

2

Breast Milk: Components with Immune Modulating Potential and Their Possible Role in Immune Mediated Disease Resistance

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Key Points

- Breast milk contains several interesting immune modulating components with specific modulating potentials, which are known to have a clear role in immune mediated disease resistance later in life.
- The development and deterioration of our immune defenses show differences as well as similarities in immunological challenges throughout life.
- Each phase in life puts specific requirements on nutrition, although no clear statement can be made based on literature as to what the exact dietary requirements are in order to fully support the immune system during life.

Key Words: Immune-modulation, protection, breast milk components, infant, adult, disease.

2.1 INTRODUCTION

The ontogeny of the immune system starts early in gestation but is not completed at birth. The highly protective germ-free environment and the need to avoid immunological interactions of the infant against the mother seems to be the main reason for this “physiological” immaturity of the immune system in newborn infants. The immaturity is characterized by deficiencies of the innate and the adaptive immune responses. The insufficient innate immune response is evident by an improper chemical barrier (1), a weak mucosal barrier integrity (2), reduced NK cell responsiveness, defective APC

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function (3), and reduced gene expression in DCs (i.e., IL-12) (4), which is accompanied by DCs biased against Th1 response induction (5). In addition, the pathogen recognition apparatus, although present does not respond properly in human neonates, resulting in, for example, impaired TLR responsiveness and pathogen recognition (1,6). Furthermore, it is increasingly recognized that regulatory T cells, which inhibit excessive immune responses thereby maintaining peripheral T-cell tolerance, are particularly abundant and potent at birth (7). The adaptive immune system still needs to mature completely and get in contact with pathogens in order to build upon a proper memory. T-cell generation (8) and function (9) in neonates is not fully developed. In addition, neonatal B cells are capable of switching to IgG1 and IgG3 during the first 2 years of life, but the switch to IgG2 and IgG3 is inadequate during this period. To compensate the lack of protection in the fetus and newborn, microbe-specific maternal IgG antibodies move across the placental barrier to provide some vital protection. After birth, breastfeeding maintains the maternal–fetal immunological link by transferring immune competence of the mother to her infant. Anti-infective compounds provide directly defense potential and immune modulating compounds stimulate the postnatal development of all levels of the immune system. Both groups of factors contribute to the protection during lactation but there is broad consensus that the immune modulation of the infant during lactation has also consequences for the immune response after lactation. The present review describes the protective and immune modulatory factors in breast milk which are considered important for the neonate defense system during the very vulnerable period immediately after birth and also for the programming of the immune system for later life.

2.2 NATURAL DEFENSES THROUGHOUT LIFE

In principle, the human body is protected by various nonspecific defense mechanisms. Pathogens that break through the mucosal surface barrier encounter two additional levels of defense, the innate and acquired immune responses. The efficient cross-talk between innate and acquired immunity enables the powerful host defense protecting us from immune-related disorders and pathogenic invaders. The innate immune response is immediately activated after infection, while the acquired immune response takes at least several days for full development. Increased susceptibility to infections and decreased immune responsiveness are indeed present during the first years of life and are in part related to the incapacity of the infant's immune system to respond properly. It is important to maintain proper levels of immune defenses throughout life as they are challenged daily. During the different phases of life, several factors influence our immune system and immune responsiveness, such as nutrition, hormonal changes during adolescence and so on. A vast amount of literature is available on the role that nutrients, that is, as present in breast milk (as reviewed in this article), have on the development of the immune system; a lot less is known about the exact requirements in the phases thereafter, that is, in toddlers, during adolescence, and in the later stages of life. Although it is clear that each phase in life puts specific requirements on nutrition, no clear statement can be made based on literature as to what the exact dietary requirements are in order to fully support the immune system during these stages in life.

The aging processes induce multiple changes in metabolism, the hormones network, the immune system, which can modulate the efficiency and effectiveness of the immune system, determining a response to stressors. For example, normal aging is associated with deregulated immune and inflammatory responses, which results in increased susceptibility toward infections in the elderly. Host resistance in general undergoes changes in both a qualitative and quantitative manner with aging as a declined T cell function is the best-characterized feature of immunosenescence. The development and deterioration of our immune defenses is schematically represented in Fig. 2.1, illustrating differences and also similarities in immune challenges throughout life.

