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Immunomodulatory Effects of Breast Milk on Food Allergy

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INTRODUCTION

Human milk (HM) is not only considered the ideal nutrition source for term infants during the first six months of life by providing nutrients needed for growth and development [1], but it also provides antimicrobial and immunomodulatory factors providing defense against infections [2, 3]. Thereby, breastfeeding provides continued exposure to the mother's immune system during the crucial window of first few months of life, when the infant's immune system is constantly developing. However, the immunomodulatory make up of HM has not been well-characterized and demonstrates a great deal of variability between mothers, which implies that the benefit of breastfeeding to the breastfed infants may differ between dyads. This can have an impact on the degree to which breast milk can provide benefit in individual mother-infant pairs (Figure 1).

Breastfeeding is currently recommended as primary prevention for allergic diseases, including food allergy (FA) [4–6]. A systematic review concluded that there is an protective effect of exclusive breastfeeding against cow's milk allergy (CMA) in early childhood among high-risk infants [7]. However, more recent studies did not find an association between FA and breastfeeding, although concluded that the evidence on FA had high heterogeneity and low quality [8], insufficient to draw conclusions about breastfeeding impact on FA [9]. The most recent population-based study from Australia, reported no association between breastfeeding and length of breastfeeding with FA at 1 year (likely underpowered for CMA)

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[10]. Unfortunately, to date the majority of studies have either lacked adequate statistical power to assess the impact of breastfeeding on FA, or have not evaluated this association at all (or only assessed food sensitization) due to methodologic problems. Randomized controlled trials are lacking for ethical reasons and the definitions of breastfeeding and allergic outcomes varies greatly between existing studies.

The only randomized trial on the topic, the Promotion of Breastfeeding Intervention Trial (PROBIT) from Belarus, designed to promote breastfeeding duration and exclusivity of breastfeeding documented a reduction in gastrointestinal infections and eczema in the 12 months in the intervention group[11]. The 6-year followup in this cohort found that this protective effect was no longer observable; however FA was not assessed [12]. Some of the discrepancy between studies may be explained by differences in HM composition, which has not been accounted for in the broad definition of breastfeeding. Breastfeeding in general may protect against wheezing and eczema by protecting against early life (viral) infections [8], but protection against FA might require more defined composition of immune factors from HM. Also, the mechanisms by which HM affords protection are largely unknown. Gene-environment interaction have also been shown to impact protection. The association between breastfeeding and food sensitization modified by single nucleotide polymorphisms (SNPs) in the interleukin (IL)-12 receptor β1, Toll-like receptor (TLR)-9, and thymic stromal lymphopoietin (TSLP) genes: for example, breastfeeding increases the risk of food sensitization in children carrying the GG genotype but decreases the risk in children carrying the GT/TT genotype of the IL-12Rβ1 [13].

Breast milk originates from secretory cells within the lactating breast. The majority of HM components including lactose, milk lipids, and a variety of milk proteins are produced in the lactating cells [14]. Beyond the major macronutrient components, HM also contains human milk oligosaccharides (HMOs), immune cells, cytokines, chemokines and hormones, immunoglobulins, critical growth factors, active enzymes including peroxidases and lysozymes, lactoferrin, and additional secretory components, soluble CD14, TLR2 and tumor necrosis factor (TNF) receptor, along with maternal diet-derived food antigens, and its own microbiome made up of bacteria and viruses [15, 16]. Previous studies have evaluated many of these HM components and their relationship with allergy development in offspring. This review discusses most recent (last 10+ years) and selected key older studies found in PubMed assessing relationship between breastfeeding and FA in infants and young children, and summarizes existing animal and human studies that have evaluated the association of human milk immunologically active components with FA in offspring, and their impact on infant gut microbiome. This includes allergens, immunoglobulins, immune complexes, cytokines, chemokines, growth factors and HMOs, and excludes enzymes, lactoferrin, sCD14, sTLR2 and sTNFR, where no data is available in association with FA.

BREAST MILK AND INFANT GUT MICROBIOME

Some of the impact of breastfeeding on infant immune system may be due to its impact on infant gut microbiome. In addition to prenatal environment, delivery mode, antibiotic treatment, and diet, the infant microbiome composition is significantly influenced by breastfeeding [17, 18]. Among breastfed infants, microbiome diversity is initially lower

compared to formula fed infants, given that HM creates an intestinal environment that gives selective advantage to highly adapted intestinal microbiota, by providing HMOs. The dominant microbes of breastfed infants (*Bifidobacteria, Lactobacilli, Enterobacteriaceae*) are surpassed by *Clostridium* and *Bacteroides* species after cessation of breastfeeding and introduction of complementary foods [19–22]. Cohort studies including the WHEALS study found that breastfeeding is one of the most influential factors in the development of the infant microbiome [18]. In humans, breastfeeding is a major source of beneficial bacterial species [23], indicating the essential role of this food source in determining the microbiota in early life that may impact the later development of allergic diseases, including FA. Kourosh et al. showed that children with IgE-mediated FA had significantly different microbial composition, particularly among *Clostridia* species, compared with controls subjects [24] Fieten et al. [25], in a study conducted in children with atopic dermatitis, found fewer of two *Bifidobacterium* species (*B. breve, B. adolescentis*) and in addition to lower numbers of *F. prausnitzii*, and *A. muciniphila* in the fecal microbiome of children with concomitant FA compared to those without FA. Finally, Fazlollahi et al found a higher alpha-diversity of microbial flora in egg-allergic children compared to non-FA controls [26]. These studies and a recent review [27] highlight that alterations in gut microbiome may be a key factor in the development of FA.

The impact of microbiome on the infant immune system is likely due to the short-chain fatty acids (SCFAs) including propionate, butyrate, and acetate that are a byproduct of microbial metabolism, and have anti-inflammatory functions [28]. A recent study found that SCFAs were altered in children who are atopic [28]. Similarly, in a mouse model, researchers found that higher levels the SCFAs acetate and butyrate may inhibit the development of FA by inducing tolerance via $CD103^+$ dendritic cells [29]. In studies of term infants, while overall SCFA levels are higher in formula-fed compared to breastfed infants, the highest levels of acetate are observed in exclusively breastfed infants [28, 30]. Taken together, these studies support the hypothesis that one mechanism of FA protection conferred via breastfeeding may be through the influence of HM on the infant gut microbiome that leads to reduction in pro-inflammatory processes.

