



Human Milk Drives the Intimate Interplay Between Gut Immunity and Adipose Tissue for Healthy Growth

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As the physiological food for the developing child, human milk is expected to be the diet that is best adapted for infant growth needs. There is also accumulating evidence that breastfeeding influences long-term metabolic outcomes. This review covers the potential mechanisms by which human milk could regulate healthy growth. We focus on how human milk may act on adipose tissue development and its metabolic homeostasis. We also explore how specific human milk components may influence the interplay between the gut microbiota, gut mucosa immunity and adipose tissue. A deeper understanding of these interactions may lead to new preventative and therapeutic strategies for both undernutrition and other metabolic diseases and deserves further exploration.

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INTRODUCTION: HEALTH BENEFITS OF HUMAN MILK

Human milk is the most efficient way to prevent child morbidity and mortality related to respiratory and gastro-intestinal infectious disease (1). It also significantly reduces the incidence of necrotizing enterocolitis (2), a serious intestinal disease in preterm newborns. The time window for breastfeeding coincides with the rapid development of the infant and its immune system and there is accumulating evidence human milk influences the child's growth trajectory and long-term health outcomes such as overweight and diabetes in later life (1, 3–5).

In this review, we discuss the role of breastfeeding in healthy growth and adipose tissue development as this is a largely unexplored area to date. Especially the contribution of individual human milk components on metabolic health remains poorly understood. Identifying human milk components that can aid in healthy postnatal growth and development could provide new preventative and therapeutic strategies for malnutrition in early life and long-term metabolic health.

REGULATION OF GROWTH BY HUMAN MILK: POTENTIAL MECHANISMS

As breastfeeding is physiological for the newborn, human milk is expected to be the diet that is most adapted to the growth needs of the infant and is therefore considered as the normative standard for infant nutrition. Breastfed infants increase more in weight, length, and fat during the first months of life, followed by a slower growth velocity up to one year of age, when compared to formula-fed infants (5). Human milk composition is extremely dynamic, and varies within a feed, diurnally, over

lactation and between mothers (6, 7). The link between the nutrients and other bioactives in human milk and growth occurs at various levels, from appetite regulation to direct sensing of nutrients by immune cells in the intestine. In the next paragraphs, we will review the multiple pathways that human milk potentially acts on to improve growth and adipose tissue development.

Protection from Infections

Infectious diseases are a major cause of growth failure (8). Therefore, the major impact of breastfeeding in early life on infectious disease prevention (1) is expected to improve growth outcomes. Indirectly, the lower antibiotic exposure in breastfed infants also has potential for profound improvement in growth as antibiotics in early life have been linked to altered growth outcomes (9–11).

Regulation of Appetite

Healthy growth promoted by breastfeeding has been linked to the establishment of infant appetite regulation and feeding pattern development (12). Two key hormones found in human milk control appetite: leptin decreases while ghrelin increases appetite and are thus thought to be involved in the regulation of milk intake, energy balance and adiposity. However, studies reporting on leptin and ghrelin in human milk and infant's weight gain and fat mass have shown inconsistent results, as discussed elsewhere (4).

A Tailored Source of Macronutrients

Breastfeeding is likely to provide the neonate with the nutrient and energy content best suited to the early stages of life. The macronutrient composition of human milk varies within mothers and across lactation but is remarkably conserved across populations (6). Lactose, the primary sugar of human milk, is the most abundant and least variable macronutrient in human milk (6). Breast milk protein content adapts to the growth requirements of the infant (13) decreasing over the first 4–6 weeks of life (6, 7). The energy content of milk correlates with its fat content, which is the most variable macronutrient in milk. Fat levels are especially high in the hind milk (last milk of a feed) and in afternoon and evening feedings (6, 7). Milk lipids, consisting for >98% of triglycerides, are packaged in milk fat globules for delivery to the infant's gastrointestinal tract. Bile salt-stimulated lipase (BSSL) is one of the key enzymes for lipid digestion in the neonate and is present in human milk to help the neonate with fat absorption. Inactive BSSL in pasteurized human milk leads to fat malabsorption and reduced growth rates in preterm infants (14). BSSL-deficient mice pups also demonstrate epithelial disruption and growth deficiency (14). Human milk also contains bile acids (15), which may aid in digestion and absorption of fat in the neonate. Circulating bile acids also activate transmembrane G protein-coupled receptor 5 (TGR5) and increase the secretion of glucagon-like peptide-1 (GLP-1) associated with decreased body weight (16). Thus, providing bile acids *via* breast milk may affect growth and body weight of the infant.