2.3 ROLE OF BREASTFEEDING

The human immune system can be easily modified during the first years of life, which is necessary to complete protection against infections and sufficiently tolerate non-harmful environmental agents. Breastfeeding is adapted to the infant's requirements and may compensate for the relative inefficiency of host defense by providing considerable amounts of both nonspecific as well as pathogen-specific secretory IgA (sIgA). These antibodies, which are formed as a consequence of the previous exposure to infectious agents by the mother, can bind and inactivate potential harmful pathogens. In addition to the antibodies, breast milk contains several other nonspecific factors that have antimicrobial effects, or provide protection to the infant through alternative routes. These factors with immunological, hormonal, enzymatic, trophic, and/or bio-activity present in breast milk may offer passive protection (10). Other factors like macrophages and leukocytes, largely present at the beginning of lactation, may exert a more modulatory effect on the neonatal immune system and provide additional protection (11). Breast milk contains several immune-modulatory compounds, including the antibodies, IgGs, IgMs, isoforms of immunoglobulins (sIgA), nucleotides, specific amino acids (taurine, polyamines), PUFA's (eicosapentaenoic acid, docosahexaenoic acid), monoglycerides, lauric acid, linoleic acid, cytokines and chemokines, soluble receptors (CD14, sTLR2), antibacterial proteins/peptides (lactoferrin, lysozyme, β -lactoglobulin, casein), prebiotics, oligosaccharides, and intact immune cells as well reviewed by M'Rabet et al. (12). Several of these components have been extensively studied on their specific immune modulating potencies in general as reviewed by Calder et al. (13).

2.4 IMMUNE MODULATION PROPERTIES OF BREAST MILK

Several reports confirm that the immunological components of human milk can influence the infant's immune response. The influence of breastfeeding compared to formula feeding on immune modulation has been studied in infants by measuring, for instance, vaccination responses, but also incidences of infections, allergies, etc. As recommended by the WHO and the International Life Science Institute, the immune response after vaccination can be taken as an objective measurement or model to evaluate the immune response (14). A vaccination response can be measured by vaccine-specific *ex vivo* cell proliferation and cytokine production and by the level of neutralizing antibodies (9) cov-

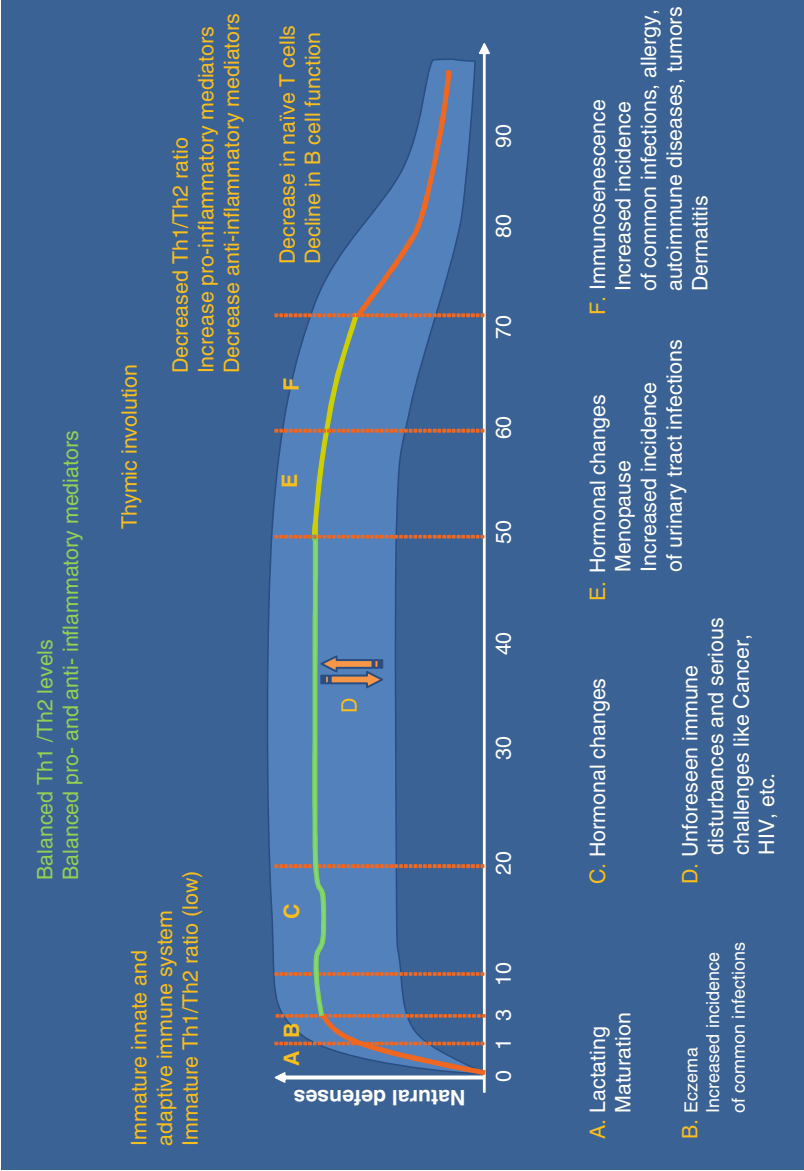


Fig. 2.1. Immunity throughout life. This figure schematically represents the level of human natural immune defenses throughout life, from the developmental stages during infancy until immune-senescence at the latest stages in life. Several stages can be identified, with unique immunological features and influences of nutrition as discussed within this review.

