Published in final edited form as:

Semin Immunopathol. 2012 September ; 34(5): 655–669. doi:10.1007/s00281-012-0323-y.

Early Life Precursors, Epigenetics, and the Development of Food Allergy¹

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Abstract

Food allergy (FA), a major clinical and public health concern worldwide, is caused by a complex interplay of environmental exposures, genetic variants, gene-environment interactions, and epigenetic alterations. This review summarizes recent advances surrounding these key factors, with a particular focus on the potential role of epigenetics in the development of FA. Epidemiologic studies have reported a number of non-genetic factors that may influence the risk of FA, such as timing of food introduction and feeding pattern, diet/nutrition, exposure to environmental tobacco smoking, prematurity and low birthweight, microbial exposure, and race/ethnicity. Current studies on the genetics of FA are mainly conducted using candidate gene approaches, which have linked more than 10 genes to the genetic susceptibility of FA. Studies on gene-environment interactions of FA are very limited. Epigenetic alteration has been proposed as one of the mechanisms to mediate the influence of early-life environmental exposures and gene-environment interactions on the development of diseases later in life. The role of epigenetics in the regulation of the immune system and the epigenetic effects of some FA-associated environmental exposures are discussed in this review. There is a particular lack of large-scale prospective birth cohort studies that simultaneously assess the inter-relationships of early life exposures, genetic susceptibility, epigenomic alterations and the development of FA. The identification of these key factors and their independent and joint contributions to FA will allow us to gain important insight into the biological mechanisms by which environmental exposures and genetic susceptibility affect the risk of FA, and will provide essential information to develop more effective new paradigms in the diagnosis, prevention and management of FA.

Keywords

Genetics; Environmental Exposure; Epigenetics; Food allergy

Introduction

Food Allergy (FA), defined as “an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food” in the recent National Institute of Allergy and Infectious Diseases-sponsored expert panel report[1], is emerging as a major clinical and public health problem not only in the U.S., but worldwide[2, 3]. FA affects more than 1-2% but less than 10% of the population[4]. More significantly, FA is the most frequent single cause of emergency room visits for anaphylaxis. FA impacts not only

¹This article is published as part of the Special Issue on Food Allergy [34:6]

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the affected individual but also those providing care and nourishment for the food-allergic individual, thus its effect on family and society is enormous[5-8]. Strict allergen avoidance, which is exceedingly difficult, is the current approach to the management of FA.

The prevalence of FA may vary by age, geographic location and possibly race/ethnicity[9]. While conclusive data are lacking, many experts believe that the actual prevalence of FA has risen substantially over the past decade, in parallel with the rise previously seen for other atopic conditions [2, 3, 10, 11]. Although the cause for the rise in prevalence remains unclear, it may partly be due to changes in environmental exposures. To date, while epidemiologic studies have linked a broad range of early-life environmental factors to the risk of FA, these findings await further replication in independent studies. Recent advances in environmental epigenetics research hold great potential to explain how early-life environmental exposures affect the incidence of diseases later in life. In this review, we will summarize pertinent literature on early-life environmental exposures and genetic susceptibility for FA, with a particular focus on potential epigenetic alterations related to the immune system and the development of FA. We will also discuss critical knowledge gaps and future directions in the field, as well as the need to integrate multi-level-factorial variables and apply cutting-edge science and technology in FA research.

A Critical Time Window to Understand the Development of Food Allergy

Most cases of FA develop in the first few years of life, suggesting that early life is a critical window for the development of FA. While production of Immunoglobulin E (IgE) in the first year of life is cyclical, IgE titers trend positively in those who are later sensitized[12]. Also, children who go on to develop allergy by age 5 have higher T_H2 cytokine responses by age 1 year[12], suggesting that allergen-specific immunologic responses within the first year of life correlate with the development of allergy. The prenatal period also is believed to be a critical window for programming, which is supported by recent findings on the relationships between maternal environmental exposures (such as smoking, diet, and microbe exposure) during pregnancy and the risk of FA in offspring[13-16]. Furthermore, infants who later developed egg sensitization were found to release less interferon-gamma and less interleukin (IL)-10 from PHA stimulated cord blood mononuclear cells[17]. While controversy exists concerning the relative impact of pre- vs. post-natal events, early life is clearly a time when immune deviation and atopy are determined.

Key Non-Genetic Factors associated with the Development of Food Allergy

There is an increasing number of epidemiologic studies focused on the relationships between environmental exposures and the risk of FA during childhood and adolescence, however, most of these studies have led to inconsistent findings. Lack[18] reviewed the possible non-genetic risk factors for the development of FA and came out several hypothesis, which include: (1) dual-allergen-exposure hypothesis, which posits that food sensitization (FS) can occur through low-dose cutaneous exposure, and that early consumption of food protein induces oral tolerance; (2) hygiene hypothesis, which suggests that early exposures to microbial pathogens could protect against subsequent atopic diseases; (3) dietary fat hypothesis, which suggests that higher intakes of ω -6 and lower intakes of ω -3 fatty acids lead to increased production of prostaglandin E2 (PGE2), and thus the development of FA; (4) antioxidant hypothesis, which stresses the anti-inflammatory effects of antioxidants in allergic diseases; and (5) vitamin D hypothesis, which takes two opposite forms: the vitamin D excess hypothesis, which suggests that vitamin D is a risk factor for allergy, while the vitamin D deficiency (VDD) hypothesis argues the opposite. The following paragraphs summarize the recent findings on the relationships between non-genetic factors and the risk of FA.

