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Health benefits of dairy lipids and MFGM in infant formula

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Abstract – Human breast milk (HBM) is the gold standard for the early nutrition of the neonates. The best way to improve infant formulas (IFs) is to mimic both the composition and the structure of HBM components. Supplementation of IF with dairy lipids or bovine milk components such as milk fat globule membrane (MFGM), in partial replacement of plant oils that are currently mainly used, has health benefits for infants. In this article, results of clinical studies on the impact of IF supplementation with MFGM and dairy lipids on psychomotor development and infectious disease prevalence in infants are reviewed and supported by recent pre-clinical studies. Numerous human studies have reported beneficial effects of MFGM supplementation on neurocognitive development and protection against infectious agents without deleterious impact on growth. Based on rodent and porcine studies, benefits of adding bovine MFGM and dairy lipids in IFs on gut digestion, physiology and protection against pathogens and inflammatory challenges have also been highlighted. However, more randomized controlled trials testing IF supplementation with bovine milk fat, and specifically apolar lipids and associated glycoproteins, must be performed to increase scientific-based knowledge, address safety concerns, and study its potential programming role of adult health.

Keywords: bovine milk fat / polar lipid / milk composition / infant formula / infant health

Résumé – Les bénéfices santé des lipides laitiers et des membranes des globules gras introduits dans les formules infantiles. Le lait maternel est l'aliment de choix à privilégier pour nourrir les nouveau-nés. Il est ainsi l'aliment de référence tant sur sa composition nutritionnelle que sur ses propriétés fonctionnelles, pour améliorer la formulation des formules infantiles (FI). L'incorporation dans les FI de la matière grasse du lait de vache ou de certains de ses composants tels que les membranes des globules gras (MFGM pour milk fat globule membrane), en remplacement partiel des huiles végétales qui sont actuellement principalement utilisées, apporte des effets bénéfiques pour la santé du nouveau-né. Dans cette revue, les résultats des études cliniques sur l'impact des MFGM et des lipides laitiers dans les FI sur le développement psychomoteur et la prévalence des maladies infectieuses et digestives infantiles sont rapportés et étayés par les résultats d'études pré-cliniques récentes. L'incorporation de MFGM dans les FI apporte un bénéfice sur le développement neurocognitif de l'enfant et sa protection vis-à-vis d'agents infectieux, sans modifier sa croissance. L'effet bénéfique de la supplémentation des FI avec des lipides laitiers et des MFGM d'origine bovine sur la digestion et la physiologie intestinale, ainsi que la protection contre des challenges inflammatoires est par ailleurs mis en évidence dans des études pré-cliniques réalisées chez les rongeurs ou le porc. Cependant, de nouvelles études sont nécessaires pour accroître nos connaissances sur le rôle fonctionnel et le mode d'action de la matière grasse laitière et en particulier, des lipides apolaires et des glycoprotéines associées aux MFGM, et ses effets potentiels sur la programmation de la santé de l'adulte.

Mots clés : matière grasse laitière / lipide polaire / composition du lait / formule infantile / santé infantile

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1 Introduction

Human breast milk (HBM) from healthy mothers is a timely-adapted and balanced source of nutrients and bioactive compounds ensuring proper growth and development of infants, and is therefore the gold standard for early nutrition of full-term infants up to six months of age. Hence, the best way to improve infant formulas (IFs) is to mimic both the composition and the structure of HBM components. A range of values for macronutrient contents in IFs is now well defined. An ideal protein content of 1.8 g/100 kcal, very close to HBM (Tab. 1), is established for bovine milk protein-based IFs on the basis of reducing the risk for rapid weight gain during infancy, a known-risk factor for overweight and obesity up to school age (Koletzko *et al.*, 2009; Weber *et al.*, 2014). HBM lactose content of 10.3–11.4 g / 100 kcal (as the main source of carbohydrates) is also closely mimicked in IFs while HBM oligosaccharides (the third largest component after lactose and lipids, 0.8–3 g / 100 kcal HBM) cannot be fully reproduced. Finally, while the lipid contents of both HBM and IFs are 5–6 g/100 kcal in average, lipid composition greatly differs as the lipid matrix of most IFs is exclusively made of a blend of vegetable oils instead of dairy fats. Only the addition of docosahexaenoic acid (DHA, 20–50 mg/100 kcal) belonging to long-chain polyunsaturated fatty acids (LC-PUFAs) of the ω3 family, is now mandatory in European IFs. However, the use of vegetable oils induces other major differences in the fat globule and triglycerides structure that may impact the developmental physiology of neonates (Le Huërou-Luron *et al.*, 2010).

The present review aims to compare lipid composition of HBM, cow milk (CM) and IF, and to highlight recent findings about lipid structure and composition effects on neuro-development, protection against infections, gut barrier functions and metabolic health in infants.