INSIGHTS FROM ANIMAL MODELS

Animal models of FA have been developed to explore the mechanisms involved in the development of diseases to normally harmless food allergens [31]. These models of FA have been utilized to dissect how maternal factors influence the susceptibility of offspring to allergies. This section focuses on the role of breast milk factors in the development of experimental FA in offspring (Table 1).

Allergen, immunoglobulins (Igs), and immune complexes (IC)

The concept of tolerance induction by allergen in breast milk has been shown in experimental asthma [32]. Aerosol allergen (ovalbumin; OVA) exposure of wild-type (WT) mothers during breastfeeding resulted in an allergen transfer to offspring through milk and the induction of allergen-specific, transforming growth factor (TGF)-β-dependent tolerance towards allergic airway inflammation. Naive offspring adopted and nursed by pre-

conceptually sensitized WT mothers with OVA and alum adjuvant intraperitoneally (i.p.) exposed to OVA aerosols during breastfeeding received maternal IC (allergen and allergen-specific immunoglobulin (Ig) G) via milk and exhibited a long-lasting allergen-specific protection from asthma [33]. In contrast, earlier studies have indicated maternal transmission of asthma susceptibility to offspring [34] from WT mothers pre-conceptually immunized with OVA/alum and exposed to OVA aerosol during pregnancy. As OVA-sensitized mothers were *not* exposed to OVA during breastfeeding, these data imply that allergen transfer via milk is critical for successful tolerance induction in offspring. Respiratory allergen from house dust mite is present in HM and primes for allergic sensitization in experimental asthma [35], suggesting that maternal exposure to environmental allergen reflected in milk may facilitate allergic sensitization, rather than protection in offspring. In conclusion, these asthma studies imply that milk-borne allergen, IC, and TGF-β may induce tolerance in offspring against asthma, while insufficient milk-borne allergen exposure or specific environmental allergen exposure of offspring may promote asthma.

Although the mechanisms of experimental asthma may not simply be applicable to experimental food allergy, these observations led to the hypothesis that allergens, Igs, and IC in milk might facilitate the induction of tolerance to food allergens in neonates. On the subject of FA, we have demonstrated that pre-conceptional peanut exposure of C3H/HeJ mothers (a substrain of C3H mice that lacks a functional toll-like receptor 4 that recognizes lipopolysaccharide) resulted in the generation of varying levels of maternal Igs in serum and breast milk. However, maternal peanut exposure preconceptionally or during pregnancy and breastfeeding had no impact on offspring's rates of peanut allergy assessed by oral and i.p. peanut challenge in a model where peanut allergy was elicited by oral immunization with peanut and cholera toxin (CT) [36]. These findings support the recommendations of no dietary restrictions for pregnant and breastfeeding mothers. Bernard and colleagues found that HM containing peanut allergens induced partial oral tolerance in peanut-sensitized young mice [37], supporting a beneficial role of milk-born allergen in decreasing disease susceptibility in offspring. A stronger immunization of C3H/HeJ mothers with oral peanut/CT and peanut exposure during pregnancy and breastfeeding indeed reduced peanut allergy risk in offspring[38]. Offspring of preconceptually peanut/CT sensitized mothers exhibited IgG1-mediated anaphylaxis in response to oral peanut challenge (first exposure). Interestingly, when sensitized mothers received peanut/CT also during pregnancy and breastfeeding, offspring were protected from anaphylaxis following first peanut challenge as well as active peanut/CT sensitization and oral peanut challenge. These results suggest that maternal immune responses during pregnancy and breastfeeding are critical in the reduction of disease susceptibility in offspring.

We have recently delineated for the first time the mechanisms of neonatal tolerance induction against FA, mediated by maternal IgG-IC and neonatal crystallizable fragment receptor (FcRn) [39]. Maternal allergen sensitization through epicutaneous route [40] prevented food anaphylaxis and allergen-specific IgE in offspring following epicutaneous sensitization and oral challenge of offspring with allergen. *This protection was mediated by FcRn-dependent transfer of maternal allergen-IgG-IC via breast milk and induction of allergen-specific Treg cells in offspring*. Neonatal tolerance was induced in offspring of naive mothers that were fostered immediately after birth and nursed by OVA-sensitized mothers.

The induction of tolerance was also observed in offspring of naïve mothers supplemented with IgG-IC during breastfeeding. Induction of oral tolerance in offspring required FcRn-dependent antigen presentation by $CD11c^+$ dendritic cells. Human breast milk containing OVA-IgG-IC induced tolerance in humanized FcRn mice, providing a particularly important evidence for the potential clinical relevance of our findings in humans. Jointly, these findings from our mouse model demonstrate that interactions of offspring FcRn and maternal IgG-IC are key components of the induction of Treg cell responses and regulation of food-specific tolerance in the neonatal period. This study provided experimental evidence for the key role played by maternal allergen-specific Igs in milk in establishing effective tolerance that prevents FA in offspring. These effects extend well past the previously described roles of maternal antibodies and FcRn in the provision of passive immunity. Additionally, such food-specific IgG antibodies are also induced during oral immunotherapy in humans and have been shown to act through FcγRIIb to suppress IgE-mediated hypersensitivity [41]. Strategies that favor maternal IgG responses might prove useful in the prevention of FA in offspring.

Vitamin A and TGF-β

In humans, increased risk of allergy during early childhood indicates insufficient immune regulation in this period of life. Also in mice, neonates (i.e. first week) are refractory to oral tolerance elicited by maternal allergen transfer via milk due to a physiological vitamin A deficiency [42]. Unsensitized BALB/c WT mothers were fed OVA in the first, second, and third week of or throughout breastfeeding and tolerance induction in offspring to OVA-induced airway inflammation was assessed. Oral tolerance induction was fully efficient only starting third week of life. Insufficient tolerance in one-week-old neonates was associated with a reduction in gut barrier, retinaldehyde dehydrogenase expression by mesenteric lymph node $CD103^+$ neonatal dendritic cells, and serum retinol levels as compared to those in adult mice. Vitamin A supplementation rescued neonatal defects and resulted in sufficient tolerance induction in one-week-old mice. Oral tolerance was dependent on interferon (IFN)-γ. These results may suggest vitamin A supplementation together with maternal allergen transfer via milk as possible interventions for allergy prevention in the neonatal stage of life.

