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**Influence of Diet on Infection and Allergy in Infants**

# Breast-Feeding and Its Role in Early Development of the Immune System in Infants: Consequences for Health Later in Life[1,2]

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## Introduction

Respiratory tract infections and gastrointestinal tract infections of both bacterial and viral origin cause the highest mortality and morbidity in neonates and infants. This is true not only for developing countries but also for industrialized countries (1). Increased susceptibility to infections and decreased immune responsiveness to these infectious agents continue to be present significantly in y 2 of life. However, it should be realized that the induction of an immune response against nonharmful common environmental antigens, such as food antigens and particular commensals (bacteria), has to be inhibited lest it give rise to undesirable, excessive, and destructive inflammatory and allergic reactions (2,3). It appears that the development of the immune system in neonates and young infants is reflected in the enhancement of "specific" immune responses to danger signals and in the induction of tolerance toward common nonharmful environmental antigens such as food components as well as the microbiota of the infant gut. It should be realized that the human immune system can be modulated easily during the first months of life (4), when it can be affected not only positively but, unfortunately, also negatively. This dichotomy is illustrated by, e.g., survival advantage after surgery early in life and survival postsurgery health consequences later on (5).

This article provides a brief overview of the current knowledge of the development of the infant immune system and possibilities for intervention and immunomodulation.

### Immune maturation in early life: late-stage pregnancy and y 1 of infancy

To prevent excessive, destructive, and adverse immunological reactions between mother and fetus that might lead to "immune abortion," the immune system of the fetus is actively downregulated during pregnancy. This is reflected by the presence of high amounts of active inhibitory T cells, also called regulatory T (Treg)[6] cells, by downregulation of antigen-specific T-cell proliferation (6–9), by the production of suppressive metabolites via indoleamine 2,3-dioxygenase (10), and by deletion of activated T cells via FasL-induced apoptosis (11). A consequence of the immunological status during pregnancy is a not yet fully active and developed immune system postpartum.

The immune system consists essentially of the innate immune system and the adaptive immune system. The innate immune system is the sum of physical barriers, chemical barriers, and the reactivity of local nonspecific cells and cells recruited to the site of inflammation. The innate nonspecific immune system is not fully developed or active in y 1 of life.

The skin and the respiratory and intestinal tracts all play pivotal roles in the innate immune response. In the latter 2 organs, the mucosal tissues form the physical and chemical barrier. In infants, the integrity of the epithelial layer is not complete, as characterized by the existence of a higher permeability of the epithelial layer in both the respiratory and gastrointestinal tracts. In adults, the creation of a low-pH environment in the stomach and the secretion of proteases and antipathogenic peptides are important features of the chemical barrier, inhibiting and killing invading pathogens. In infants, the secretion of these compounds is not fully developed (12,13). Another example of the physical barrier in the gastrointestinal and respiratory tracts is the group of glycoproteins, such as mucins, covering the entire epithelial layer as mucus. The composition and glycosylation of the mucus layer differ significantly between neonates and adults. As a consequence, this may lead to differences in the composition of the gut microbiota between neonates and adults, which in turn might play a role in different susceptibilities to pathogens (14,15).

Granulocytes comprise a subset of immune cells that play a crucial role in innate immune responses. It is known that neonatal neutrophils are reduced in number. In addition to a reduced number of neutrophils, functional impairment of innate immune responses is reflected by a reduced expression of complement receptor CR3, diminished expression of L-selectin, impaired

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[6] Abbreviations used: APC, antigen-presenting cell; BCG, bacillus Calmette-Guérin; DC, dendritic cell; ID, idiotypic antibody network; MHC, major histocompatibility complex; Th1, T helper 1; Th2, T helper 2; TLR, Toll-like receptor; Treg, regulatory T cell.


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chemotaxis, rolling adhesion, transmigration, and lamellipodia formation. Neonatal neutrophils have a reduced capacity to upregulate CD14 as well.

Antigen-presenting cells (APC) play an important role in the innate immune system as well. These cells trigger and initiate the specific adaptive immune response by taking up antigens and subsequently presenting them to lymphocytes, such as T cells. Overall, APC activity in neonates is less than that in adults. Several mechanisms play a crucial role in the reduction of neonatal APC activity. First, the neonatal APC activity is intrinsically lower because of alteration in signaling cascades compared with adult cells. Second, there is a defective interaction between APC and T cells, and third, the function of APC is downregulated by Treg cells very efficiently (16).