Somatotropic Axis

Postnatal growth is driven by the activity of the somatotrophic axis (17, 18). Newborns produce Growth Hormone (GH) in the pituitary gland which stimulates the production of Insulin-like Growth Factor-1 (IGF-1) by the liver and peripheral tissues. GH receptor and IGF1 receptor signaling promote organ and systemic growth (19). The infant also receives exogenous GH through breast milk. GH concentrations are higher in colostrum than in mature milk (20), and levels in the serum peak around birth and then gradually decline (19). IGF and IGF-binding proteins are also abundantly present in milk, especially in colostrum (20) but the role of IGF-1 in growth trajectories and adiposity in early life remains poorly understood with conflicting data reported (21). Most studies failed to provide evidence for sufficient absorption of IGF-1 to alter systemic IGF concentrations (22), which increase from birth to weaning (19). As such, direct contribution of milk-derived IGF-1 to somatic growth in infants seems unlikely (22) but it may be important for gut epithelium development and thereby nutrient absorption and gut integrity-related immune homeostasis (see below). Human milk may also increase systemic IGF-1 indirectly *via* branched amino acids present in milk proteins such as casein (22).

Healthy Adipose Tissue Development

In humans, adipose tissue appears early in the second trimester of the pregnancy (23). Both white and brown adipose tissues are key for energy homeostasis. White adipocytes store excess energy as triglycerides and release these when needed. Adipocytes also secrete various hormones such as leptin, adiponectin, and resistin and produce adipokines (adipose cytokines) such as TNF- α , IL-1 β and IL-6 regulating insulin activity and glucose metabolism and contributing to tissue energy homeostasis (24). On the other hand, brown adipocytes have the ability to burn off lipids as heat (25). These adipocytes can also emerge within white adipose tissue (WAT) and this so-called beige adipose tissue is abundant in early life and undergoes a reduction with age (25, 26). To understand the influence of human milk on growth it thus appears fundamental to elucidate whether human milk acts on adipose tissue development and function. Currently the knowledge is very scarce in this area.

Adipogenesis

During a process called adipogenesis, progenitor cells develop into preadipocytes and subsequently mature, lipid-laden adipocytes (27). Adipocyte progenitor cells are committed to becoming mature adipocytes in fetal and early postnatal life (28, 29). Leptin and adiponectin can stimulate the differentiation from preadipocytes into adipocytes *in vitro* (30, 31). It should however be noted that the literature reports contrasting findings for breast milk hormones and adipokines in relation to adiposity *in vivo*, which is discussed in a recent systemic review by Mazzocchi et al. (4). Further studies are needed to clarify the roles of bioactive components in breast milk in relation to body composition. Other breast milk factors such as lactoferrin (32) and short-chain fatty acids (SCFA) (33, 34) have also been found

to increase adipogenesis *in vitro*. SCFA are microbiota-derived metabolites that are most likely produced by the maternal gut microbiota and enter the milk *via* the circulation (35). In addition, milk oligosaccharides are fermented in the colon of the neonate generating SCFA (36, 37). SCFA can stimulate adipogenesis through G protein-coupled receptors (GPCR) signaling (33) and inhibition of histone deacetylase activity (34). Thus, as epigenetic regulators SCFA may have the potential to program adiposity. On the other hand, inflammatory cytokines such as TNF- α reportedly inhibit adipogenesis (38, 39), highlighting the potential importance of anti-inflammatory compounds in human milk. While there are no studies today on the direct influence of human milk on adipose tissue development, we can postulate that the nutrient content and anti/pro-inflammatory profile of human milk will influence adipocyte ontogeny. This deserves to be addressed in future research.

Adipose Tissue Hypertrophy and Proliferation

Excess nutrients are stored in white adipocytes as lipid droplets in response to insulin (40). Studies in mice have identified that once adipocytes increase in size in response to excess nutrient load during the early post-weaning period, a subsequent expansion of progenitors occurs due to increased systemic IGF-1 levels (41). If these cells encounter another dietary challenge in adulthood they increase in numbers, resulting in higher adipose tissue mass (41). Protein restriction in mice at weaning resulted in reduced adipocyte proliferation and growth restriction. These young mice increased their food intake in order to adapt, and this continued into adulthood (42). In culture, adiponectin has been shown to promote proliferation and increase lipid content of adipocytes (31). These studies show the importance of the diet for lipid accumulation and adipocyte proliferation, suggesting a significant role for the growth-adapted energy and nutrient content of human milk for adipose tissue expansion in early life.