ering both the efficiency and magnitude of antigen-specific T and B cell responses. For example in 12-month-old children receiving breast milk, an increased production of IFN-gamma and increased percentage of CD56+CD8+ cells (activated cytotoxic T cells) after measles–mumps–rubella vaccination were seen, as compared with formula-fed infants. In addition, cytokine responses to measles, mumps, and rubella vaccination differed between the two types of nutrition (15). These results are suggestive of a more Th1 type of responsiveness in breastfed infants as compared to formula-fed infants.

2.5 ANTI-INFECTIVE PROPERTIES OF HUMAN MILK

Several studies have shown the protective capacity of breast milk. It is known that breastfeeding reduces the incidence of gastrointestinal and nonenteric infections in infants because of its antimicrobial activity against several viruses, bacteria, and protozoa as reviewed by Chirico et al. (16). It was shown in a recent meta-analysis that infants who were breastfed for more than 4 months showed a significant reduced incidence of respiratory tract infection requiring hospitalization, as compared to infants who were not breastfed (17). In addition, the risk for infectious diarrhea is higher in nonbreastfed infants, than for infants receiving human milk. Other studies showed that breastfeeding provides protection against urinary tract infections and otitis media (18, 19). It can reduce infant mortality, and protect, for instance, against neonatal meningitis and septicemia. In addition, protection is also clearly demonstrated against respiratory infections. These studies show the clear protective nature of human milk against all sorts of invasive pathogens. In addition to that, human milk has been shown to reduce the development of inflammatory conditions such as allergy (20), Crohn's disease, ulcerative colitis, and protect possibly against certain other immunological diseases such as insulin dependent diabetes and tumors in infancy (21, 22). This, moreover, emphasizes the diversity of activity and active components present in human breast milk.

2.6 ANTI-INFLAMMATORY PROPERTIES OF BREAST MILK

During the bacterial colonization of the newborn's mucosal surfaces, including the skin and gut, a huge amount of microbial components are brought in acute contact with the sterile neonate. The coordination of the inflammatory response developed after this first contact is of vital importance. The epithelial layer, together with the intra-epithelial and lamina propria immune competent cells, is the most important player in regulating the recognition of microorganisms and maintenance of gut homeostasis. Spontaneous integrin expression on several lymphocytes at 6 months of age was reported significantly lower in breastfed than formula-fed infants, which is indicative for the anti-inflammatory potency of human breast milk.

2.7 THE ONSET OF ALLERGIES VS. BREAST MILK

According to the hygiene hypothesis, for instance, the exposure of microbial components including TLR agonists early in life serves to polarize the immune response away from Th2 responses toward a more Th1 type of response, thereby reducing the

onset of allergy and/or atopy. Consistent with this hypothesis is the inverse epidemiological relationship between the decreasing rate of common infections (in industrialized countries) and the parallelly increasing rate of allergy and autoimmune diseases. However, the improving vaccination strategies occurring simultaneously may hamper this view. It is clear, however, that the onset of allergy is influenced by breast milk as well as atopy-related disorders (23–25) although some controversy exists regarding the beneficial length of breastfeeding (26–28). In a multidisciplinary review of the literature (1966–2001) van Odijk et al. (23) showed that exclusive breastfeeding reduces the risk of asthma, particularly, strong effects in infants with atopic heredity. These protective effects increase with the duration of breastfeeding (up to at least 4 months). These protective effects of human breast milk seem to persist at least during the first decade of life.