Lower IL-12p70 production and IL-12p35 mRNA production was found in cord blood dendritic cells (DC) compared with adult blood DC after a variety of stimuli (17–21). Moreover, the absolute number of DC is not affected by age, although the expression of major histocompatibility complex (MHC) class II and costimulatory molecules is lower on cord blood DC (19–22). The reduced production of IL-12 by cord blood DC might be compensated by a higher production of IL-23, another Th1-type cytokine (22).

Reduced expression of MHC class II and costimulatory molecules might result in less activation of DC and subsequently hampered signaling toward T cells. Whole-blood stimulation leads to lower IL-12p70 and IFN$\alpha$ production and to higher IL-10 production compared with adult whole-blood stimulation (23). Similar effects were found for monocyte-derived DC (18,24).

However, neonatal DC can be activated and skewed toward a Th1-type immune response very efficiently. For instance, expression of CD80 and CD86 and production of IL-12 could be elevated by costimulation with bacterial CpG DNA or IFN$\gamma$ (25–28). Highly purified $CD14^+$ DC show similar IL-12 production and IFN$\gamma$ production as adult DC (29,30), indicating that the impaired IL-12 production and APC function are not merely intrinsic properties of neonatal APC but that the interplay between DC and T cells is altered as well.

The impaired activity of cord blood DC is reflected in a reduced capacity in phagocytosis and endocytosis (18,24). The latter report is highly interesting because the phagocytosis was directed against debris from dying cells, both apoptotic and necrotic cells. Apoptosis plays an important role in the morphogenesis of the fetus. Perhaps the diminished DC activity is not important only for the induction of tolerance against maternal proteins but also to avoid destructive inflammation during the development of the fetus as well. In accordance with this hypothesis, DC remain immature during development because of tolerance-inducing exosomes that contain morphogens (31). Follow-up research is essential to prove this hypothesis.

Because of the recent hygiene hypothesis, attention has been paid to the role of Toll-like receptors (TLR) in the immune response and immune development. TLR play an important role in sensing bacterial products and in activating and skewing the immune system. Although the expression of TLR on neonatal macrophages and monocytes is similar to that in adults, TLR signaling itself is different in infants because TLR stimulations in response to TLR1–7 agonist are different. The production of Th1 cytokines TNF$\alpha$, IFN, IL-12, and IL-1$\beta$ are downregulated, whereas IL-6, IL-8, IL-10, and IL-23 are unregulated compared with adult production (13).

After birth, a rapid activation of the acute-phase response is induced. The acute-phase response plays an essential role in the innate immune response. Although the acute-phase response is caused by stress and hypoxia during labor and uterine contractions, the response might play a role in the clearance of any microbial product that the neonate encounters during its acquaintance with the extrauterine environment. The acute-phase response is mostly IL-6 driven together with a preserved IL-23, IL-17 axis (13). This is in accordance with the notion that TNF$\alpha$ and IL-1$\beta$ signaling, 2 other cytokines involved in the activation of the acute-phase response, are downregulated during pregnancy to avoid miscarriages (32). Perhaps downregulation of TNF$\alpha$ and IL-1$\beta$ signaling might avoid excessive and destructive inflammation during the first days of life as well.

The interplay between DC and T cells determines the fate of T-cell responses and the general T-cell repertoire. As nicely reviewed by Marchant and Goldman (33), neonatal T cells contain high concentrations of T-cell receptor excision circles, which are episomal DNA by-products produced after T-cell receptor rearrangements. They have a high cell turnover with long telomeric sequences, because of high telomerase activity. Neonatal T cells have an increased susceptibility to apoptosis that can be prevented by IL-2; they proliferate after IL-7 and IL-15 stimulation (33–35). Neonatal T cells are effective in producing IL-2 and TGF$\beta$, but they produce only 50% of TNF$\alpha$ and only 10% of IFN$\gamma$ and IL-4 compared with T cells from adults. Still, T cells of the neonate are able to respond to environmental antigens (36).

Recently it has been reported that DC-T cell interactions in Hassal bodies (in the thymus) are important for the generation of Treg cells (37). Because infants have a larger thymus and a high thymic output (T-cell receptor excision circles), this might play a crucial role in the induction of "immune" tolerance. Indeed $CD25^+$ Treg cells are present at high numbers during fetal life (6,8,38,39).