Feeding Pattern and the Timing of Food Introduction

The ability to avoid FA by manipulating the diet during pregnancy or early infancy remains controversial. Many studies have investigated the role of breastfeeding on the risk of atopy and FA, with results varying from a protective[19-21] or neutral effect[22-26] to a disease-promoting effect[27-29]. The review by Host et al. in 2008 supports the effectiveness of dietary regimen in preventing allergic diseases, including exclusively breastfeeding for at least 4-6 months, or, in the absence of breast milk, formula with documented reduced allergenicity for at least the first 4 months, combined with avoidance of solid food and cow's milk for the first 4 months[30]. However, the American Academy of Pediatrics has withdrawn their recommendations about food avoidance during pregnancy and early infancy, and replaced them with comments regarding the lack of current evidence related to delaying the timing of the introduction of complementary foods beyond 4 to 6 months of age in preventing the occurrence of atopic disease[31]. Some other studies have shown that prolonged breastfeeding and/or delayed introduction of these food allergens may increase the risk of FA. For example, Koplin et al. found that delayed introduction of egg appears to be a risk factor for egg allergy, although no association was found for duration of breastfeeding and age at introduction of the solid food[32]. Similar results were found between the introduction of milk and milk allergy[33], the introduction of peanut and peanut allergy[34], as well as the introduction of cereal grain and wheat allergy[35].

The inconsistent results for the relationships of breastfeeding and the timing of food introduction with the risk of atopy and/or FA may partly be due to the fact that these relationships are modified by other factors including a child's age[36], gender[37], family history of allergy[37, 38], the existence of other allergic diseases[39, 40] and genetic backgrounds[41]. In a cohort composed of 594 maternal-infant pairs, Joseph et al. reported that complementary food introduced at <4 months of age was associated with a reduced risk of peanut sensitization by age 2 to 3 years, but only for children with a parental history of asthma or allergy[40]. Our study showed that, in a family-based Chicago Food Allergy cohort, later formula and later solid food introduction was associated with a lower risk of FA in children without eczema, but not in children with eczema[39]. In our inner-city, multi-ethnic prospective Boston Birth Cohort (the BBC), we reported that prolonged breastfeeding was associated with increased FS, and that such a positive association was dependent on functional genetic variants in the *IL12 receptor beta 1 (IL12RB1)*, *thymic stromal lymphopoietin (TSLP)*, and *toll-like receptor (TLR) 9* gene. This study underscores the importance of evaluating the effects of breastfeeding in the context of individual genetic backgrounds[41].

Nutritional/Dietary Factors

Vitamin D is increasingly recognized as an important regulator of immune response[42-44]. It may have a number of tolerogenic effects on dendritic cells (DCs)[45] and on the differentiation of T-regulatory (T-reg) cells[46, 47], and may have direct effects on B cells to promote IL-10 production and decrease IgE production[48]. Vitamin D has been proposed to mediate the observed associations between season of birth and childhood FA[49] and/or food-induced anaphylaxis[50], as there is inadequate UVB intensity for the synthesis of active vitamin D in winter. The role of vitamin D has also been indirectly reflected by geographic studies, which indicate that a higher prevalence of allergic disease occurs in areas further away from the equator[51-55]. This evidence, however, was not completely supported by studies using supplemental intake and/or a direct measurement of plasma/serum vitamin D level. Elevated serum 25(OH)D was not associated with sensitization to common aeroallergens and food allergens (milk and egg) in the National Health and Nutrition Examination Survey (NHANES) III[56]. In comparison, results from the

NHANES in 2005-2006 showed that 25(OH)D deficiency (<15 ng/mL) was associated with increased sensitization to peanut, ragweed and oak when compared with sufficient vitamin D levels of >30 ng/mL[57]. Nwaru et al. found that maternal intake of vitamin D during pregnancy was inversely associated with FS[16]. Gale et al. found that maternal 25(OH)D in late pregnancy was positively associated with eczema and asthma when children were 9 months and 9 years old, respectively[58]. These conflicting results may support two opposite hypotheses. Wjst postulated that excess vitamin D might be associated with increased risk of allergic diseases based on its effects on the T_H1/T_H2 shift to T_H2 dominance, parallel patterns of increased vitamin D supplementation and a “Western lifestyle” [59, 60]. In contrast, Litonjua and Weiss[61] postulated that vitamin D might protect against allergies because both VDD and allergic diseases are associated with African American race, obesity, higher latitude, and immigration to westernized countries, which should not be considered a coincidence.. Additionally, 1,25(OH)₂D has been demonstrated to maintain mucosal barrier integrity [62], and thus, lower vitamin D status could lead to an exposure to abundant food allergens. Our recent study in the BBC reported that cord blood VDD (<11 ng/ml) increased the risk of FS only among children carrying the CC/CT genotype in the *IL4* gene (rs2243250), which may indicate that the relationship between vitamin D and FS may be modified by genetic variants [63].