2.8 DURATION OF BREASTFEEDING

While discussing maternal factors and their influence on the immune system, it is important to recognize that human milk composition differs in time elapsed postpartum, in density, and composition. The favorable duration of breastfeeding differs between country and continent, due to the environmental challenges and cultural opinions. Several studies have been performed to determine the optimal duration of breastfeeding. In general, it can be stated that breastfeeding for less than 2 months may be deleterious because of lack of exposure to the protective factors in breast milk. In addition, there are some indications that breastfeeding for longer than 8 months is associated with increased BMI and percentage of body fat in later life (29). Currently, it is recommended to breastfeed exclusively during the first 6 months of infant life. Although breastfeeding can prevent 13–15% of child deaths in low-income countries, in some circumstances, breastfeeding can present a terrible dilemma, for instance, in the risk for transition of pathogens like HIV. Through breastfeeding, over 300,000 children are infected with HIV every year, as estimated by UNAIDS. However, a significant increase in early mortality was identified in studies in Kenya (11% vs. 9%) and Botswana (9.3% vs 4.9%; $P = .003$) in formula-fed versus breastfed infants (30). When HIV-positive mothers breastfeed exclusively, infection with HIV of their babies is relatively low (4%). This risk is lower than that in babies who receive other food or liquids in addition to breast milk before 6 months of age. Exclusive breastfeeding protects the integrity of the intestinal mucosa of the infant, which may thereby be a more effective barrier to HIV infection. Therefore, it has been advised that in developing countries, early exclusive breastfeeding reduces the risk of postnatal HIV-1 transmission and increases HIV-free survival (31). However, in better resourced areas, these differences have not been reported. This reinforces the UNAIDS guidelines on breastfeeding for HIV-infected mothers – namely, “where replacement feeding is acceptable, feasible, affordable, sustainable, and safe, avoidance of all breastfeeding is recommended, otherwise exclusive breastfeeding is recommended for the first few months of life.” The WHO established a global determined goal, which states that in 2010 within the healthy population at least an initiation rate of 75% breastfeeding should be possible to reach. In addition, a breastfeeding rate of 50% at 6 months and 25% at 1 year is favorable. Although initiation rates approach 70%, rates at 6 months (33%) and 1 year (18%) currently remain low; in 2009, these goals have not been reached yet.

2.9 IMMUNE MODULATION CAPACITY OF SPECIFIC COMPONENTS AND EFFECT LATER IN LIFE

Researchers are actively investigating how dietary modifications that influence the immune system can be used to reduce the risk of various diseases or to improve their management. Most host defense mechanisms are impaired in malnutrition, even if the nutritional deficiency is only moderate in severity. Protein-energy malnutrition is often accompanied by deficiencies of micronutrients such as vitamin A, vitamin E, vitamin B6, vitamin C, folate, zinc, iron, copper, and selenium. For example, the rapid proliferating T cells responding to pathogens are especially affected by the lack of essential nutrients, resulting in a decrease in their numbers. Severe and chronic malnutrition may even lead to atrophy of the thymus and other lymphoid organs affecting the basis of our immune apparatus. The possibility that supplementation with certain nutrients, like vitamin C, D, or E, at levels above the Recommended Dietary Allowances (RDA), and food constituents such as probiotics and prebiotics may improve immune function in vulnerable individuals, like the elderly or immune compromised, but also in the general population is subject to increasing research. Compounds with specific immune

Table 2.1
Immune modulating breast milk components^a

Components	Activity	References (infant)	References (adult)
<i>Carbohydrates</i>			
Oligosaccharides, glycoconjugates	Modulation of microbiota and immune function, antiadhesive function	(66–68)	(69, 82)
<i>Antioxidants</i>			
Vitamin A, C, E, catalase, glutathione peroxidase, lutein, etc.	Radical scavenging, anti-inflammatory activity	(63, 70)	(62)
<i>Lipids/PUFAs</i>			
Free fatty acids, monoglycerides	Antimicrobial and antiviral effects	(10)	(73)
Arachidonic acid, docosahexaenoic acids, etc.	Modulation of prostaglandin production Immune modulation	(71, 72)	
<i>Carrier proteins</i>			
Lactoferrin, transferrin, vitamin B-12 binding protein, steroid binding protein, α -lactalbumin, κ -casein	Antimicrobial activity, immune modulation, microbicidal effect and iron binding capacity	(74–76)	(35, 36, 77).
<i>Bacteria</i>			
Bifidobacteria, Lactobacillus	Modulation of microbiota and immune function	(78–81)	(55, 59)

^aThe list is a small selection of immune modulating compounds present in breast milk, with the focus on immune-modulating ingredients which are also used in daily diet/supplements to improve immune functions

modulation capacity present in breast milk and used to supplement daily diet are depicted in Table 2.1 and some of which are discussed below in more detail.