In addition to the overall impaired neonatal T-cell functions, cytotoxic T-cell functions are limited as well, resulting in less proliferation and "immature" cytokine profiles. Because of defects in IFN$\gamma$ production, natural killer cell activity is impaired as well (40).

Humoral immune responses are also different between adults and young infants. Although the number of B cells in the neonate is very high, the maturation of plasma B cells is not yet completed at birth, leading to a defective antibody isotype switching. As a consequence of the relative T-cell and B-cell immaturity, neonates are capable of only rapid IgM and anti-IgM responses. Neonatal B cells are efficient in their capacity to produce IgE if they are stimulated by exogenous IL-4. However, because of the minimal level of IL-4 produced by neonatal T cells, the level of IgE production by neonatal B cells is very low (41). During the first 2 y of life the switch to IgG1 and IgG3 is functional in the neonate, whereas the switch to IgG2 and IgG4 is inadequate in this period. Serum sIgA levels can reach adult levels within a few weeks under heavy microbial exposure (42). Many bacteria are targeted by sIgA in human milk, including *E. coli*, *Shigella*, *Salmonella*, *Campylobacter*, *Vibrio cholerae*, *H. influenzae*, *S. pneumoniae*, *Clostridium difficile* and *C. botulinum*, *Klebsiella pneumoniae*, as well as the parasite *Giardia* and the fungus *Candida albicans* (43).

As recommended by the WHO International Life Science Institute (44), the immune response after vaccination can be used as a model or measure for controlled exposure to antigens. This model is used in young infants to compare the in vivo immune response between infants and adults. In most cases, the response is studied by vaccine-specific ex vivo cell proliferation and cytokine production and by levels of neutralizing antibodies. The data are nicely reviewed by Marchant and Goldman (33). In





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general, in infants an antigen-specific immune response can be generated. The reaction is mostly characterized by a Th2-type response as reflected by high production of Th2-type cytokines and high levels of antigen-specific type 2 immunoglobulins. This is the case for vaccines such as hepatitis B (45), polio (46), and measles (47). Some vaccines, for instance antituberculosis bacillus Calmette-Guérin (BCG) vaccine (48) or whole-cell pertussis vaccine (49), do induce a Th1 response in infants, indicating that a Th1 response can be generated in infants, although less efficiently. Some studies in which BCG is used as an adjuvant for unrelated vaccine antigens show that BCG merely induces both Th1 and Th2 responses in infants (50), again indicating that a Th1 response can be induced in infants when triggered with a strong immune inducer.

### Consequences of impaired immune maturation

Data support the hypothesis that delayed or impaired maturation of the immune system early in life can result in immune dysfunction later in life, leading to, e.g., allergy or atopy (51). The production of IL-10, a cytokine released by Treg cells, is lower in cord blood DC of neonates of atopic mothers compared with nonatopic mothers after TLR-2 stimulation with peptidoglycan. (52). A lower number of IL-12-producing cells was found in both unstimulated (53,54) and LPS-stimulated immune cells (55) in children from allergic mothers. The expression of HLA Class II on monocytes is lower in children in whom allergy emerged within the first 2 y of life (56). Although the DC distribution did not differ in cord blood of healthy neonates compared with cord blood DC in neonates that acquired atopy at a later age, the number of immature plasmoid DC (CD11c-CD123low+, DC) was increased in children who acquired atopic dermatitis compared with healthy nonatopic children (57), whereas the amount of mature plasmoid DC (CD11c-CD123high+) was decreased significantly.

Maternal atopy is found to be associated with high $CD4^+IL\text{-}13^+$ cord blood cells and stronger Th2 IL-13 responses to the milk allergen $\beta$-lactoglobulin (55,58). Atopic diseases at 1 y of age have been associated with high IL-13 production and $CD4^+IL\text{-}13^+$ cells in cord blood as well (59).

It is of great interest to note that the development of atopy in childhood is associated with a reduced capacity to develop immunological memory against BCG immunization during infancy (60) and slower development of responses to diphtheria/pertussis/tetanus vaccination (61).