Dietary fat is another nutritional factor that may play an important role in regulating the immune system. It has been suggested that ω-6 long-chain polyunsaturated fatty acids (LC-PUFAs) may lead to the production of PGE₂, which can inhibit the production of T_H1 cytokines[64] and promote synthesis of T_H2 cytokines[65]. In comparison, ω-3 LC-PUFAs may inhibit PGE₂ synthesis. A decrease in consumption of ω-3 or ω-3/ω-6 LC-PUFAs has been proposed to account for the increased prevalence of allergic diseases, which has been supported by some but not all studies. For example, ω-3 LC-PUFAs supplementation during pregnancy is reported to be associated with decreased mRNA levels of T_H2-related molecules in the fetus[66]. Kull et al. in a large prospective birth cohort (n=4089), found that regular fish consumption (the main source of -3 LC-PUFAs) during the first year of life was associated with a decreased risk of allergic disease and FS by 4 years of age[67]. A randomized placebo-controlled trial, in which 145 pregnant women received daily maternal supplementation with either 1.6 g eicosapentaenoic acid (EPA) and 1.1 g DHA (ω-3 LC-PUFAs group) or a placebo from the 25th gestational week to an average of 3-4 months of breastfeeding, showed that infants in the ω-3 LC-PUFAs group had a lower prevalence of FA than those in the placebo group during the first year of life[14]. Inconsistently, a multicenter, randomized controlled trial showed that the incidence of parent-reported FA over the first 18 months of life was comparable in preterm infants (>33 weeks' gestation) who were breastfed by the mother taking either tuna oil (high-docosahexaenoic acid [DHA] diet) or soy oil (standard-DHA diet) [68]. A study by Ullam et al. found that early introduction of fish had no influence on fish allergy[69]. The meta-analysis conducted by Anandan also suggests that ω-3 or ω-6 LC-PUFAs may be unlikely to play an important role in preventing FA and/or other allergic diseases[70].

Antioxidant supplements including vitamin C, E, and β-carotene. Vitamin E is reported to suppress IL-4 levels in human peripheral blood T cells by blocking the binding of transcription factors to two important IL-4 promoter binding sites[71]. Data from the NHANES III showed that allergic skin sensitization were less common in participants with higher serum level of Vitamin E[72]. However, another study reported that vitamin E intake was associated with an increased risk of allergic sensitization at age 5[73]. Sato et al. demonstrated that mice fed β-carotene produced more T_H1 cytokines and less T_H2 cytokines than those in the control group, suggesting that β-carotene may contribute to T_H1/T_H2 balance, which leads to reduced IgE production[74]. Using a semi-quantitative food frequency questionnaire, β-carotene intake was found to be associated with a reduced risk

of allergic sensitization at age 5, and with decreased total IgE level[73]. A higher concentration of vitamin C in breast milk also was associated with a reduced risk of atopy in infants[75]. Children who reported taking multivitamins before or at age 4 years had a decreased risk of FS[76]. Early vitamin supplementation also was significantly associated with a decreased risk of FA in exclusively formula-fed children[77]. Other nutritional/dietary factors, such as vitamin A, zinc and a Mediterranean diet have been reported to protect against asthma[78]. Hollingsworth et al. reported that in mice, a maternal diet supplemented with methyl donors may exacerbate the severity of allergic airway disease[79]. However, several studies in humans reported no associations of maternal folic acid supplementation during pregnancy with atopy[80], asthma[81], or FA[82]. The associations of these dietary factors with the risk of FA warrant further investigation.

Environmental Tobacco Smoke (ETS)

Kulig et al. reported that children pre- and post-natally exposed to ETS had a significantly higher risk of FS during the first 3 years of life[15]. Lannero et al. demonstrated that, although there was no association for maternal smoking during pregnancy, a dose-response effect was revealed between parental smoking in early infancy and an increased risk of IgE sensitization to inhalant and/or food allergens[83]. In a German prospective multicenter birth cohort, Keil et al. found that maternal smoking during pregnancy significantly increased the risk of allergic sensitization in children with one or two allergic parents[84]. Inconsistently, Raheerison et al. reported that children with exposure to maternal ETS during pregnancy were at a higher risk for sensitization to house dust mites, but not for FS[85]. Strachan et al. reported that parental smoking, either before or immediately after child birth, is unlikely to increase the risk of allergic sensitization in the child [86]. In a Finnish population, maternal smoking was even found to be associated with a decreased risk of cow's milk allergy in infants up to 2 years of age[87].