Beiging

Neonates are born with beige adipose tissue-dominated fat depots. The energy content of human milk has the potential to influence adipose tissue beiging, as it has been shown that restricting calorie intake in young mice reduces the expression of brown adipose tissue (BAT) markers such as uncoupling protein 1 (UCP-1) in WAT at weaning (43). Another study has demonstrated that a high-fat diet in young mice that were exposed to a low-protein diet prenatally prevented the differentiation of precursors into beige adipocytes (44). Leptin and adiponectin promoted beiging of WAT in mice (45, 46) and lactoferrin upregulated UCP-1 expression in brown adipocytes in culture (47). The lipid composition of human milk is key for beige adipose tissue development. A recent study in mice demonstrated that breast milk-specific alkylglycerols sustain beige adipocytes through adipose tissue macrophages. Macrophages metabolize the alkylglycerols into platelet-activating factor (PAF), which leads to IL-6 secretion. Subsequently IL-6/STAT3 signaling in adipocytes triggers beige adipose tissue development. Therefore, breast milk intake delays

the reduction of beige fat in early life, and reduces fat accumulation (48). Importantly, these lipids are absent in formula or the adult diet and the replacement of beige adipose tissue by WAT is accelerated in obese children (49). In addition, human milk SCFA levels are inversely associated with infant weight gain and adiposity and thus might protect from excess weight gain in early life (50). Although the exact mechanisms remain to be determined, milk-derived SCFA may contribute to the regulation of adiposity *via* the activation of BAT increasing energy expenditure (51, 52). These studies suggest that human milk energy content and lipid composition are key for healthy adipose tissue development and energy expenditure.

Adipose Tissue Immune Homeostasis

The adipose tissue does not only comprise adipocytes as its stromal vascular fraction contains heterogeneous cell populations such as mesenchymal progenitor/stem cells, preadipocytes, endothelial cells, pericytes and immune cells. Data from adult experimental models highlight that these cells also play an important role in controlling adipocyte energy metabolism. Regulatory T cells (Treg) support adipose tissue function by keeping local and systemic inflammation in check and promoting insulin sensitivity (53). Both visceral and subcutaneous WAT have low fractions of CD4⁺ FoxP3⁺ Treg cells at birth. In the visceral WAT Tregs accumulate over time and account for over half of T cells in lean adult mice (54). Besides Treg, type 2 immunity is required in the adipose tissue for optimal energy metabolism as it leads to the activation of eosinophils and alternately activated M2-type macrophages. Together these cells act to promote browning, which can reduce adiposity (55, 56) as described above.

Human milk has the potential to assist in adipose tissue homeostasis by preventing chronic systemic inflammation, which is linked to preserving the gut mucosal barrier (discussed in more detail below). Reducing circulating lipopolysaccharide (LPS) concentrations lowers pro-inflammatory gene expression in visceral WAT, dampening local WAT inflammation and improving insulin sensitivity (57). As lipids do not only serve as an energy substrate, but also have an important role in cell signaling, the quality of lipids in human milk is of interest for the development and inflammatory status of the neonate. Long chain n-3 polyunsaturated fatty acids (PUFA) are generally considered protective against inflammation (58) and have been shown to decrease the infiltration and cytokine production of inflammatory macrophages in adult adipose tissue (59). Although the key role of PUFA for development in early life (e.g. for neural development) is widely recognized, its importance for growth and metabolic health in infancy remains unclear. The interaction of SCFA with adipose tissue is relevant for the prevention of metabolic disease and its associated inflammation (60). SCFA have anti-inflammatory properties and reduce the expression of inflammatory cytokines and chemokines as well as leukocyte infiltration in adipose tissue (61). SCFA however also induce leptin secretion, which can induce a proinflammatory cytokine profile (30, 60, 62). Lactoferrin has been demonstrated to decrease inflammatory markers in adipocytes (32). The relevance for this in early life remains unknown and requires further investigation.

However, the examples above illustrate that mediators present in human milk, or generated in the infant's gut from milk components, can support adipose tissue homeostasis.