Consequences of an impaired immune maturation for the onset of autoimmunity are not yet known. Some studies suggest that breast-feeding may protect against type 1 diabetes, and others suggest a protective effect against multiple sclerosis and rheumatoid arthritis as well. However, the results are still controversial, and further research is needed (62). An interesting research hypothesis is to test the role of IL-6 and TGF$\beta$ in the onset of autoimmune diseases in infants (63,64). Because IL-6 and IL-23 are present in the serum of infants, and breast milk contains both IL-6 and TGF$\beta$, there might be improper Th17 cell activity in infants who develop autoimmunity later in life. Th17 cells have been shown to be involved in autoimmune disorders and are a newly identified subset of T cells (**Fig. 1**).

### The interplay among genes, nutrition, and environment

The interplay between mother and child during pregnancy and after birth and the introduction of nutrition (breast-feeding and

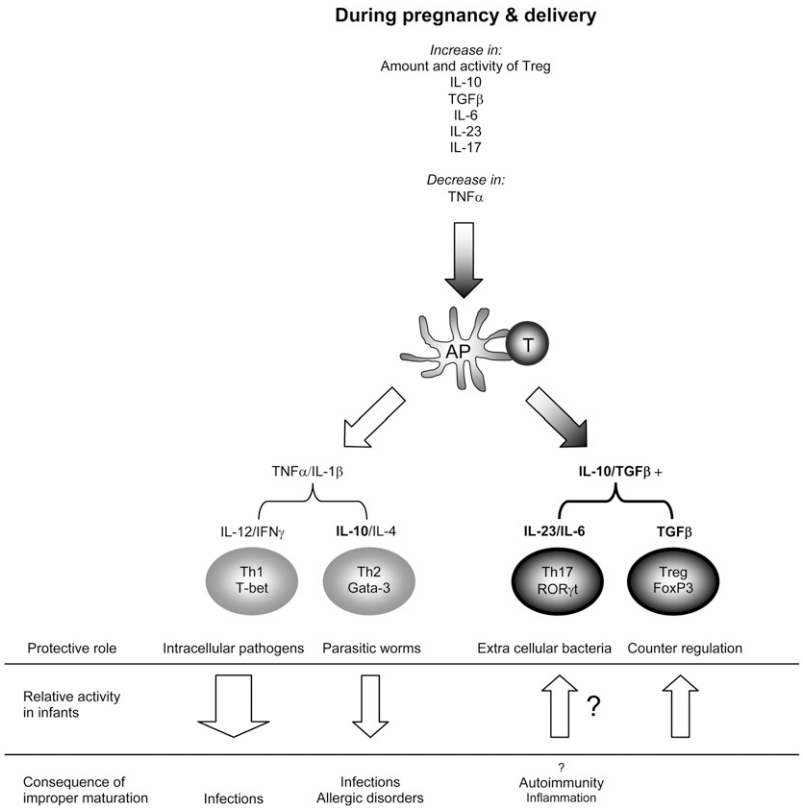


**FIGURE 1** Relative activity of different T-helper subsets in infants compared with adults and the possible consequence for acquiring immune disorders. The development and differentiation process of T-helper subsets are shown as illustrated by Reiner (89). As described in the text, during pregnancy, Th1 and Th2 activity in infants is downregulated via increased production of IL-10 and TGFβ and activity of Treg cells compared with adults. Also, stress responses are altered as characterized by an increase in IL-6, IL-23, and IL-17 production, whereas TNFα and IL-1β production are tempered. Because Th17 cells have been only recently discovered, no knowledge is available on the activity of this subset in infants. However, based on levels of IL-6, IL-7, and IL-23 found in serum in infants, it is postulated that the activity of Th17 is increased in infants. Investigations are needed to prove this. The differential development process of each T-helper subset does not exclude the interaction between T-cell subsets. For instance, Th1 cells are known to produce IL-23 and thereby to activate the formation of Th17 cells (90). Maturation of the immune response in infants is characterized by a higher induction of an antigen-specific Th1 response compared with an antigen-specific Th2 response and downregulation of a Treg cell response. Improper orchestration of the development of the different subsets of T cells might lead to immune-related disorders. For example, delayed induction of Th1 responses and subsequent relatively higher Th2 and Th17 activity with simultaneous loss of Treg cells during maturation might lead to uncontrolled immune responses. Data suggesting the onset of allergy via this mechanism are also described. There are no data to support the hypothesis for autoimmunity.





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the introduction of solid foods) influence the development of the immune system of the child. Breast milk can be a source of antigens to which the immune system becomes tolerant easily. Breast milk provides factors that modulate immune maturation and subsequently the immune response. Breast milk provides factors that influence the microbiota and in turn affect antigen exposure and immune maturation (3).