2 Compared lipid composition and milk fat globule structure of human breast milk, cow milk and IFs

The metabolizable energy content of HBM and CM is approximately 65–70 kcal/100 mL, one half being provided by fat. The estimated total fat intake of fully breast-fed infants is approximately 5.5 kg during the first six months of life (Koletzko *et al.*, 2011). Lipids in HBM and CM represent on average 3.6 g/100 mL with more than 97% as triglycerides (TAG), small amounts of mono- and diacylglycerides (MAG, DAG), around 1% of phospholipids and 0.5% of sterols, mostly cholesterol (Tab. 1) (Bourlieu *et al.*, 2015). HBM and CM lipid composition are characterized by a large diversity of fatty acids (FAs) (over 400 FAs with variable chain lengths and unsaturations), a wide variability of LC-PUFAs, and a unique stereospecific structure with palmitic acid primarily esterified at the *sn-2* position (~ 70% in HBM and 45% in CM) and unsaturated FAs mainly at the sn-1,3 positions (oleic acid is the major monounsaturated FA, 17–47% of milk total FAs). The HBM contains a lower percentage of saturated FAs, including short-chain FAs, compared to CM. It is noticeable that the energy and macronutrient contents of HBM and CM vary depending on the lactation period, the time of the day and also within feedings. In addition, HBM and CM lipid composition is greatly influenced by maternal diet (Lock and Bauman, 2004; Jensen, 2006; Innis, 2007; Delplanque *et al.*, 2015).

The steady IF composition is designed to meet the nutrient requirements of infants for the whole first six months of life. IF lipid composition, quantitatively close to average mature HBM, greatly depends on the blend of the different fat sources used. IFs containing dairy fats were primarily used in the first part of the 20th century, but are nowadays very limited. Most IFs rather contain plant lipids, such as palm oil, coconut oil, sunflower oil or soy oil. Coconut oil provides short- and medium-chain FAs as do dairy lipids, and palm oil has, like dairy lipids, a high palmitic acid content. However, palmitic acid differs according to the lipid sources by the stereo-specific positioning of FAs on the glycerol molecule, with the higher percentage of esterification at the sn-2 position in dairy lipids compared with palm oil. This position is of great nutritional importance as long-chain saturated FAs in the sn-2 position are more easily and efficiently digested and absorbed (Innis, 2011). Due to their content in plant oils, IFs usually contain more LC-PUFAs of the ω3 and ω6 families than HBM (for ω3 PUFA 11.6–26.0% of total FAs in HBM *vs.* 13.6–21.9 % of total FAs in IFs; for ω6 PUFA 0.85–3.57 % of total FAs in HBM *vs.* 1.9–3.7 % of total FAs in IFs). However, LA:ALA and ARA:DHA ratios are within the same range of values in IFs and HBM, *i.e.* from 3.5 to 12 and from 1.0 to 4.0, respectively (Delplanque *et al.*, 2015).

Another important difference between HBM and IFs is the ultrastructure of the fat emulsion. HBM fat is organized under its native form into dispersed globules enveloped by a biological membrane called milk fat globule membrane (MFGM) resulting from the secretion of fat globules from the epithelial cells of the mammary gland. Fat globules are coated with three layers: an internal protein layer, an intermediate layer both consisting of phospholipids, and an external layer mainly consisting of high-molecular weight glycoproteins. HBM glycoproteins display branched oligosaccharide structure on their surface whereas oligosaccharides would be absent or present at a low level in CM. Milk fat globules (MFG) have a mean diameter around 3–5 μm but present a large range in size distribution (0.1–15 μm) in both HBM and CM. In contrast, IF fat is dispersed in the micellar phase of the formula by homogenization of vegetable oils in the presence of dairy proteins. This process results in a stable micro-emulsion of vegetable lipids mainly stabilized by caseins in the form of small lipid droplets with an average diameter of less than 0.5 μm without membrane coating (Bourlieu *et al.*, 2017).

3 Health benefits of MFGM supplemented IFs

MFGM is highly structured and contains membrane-specific proteins (mainly glycoproteins that represent 70% of MFGM dry matter), polar lipids (phospholipids and glycosphingolipids that represent 25% of MFGM dry matter), but also apolar lipids such as cholesterol (2% of MFGM dry matter) and cerebrosides (3% of MFGM dry matter) (Dewettinck *et al.*, 2008). The proteome of HBM and CM MFGM includes 200 to 250 identified proteins

Table 1. Compared human breast milk, cow milk and infant formula composition.
Adapted from (Malacarne *et al.*, 2002; Brenna *et al.*, 2007; Ballard and Morrow, 2013; Delplanque *et al.*, 2015).