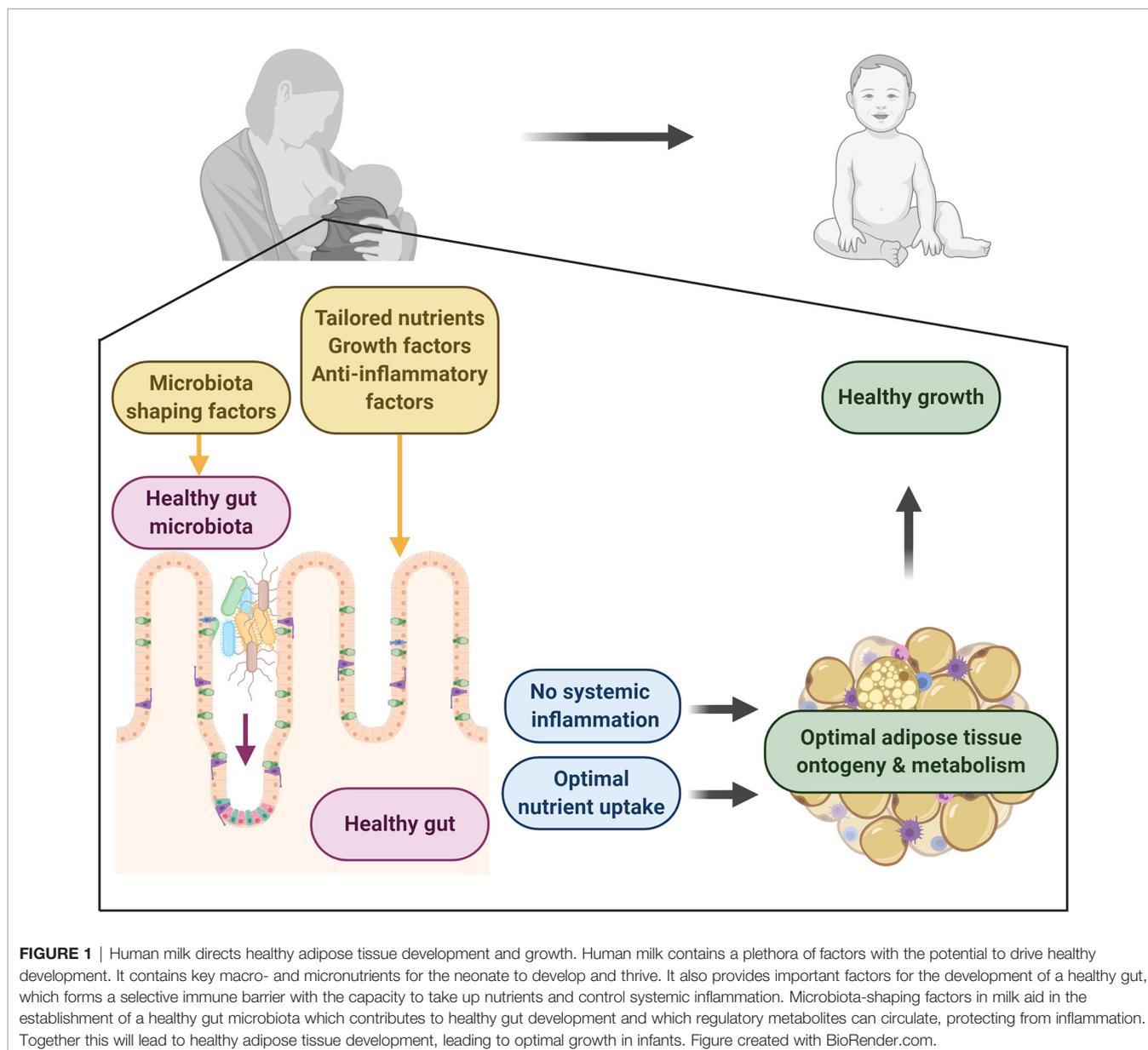
Gut (immune) Function and Metabolic Homeostasis

In the next paragraphs we will provide a more detailed overview about the link between human milk, gut (immune) function and metabolic health (see **Figure 1**). Research in adults, both in mice and humans, has demonstrated a key role for the gut in regulating metabolic homeostasis and energy storage. The intestinal mucosa is important for the uptake of food-derived nutrients and microbiota-derived metabolites. It also represents

an immune barrier that prevents the invasion of pathogens and an inflammatory response to contents in the lumen. In addition, insulinotropic hormones (incretins) including GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) are secreted from enteroendocrine cells and control glucidic metabolism. However, there is a lack of literature on the role of gut ontogeny in relation to growth and metabolism.

Intestinal Mucosa

The infant's gut starts off permeable due to its immaturity (63, 64), allowing for increased intestinal absorption of intact proteins compared to the adult (65, 66). This may facilitate the intact absorption of bioactive factors present in breast milk.