The content of breast milk has evolved over millions of years not only to provide nutrition but also to protect the offspring from infections and to induce immunological tolerance against common nondangerous compounds. It is generally thought that each individual mother provides for the specific developmental needs of her individual child, which are rapidly evolving during the first months of life (65). However, what is the immunological consequence if the mother is genetically or environmentally disposed to cause improper immune maturation in her offspring and subsequently transfers, indirectly or directly, immunological disorders?

## Breast milk and its immune-modulating compounds

The concept that breast-feeding can modulate the immune system despite a genetic predisposition has been supported by fundamental experiments using specific strains of mice. If $rag2^{+/-}$ mouse pups, mice that do not contain T cells, are breast-fed after birth by $rag2^{-/-}$ mice, the immune response as measured by antigen-specific immunoglobulins is impaired, whereas $rag2^{+/-}$ pups breast-fed on $rag2^{+/+}$ mice showed specific immune responses (66).

Antibodies in milk were detected in 1903 by Schlossman and Moro. Maternal antibodies do have immune-modulating effects in the offspring. Availability of maternal antibodies during pregnancy is guaranteed by transport across the placenta by neonatal Fc-receptors. After birth, immunoglobulins are found in colostrum and mature breast milk.

IgG and IgM are transferred from mother to her infant via breast milk. As for IgA, it is known that these antibodies protect the infant against infections passively. They also influence the immune repertoire of the offspring. The repertoire of idiotypic (ID) antibodies, T-cell clones, and B-cell clones is determined by antiidiotypic interactions of the autologous host, in this case the receiving infant. This idiotypic network has been postulated by Jerne (67) in the early 1970s. Subsequently, in the late 1970s and early 1980s, many experiments were performed to establish the effect of maternal antibodies on the immune response in offspring, to prove that the ID network does play a role in the immune response of offspring (68). A systematic review of all these data concluded that maternal ID and anti-ID interactions during the first 3 wk of life in mice induce immune imprinting (programming) and are decisive for the repertoire of T cells and B cells. The effects of maternal antibodies on the immune response later in life in the offspring are shown repeatedly, as reviewed by Lemke et al. (68) (**Table 1**).

There are serious indications that breast-feeding modulates vaccination responses in infants positively as compared with formula-feeding in children. Measles, mumps, and rubella vaccination resulted in significant changes in $CD8^+$ T cells, natural killer cells, and mitogen-induced IFN$\gamma$ production compared with baseline in 1-y-old breast-fed children but not in formula-fed children. No differences were observed in mitogen-induced IL-4 or IL-10 production, suggesting enhanced development of Th1 responses in breast-fed children (69). Another study demonstrated that breast-feeding induced higher serum antibody responses to oral polio vaccination but not to other systemic vaccines (70). In addition, multiple reports in literature show that breast-feeding lowers the incidence of infections (71–73) and atopy-related disorders (74–78).

In contrast, there are some studies showing a higher risk of developing allergic diseases and sensitization if duration of breast-feeding is relatively long in asthmatic mothers. The most recent of these (79) reported that New Zealand children were more likely to develop allergic diseases and sensitization at 13 y of age if they had been breast-fed ($n = 504$) compared with formula-fed infants ($n = 533$). The duration of breast-feeding was also positively associated with the onset of allergic diseases in these children. Other studies, including a German investigation (80,81) and a report from North America (82), documented an increased risk of asthma in breast-fed children whose mothers were asthmatic, compared with those without maternal asthma. These data suggest that the genetic predisposition of the mother is reflected in the composition of breast milk and subsequently leads to alteration of the immune response in the children.

The studies cited above are highly controversial because systematic reviews still show a protective effect of breast-feeding against allergic diseases (76–78). However, it should be noted that most studies only compare infants with paternal and maternal heredity for atopic disease and do not correct for other factors in the analysis. In addition, confounding factors for the onset of asthma are respiratory infections, and, as discussed

