhamnosus* are not seen in all studies [42]. A recent meta-analysis suggests a preventive effect on eczema, particularly in studies that combine prenatal and postnatal supplementation [43], although exclusive prenatal supplementation was not effective [44•]. One preliminary study suggests that maternal supplementation during pregnancy and lactation (with no direct infant supplementation) may be sufficient [45•]. If confirmed in other settings, this would simplify the administration. The meta-analysis also advised caution based on considerable heterogeneity (in strains, dosages, timing, and delivery of supplementation; study populations; and clinical outcome measures), which makes comparison and interpretation complicated [43].

Notably, no consistent evidence indicates that any probiotics prevent other allergic conditions or sensitization. However, long-term outcomes (including respiratory allergies) of these study cohorts are not satisfactorily evaluated and are limited to two reports [46, 47]. At this stage, there is not enough evidence to recommend probiotics in the prevention or treatment of allergic disease [41•]. Several ongoing clinical trials may provide further insight.

Fermentable Dietary Fiber and Oligosaccharides

Dietary fiber and oligosaccharides are important for gut health, particularly in promoting favorable colonization

[18]. Direct effects on the immune system also have been demonstrated. These undigested dietary components are fermented to produce short-chain fatty acids (SCFAs) with anti-inflammatory properties [48••]. Modern diets with less dietary fiber therefore may be contributing to the epidemic of immune disease by leading to less favorable colonization patterns (which are already implicated in less tolerogenic properties) [49, 50] and by reducing substrates for production of anti-inflammatory SCFAs. Thus, less favorable colonization patterns together with declining intake of dietary fiber also may be implicated in the failure of immune tolerance and the mounting propensity for both inflammatory autoimmune and allergic diseases.

Earlier epidemiologic studies suggested an association between low intake of dietary fiber and allergic conditions [51], and preliminary allergy prevention studies suggest an allergy protective effect of neonatal supplementation with “prebiotic” oligosaccharides [52, 53•]. Direct immunologic effects of oligosaccharides in human studies and animal models also provide a further basis to explore soluble dietary fiber in promoting immune tolerance and prevention of immune disease [19, 20].

Antioxidants

Modern dietary changes additionally include decreasing intake of antioxidants (eg, vitamin C, vitamin E, β -carotene, zinc, and selenium). Lower intake of antioxidant-rich foods has been associated with reduced pulmonary function [54]. Preliminary evidence indicates that antioxidant status in pregnancy may influence susceptibility to allergic disease. Reduced maternal consumption of antioxidant-rich foods and vitamin E has been associated with increased risk of developing childhood wheeze [55], asthma, and sensitization [54]. A recent meta-analysis concluded that higher maternal dietary vitamin E intake was protective against wheeze [56•]. However, because of concerns regarding adverse effects [57], these epidemiologic associations have not been confirmed in intervention studies thus far. Although not designed for allergy prevention, a recent randomized controlled trial reported no improvement in infant respiratory outcome following maternal high-dose vitamin C and E supplementation in the attempt to reduce pre-eclampsia [58]. Rather, infants of the mothers who were given high-dose vitamin C and E had increased health care utilization.

Antioxidant status has documented effects on regulatory T cells [59] and antigen-presenting cells [60]. Theoretically, this could favor development of T-helper type 1 and inhibit T-helper type 2 responses. Maternal antioxidant intake likely influences the fetal antioxidant status, with possible effects on tolerance induction and development of childhood allergy [1]. However, because of the lack of

intervention studies and concerns about adverse effects [57], a healthy, balanced diet rather than specific vitamin supplementation should be promoted at this stage.

Vitamin D

There is growing appreciation that vitamin D may also play an important role in the development of immune tolerance. Vitamin D has immunomodulatory properties, including effects on epithelial cell, B-cell, T-cell, and dendritic cell functions [61]. Higher intake of vitamin D during pregnancy has been associated with reduced wheeze [56•, 62], asthma and allergic rhinitis [63], and eczema [62], although another study observed higher maternal levels increasing infant risk [64]. This was followed by a recent report that cord blood 25-hydroxyvitamin D levels are inversely associated with the risk of respiratory infections and early childhood wheeze [65•]. Notably, an association between maternal intake of vitamin D and the expression of tolerogenic genes in cord blood has also been reported [66•], providing further support to a link between vitamin D status during pregnancy and tolerance induction. Further studies are needed to clarify the role of vitamin D in the induction of immune tolerance and the subsequent risk of developing allergic disease.

Folate

The recent understanding that folate, a dietary methyl donor, can alter gene expression through epigenetic mechanisms has led to emerging interest in the role of this and related dietary nutrients in immune development. Patterns of DNA methylation stably regulate gene expression patterns and are fundamental to cell differentiation. Significantly, because epigenetic changes are transmitted with each cell division, patterns of early gene expression have lasting implications for subsequent development and disease risk and are potentially heritable with transgenerational effects [6].