Prematurity and Low Birthweight

Prematurity is proposed to be associated with increased intestinal permeability and increased food antigen uptake[88, 89], which may lead to an increased risk of IgE-mediated FA in premature children. Very low-birthweight (LBW) preterm infants also are considered to have a wide range of immature digestive and absorptive functions, which might cause increased macromolecular absorption[90], leading to FA. Lucas et al. reported that LBW infants who received cow's milk formula developed latent systemic sensitization more rapidly than infants born at term[91]. A recent study in a national sample of U.S. children showed that children aged 6-12 years who were born with very LBW were more likely to have reported FA compared to children with normal birthweight[92]. However, findings from other studies have questioned the role of prematurity/LBW in the development of FA. Martino et al. compared 80 preterm infants with 80 sex-matched and age-matched full-term infants at a mean age of 16 months and found no difference in frequency of positive skin tests to foods between the two groups[93]. In the 1995 Manitoba Birth cohort composed of 13,980 children, Liem et al. found no association for prematurity and LBW with the risk of FA in childhood[94]. Similarly, in the BBC, we found that prematurity was associated with an increased risk of recurrent wheezing, while no such associations were found for either FA or eczema[95]. In a Japanese study, the prevalence of FA in LBW infants (8.1%) was found to be significantly lower than that in infants with normal birthweight at 18 months of age (11.2%)[96].

Microbial Exposure and the Hygiene Hypothesis

The revised hygiene hypothesis proposes that changes in the intestinal colonization pattern during infancy are an important reason for the increased prevalence of allergy[97, 98]. These

changes can be caused by Cesarean delivery, presence of siblings, antibiotic use, child care and pet/farm exposure. From a German prospective multicenter birth cohort of 2500 infants, Negele et al. reported a significant positive association between Cesarean delivery and specific food IgE[99]. The meta-analysis by Bager et al. showed that Cesarean delivery was associated with increased risk of FA and other allergic phenotypes[100]. Metsala et al. found that Cesarean delivery was associated with increased risk of cow's milk allergy in infants up to 2 years of age in the Finnish population[87]. Similar results were found by other studies for milk allergy[101] and egg allergy[102]. Using a logistic regression model, Dioun et al. found that being first born was an independent predictor of FA[103]. However, another study showed that having an older brother may delay the onset of IgE sensitization but may not prevent IgE sensitization[104]. Treatment with antibiotics in early infancy was also found to contribute to an increased risk of atopy in children[105]. Pet exposure at 0-2 years and at 0-5 years may protect against IgE sensitization until 5 years of age[106]. In an animal model, Lewis et al. provided direct evidence that an early-life farm environment, by affecting microbial colonization, is associated with both local development of regulatory components of the mucosal immune system and immune responses to food proteins at weaning[107]. Ege et al. showed that prenatal exposure to stables may significantly protect against atopic sensitization and upregulate the expression of receptors of the innate immune system including *TLR2*, *TLR4* and *CD14*[13]. Schaub et al. reported that maternal farm exposure during pregnancy increases the number and function of cord blood T-reg cells associated with lower T_H2 cytokine secretion and lymphocyte proliferation on innate exposure[108], all suggesting that farm environment exposure may affect the susceptibility of FA.

Sleep Duration

In school-age children (especially adolescents), sleep duration has decreased over the last several decades[109, 110]. This decrease has occurred in parallel with an increase in both obesity[111] and FA[112, 113]. Epidemiologic studies have linked altered short sleep duration to systematic inflammation[114, 115] and immune regulation[116]. Van Leenwen et al. reported that sleep restriction resulted in an elevated production of pro-inflammatory cytokines[117] (IL-1 β , IL-6 and IL-17), which may play important roles in immune defense[118]. Indeed, short sleep duration may even set up a positive feedback loop with inflammation since IL-13 and IL-4 given exogenously act to decrease sleep in animal models[119, 120]. In a Chinese twin cohort, we were the first to investigate the potential relationship between sleep duration and allergen sensitization, and we demonstrated that short sleep duration was associated with increasing sensitization to food allergens and aeroallergens in a dose-response manner[121]. These findings require further validation.

Antacid Medications

Antacid medications may increase the gastric pH and substantially interfere with the digestive function of the stomach, leading to the persistence of labile food protein during gastric transit, which may have a major effect on the development of FA[122]. Results from a mouse model suggest that the use of antacids lead to an enhanced risk for FA[123-126]. In 152 adult patients, Untermayr et al. reported that the relative risk to develop food-specific IgE after antacid treatment was 10.5 (95%CI: 1.4-76.5)[127].

Race/Ancestry

Non-White race[128] and non-Hispanic Black race[129, 130] have been reported as potential risk factors for FA. In telephone surveys, shellfish allergy was reported at a significantly higher rate among Black subjects than White subjects (3.1% vs. 1.8%)[130]. Yet, self-identified ethnicity and reported origin of parents and grandparents is imprecise

compared to a genetic estimation of individual ancestry[131, 132]. The use of ancestry informative markers (AIMs) allows genetic ancestry to be easily and inexpensively estimated in admixed populations such as African Americans and Latinos[133-135]. In the BBC, we previously reported that African ancestry (estimated based on 150 AIMs markers) was associated with an increased risk of FS, and with an increased odds of egg sIgE levels 2 kUA/L and peanut sIgE levels 5kUA/L[136].