**TABLE 1** Known effects of maternal antibodies on the immune response in the offspring in mice[1]

| Short description of effect | Summary of studies |
|---|---|
| Improvement of immune function | Quantitative improvement of immune responses were found as measured by the enhancement of antigen-specific immune responses, conversion of a primary into a secondary humoral response. Induction of antigen-reactive IgM antibodies in nonimmunized F1 animals by maternal immunization with antigen or antiidiotype antibodies. |
| Improvement of immune function in F2 progeny | Maternal immunization(s) or transfer of quaternary monoclonal antihapten (2-phenyl-oxazolone) antibodies induce IgM antibody formation in nonimmunized F1 mice and production of secondary antibody titers after primary immunization of F2 progeny. Moreover a diversification of the primary antibody repertoire was found together with a selection of primary antibodies with strongly enhanced affinities. |
| Increase of resistance against infections and tumors | Maternally derived antiidiotype antibodies can protect adult mice against microbial infection or tumor cell growth. |
| Inhibition of allergic responses | Allergen- and isotype-specific suppression of IgEresponsiveness. Maternally derived immune or exogenous monoclonal IgG antibodies inhibit systemic and airway IgE responses. The effects are only found until age 4 mo; IgE suppression is then prolonged until age $>$ 1 y. Maternal IgG thus reverses a seemingly genetically based IgE high-responder state into non- or low responsiveness |
| Transfer of autoimmunity | Abrogation of autoantibody transfer from mother to child prevents the incidence of diabetes in NOD mice later in life. |

[1] The data presented in this table are taken from Lemke et al. (68) and references therein and from Greeley et al. (83).





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above, breast-feeding does protect against respiratory infections. Most studies do not correct for this phenomenon.

The evidence in regard to autoimmune diseases is very poor. Sjögren's syndrome, a syndrome caused by autoantibodies against Ro/Sjögren's syndrome A antigen and lupus/Sjögren's syndrome B antigen and systemic lupus erythematosus and autoimmune ovarian diseases are examples in which maternal transfer of autoimmunoglobulins might play a role in the onset of the disease in the infant (68,83). Similarly as in allergic disorders, infections play an important role in the onset of autoimmunity (84). It is very difficult, therefore, to prove the concept in epidemiological studies.Although there are indeed indications that breast-feeding influences the development of the immune system in infants, unfortunately, not all compounds in breast milk responsible for immune modulation have been discovered as yet, and this area needs more research attention.

In addition to IgGs and IgMs, breast milk contains other immune-modulatory compounds as well, including nucleotides, specific amino acids (taurine, polyamines), PUFA (eicosapentaenoic acid, docosahexaenoic acid), monoglycerides, leuric acid, linoleic acid, cytokines (IL-8, IL-7, TNF$\alpha$, adiponectin, leptin), isoforms of immunoglobulins (sIgA), soluble receptors (CD14, sTLR2), cytokines and chemokines, antibacterial proteins/peptides (lactoferrin, lysozyme, $\beta$-lactoglobulin, casein), and intact immune cells. **Table 2** includes a list of compounds that can be found in breast milk with experimental proof for immune modulation in mice and/or humans.

Recently much attention has been paid to the effects of probiotics, prebiotics, or oligosaccharides and polyunsaturated fatty acids. Several reviews have appeared in this area recently (3,85).

To indicate current knowledge of immune-modulatory compounds from breast milk, a brief summary is given on the known effects of the gut microbiota. It is known that the maturation of the gastrointestinal tract is influenced by the microbiota. This was already shown in 1905. The microbiota of breast-fed infants contains more bifidobacteria than that of adults or formula-fed infants. This has been described repeatedly. The microbiota