To assess the duration of oral tolerance induced by breast milk towards FA, BALB/c WT mothers were pre-conceptually immunized i.p. with OVA/alum then fed OVA during breastfeeding while nursing offspring from unsensitized mothers [43]. Breastfeeding by OVA- mothers resulted in a decrease in frequencies of allergic diarrhea and serum levels of mast cell proteinase-1 following repeated oral OVA challenges in 6-week-old, but not in 13-week-old, offspring. Supplementation with TGF-β after weaning till 12 weeks prolonged protection against diarrhea and improved gut barrier in 13-week-old mice breastfed by OVA- mothers. Although the precise mechanisms responsible for allergic diarrhea are not fully understood, expansion of intestinal mast cells is a common phenomenon in food allergic patients [44, 45] and has been associated with disease severity in experimental FA models [46, 47] Breastfeeding by allergen-sensitized mothers together with offspring TGF-β supplementation may provide long-lasting prevention of allergic diarrhea and intestinal mast cell expansion.

Food-specific IgG and food allergen-immune complexes are present in sera and breast milk of healthy human subjects [48–53]. Allergen-sensitized female mice in these studies above are not necessary allergic or atopic but were used to investigate the role of maternal allergen and allergen-specific immunoglobulins in milk in influencing offspring allergies. Analysis of how atopic status of mothers may influence tolerance induction or food allergy in offspring in humans will be an important future issue to be addressed. One of the critical advantages of using mouse models to study the impact of breast milk on the development of FA in offspring is that sensitization or tolerance can be induced to specific allergens under controlled environmental conditions within defined genetic backgrounds at specific timing, which is not possible in human subjects. This aspect of mouse models allows extensive and precise investigations into the mechanisms involved in maternal-fetal interaction during breastfeeding period, such as identification of possible triggers of food sensitization, as well as pathways involved in the induction of tolerance towards FA. Increasing animal studies underscore the critical role of breast milk in the induction of tolerance towards FA in offspring.

HUMAN MILK IMMUNOMODULATORY COMPONENTS AND FOOD ALLERGY

Dietary allergen and maternal diet

Debate over whether the presence of food antigens in HM results in sensitization or tolerance in infants is ongoing. The detection of specific dietary antigens in HM following maternal consumption has been well established for a wide variety of food proteins, including ovalbumin [54, 55], β-lactoglobulin [56, 57], gliadin [58], and peanut [37, 59–61]. Although maternal ingestion of dietary allergens can induce symptoms in some sensitized infants [62], this is certainly not always the case. Furthermore their role in the initial sensitization to foods remains unclear, and the currently available evidence does not support restriction of the maternal diet during pregnancy or lactation [5].

In an effort to account for variation in maternal dietary patterns, several studies have evaluated the relationship between intake of allergenic foods during lactation and FA outcomes in offspring [63, 6465, 666768–7172] (Table 2). Studies evaluating peanut consumption during lactation reported mixed findings; two reported no association [63, 64], two studies found reduced risk of peanut sensitization or FA [65, 66], and one study found that maternal consumption during lactation increased the infant's risk of peanut allergy [67]. One study evaluating maternal peanut and tree nut consumption during the peri-pregnancy period found that higher levels of consumption in non-allergic mothers resulted in protection from peanut and tree nut allergy in the infant [72]. This study did not report the independent effect of consumption during lactation, however. Studies evaluating cow's milk, egg, and other allergens found no association between maternal diet during lactation and risk of allergy or sensitization [68–71]. A number of methodological considerations may explain the discrepant findings between studies. Definitions of exposure (estimates of maternal consumption during lactation, along with breastfeeding intensity and duration) and outcome (oral food challenge diagnosed FA, self-report FA, sensitization on skin prick test or allergen specific IgE) are not utilized systematically between studies, making associations difficult to compare directly. Many of these studies have relatively small sample sizes, relying on small numbers of events

(FA detection) for statistical analysis. Several of the studies found no association between maternal diet during lactation and FA outcomes, however very small numbers of subjects in these studies experienced these outcomes [68, 69], generating significant concerns about the risk of type II error. Another important factor to consider is that the high concordance between maternal diet during pregnancy and lactation further complicates evaluating these associations separately [6473, 74], however statistical control for maternal diet during pregnancy is likely necessary for obtaining an unconfounded effect estimate of the association of interest. If we assume that maternal diet during pregnancy is associated with FA risk in the offspring, and that maternal diet in pregnancy is also tightly associated with maternal diet during lactation, then this variable meets the classical definition of a confounder, and should be adjusted for in statistical models (Figure 2). Randomized controlled trials would be an optimal tool for eliminating these statistical concerns. Given the large variability in findings reported and numerous methodological concerns, observational studies that evaluate maternal diet during lactation (and do not consider the composition of HM) thus far have not been able to conclusively determine the role played by maternal dietary antigens in HM in the development or prevention of food allergy.

One of the major limitations of studies that do not measure dietary antigens and rely on maternal dietary intake as a proxy measure, is potentially significant misclassification of a child's exposure to these antigens via HM. Several reports have found large inter-individual variation in food allergens in HM, and have demonstrated that a non-trivial proportion of women had undetectable levels of food allergens following consumption of these foods. Following cow's milk consumption, 15% - 47% of subjects had no detectable β-lactoglobulin in HM [56, 57]. Over 25% of mothers in egg consumption arms of a randomized trial demonstrated no detectable OVA in their milk [54], and in a randomized cross over trial, 24% of mothers never demonstrated detectable OVA in their milk[55]. Following peanut consumption, 52% of women had no detectable peanut proteins [61], and 72% had no detectable Ara h2, the most potent allergenic peanut protein, in breast milk [59]. Beyond the presence or absence of detectable antigen, it is important to note that for women with detectable levels of food antigens in their HM, the timing of the onset of detection, the peak concentration, and the duration throughout which the food protein is detectable also varied greatly from subject to subject. The sources of variability in these factors (timing, concentration and duration of detection) are likely multifactorial, and have been shown to be unrelated to mammary epithelial permeability [54], suggesting that perhaps the variability may be in part due to differences in maternal intestinal permeability to these antigens.