Other Factors

Boys appear to be at a higher risk for FA than girls[128, 129]. *Obesity* may be an inflammatory state associated with increased risk for FA[137]. *Alcohol consumption* is a documented risk factor for increased specific IgE levels against food antigens in adults[138]. *Air pollution exposure* during the first year of life was associated with an increased risk of FS at year 8[139]. In a nested case-control study in Finland composed of infants up to 2 years of age, low socioeconomic status, high maternal age, number of previous deliveries and/or *previous pregnancies* were all associated with the risk of cow's milk allergy[87]. In the BBC, we found that *gestational diabetes* was associated with both FS and cord blood IgE independent of fetal growth and maternal obesity[140]. A recent study further reported that *U.S.-born* children and adolescents had higher odds of FS than foreign-born children, and among the U.S.-born group, children of immigrants were at the highest risk[141].

Genetics and G×E Interactions associated with the Risk of FA

As we reviewed previously [142], FA is under strong genetic control, while the genetic variants accounting for the susceptibility of FA remain largely unknown. Candidate gene association studies, which have focused on one or more candidate genes selected based on an understanding of biological mechanisms underlying the disease, represent the main approach used to map genetic variants associated with FA. One of the major limitations of these candidate gene association approaches is that it depends on *a priori* knowledge to select promising candidate genes, which ultimately is unsuccessful in identifying novel genetic variants relevant to complex traits. To date, more than 10 genes, have been linked to FS and/or FA in at least one single study. These genes include the HLA class II gene family (*HLA-DRB1*[143, 144], *HLA-DQB1*[143], *HLA-DPB1*[143]), *CD14* [145], *forkhead box P3*(*FOXP3*)[146, 147], signal transducer and activator of transcription 6 (STAT6)[148], *serine peptidase inhibitor, kazal type 5* (*SPINK5*)[149], *IL10*[150], *IL13*[151], *NLR family, pyrin domain containing 3*(*NLRP3*)[152], and *filaggrin* (*FLG*) genes[153], most of which may be involved in antigen presentation and/or a shift of the immune system towards a T_H2 response. Further replications in different populations are need for these genes. We expect that the use of the state-of-art, hypothesis-free genome-wide association (GWA) approach in FA research will potentially lead to a steeper increase in the identification of novel genetic variants associated with the susceptibility of FA.

It has been recognized that the process of identifying the genetic markers of human complex traits is highly time-consuming and labor-intensive, which, even worse, will potentially lead to a small number of confirmed susceptibility genes, leaving a long list of genes with inconclusive findings. One potential explanation for these difficulties might be the presence of gene-environment and/or gene-gene interactions. A few studies have reported that the genetic susceptibility of atopy and/or allergic phenotypes is dependent on environmental exposures such as birth order[154], prenatal or postnatal exposure to ETS[155, 156], air pollution[157, 158], day care[159], diet[41, 63] and microbial exposures[160-164]. In comparison, only limited studies have been designed and conducted to particularly focus on FS and/or FA. For example, the *GSTP1* Ile105Val polymorphism has been shown to modify the effect of air pollution on allergic sensitization to inhalant and/or food allergens[157]. In

addition, our group recently reported that breastfeeding was associated with an increased risk of FS, and that this effect was significantly modified by genetic variants in the *IL12RB1* (rs425648), *TLR9* (rs352140) and *TSLP* (rs3806933) genes, individually. More importantly, we found that the interaction between the combined genotypes of the 3 SNPs and breastfeeding on FS was even stronger[41]. In the same cohort, we also found that VDD significantly interacted with the *IL4* gene polymorphism on the risk of FS. Similar but weak interactions were also found for SNPs in the *MS4A2* (rs512555), *FCER1G* (rs2070901), and *CYP24A1* genes; and when all four SNPs were simultaneously considered, a strong gene-VDD interaction was evident[63]. An even smaller number of studies have been carried out to explore the role of gene-gene interaction on the susceptibility of FS and/or FA. Liu et al. reported that, among unrelated German children from a multicenter atopy study, the effect of *IL13*-1112TT genotype on FS was modified by polymorphisms in the *IL4* receptor alpha (*IL4RA*) gene[151]. Clearly, based on the important evidence uncovered through these limited studies, further studies to explore the role of G×E and G×G interactions in determining FA will help to elucidate the mechanisms through which genes and environment work together to determine the risk of FA.

Epigenome: An Epicenter for Understanding Human Health and Disease

Epigenetic modifications, which are heritable changes in gene expression other than those in the DNA sequence[165, 166], fall into three main categories: *DNA methylation*, a covalent modification at the carbo-5 position of cytosine in the CpG dinucleotide; *histone modifications*, which affect alterations in nucleosomal packaging and high-order folding of chromatin; and *aberrant expression of microRNAs*, which is capable of post-transcriptionally regulating the expression of a cohort of cognate target genes[167]. The epigenome can change and adapt to environmental stimuli over a relatively short time period, and is also subject to epigenetic ‘drift’ over the life-course in response to both environmental and stochastic factors[168]. The plasticity of the epigenome has been demonstrated in many elegant models showing how variation in early life environmental exposure can profoundly alter the phenotype of genetically-identical offspring through epigenetic effects[169, 170]. Both animal models and human studies implicate the intrauterine period as a sensitive time for the establishment of epigenetic variability[169, 171, 172], which in turn influences risk for a range of disorders that develop later in life. There is growing recognition that epigenetic mechanisms are critical to normal human development and play an important role in complex human diseases[173-175]. Two of the most comprehensively studied epigenetically-regulated phenomena in mammals are genomic imprinting and X-chromosome inactivation.