**TABLE 2** Compounds in breast milk with immune-modulating capacities[1]

| Components | Activity | References |
|---|---|---|
| Proteins | | |
| Cytokines/chemokines | Immune modulation | |
| TGF$\beta$, IL-10, etc. | Antiinflammatory effects | (28,91–96) |
| TNF$\alpha$, IL-1$\beta$, IL-6, etc. | Proinflammatory effects | |
| IL-4, IL-5, IL-13 | Stimulation of Th2 immunity | |
| IFN$\gamma$, IL-2, IL-12 | Stimulation of Th1 immunity | |
| IL-8, eotaxin, RANTES, etc. | Chemoattractant function | |
| Soluble receptors/antagonists | Antiinflammatory effects | (97,98) |
| sCD14, TNFR I and II, IL-1RA, etc. | | |
| Defensins | Antimicrobial activity | (99) |
| sIgA, IgM, IgG antibodies | Antiadhesive, antiinfective effects | (100,101) |
| Hormones/growth factors | Stimulate barrier function, gut development, immune modulation | (102–106) |
| Prolactin, leptin, IGF-1, etc. | | |
| Enzymes/abundant proteins | Antimicrobial activity, immune modulation | |
| Lysozyme | Microbicidal effects, immune modulation | (107,108) |
| Lactoferrin | Microbicidal effects, iron-binding capacity, immune modulation | (109,110) |
| $\alpha$-Lactalbumin | Antimicrobial peptides on digestion | (111) |
| $\kappa$-Casein | Contains an antiadhesive carbohydrate component | (112) |
| Haptocorrin | Antimicrobial activity by vitamin B-12 binding | (113) |
| Lactoperoxidase | Antimicrobial activity | (114) |
| Carbohydrates | | |
| Oligosaccharides, glycoconjugates | Antiadhesive function, modulation of microbiota and immune function | (85,115,116) |
| Antioxidants | Radical scavenging, antiinflammatory activity | (117) |
| Vitamins A, C, E, catalase, glutathion peroxidase, etc. | | |
| Lipids | | |
| Free fatty acids, monoglycerides | Detergent-like antimicrobial and antiviral effects | (118) |
| PUFA | Immune modulation, modulation of prostaglandin production | (38,119) |
| Arachidonic acid, docosahexaenoic acid, etc. | | |
| Nucleic acids | | |
| Nucleotides, nucleosides, oligonucleotides | Enhancement of antibody production, metabolic effects | (70,120,121) |
| Subcellular components | | |
| Gangliosides | Modulation of microbiota and immune function | (122,123) |
| Exosomes | Immune modulation, induction of Treg cells | (124) |
| Cells | | (125,126) |
| Neutrophils, macrophages | Antimicrobial activity | |
| T and B lymphocytes | Possible impact on immune maturation | |
| Bacteria | Modulation of microbiota and immune function | (127,128) |
| Bifidobacteria | | |

[1] The list as shown depicts only compounds that can influence the immune system in the offspring in well-nourished circumstances. For instance, zinc is not depicted in the list, although zinc deprivation/malnourishment does lead to immune deficiency in the offspring.





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species are thought to acidify the content of the gastrointestinal tract and therefore inhibit its colonization by pathogenic (pH-sensitive) bacteria (reviewed by Vos et al. (85)). Recent work suggests that viable bacteria are present in breast milk. Bacterial DNA is transported from the mother's intestine to the mammary gland via an endogenous cellular route (86).

Data from domestic and experimental animals and epidemiological studies suggest that the microbiological environment of the infant plays a crucial role in the maturation of the immune system. In particular, research has been performed on the role of the commensal microbiota of the gastrointestinal tract. Infections, in particular in the gastrointestinal tract and the respiratory tract, may also contribute to the maturation of the immune system. Most articles are focused on the upregulation of the Th1 response (51). Although the targets of the microbial agents are not as yet fully known, it is thought that APC play a pivotal role (87).

Most studies have dealt with the effects of specific probiotic strains or prebiotics in infants on allergic symptoms and the incidence and severity of infections. Long-term effects of changing the microbiota on the immune system of the offspring have not yet been studied (85). Therefore, the question remains whether other immune-modulating compounds from human breast milk can have the similar long-term effects as described in mice.

## Summary

Because of the interaction between mother and child during pregnancy, excessive and destructive inflammatory responses must be avoided during the development of the fetus. Active inhibition of the immune system of the fetus to inhibit "immune abortions" results in an immature immune system at birth and during the first years of life, making the child susceptible to infections and immune disorders.

The development of the immune system in infants is characterized by the induction of an antigen-specific immune response and maintenance of immunological tolerance against commonly found compounds in the environment of the infant. Improper immune maturation may lead to lifetime immunological disorders such as allergic disorders and autoimmunity.

The interaction between mother and child postpartum plays an important role in the development of the infant's immune system. The immunological memory of the mother is passed to her infant via breast milk, and breast milk contains a variety of immune-modulating compounds causing immunological imprinting and programming (88).

This review clearly illustrates that knowledge of the development of the immune system in infants has numerous black holes. Investigations on the interplay between mother and child after birth, including studies of the content of breast milk, are needed to support the described concepts. Because the active downregulation of the immune system during pregnancy and infancy shows similarities with immunological tolerance in later life (2), the investigations will not only fulfill our academic curiosity but will also lead to new targets and therapeutics to prevent and/or inhibit allergies and autoimmune diseases.

Other articles in this supplement include references (129–138).

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