Maternal dietary intake has been shown to impact infant immune markers that likely alter the risk of FA development. Metcalfe found that high dose egg exposure in the mother resulted in higher levels of specific IgG_4, a marker of exposure and possible immune tolerance in breastfed infants, compared to mothers in low or no egg arms of the trial [54]. Similarly, our study found that mothers who restricted cow's milk intake during lactation had infants with lower levels of specific IgG_4 [75]. These data suggest that the effect of dietary antigens in HM on immune markers of exposure in offspring have demonstrated benefit among subjects with detectable levels of food antigen.

Taken together, findings from existing epidemiological studies evaluating the relationship between maternal diet during lactation and FA outcomes in offspring are limited in their explanatory power due to the inability to control for wide inter-individual variation concentration of food antigens in HM. Importantly, the maternal diet during lactation influences HM composition in ways that antigen concentration along with food-specific immunoglobulins in humans [75]. This may be confounded by maternal diet during pregnancy, which itself may be protective [76]. Additional large-scale studies that carefully evaluate the concentration of dietary antigens in HM and the associated risk of allergic disease will be needed to clearly elucidate these complex relationships.

Immunoglobulin A (IgA)

IgA is the fifth most prevalent component in HM, with smaller amounts of IgG and IgM in HM [77]. Present mostly in secretory form, secretory IgA (SIgA) controls gut microbiota and intestinal homeostasis [78]. Plasma cells in the lamina propria of the gut produce mucosal IgAs, which are transported by the polymeric immunoglobulin receptor (pIgR) across the epithelium [79]. B cells originating from the maternal gut migrate to the mammary tissue via the “enteromammary link”, and secrete specific IgA that enters HM [80]. This process is regulated by the mucosal vascular addressin MadCAM-1, a protein that interacts with both the mucosa-associated CCR10 [81] and the gut-targeting receptor $\alpha_4\beta_7$ integrin [82]. Given the interaction between these components, it is hypothesized that that the specificity of IgA in a mother’s milk is a reflection of the antigenic exposure her immune system experiences to dietary proteins in her gut.

Consistent with prior reports [83, 84], in a prospective birth cohort oversampled for factors that confer high risk of FA development, we found that increased levels of both total IgA [85] and cow’s milk-specific IgA [75] in HM were associated with protection against CMA. Maternal exposures dictated by geography, microbial burden, contact with animals (specifically farm animals and cats), are likely a major determinant the levels and specificity of the IgA observed in HM [77]. We also showed that a restriction of cow’s milk from the maternal diet was associated with reduced levels of cow’s milk-specific IgA levels in HM when compared to mothers with unrestricted diets [75], implying that the dietary antigenic exposure of the maternal immune system via the gastrointestinal tract shifts the antibody specificity observed in HM. This could be the reason why maternal diets restricting highly allergenic foods may not be advantageous in prevention of FA. We also showed the IgA in HM had different specificity to cow’s milk antigens than the IgA in serum, indicating that distinct antibody-producing lymphocytes likely contribute to HM and serum IgA, thereby providing further evidence of the “enteromammary link” [86]. This evidence suggests that maternal diet influences the specific IgA composition of HM. An active connection between immune tissues in the maternal gut and the mammary gland results in a HM-specific IgA profile influenced by the mother’s dietary exposures.

While the precise function of HM IgA remains unclear, it is believed to provide passive protection until infant production of IgA commences after birth [87]. During lactation, IgAs also influence the microbiome composition of the infant, conferring protection to colitis in adulthood [78]. In summary, the IgA found in HM is shaped by many factors, including

maternal exposures that vary based on diet, geographical location, exposure to microbes, among others. These immunoglobulins are likely an important factor in the prevention of CMA in the infant. There are no studies assessing the impact of immunoglobulins or antibodies in other FA.

Cytokines, chemokines and growth factors

HM contains numerous immunomodulating cytokines that stimulate or suppress immune cells [77]. Whereas some are found in relatively low concentrations in HM, others, such as TGF-β is found in larger quantities [88]. Inter-individual variation in HM cytokine levels may stem from differences in microbial exposures; TGF-β, IFN-γ, and IL-10 levels vary based on maternal country of origin and country of residence [77].

TGF-β is a key regulatory cytokine involved in the inhibition of Th1 and Th2 pathways, and thus far, is the most well studied soluble factor in HM. Considering all three isoforms, TGF-β is the predominant cytokine in HM, the most common isoform being TGFβ2 [77]. TGF-β is involved in the induction of production of specific IgA and intestinal epithelial cell maturation [89]. A 2010 review by Oddy and Rosales included 12 studies conducted in humans, and reported that 8 of the studies found that higher levels of TGF-β1 or TGFβ2 resulted in lower risk of atopic outcomes in the first years of life [90], however the results from other studies differed. A summary of association between TGF-β and the development of FA can be found in Table 3. Although three studies did not find an association between TGFβ1 (and in one also TGFβ2) levels in milk and FA, two studies have found higher levels being associated with lower risk of FA. Among the latter two studies, the first study of FA showed that mothers of infants with IgE-mediated CMA had lower TGFβ1 concentrations in colostrum than mothers of infants with non-IgE-mediated CMA, and that the concentration of TGFβ1 in healthy controls fell between these two groups [91] (Table 3). The second study found a protective association between a group of several pro-inflammatory and regulatory cytokines (including TGF-β1) in HM and CMA [88]. Based on these studies, the role of TGF-β levels on FA development has not been conclusively determined, and may differ among different types of FA. Additional studies specifically evaluating FA are needed to better understand the influence of TGF-β on this process.