2.9.1 *Proteins*

Major nutrient groups with several important bioactive factors are the proteins, including immune-globulins, lactoferrin, lysozyme, α -lactalbumin and casein. Lactoferrin is a proteolysis-resistant glycoprotein and one of the most abundant proteins in human milk. An impressive range of effects have contributed to lactoferrin which include direct antimicrobial activities against a large panel of microorganisms, including bacteria, viruses, fungi, and parasites, and anti-inflammatory effects in addition to anticancer activities. Lactoferrin limits bacterial and fungal growth by competing for essential iron and may act as an alarmin to promote the recruitment and activation of APCs and antigen-specific immune responses (32–34). In addition, epithelial growth-promoting activities have been associated with lactoferrin. Ingesting lactoferrin relieves some symptoms of *H. pylori* gastric infection and increases the eradication of *H. pylori* in the stomach (35). In addition, benefits have been shown on rotaviral gastroenteritis and the possible inhibition of colorectal adenoma development. This indicates that protective immune modulatory proteins are present in human milk and may be of use in disease-specific conditions. The exact mechanism of action as well as the benefit for healthy adults still needs to be addressed.

Besides lactoferrin other interesting proteins are present in human breast milk including the enzyme lysozyme which inhibits the growth of many bacterial species by disrupting the bacterial cell wall, more specifically, the proteoglycan layer. In addition, casein may inhibit the adhesion of various bacteria at different epithelial sites. Lactalbumin is part of an enzyme complex that synthesizes lactose, and upon modification seems to contribute to the apoptosis of malignant cells. The anti-secretory factor is a protein present in most tissues in the body, and the plasma levels of anti-secretory factor can be increased by exposure to bacterial enterotoxins and to specially processed cereals. The anti-secretory effect has been shown in patients with secretory diarrhea, and the additional anti-inflammatory effect of anti-secretory factor has been demonstrated in ulcerative colitis and Crohn's disease (36).

2.9.2 *Lipids*

Another major nutrient and energy source in breast milk are the lipids, including long chain polyunsaturated fatty acids (PUFA), triglycerides, glycosphingolipids and free fatty acids (FFA). Monoglycerides, digestive products of triglycerides and some FFAs may have some lytic effect on viruses. Glycosphingolipids have been hypothesized to be one of the non-immunoglobulin compounds in human milk that can contribute to the protection against pathogens. Preterm infants given an adapted milk formula with gangliosides had fewer *E. coli* in feces and higher bifido-bacterial count than infants fed normal control formula (37). PUFAs such as arachidonic acid (AA) of the omega-6 (n-6) family and eicosapentaenoic acid (EPA), gamma-linoleic acid (GLA), and docosahexaenoic acid (DHA) of the omega-3 (n-3) family can potently alter the functioning of immune cells. In general, diets rich in n-3 PUFA tend to inhibit excessive immune responses which are associated with chronic inflammatory diseases such as asthma and

rheumatoid arthritis among others, as nicely reviewed by Riediger et al. (38). Whereas diets rich in n-6 PUFA tend to promote immune responses, which can lead to inflammation affecting chronic inflammatory diseases. The ratio of n-6 to n-3 PUFA may therefore be more important than the absolute amount of each of these classes of fatty acids in the diet. The basis for the anti-inflammatory properties of dietary fatty acids like EPA and GLA is their ability to replace AA ultimately as substrate for the synthesis of eicosanoids.

n-3 fatty acids are required for normal conception, growth, and development of an embryo. During the third trimester, approximately 50–60 mg/day of maternal DHA stores are transferred to a fetus via the placenta. Fish oil supplementation modulates immune function in healthy infants (39). Human milk contains DHA, and several organizations recommend supplementing infant formulas with DHA for infants and premature infants. DHA is particularly highly concentrated in the brain and retinal membranes, especially in photoreceptors, and is therefore assumed to play a critical role in both vision and cognitive function. However, several studies show either no improvement or slight improvement in visual acuity of infants receiving DHA supplemented to the infant formula compared to controls (40, 41).