Immune Development is under Epigenetic Regulation

The kinetics and balance of naïve CD4⁺ T-cell differentiation into T_H1 or T_H2 effector cells is critical to the development of FA, since a relatively T_H2-skewed status predisposes an increased risk of allergy[176]. A growing body of studies support that T_H2 cell differentiation is under epigenetic regulation[177-179][180-184]. Methylation of the *IFNG* gene promoter, which can be reversed with a DNA methyltransferase (DNMT) inhibitor *in vitro* and *in vivo*[177], is the main epigenetic control of T_H1 lineage commitment. CpG sites -295, -186, and -54 upstream to the transcription start site of the *IFNG* promoter in cord CD4⁺ T-cells were demethylated under T_H1-polarizing conditions, whereas the majority of these sites were methylated under T_H2-polarizing conditions[178]. After allergen sensitization/challenge, DNA methylation at the *IFNG* promoter was significantly increased, which was correlated with decreased *IFNG* cytokine expression[177], leading to a T_H2-skewed response. In comparison, demethylation of T_H2-associated cytokines, such as IL-4, may be critical to T_H2 lineage commitment. Lee et al. reported that the 5’ region of the IL-4

locus was hypermethylated in naïve T-cells and became specifically demethylated in T_H2 cells[179]. Among the four Dnase I hypersensitive sites in the T_H2 cytokine locus control region, DNase I hypersensitive site 7 undergoes rapid, Th2-specific demethylation on TCR stimulation[180]. DNA methylation is also involved in STAT6 expression in human T-cells[185], which is an important transcriptional factor implicated in the T_H2 commitment linkage. Current evidence also indicates that DNA hypomethylation is a prerequisite for *FOXP3* expression and T-reg differentiation[181-183]. The level of *FOXP3* demethylation in cord blood is associated with the more efficient suppressive capacity of T-reg cells, and is positively correlated with Th2 cytokines (IL5 and IL-13) following LpA-stimulation[184].

The role of histone acetylation/deacetylation in regulating T-cell development and function has been previously reviewed[186, 187]. Multiple histone deacetylase (HDACs) that regulate chromatin remodeling, gene expression and protein function are expressed in Foxp3+ T-reg cells. Administration of an HDAC inhibitor *in vivo* may lead to increased *FOXP3* gene expression and a suppressive function of T-reg cells[188, 189]. Recent studies also support the involvement of microRNAs in regulating the immune system[190-193]. For example, miR-146, an NF-kappaB-dependent gene, is involved in the negative regulation of TLRs and cytokine signaling[190]. miR-155 may play a role in the *in vivo* control of specific differentiation processes in the immune response[191]. This gene is overexpressed in patients with atopic dermatitis, and may contribute to chronic skin inflammation by increasing the proliferative response of Th cells through down-regulating the production of CTLA-4[192]. miR-126 suppresses the effector function of Th2 cells and the development of allergic airway disease[194]. Other miRNAs, such as miR-21[195], miR-181a[196], miR-133b[197] and miR-206[197] may also play a role in the regulation of immune cell development and function.

Limited studies are available that directly investigate the associations between epigenetic alterations and allergic phenotypes. Pascual et al. found that three characterized populations, including house dust mite (HDM) allergic subjects, and aspirin-intolerant asthmatics and controls, had different methylation patterns at limited numbers of loci in CD19+ B lymphocytes. Among these loci, *CYP26A1* is one of the genes that may play a role in the immune system[198]. In mice, Liu et al. demonstrated that altered methylation in two genes, *IL-4* and *IFNG*, was significantly correlated with a change in IgE levels. Breton and colleagues were the first to study DNA methylation levels in the asthma-specific candidate genes, and demonstrated that DNA methylation levels in the *arginase* gene, but not the *nitric oxide synthase* gene, were inversely associated with exhaled nitric oxide in children with asthma, suggesting a possible role of DNA methylation in the regulation of nitric oxide production[199]. Consistent differences in methylation and expression patterns were also observed for the prostaglandin D2 receptor gene between asthmatic patients and controls[200]. No studies have directly investigated the role of epigenetics in FA.