New and ongoing studies evaluating the impact of additional cytokines and chemokines present in HM the development of atopic conditions has shown variable results[77]. Several authors report an absence or very low concentrations of several of these bioactive substances including IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IFN-γ, CCL5, CXCL8, CXCL10, and TNF-α. These studies have shown no relationship between these compounds and atopy development [77]. Table 3 summarizes the current literature evaluating the relationships between cytokines and FA development [72, 8891–96]. Our study showed that protection against CMA was associated with the levels of IL-1β, IL-6, IL-10, and TGF-α1 in HM [88]. It is not possible to determine from this study whether these chemokines and cytokines are biomarkers of the mechanism that confers protection from CMA, or if they are directly related to the process of protection. However, given that these factors promote differentiation of Th17 cells, the production of IgA, and crosstalk between the RORγt$^+$ innate lymphoid cell (ILC)-3 population and gut macrophages [88], it is plausible that these

chemical factors we detected in HM samples are directly involved in promoting protective immunomodulation. Another study reported that increased IL-13 concentration in both colostrum and mature HM were associated with lower risk of FA and eczema, respectively by parent report. These authors found no significant association between levels of IL-2, IL-4, IL-5, IL-10, IL-12 and IFN-γ with either of these conditions or wheeze [95]. Finally, a recent study using the case-cohort design among the EDEN birth cohort showed a positive association between the concentration of IL-2, CXCL10, and TNF-β and reported FA in childhood [96]. Higher concentrations of IL-1β and IL-17 were found in mothers who reported increased physical activity [77]. Overall, maternal atopic status was not systematically associated with cytokine levels in HM [88]. Overall, these studies demonstrated the strongest association between high levels of TGF-β and perhaps some other regulatory and inflammatory cytokines and decreased FA risk, but data are few and to some extent conflicting.

Human milk oligosaccharides (HMOs)

HMOs are abundant sugar chains found exclusively in HM. During the period of exclusive breastfeeding, the infant's gut microbiome feeds primarily off of these HMOs, which promotes the growth of Bifidobacteria and Bacteroides species, leading to their predominance in the gut microbiome of exclusively breastfed infants [97]. The infant in unable to digest these HMOs, which originate as lactose molecules that are modified by a series of glycosyltransferases, enzymes which are encoded by the genes responsible for the Lewis blood groups and secretor status. Two fucosyltransferases FUT2 (secretor gene) and FUT3 (Lewis gene) are responsible for the addition of fucose. Mothers express a unique set of enzymes and synthesize their own variety of HMOs based on which allelic variants they express. Resulting from this genetic variation, HM demonstrates significant inter-individual heterogeneity in HMO composition, both in terms of the oligosaccharides present and their relative abundance. This variation indicates that breastfed infants are exposed only to certain HMOs in their mother's milk. 15-25% (varying by ethnic background) of mothers lack a functional lack a functional FUT2 enzyme (FUT2−/−) [98, 99] and are labeled non-secretors, given that they lack all HMOs containing alpha-2 linked fucose [100]. Infants who receive HM from non-secretor mothers have microbiota with later establishment of bifidobacteria predominance [101]. The study by Sprenger et al. found that infants fed by non-secretor mothers who were born by cesarean section had an increased risk of developing IgE-associated atopic dermatitis [100]. This study did not evaluate the risk of FA development, nor did it consider the concentration of individual HMOs. In our study, infants fed HM containing low concentrations of Lacto-N-fucopentaose (LNFP) III had a higher risk of developing CMA compared to infants who received HM with higher levels of this oligosaccharide [102]. Similarly, in a report from the Canadian Healthy Infant Longitudinal Development (CHILD) study, authors evaluated the association between HMO profiles and food sensitization at 12 months, and found that the presence of specific HMOs conferred reduced risk of food sensitization in the infant [103]. Taken together, these findings suggest that specific HMO profiles may result in protection from the development FA, and that this protection may be conferred via their impact on infant gut microbiome.

The protection observed in these studies may be due to the effect of HMOs on gut microbiome or direct effects on immune cells. Certain HMOs have demonstrated anti-inflammatory characteristics, and promote the maturation of the gastrointestinal immune system. Other HMOs inhibit intestinal cell growth, while others interact with dendritic cells via the lectin receptor DC-SIGN (Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbng Non-integrin) [77]. Additional studies with a focus on the specific HMO composition of HM will be required to more clearly elucidate the role of these compounds in mechanisms of atopic disease development and prevention.

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

The composition of immunologically active substances and significant interpersonal variation of HM has yet to be fully described. Past epidemiologic studies have often failed to account for these variables, and have historically operationalized HM exposure crudely, and in ways that may obscure associations of interest. Additionally, the outcome definitions for FA also vary from study to study, with some authors utilizing gold standard oral food challenge, others relying on clinical diagnosis, and still others reporting associations with evidence of sensitization. These challenges, in combination with a number of factors that have historically not be accounted for including wide variation in biologically active components in HM, differences in maternal diet, microbial exposures, and geographical differences, it is of no surprise that findings have been inconsistent in the literature thus far. Due to ethical considerations given the established benefits of breastfeeding, large scale randomized trials with assignment to infant diet type are lacking, which makes simultaneously controlling for all of these factors very challenging. To date, most studies have lacked the statistical power to properly evaluate the relationship between breastfeeding and FA, or have avoided FA as an outcome altogether due to these challenges.

Improved understanding of maternal-offspring interactions from animal models, in parallel with human studies will contribute to the development of novel strategies through breastfeeding to prevent and treat FA. The challenges with animal studies include its limited applicability to human systems. In rodents, FcRn functions in the neonatal period, transporting maternally derived IgG in milk across the epithelial barrier in the gut, whereas in humans FcRn transports robustly maternal IgG to the fetus across placenta 104. Furthermore, the composition of breast milk differs between these species; as an example milk oligosaccharides are much more complex in human than in mouse. Also, the ratio of IgA to IgG differs in human and murine milk. These and other differences may limit the ability to fully translate findings in animal studies to those mechanisms that are biologically similar, although the strengths of animal models include being able to answer specific questions that are difficult or unethical to address in human subjects.