As touched upon above, from the adult situation it is known that defects in the integrity of the gut barrier can also result in systemic translocation of bacterial/gut-derived material leading to endotoxemia, which contributes to chronic low-grade inflammation and metabolic dysfunction (67–69). In healthy cases a structural barrier of epithelial cells proliferates in early life and restricts the entry of foreign (bacterial) material into the systemic circulation (63, 70). Studies in young infants demonstrate the major beneficial effect of human milk as compared to formula for the development of gut barrier integrity (64, 71). This is most probably related to breast milk factors required for epithelial cell maturation and function, including epidermal growth factor (EGF) (6, 72), IGF-1 (22), transforming growth factor (TGF)- β (73), lactoferrin (74), vasoactive intestinal peptide (VIP) (75), vitamin A (37, 76) and SCFA (36, 37). Analysis of epithelial cells obtained from stool samples at 3 months of age demonstrated differential expression of over 1,000 genes between breastfed and formula-fed infants (77). The importance of the gut barrier in early life for energy metabolism is highlighted in infants with chronic intestinal inflammation. These infants show poor nutrient absorption leading to macro- and micronutrient deficiencies and the use of energy for the inflammatory response, resulting in impaired growth and physical development (78).

A population of innate gut immune cells, innate lymphoid cell type 3 (ILC3), represents a potentially important target for control of energy metabolism by breastfeeding. These cells develop *in utero* under the influence of maternal vitamin A and aryl hydrocarbon receptor (AhR) ligands (79, 80). AhR ligands, originating from the maternal microbiota, are also detected in breast milk and stimulate the development of ILC3 in the intestine of the neonate (80, 81). Mouse models suggest that these cells could be key in the regulation of inflammation and energy metabolism after weaning. Through the secretion of IL-22, ILC3 control the expansion of inflammatory bacteria in the gut (82) and promote a strong epithelial barrier (57), both preventing chronic inflammation. IL-22 also enhances PYY levels, an anorexic gut hormone reducing food intake (57), and is likely involved in the control of lipid uptake. Studies show that IL-22 reduces lipid transport (82) resulting in lower body weight (83) while others describe that IL-22 enhances lipid uptake and export to the adipose tissue, and therefore increase body fat (84). IL-22 secretion by ILC3 is controlled by bacterial activation of Toll-like receptor-MyD88 signaling (46). VIP, secreted from enteric neurons upon food consumption, also appears important for regulation of IL-22-producing ILC3 in the gut. However, divergent effects were observed in two recent studies (83, 85). It may be of interest to investigate the role of VIP in regulating this pathway in early life, as human milk contains ~100pg/mL VIP (86). The studies described here show that various milk components can improve the intestinal barrier and prevent chronic systemic inflammation and thus support adipose tissue homeostasis.

Gut Microbiota and Metabolic Health

Perhaps the clearest links between human milk, the gut and metabolic outcomes are related to the gut microbiota. Microbial signals such as microbe-associated molecular patterns (MAMPs)

and bacterial metabolites such as SCFA modify local mucosal and systemic immune responses (36), as described above. In the adult, changes in the gut microbiota composition influence energy extraction (87), inflammation (68, 88), metabolic signaling (89) and browning of adipose tissue (90). Because the intestinal microbiota establishes as the adipose tissue and immune system develop, microbiota disruption during the early time window can impair host metabolism, body composition and healthy postnatal growth. Infants with undernutrition show persistent microbiota immaturity (91–93) which correlates with anthropometric growth measurements (93). On the other hand, Caesarean section (94–96), lack of breastfeeding (3) and the use of antibiotics (9–11) are associated with gut dysbiosis and being overweight in childhood. The impact of early life antibiotics on adiposity can remain after ceasing of antibiotic treatment, even though the microbiota recovers, highlighting that alterations in the critical window can have long-term effects (97, 98).