Animal models demonstrate that maternal supplementation with dietary methyl donors in pregnancy induces hypermethylation of key regulatory genes in lung tissue, with subsequent allergic airways disease in the offspring [3]. In humans, folic acid supplementation during pregnancy has been linked to increased risk of asthma and respiratory disease in infants [67, 68]. This was followed by a report from an observational study that higher folate status in pregnancy is associated with increased risk of asthma at 3 years of age [69•]. There have been links between folate status in the postnatal period and allergic disease, but if anything, folate was noted to be protective [70]. This provides further evidence that the effects of dietary exposures may vary with developmental stage.

Currently, no specific changes to the recommendations for folate supplementation in pregnancy can be given based on the results of these observational studies. However, there has been an urgent call for additional studies to address the role of folate in pregnancy.

Dietary Allergens

It is becoming increasingly clear that allergens are not driving the allergy epidemic, and it seems more likely that this is due to other multifaceted environmental changes. Previous food allergen avoidance strategies have been ineffective, probably because complete avoidance is impossible and sensitization may still occur through other, less tolerogenic routes (eg, the skin) [71]. With the understanding that specific oral tolerance is an antigen-driven process, there is now focus on earlier, regular exposure to allergenic foods to promote tolerance.

Most current recommendations reflect the lack of evidence that delaying the complementary feeding (beyond 6 months) or avoidance of specific “allergenic” foods (eg, cow’s milk, eggs, peanuts, tree nuts, and seafood) prevents allergic disease [72, 73]. Based on this and emerging evidence that food allergen avoidance may even lead to an increase in food allergy [72, 74•], eczema [75, 76], and sensitization [77•], most expert organizations now recommend introduction of complementary foods from 4 to 6 months of age, with no specific delay in “allergenic foods” [73, 78–80]. Some reports suggest that starting complementary foods before 3 to 4 months of age may increase the risk of allergic disease [81], possibly because colonization is not fully established and the gut is more permeable.

The first randomized controlled trials to investigate whether early introduction of specific allergenic foods will induce tolerance and reduce the risk of allergic disease are now under way. The results are expected to provide further understanding of the role of early allergen exposure in tolerance induction. Whatever the results, it remains important to interpret the findings in the wider context of other modern environmental changes. Ultimate approaches will be those promoting an optimal “tolerogenic” microenvironment in the gut during the time of first allergen encounter, again stressing the critical role of gut microbial colonization, breastfeeding, and other dietary immunomodulators.

Genetic and Environmental Interactions: Inferences for Future “Personalized” Dietary Interventions

Emerging evidence indicates that genetic and environmental interactions may explain individual variability in

response to dietary interventions. Preliminary studies demonstrated functional polymorphisms in the metabolic pathways of several of the dietary factors that have been reviewed above, including folate [82] and fatty acid metabolism [83], although more studies are needed. For example, variations in folate metabolism conferred by the MTHFR (C677T) genotype have been associated with allergic disease [82] and asthma [84], although not unambiguously [85].

Functional genetic polymorphisms confer individual susceptibility to disease, but they can also confer differences in the biological effects of an environmental exposure. Environmental changes that increase the risk of allergic disease in a subgroup of individuals (ie, with a specific functional genetic polymorphism) may have no effects (or reverse effects) in other individuals. The inference for dietary interventions is that effectiveness may vary with specific genetic polymorphisms, leading to the concept of *personalized dietary intervention*. This implies that ideal interventions to prevent disease will need to be individualized according to genetic “profile.” Further adding to this complexity, the effect of a genetic polymorphism on disease risk can also vary with the level of a specific environmental exposure. Although not related to diet, an illustrative example of this is seen with microbial exposure in which genetic polymorphisms confer different risk depending on whether children are raised in a “low” versus a “high” microbial burden environment [86]. Similar complex interactions with dietary factors could have implications for diet supplements. For example, increasing levels of specific dietary components could create unexpected or paradoxical relationships between genetic polymorphisms and disease risk. This highlights the need to regard interventions cautiously, with consideration of these potentially complex interactions.

Conclusions

The developing immune system is highly dependent on dietary nutrients and therefore is susceptible to dietary changes during the prenatal and postnatal period. Mounting evidence indicates that complex changes in dietary factors with modern diets may be contributing to the rising rates of immune disease. Despite the fact that there are still uncertainties and contradictions in the literature, these do not mean that dietary factors do not have significant effects. Rather, this is more likely to reflect our inadequacy to study diet in ways that take into account the complexity of interactions. Dietary factors need to be studied in ways that allow for analysis of these interactions as well as those with other modern environmental exposures and genetic factors. This may ultimately lead to personalized early interventions that are tailored according to genetic predisposi-

tion. It remains highly likely that dietary interventions will play a key role in the promotion of immune tolerance and in prevention of immune disease.

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- Of major importance

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