The studies reviewed highlight the complex, variable composition of HM, and the impact that differences in HM characteristics may have on FA development or prevention. The biologically active components of HM may either directly impact FA risk, or perhaps indirectly influence this process through impact on gut microbiota or other still unknown mechanisms. Dietary allergens in HM in combination with immunoglobulins may provide a tolerogenic environment, explaining the reduced risk seen in some studies. Based on all of

the information available to date, it is clear that it is critical to consider the combination of each of these factors, and that the impact of this complex system considered together is likely greater than the sum of each individual part. In order to enhance our understanding of this system, future studies must evaluate the networks of bioactive components in HM, their impacts on the development of the infant immune system and microbiome as a system, and recognize that this field is still “in its infancy”. Clarification of the role of these HM components may lead to key targets for the primary prevention and potential treatment of FA. Large prospective cohort studies that include careful characterization of exposure to these key HM components, as well as careful outcome consideration would provide critical evidence regarding mechanisms and targetable factors in the development of atopic diseases.

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Abbreviations:

CMA	cow’s milk allergy
CT	cholera toxin
FA	food allergy
FcRn	neonatal crystallizable fragment receptor
HM	human milk
HMO	human milk oligosaccharide
IC	immune complex
Ig	immunoglobulin
IL	interleukin
ILC	innate lymphoid cell
INF	interferon
i.p.	intraperitoneal
OVA	ovalbumin
SCFA	short-chain fatty acid
SNP	single nucleotide polymorphism
TGF-β	transforming growth factor-β

TLR	Toll-like receptor
TSLP	thymic stromal lymphopoietin
TNF	tumor necrosis factor
Treg	regulatory T cell
WT	wild type

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KEY MESSAGES

- Breastfeeding is recommended to prevent the development of allergic diseases, however studies have not adequately assessed the role of human milk in food allergy.
- Potential benefits against food allergy may differ between infants given differences in immunomodulatory composition of human milk between mothers - differences not captured in epidemiologic studies.
- The protection against allergy development provided by human milk may be due to impact on the infant gut microbiome or via direct effects on immune system.
- High levels, ratios or combinations of certain human milk immune factors (IgA, cytokines, oligosaccharides) are associated with reduced risk of food allergy in the infant; it remains uncertain whether these are directly protective, or biomarkers of transferred protection. The role of food antigens in human milk in initial sensitization or tolerance induction is unclear.
- Animal studies highlight potential mechanisms of protection provided by antigens, TGF-β, and immunocomplexes, yet their relevance is poorly understood in humans.
- Studies evaluating the impact of breastfeeding and human milk composition on food allergy are needed.

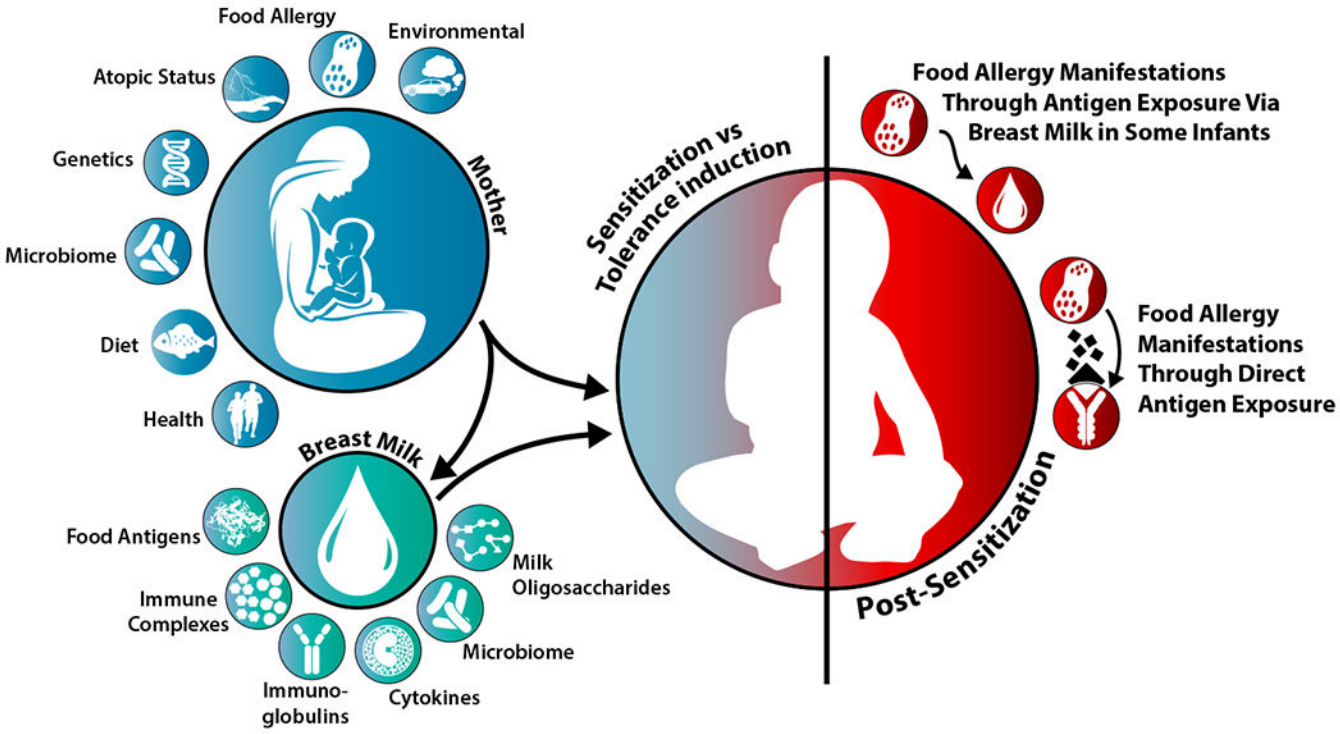

Figure 1.

Maternal and breast milk factors that influence the development of the neonatal immune system.