Epigenetics as a Potential Mechanistic Link between Environmental Exposures and FA

Epigenetic alterations are among the mechanisms by which prenatal and early-childhood environmental exposures affect disease risk later in life. Such environmental stimuli include diet/nutrition[201-204], xenobiotic chemicals[205, 206], maternal behavior[207], tobacco smoke[208, 209], and psychosocial stress[210], some of which are the potential risk factors of atopy and FA. Despite the lack of direct evidence, our current understanding of environmental epigenetics supports the hypothesis that epigenetic alterations are one of the mechanisms mediating the effect of pre- and post-natal environmental exposure on the development of FA. Below we summarize the findings regarding the epigenetic influences associated with the environmental risk factors of FA.

Nutrition/Diet

Dietary methyl donors and co-factors, such as folic acid, betaine, vitamins B12, B6, B2, and zinc, are necessary to one-carbon metabolism, which provides the methyl group for DNA methylation. Hollingsworth and colleagues reported that in mice, *in utero* supplementation with methyl donors is associated with altered DNA methylation of 82 gene-associated loci and decreased transcriptional activity. One of the genes was runt-related transcription factor 3, which may negatively regulate allergic airway disease. This study strongly suggests that dietary factors can modify the heritable risk of allergic airway disease through epigenetic mechanisms during a vulnerable period of fetal development in mice[79]. It remains unknown whether other dietary factors, such as vitamin D, fatty acids and dietary antioxidants, act on immune function and/or the development of FA via epigenetic mechanisms.

Exposure to ETS prenatally has been linked to aberrant global methylation in the placenta and cord blood, as well as in children and adults by several[208, 211-213] but not all[214] studies. In buccal cells of 348 children, Breton et al. reported that children who are prenatally exposed to ETS may have aberrant global and gene-specific DNA methylation levels[208]. Among the 8 genes with differential DNA methylation levels between exposed and non-exposed children, *AXL* and protein tyrosine phosphatase, receptor type, O (*PTPRO*) genes were further validated using pyrosequencing[208]; however, it is unclear whether these two genes are involved in the development of the immune system. Exposure to ETS has also been found to reduce HDAC2 expression and HDAC activity, which may account for the enhanced expression of inflammatory mediators (GM-CSF, IL-8 and TNF α) by ETS[215]. This study may indirectly indicate an epigenetic mechanism linking exposure to ETS and FA since TNF α and IL-8 are involved in the regulation of the immune/inflammatory mechanism[215].

Microbial Exposure and the Hygiene Hypothesis

Although further validation is needed, low microbial exposure during early life has been proposed to increase the risk of allergic disease by reducing demethylation of the *IFNG* gene of naïve T-cells[216]. A recent study by Brand et al. showed that asthma-protective effects by prenatal A lwoffii F78 exposure were dependent of altered *IFNG* production, and that such prenatal exposure may be associated with a significant change in H4 acetylation at the *IFNG* and *IL4* promoters, which were positively associated with IFN- γ and *IL4* protein level[217]. Additionally, offspring of mothers with farm milk exposure during pregnancy were found to have increased *FOXP3* demethylation; in parallel, cord blood T-reg cell counts in these offspring were increased with maternal farming exposure and associated with higher *FOXP3*[108].

Air Pollution

It is also likely that the effects of pollutants on immune function are mediated by epigenetic modification. Exposure to black carbon, a tracer of traffic particles, has been linked to decreased DNA methylation of long interspersed nucleotide element -1, but not of Alu repeat elements, although whether such a change could affect immune function and/or allergic susceptibility remains to be determined[218]. Perera et al. reported that prenatal exposure to polycyclic aromatic hydrocarbons, measured from backpacks worn by pregnant women, was positively and significantly associated with methylation of the 5'-CpG islands in the acyl-CoA synthetase long-chain family member 3 (*ACSL3*) gene, a member of the *ACSL* gene family which encodes key enzymes in fatty acid metabolism[219]. Due to the anti-inflammatory and immune-modulating effect of several fatty acids such as dietary ω -3 and ω -6 LC-PUFAs, it is possible that hypermethylation of this gene in T helper cells may affect the susceptibility to allergy. A mouse model undergoing intranasal sensitization to

A. fumigatus demonstrated increased total IgE resulting from combined exposure to inhaled diesel exhaust particles and *A. fumigatus*, which is significantly associated with hypermethylation at CpG⁻⁴⁵, CpG⁻⁵³, CpG⁻²⁰⁵ site of the *IFNG* promoter and hypomethylation at CpG⁻⁴⁰⁸ of the *IL4* promoter [220]. By studying asthmatic children living in either the highly polluted Fresno area or lesser polluted Stanford areas of California, Nadeau et al. reported that children with greater exposure to air pollution were more likely to have increased DNA methylation of the *FOXP3* locus and impaired T-reg function [221]. The epigenetic regulation of responses to ambient air pollutants and their associations with the development of allergic disorders also has been reviewed by Hong et al [222].