Inappropriate immunologic activity, including inflammation, is a characteristic of many common human disorders. The oral supplementation of n-3 PUFAs has been evaluated in various clinical studies for their immunomodulatory capacity. Despite some inconsistencies in literature, it is clear that the addition of n-3 PUFAs like EPA and GLA to the diet leads to marked decreases in AA-derived eicosanoids and pro-inflammatory cytokines. Moreover, oral EPA and GLA have shown to be beneficial in patients with chronic inflammatory bowel disease not only in extending episodes of relapses but also reduced mucosal inflammation and production of local inflammatory mediators. In addition, it has been suggested that n-3 LCPUFA may inhibit atherosclerosis development by blocking the production of cytokines which promote inflammation. For example, the supplementation of 1.5 g/day AA for 7 weeks increased PGE2 production by leukocytes. In another study, 18 g/day of fish oil (equivalent to 5 g of n-3 LCPUFAs) suppressed several indices of non-specific and specific immune responses in healthy men. The dietary intake of fish, containing high levels of n-3 LCPUFAs, may as well be protective against asthma. It is believed that the production of mediators involved in allergic responses is affected by the balance between the two types of PUFA. However, evidence from clinical trials with n-3 LCPUFA supplementation is not conclusive herein. In conclusion, EPA- and GLA-rich supplements have been used to attenuate inflammatory processes in various chronic and autoimmune diseases, for example, rheumatoid arthritis (RA), inflammatory bowel disease (IBD), asthma, psoriasis, and multiple sclerosis. In each of these situations, the benefits of decreased production of PGE2 and proinflammatory cytokines are evident. In addition, EPA and DHA give rise to resolvins, which are anti-inflammatory and inflammation resolving. Human immune cells are typically rich in AA, but AA, EPA, and DHA contents can be altered through the oral administration of EPA and DHA already within few days (42). This results in a changed fatty acid composition of the immune cells which also affects phagocytosis, T cell signaling, and antigen-presentation capability. The immune cell-membrane is important in lipid raft structure and function, and membrane trafficking, suggesting an important role for fatty acids affecting the immune cell function through a variety of complex mechanisms.

2.9.3 Carbohydrates

Carbohydrates in breast milk mainly function as important nutrients for energy production and consist of lactose, oligosaccharides, and glycoconjugates. Prebiotics are nondigestible food ingredients, generally oligosaccharides, that modify intestinal microbiota balance by stimulating the growth of beneficial bacteria, such as bifidobacteria and lactobacilli (43). A clear bifidogenic effect has been ascribed to the nondigestible oligosaccharides present in human breast milk on the gut microflora, and a positive effect on the incidence of infections at short term and possibly also long term. In addition, however, the direct effects of human oligosaccharides on immune cells cannot be excluded. Human milk derived nondigestible sialylated and fucosylated oligosaccharides, may directly inhibit the adhesion of pathogens to the mucosal surfaces (44) and protect the infant against, for instance, infectious diarrhea (45). They may as well indirectly produce a protective and immune modulatory result through a prebiotic effect on the infant intestinal microflora (46). These responses/mechanisms whereby carbohydrates and prebiotics can modulate the immune response were reviewed in depth by Vos et al., and are therefore not discussed in detail herein (47).

The complex prebiotic carbohydrate are found only in trace amounts in cow's milk but are a substantial portion of human milk sugars. The addition of carbohydrates as prebiotics to infant formula is a subject of increasing investigation, since these oligosaccharides may create a bifidogenic effect on the flora of the gut, in an attempt to reduce the number of latent invasive bacteria. In addition, several studies indicate that a mixture of oligosaccharides (fructo-oligosaccharides and galacto-oligosaccharides) was shown to reduce the incidence of infections and atopic dermatitis during the first 6 months of life (48). This protective effect of oligosaccharide supplementation early in life was still present beyond the intervention period up to 2 years of life (49, 50).

These data clearly illustrate the protective and immune modulatory factors in breast milk as important to the neonate defense system during the vulnerable period immediately after birth but as well as for the programming of the immune system for later life.

Impairment in microbiota composition can be addressed by using prebiotics. It is indicated in some studies that the oligofructose consumed by toddlers increases fecal Bifidobacteria counts and decreases fecal Clostridia counts during consumption. Besides the microflora changes, some but limited evidence is available on the immunological effect of given prebiotics in adults (83); few studies are even available in adolescents. Other benefits relate to improving bone health, reducing the risk of colorectal cancer, boosting immunity, and enhancing satiety and aiding weight management. In terms of bone health, studies in humans (51, 52) have shown that inulin/oligofructose supplementation to a diet results in more absorption of calcium, accumulation of bone mineral and improved trabecular network structure. In addition to reported immune modulation induced through the ingestion of prebiotics, more health benefits are reported through modulation of the gut microbiota via prebiotic ingestion which may improve or prevent the disruption of intestinal permeability in humans (53, 54).

The glycoconjugates although not that abundantly present in breast milk may be essential in inactivation and binding to specific bacterial (*V. cholera*) and viral ligands (rotavirus).