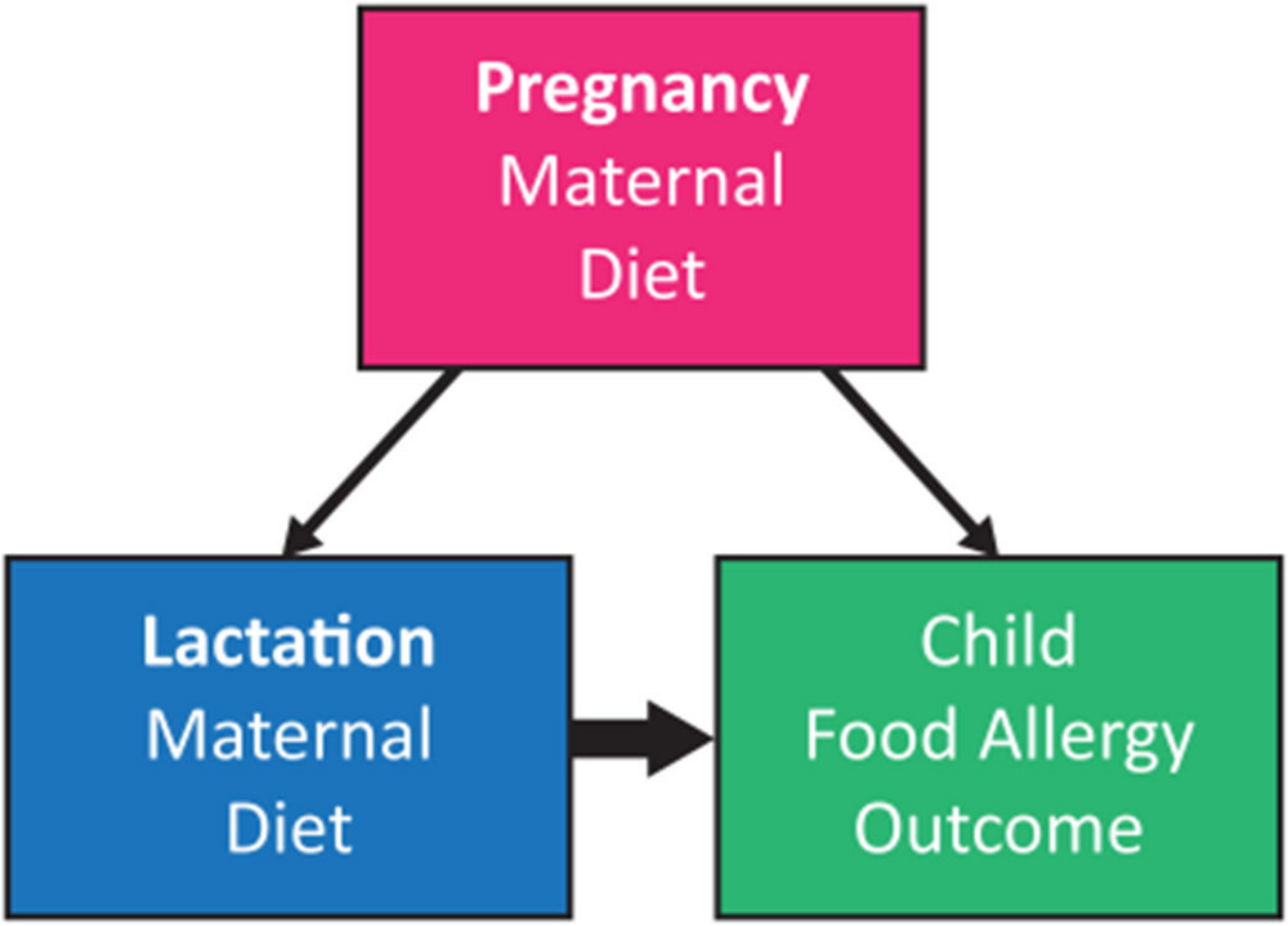

Figure 2.

In order to estimate the effect of maternal diet during lactation on FA outcomes in the offspring (bold arrow), it is necessary to control for the effect of maternal diet during pregnancy. Without statistically controlling for this variable given its association to both the outcome (child FA) and the exposure (maternal diet during lactation), the resulting effect estimate would not reflect the true association of interest.

Table 1.

Studies assessing the association between maternal allergen exposure and tolerance in offspring.

Study	Mouse strain	Allergen	Maternal sensitization (route, timing)	Maternal allergen exposure (route, timing)	Cross-fostering by sensitized mothers	Offspring outcome	Maternal impact on offspring allergies	Comments
Verhasselt 2008 [32]	BALB/c	OVA	n/a	aerosol, lactating	Yes	Asthma	Protection	Protection is milk TGFβ dependent
Mosconi 2010 [33]	BALB/c	OVA	i.p., preconceptual	aerosol, lactating	Yes	Asthma	Protection	Protection is milk IC dependent
Turfkruyer 2016 [42]	BALB/c	OVA	n/a	Oral, lactating	No	Asthma	Protection	Inefficient neonatal tolerance is due to vitamin A deficiency
Hamada 2003 [34]	BALB/c	OVA	i.p., preconceptual	aerosol, preconceptual and pregnancy	No	Asthma	Asthma exaggeration	Lack of maternal allergen exposure during lactating
Macchiaverni 2014[35]	BALB/c	Der p	i.n. preconceptual	i.n., lactating	Yes	Asthma	Sensitization	
Jarvinen 2015 [36]	C3H/HeJ	Peanut	Ad libitum, preconceptual	Ad libitum, pregnancy and lactating	No	FA	No impact	
Bernard 2014[37]	BALB/c	Peanut	n/a	n/a	No	FA	Protection	Human milk containing peanut and peanut-IC prevents sensitization in mice
Lopez-Exposito 2009[38]	C3H/HeJ	Peanut	Oral, preconceptual	Oral, pregnancy and lactating	No	FA	Protection	
Ohsaki 2018[39]	BALB/c	OVA, peanut	Epicutaneous, preconceptual	Epicutaneous, pregnancy and lactating	Yes	FA	Protection	Milk IC-offspring FcRn axis induces neonatal tolerance
Rekima 2017[43]	BALB/c	OVA	i.p., preconceptual	Oral, lactating	Yes	FA	Protection	Milk allergen and TGFβ supplementation protect offspring against FA

n/a, not applicable; i.p., intraperitoneal; i.n., intranasal; OVA, ovalbumin; Der p, Dermatophagoides pteronissinus; TGFβ, transforming factor-β; IC, immune complex; FcRn, neonatal crystallizable fragment receptor; FA, food allergy;

Table 2.