Breastfeeding status is the most significant factor associated with microbiota structure in early life (99–104). Breast milk bacteria contribute to the seeding of the infants gut microbiota, and this is dependent on breastfeeding exclusivity and duration (102). These bacteria most likely originate from the mother as well as other exogenous sources such as the home environment and infant mouth (102). Bacteria transferred through human milk include species such as *Rothia*, *Veillonella* and *Bifidobacterium* that can influence immune homeostasis (102). The microbiota of healthy, exclusively breastfed infants is dominated by *Bifidobacterium*, which is linked to health benefits such as improved gut barrier function (92). A recent cohort showed that the abundance of *Enterococcus* in the infant gut, seemingly due to the lower abundance in maternal breast milk, inversely correlated with infant body weight and fat as well as leptin levels (105). A recent mouse study identified bile acids as potent drivers of intestinal microbial maturation in early life (106), and potentially human milk bile acids may contribute to this effect. Human milk also provides the neonate with large amounts of antimicrobial factors such as lactoferrin, which can further shape the early microbiota (103). Of large interest to date are prebiotic factors such as human milk oligosaccharides (HMOs), which support the growth of beneficial bacteria and can alter colonization patterns in the neonate (103). HMOs are a group of complex sugars that are the third most abundant solid component of human milk, and though non-nutritive to the infant they have many properties besides their role as prebiotics. The influence of HMOs on growth is therefore most probably multi-factorial and beyond its prebiotic activity includes inhibition of pathogen adhesion and host invasion, local and systemic anti-inflammatory effects (107) and modification of the metabolism in the microbiota as well as the host (108). A study amongst Malawian mothers with undernourished infants has demonstrated that milk oligosaccharides are less abundant in breast milk of mothers with stunted infants. This study also showed a causal, microbiota-dependent relationship between sialylated milk oligosaccharides and growth promotion in malnourished

animals (108). An elegant mouse study by Cowardin et al., demonstrated that sialylated milk oligosaccharides, but not the most abundant HMO 2'fucosyllactose (2'FL), decreased bone resorption, leading to an increase in bone volume and growth in a similar low resource setting (109). In a healthy population, human milk 2'FL was positively associated with growth in infancy and early childhood, whereas high concentrations of lacto-N-neo-tetraose (LNnT) were associated with reduced body fat and growth (110–112). Overall, HMO diversity was inversely associated with infant fat mass (110) and childhood growth (112). Maternal exercise induced 3'-sialyllactose in human milk, and this HMO improved metabolic health and protected from the harmful effects of high-fat diet feeding in adult mouse offspring (113). These recent studies all point out the importance of HMOs for healthy growth in early life.

PERSPECTIVE

Studies addressing the link between human milk composition and infant growth are important to strengthen our understanding of both the short- and long-term health-promoting effects of breast milk. Here we demonstrate that various nutritional, bioactive, growth and immunological factors in human milk may play a role in healthy growth and adipose tissue development in infants. The mechanisms that mediate these positive effects of breastfeeding on growth outcomes remain unclear but the evidence there is today shows this may be related to strengthening the gut barrier and microbiota development, facilitating immune and metabolic homeostasis.

Future Research

As both the rates of undernutrition and overweight are alarmingly high (114–116), it is important to identify interventions that effectively promote healthy growth of children. Research on the role of human milk on adipose tissue development is scarce. There are large gaps in knowledge on the direct and indirect impact of human milk and breastfeeding on adipogenesis, adipose tissue expansion, being of adipose tissue as well as the immune function of the fat depot that deserves to be filled.

The engagement of specific metabolic pathways profoundly affects immune cell differentiation and function. Metabolic programming is, amongst other factors, controlled by the

availability of nutrients. Identifying the metabolic requirements and specific nutrients of immune cells in the intestine and adipose tissue in early life, could help to further understand immune homeostasis and healthy growth in infancy. Recently Met-flow (117) has come in the picture as an accessible technique capturing the metabolic state of immune cells that may help answer this question in more detail.

The dynamic composition of human milk, varying significantly within a feed, diurnally and over the course of lactation may play an important role in the healthy development of the infant. This topic needs to be further explored for better understanding of the early diet and healthy growth. Recent evidence point towards the cyclic regulation of ILC3 cells in the intestine, which is linked to the circadian clock as well as food intake (83, 85). As the newborn gut is dominated by innate immune cells (118), the dynamic composition of milk may be of importance for optimal immune development in the intestine and beyond, contributing to metabolic homeostasis.

Conclusion

The interplay between the gut microbiota, gut mucosa and adipose tissue metabolism is the focus of much research in the adult. This mini-review highlights how this crosstalk might be crucial for a healthy start in life and the key role human milk may play in driving this. Future research will need to replace extrapolation from the adult by evidence gained in the newborn. This will allow the development of (human milk-inspired) child-tailored approaches for metabolic disease prevention.

AUTHOR CONTRIBUTIONS

LV and VV wrote, edited, and revised the manuscript together. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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