2.9.4 *Bacteria*

At the time the fetus leaves the protective germ-free environment, it lacks antigenic experience and stable flora on all mucosal sites, including the skin and the gastrointestinal tract. The intestinal microbiota is important in several aspects related to the digestion of food and establishment, and the maintenance of gastrointestinal immune defensive barrier. A stable microbiota composition will improve the resistance to colonization by pathogens; it controls proliferation and differentiation of epithelial cells. By definition, a probiotic is a life microorganism which has a health benefit on the host. Specific strains of probiotic bacteria exert different effects on the immune system. Therefore, a generalization of the category would be inaccurate and misleading. The effects of probiotic strains on gut health in adults is well established, as well indicated by a meta-analysis in *The Lancet* (55). Feeding with breast milk may add to the development of a healthy intestinal microflora. At the age of 1 year, differences still exist in microbiota composition of formula and breastfed infants (56). The intestinal microbiota composition of breastfed infants is less diverse, more bifidogenic than bottle-fed infants. Several components of breast milk can contribute to this observation, including the presence of some bacteria or bacterial fragments (57) as well as prebiotics like nondigestible oligosaccharides or certain peptides. Positive effects have been described as to the development of the gut toward a more bifidogenic environment (58).

One of the most common gastrointestinal complications in premature babies is necrotizing enterocolitis. A meta-analysis of different organisms used as probiotics in this situation has shown that results are generally positive [Deshpande G, Rao S, Patole S. Probiotics for prevention of necrotizing enterocolitis in preterm neonates with very low birthweight: a systematic review of randomized controlled trials. *Lancet* 2007; 369:1614–20]. Again, caution is needed in that it may not be applicable for all probiotics. As the inexperienced newborn is stabilizing its microbiota in conjunction with immune responsiveness during the first months of life, a disturbance of this delicate balance may involve serious risks; additionally, the effects on immune responsiveness later in life are not defined.

The immune-enhancing potential of probiotics has been reported frequently; the mechanism by how these effects may be occurring, however, has not been elucidated. Recently, some evidence of how probiotics may influence the immune system in humans in the short term, that is, directly after intake, has been published by the group of Kleerebezem (59). The study identified changes in mucosal gene expression patterns and cellular pathways, through the ingestion of life or death *bacteria*, in healthy adults. Although the differences indicated are minimal, the difference between the form of which these probiotics are supplemented (i.e., life vs. death) is remarkable, although not surprising since the immune system in the gastrointestinal tract is highly trained to identify /respond to possible life intruders, and neglect non-harmful agents present in our daily diet. Unfortunately, no differences between different probiotic strains have been studied yet, and the effect on longer term remains to be elucidated.

The consumption of a combination of probiotics and prebiotics also called synbiotics may approach the composition of breast milk even more, and may add individual value to the development of improved gut health and immune health (60). One recent study reports in elderly at least an additive effect on the use of a probiotic strain in addition

to a prebiotic disaccharide, increasing the levels of bifidobacteria and improving mucosal functions like bowel movement (61). However, clinical studies are clearly required to identify the individual effects of the probiotics, probiotic strains, and prebiotics in order to establish the existence of real synbiotic benefits.

2.9.5 Antioxidants

Human milk has tremendously important anti-inflammatory effects, which are in part mediated through oxygen radical scavenging. Factors contributing to the antioxidant capacity of breast milk are α -tocopherol, β -carotene, ascorbic acid, and l-histidine. Vitamins including vitamin A, C, and E have anti-inflammatory effects due to oxygen radical scavenging, and may be immunomodulatory. These antioxidants act both at the mucosal level and after absorption systemically (α -tocopherol, β -carotene). Glutathione peroxidase can decrease inflammation by preventing lipid peroxidation. The effects of vitamin E supplementation have been shown to be variable and dependent on several confounding factors like the severity of vitamin E deficiency, dosage used, and age of individuals and other factors. In the elderly, an enhanced cell-mediated immune response and decreased prostaglandin E2 production were seen when they were given high concentrations of vitamin E. A mechanistic explanation for the enhanced immune function with vitamin E supplementation in the elderly could be besides the prevention of oxidative damage in immune cell membranes, the fact that high concentrations of prostaglandin E2 may inhibit T cell function and proliferation.

Like vitamin E, vitamin C is an antioxidant and present in several vegetables and fruits. A high concentration of Vitamin C is found in immune cells and is used rapidly during infection. The mechanisms whereby vitamin C affects the immune system are hardly understood. Vitamin C may modulate the functions of phagocytes, production of cytokines, proliferation of T lymphocytes, and gene expression of monocyte adhesion molecules. Numerous controlled trials in human volunteers have been conducted to evaluate the effect of vitamin C on the incidence and severity of common cold. People who regularly take high dosages of vitamin C seem to have a slightly shorter duration of common colds (about 10%) than those who do not. Although, no effect of vitamin C supplementation were seen on the incidence of common colds in the normal population, a clear reduction (up to 50%) was seen among people that are regularly stressed by, for instance, physical activity (like marathon runners) (62).