Recent studies evaluating maternal diet including or excluding allergenic foods during lactation (+/− pregnancy) and FA/sensitization in offspring

Citation, location	Number of subjects[§]	General population or high risk for atopy	Exposure	Outcome	Adequate statistical adjustment[†]	Study Design	Impact of intake during pregnancy	Impact of intake during lactation	Comments
Peanut									
Du Toit 2008[66], UK and Israel	176	General population	Infant and maternal consumption vs no consumption between countries (Israel vs UK) (grams and frequency monthly)	FA (self-report followed by SPT, IgE, or OFC)	No	Retrospective	No association	Protective	Early infant exposure to peanut showed strongest protective effect
Fox 2009 [63], UK UK	443	2 control groups; a general population group and a high risk (egg allergy) group	Maternal consumption vs no consumption (g/week)	FA (≥95% predictive value on SPT, IgE or OFC)	Yes	Case-control	No association	No association	Maternal effect disappeared when adjusted for household peanut exposure
Des Roches 2010 [67], Canada Canada	403	General population	Maternal consumption (frequency)	FA (clinical history plus positive SPT or IgE)	Yes	Case-Control	Increased risk	Increased risk	
Sicherer 2010 [64], USA	503	High risk	Maternal consumption (≥2 times per week vs < 2 times per week)	High level sensitization (IgE ≥ 5 kU/L)	Yes	Retrospective	Increased risk	No association	
Frazier 2014 [72], USA	8205	General population	Maternal consumption (servings per week) of peanuts *and* tree nuts during peripregnancy period (exposure captured via survey completed closest to index birth)	Physician reviewed self-report FA diagnosis		Prospective cohort		Protective	Did not evaluate lactation and pregnancy separately. Greatest benefit seen in mothers without peanut/ tree nut allergy
Pitt 2017 [65], Canada Canada	342	High risk	Maternal consumption while lactating (ever vs never)	Sensitization (positive SPT)	Yes	Prospective cohort (nested)	Not assessed	Protective[#]	
Cow's milk, egg and others									
Herrmann 1996[68], Germany Germany	99 -120	High risk	Maternal unrestricted vs restricted diet (cow's milk and egg) during pregnancy and lactation, vs lactation only	Sensitization (IgE ≥0.35kU/L)	No	Non-randomized comparison	No association	No association	
Hattevig 1999[69], Sweden Sweden	115	High risk	Maternal unrestricted diet during lactation vs	Sensitization (SPT and IgE ≥0.35PRU/ml)	Yes	Non-randomized comparison	Not assessed	No association	

Citation, location	Number of subjects[§]	General population or high risk for atopy	Exposure	Outcome	Adequate statistical adjustment[†]	Study Design	Impact of intake during pregnancy	Impact of intake during lactation	Comments
			restricted diet (cow's milk, egg, fish)						
Nwaru 2011[70], Finland (DIPP Nutrition study, 1998 – 2000)	1018	High risk for type 1 diabetes (all with HLA-DQB1)	Maternal consumption of foods (z-scores) during lactation (milk and egg)	Cow's milk, egg and wheat sensitization (IgE ≥0.35kU/L)	Yes	Prospective cohort	Not assessed	No association	
Tuokkola 2016[71], Finland (DIPP Nutrition study, 1997-2004	2820	High risk for type 1 diabetes (all with HLA-DQB1)	Maternal consumption of milk during pregnancy and lactation (quartiles – 1st vs 2nd and 3rd, 4th vs 2nd and 3rd)	Cow's milk allergy[≠] (physician diagnosis or self-report)	Yes	Prospective cohort	Protective	No association	Using the same cohort as above study does

Abbreviations: FA - FA, SPT - skin prick test, IgE - immunoglobulin E, OFC - oral food challenge, NS = not significant

[§]N included in lactation specific analyses

[†]Includes (at minimum) adjustment for atopic status of family and/or subject if different between comparison groups

[#]Among group with maternal peanut consumption during lactation and introduction to infants before 12 months, no adjusted effect estimate reported for peanut consumption during lactation without interaction with direct ingestion because this was highly significant (p = 0.003).

[≠]Registry-obtained physician diagnosis used to justify cost of non-cow's milk formula, or self-report if breastfed or diagnosed at > 1 year of life

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Table 3.

Studies assessing the association between cytokine levels in HM and FA in infants.

Study	Number of subjects	Duration of followup	Cytokines assessed	FA
Saarinen 1999 [91], Finland	6209	12 months	TGFβ-1, TGFβ-2	Higher TGFβ-1 levels in colostrum are associated with infants who develop IgE-mediated cow's milk allergy versus non-IgE-mediated cow's milk allergy; healthy controls were found in between
Bottcher 2003 [92], Sweden	53	2 years	IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, IL-16, IFN-γ, TGFβ-1, TGFβ-2, RANTES, eotaxin	No significant association
Snijders 2006 [93], Netherlands	315	2 years	IL-12 or TGFβ-1 (IL-10 undetectable)	No significant association
Kuitunen 2012 [94], Finland	364 (colostrum) 321 (BM)	2 years	IL-10, TGFβ-1	No significant association
Järvinen 2015 [88], Finland	145	2 years	IL-1α, IL-1β, IL-6, IL-10 PDGF-BB, CCL27, VEGF, TSLP, CCL11, CXCL10, and CXCL11, CCL22, TGFβ-1, TNF-a and -b, CCL1, CCL17, IL-31, eotaxin 3, CXCL9, IL-5, GM-CSF, and IL-12p70	Higher levels of IL-1β, IL-6, IL-10, and TGFβ-1 in HM showed association with cow's milk tolerance
Munblit 2017 [95], United Kingdom, Russia and Italy	398	6 months	IL-2, IL-4, IL-5, IL-10, IFNγ, IL-12, IL-13, HGF, TGFβ-1, TGFβ-2, TGFβ-3	Higher IL-13 levels associated with protection, otherwise no significant association
Berdi 2018 [96], France	263	5 years	Eotaxin, CX3CL1, CXCL1, IL-8, CXCL10, CCL7, CCL22, CCL2, CCL3, CCL4, RANTES, IFNα2, IFNγ, IL-10, IL-12p40, IL-12p70, IL-15, IL-17A, IL-1RA, IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-13, sCD40L, TNFα, TNFβ, EGF, FGF-2, G-CSF, Flt3L, GM-CSF, PDGF-AA, PDGF-BB, TGFα, VEGF	Higher levels of CXCL10, TNFβ and IL-2 associated with protection against FA