Epigenetics in relation to Immune-related Genetic Variations and G×E Interaction

Epigenetic marks are heritable and appear to be associated with DNA variants [169, 223-225]. A study of DNA methylation in monozygotic twins highlighted the contribution of both intrauterine environmental and underlying genetic factors to the establishment of the neonatal epigenome [169]. Some studies demonstrated that allele-specific DNA methylation is widespread across the genome, most of which can be strongly influenced by the sequence of adjacent SNPs [223, 224]. By integrating SNP data from GWAs and DNA methylation data, a study reported that numerous CpG sites are regulated by genetic variants in *cis* and/or *trans* manner [225]. Moreover, genetic variants in genes involved in the one-carbon metabolism pathway, phase 1 and 2 detoxification, DNA repair pathway, or genes encoding chromatin protein and chaperone protein, may also influence DNA methylation [226]. A recent study on *CD14* gene polymorphisms, one of the candidate genes of FA [227], reported that the reduced effect of *CD14* polymorphisms on sCD14 levels from early to late childhood parallel a small but significant increase in *CD14* methylation during the same period [227], suggesting that DNA methylation may mediate the effect of genetic variants on the development of FA via altered protein expression.

Epigenetic status also may be influenced by G×E interactions. For instance, homozygosity (TT) for the functional variant (C677T) of the methylenetetrahydrofolate reductase gene, which encodes a thermolabile protein with reduced enzymatic activity, is associated with reduced global DNA methylation, but only in the presence of low folate levels [228]. Another study demonstrated that pre-natal exposure to ETS was associated with global and gene-specific DNA methylation; this association varied by detoxification gene variations (*GSTM1* and *GSTP1*). These studies have provided indirect evidence that epigenetic alteration is one of the mechanisms by which to explain G×E interactions identified for the allergic phenotypes.

Research Gaps and Future Directions

A major challenge in FA research and prevention is that FA is a complex trait and there is limited knowledge regarding early life precursors that can be reliably used for the purposes of early risk assessment, prediction and prevention of FA. Despite the fact that most FA and FS develop in a critical period during the first few years of life, most previous FA studies have only focused on older age groups or children who have already developed FA. It also is critical to perform randomized, controlled interventional studies to determine the relative causal effects of identified environmental risk factors on the incidence of FA. Studies focused on the genetic susceptibility and gene-environmental interactions of FA are very limited. Given the complex biological pathways and mediators involved in FA, a comprehensive genome-wide search is the best available approach to identify novel genes that would not naturally be suspected due to our very limited understanding of the immune

mechanisms of FA and lack of candidate genes. Future studies focused on the epigenetic and epigenomic alterations of FA hold tremendous promise for translational medicine, much due to the reversible nature of epigenetic alterations and the promise of therapies that may restore the ‘normal epigenome’ by activating or silencing disease-related genes.

Our current knowledge supports the understanding that FA, like other complex diseases, is caused by a complex interplay of multiple factors including well-recognized epidemiological and clinical factors, genetic variants, gene-environment interactions, and epigenomic marks. Thus, studies which only address one or two factors or aspects at a time will not be able to fully explore the etiology and biological mechanisms underlying the development and progression of FA. This underscores the need for large-scale prospective birth cohort studies to simultaneously identify the inter-relationships of early life adversities, genetic susceptibility, epigenomic alterations and the development of FA. The identification of these key factors will allow us to gain important insight into the biological mechanisms by which environmental exposures and genetic susceptibility affect immune function and then the risk of FA, and will contribute to the development of new paradigms for the diagnosis, prevention and management of FA.

Acknowledgments

Drs. Wang and Hong have been supported in part by the Food Allergy Initiative; the National Institute of Allergy and Infectious Diseases (PI: Wang, R21AI079872, R21AI088609, U01AI090727); and the Department of Defense (PI: Wang, W81XWH-10-1-0123). We thank Tami Bartell for English editing.

Abbreviation

ACSL	actyl-CoA synthetase long-chain family, member 3
AIMs	ancestry informative markers
BBC	Boston Birth Cohort
CTLA4	cytotoxic T-lymphocyte-associated protein 4
CYP24A1	cytochrome P450, family 24, subfamily A, polypeptide 1
DCs	dendritic cells
DNMT	DNA methyltransferase
ETS	Environmental Tobacco Smoke
FA	Food allergy
FCER1G	Fc fragment of IgE, high affinity I, receptor for; gamma polypeptide
FLG	filaggrin
FOXP3	forkhead box P3
FS	food sensitization
GSTP1	glutathione S-transferase pi 1
GWA	genome-wide association
HDACs	histone deacetylase
IFNG	interferon, gamma
IgE	Immunoglobulin E
IL	Interleukin

IL12RB1	IL12 receptor, beta 1
IL4RA	IL4 receptor alpha
LBW	low birthweight
MS4A2	membrane-spanning 4-domains, subfamily A, member 2
NHANES	National Health and Nutrition Examination Survey
NLRP3	NLR family, pyrin domain containing 3
PGE2	prostaglandin E2
PTPRO	protein tyrosine phosphatase, receptor type, O
LC-PUFAs	long-chain polyunsaturated fatty acids
SPINK5	serine peptidase inhibitor, kazal type 5
STAT6	signal transducer and activator of transcription 6
TNFα	tumor necrosis factor, alpha
T-reg	T-regulatory
TSLP	thymic stromal lymphopoietin
TLR	toll-like receptor
VDD	vitamin D deficiency

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