Like vitamins C and E, carotenoids (including the precursor of vitamin A, β -carotene) are antioxidants. In contrast to vitamin C and E, Vitamin A is an example of a dietary component that enhances the immune system and has become a part of standard medical practice. Vitamin A is found to enhance the regeneration of damaged mucosal epithelium and improves phagocytic activity of neutrophils and macrophages. In vitamin A deficiency, the ability of gut immune cells to produce antibodies (IgA and IgG) against bacterial toxins is compromised. Supplementation with vitamin A restores this defect, and is known to reduce severe illness induced by measles and shorten the duration of the infection. However, the benefit of vitamin A supplementation seems not to be limited to deprived populations, but is rather effective during vitamin A-depriving infections like measles. Moreover, carotenoids including β -carotene, which is widely distributed in plants, and lycopene, a carotenoid found in tomatoes, are found to be beneficial for individuals with a compromised immune system. Epidemiological studies

suggest that the risk of respiratory infections is reduced when diets are rich in carotenoids. In particular, in the elderly, a recovery of declined NK cell activity to normal levels was observed following β -carotene supplementation. In contrast, in healthy adults with adequate carotenoid intake and normal immune responses supplementation with carotenoids did not further improve immune responses.

One of the vitamins important for infant's development, but not supplied in high amounts through breast milk, is vitamin D (63). Exclusively breastfed infants are indeed at higher risk of vitamin D deficiency than formula-fed infants. Therefore, some guidelines subscribe the supplementation of Vitamin D drops containing 200 IU to be given to all breastfed infants starting in the first 2 months of life. Vitamin D-deficient or insufficient neonates are at an increased risk of being affected by hypocalcemia and rickets. Serum calcium concentrations and bone metabolism in adults are related to Vitamin D levels. Although vitamin D deficiency increases neonatal hypocalcemia risk, it is unclear whether vitamin D insufficiency causes hypocalcemia. Increasing evidence from observational studies in infants at older ages, indicate that vitamin D insufficiency and deficiency might increase the risk of chronic diseases such as type 1 diabetes and multiple sclerosis. However, clear randomized trials on this association need to be conducted before clinicians can recommend vitamin D supplementation to reduce the incidence of type 1 diabetes. In the last decades, observations accumulated that vitamin D deficiency leads to more often and more serious respiratory infections than in individuals with sufficient vitamin D plasma levels. It has even been speculated that the increasing incidence of respiratory infections in the winter season could originate from a latent vitamin D deficiency, since solar radiation beyond 45° latitude is considerably lower in winter than in summer. Specific immune cells, that is, the macrophages, contain enzymatic capacity to make biologically active forms of vitamin D in addition to the liver and kidney. Interestingly, toll-like receptor stimulation in macrophages enhances the conversion of vitamin D precursor into active vitamin D as well as the expression of the vitamin D receptor. Vitamin D in macrophages regulates the production of an endogenous antibiotic called cathelicidin and modulates the pattern of cytokine secretion. Both cathelicidin and the cytokines enhance the defense against pathogens. Obviously, vitamin D is a key link between toll-like receptor activation and antibacterial responses in innate immunity.

2.9.6 Nucleotides

Nucleotides, nucleosides, nucleic acids, and related products in human milk are important in a number of cellular functions and have been shown to enhance immune function in infants. A variety of different roles have been assigned to ingested nucleotides, including supporting energy metabolism (ATP), nucleic acid production and their messengers (RNA, DNA and cAMP, cGMP, ADP respectively), coenzymes in metabolic processes (NAD, CoA), signal transduction molecules (cAMP), and carrier molecules in synthetic reactions (UDP, GDP, CMP). Although nucleotides are not essential nutrients, they are important in situations of increased demand and metabolic activity such as infection, or rapid growth (64). Mean values of the total potentially available nucleosides as measured in breast milk in different populations are used to guide the addition of nucleotides to infant formula. In some clinical studies, small benefits have been attributed to the addition of nucleotides to infant formulas, including

fewer episodes of diarrhea and higher plasma levels of IgA and IgM. The proposed mechanisms of action contributed to nucleotide-induced effects include increased iron absorption, increased growth of *Bifidobacterium*, improved development, and repair of the gastrointestinal mucosa, in addition to improved systemic immune responses including increased NK cell activity and IL-2 production.

2.10 CONCLUSIONS AND PERSPECTIVES

The list of bioactive factors present in human breast milk is still incomplete as investigators are continuously identifying new components like cathelicidin antimicrobial peptides (65). In addition the specific action and contribution toward the protective and immune modulatory capacity of breast milk from the individual components with their potential as ingredients supplemented to daily diet is still to be determined. The current knowledge of immune modulating components present in breast milk and their immune modulating potential including their possible role in immune mediated disease resistance later in life remains an increasingly important subject for research.

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