/ 100 ml	Human milk	Cow milk	Infant fomula[a]
Energy (Kcal)	65–70 (57–83)	67.4 (65–71.2)	60–70
Proteins (g)	1.20 (0.9–1.7)	3.25 (3.1–3.8)	1.1–2.1
Caseins (g)	0.37 (0.32–0.42)	2.51 (2.46–2.80)	0.4–0.8
α-Caseins (%)	11.8 (11.1–12.5)	48.5 (48.3–48.5)	
β-Casein (%)	64.8 (62.5–66.7)	35.8 (35.8–37.9)	
κ-Casein (%)	23.5 (22.2–25.0)	12.7 (12.7–13.8)	
Size of micelles (nm)	64	182	
Whey proteins (g)	0.76 (0.68–0.83)	0.57 (0.55–0.70)	0.6–1.3
β-lactoglobulin (%)	Absent	20.1 (18.4–20.1)	
α-lactalbumin (%)	42.4 (30.3–45.4)	53.6 (52.9–53.6)	
Immunoglobulins (%)	18.2 (15.1–19.7)	11.7 (10.1–11.7)	
Serum albumin (%)	7.6 (4.5–9.1)	6.2 (5.5–7.7)	
Lactoferrin (%)	30.3	8.4	
Lysozyme (%)	1.66	Traces	
Caseins/Whey proteins	30–40/60–70	80/20	40/60
Fat (g)	3.2–3.6 (1.2–5.2)	3.6 (1.2–7.9)	2.6–4
Triglycerides (%)	98.1–98.8	97.0	
Phospholipids (%)	0.26–0.8	1.5	≤ 7
Cholesterol (mg/100 mL)	10–20	1.0–33	Absent
% Fatty acids relative to total fatty acids			
Butyric (C4:0)	0.1	1.4 (1.4–3.3)	nq[b]
Caproic (C6:0)	0.2	2.1 (1.6–2.2)	0.1
Caprylic (C8:0)	0.3 (0.1–0.3)	1.7 (1.3–1.8)	1.0–1.5
Capric (C10:0)	2.0 (1.1–2.1)	3.5 (3.0–3.6)	0.9–1.3
Lauric (C12:0)	6.8 (3.1–7.2)	3.9 (3.1–4.0)	7.8–11.5
Myristic (C14:0)	10.4 (5.1–10.9)	12.6 (13.0–14.2)	4.0–5.5
Palmitic (C16:0)	28.1 (20.2–29.6)	29.5 (24.0–42.7)	18.2–25.4
Palmitoleic (C16:1)	3.5 (3.5–5.7)	1.7	0.1–0.2
Stearic (C18:0)	6.9 (6.0–8.6)	13.3 (5.7–13.7)	3.5–4.0
Oleic (C18:1)	33.6 (33.3–46.4)	26.3 (16.7–27.1)	28.4–40.8
n-6 PUFA			
Linoleic (C18:2)	17 (6.0–24)	2.9 (1.6–3.0)	13.3–18.5
Arachidonic (C20:4)	0.5 (0.25–0.75)		Added:0.2–0.6 / not added: nq
n-3 PUFA			
α-linolenic (C18:3)	1.7 (1.0–3.4)	1.1 (0.5–1.8)	1.6–2.4
Docosahexaenoic (C22:6)	0.32 (0.10–0.60)		Added:0.2–0.3 / not added: nq
Carbohydrates (g)	7.4–7.8 (6.0–9.6)	4.5	5.4–9.5
Lactose (%)	85	100	47–100
Oligosaccharides (%)	0.5–2.0	Traces	
Maltodextrin (g)	Absent	Absent	1.1–2.6
Minerals (g)	0.21	0.90	0.25–0.50
Na (mg)	16	48	12–42
Ca (mg)	33	125	30–98
K (mg)	16.5	100	36–112
Fe (mg)	0.05	0.03	0.2–0.9
Mg (mg)	5	10	
P (mg)	20	84	

Mean value and, between brackets minimum–maximum values, reported in literature.
[a] Lipid composition provided in this table is that of an infant formula based of a blend of plant oils including palm oil and coconut oil, as an example of infant formula made with plant oils as lipid source.
[b] Nq, non quantifiable amount ($< 0.05\%$).

(Hernell *et al.*, 2016). Growing interest of supplementing IFs with MFGM comes not only from its individual components that have proven bioactivities, with reported impact on brain development and cognitive functions, immunity and gut physiology, but also from the benefits associated to the combination of these components and their structural organization. The persistence of MFGs in the upper intestine allows the discharge of bioactive components in the distal intestine, contributing to their physiological impacts. In the following section, health benefits of supplementing IFs with MFGM will be reviewed.

3.1 MFGM improves brain development

A large observational study (> 17 000 healthy infants) has provided strong evidence for an advantage of breastfeeding compared to IF-feeding on infant cognitive development, suggesting that HBM components are important for an optimal neurodevelopment of infants (Kramer *et al.*, 2008). Results of a randomized trial including < 2 months of age infants fed a MFGM-supplemented, low-energy, low-protein experimental IF showed a positive association with neurocognitive development. At 12 months of age, the cognitive score (Bayley Scales of Infant and Toddler development tests) was significantly higher in the MFGM-supplemented experimental IF group than in the standard IF group but was not significantly different from that of breastfed infant group (Timby *et al.*, 2014a, b). Beneficial effects on emotional and behavioral regulation were also reported in preschool children consuming MFGM concentrate in chocolate formula milk for 4 months (Veereman-Wauters *et al.*, 2012). Magnetic resonance imaging of piglet brain opened a new insight on underlying mechanisms. MFGM combined with prebiotics and lactoferrin induced differential localization in grey and white matter tissue concentrations suggesting an accelerated early postnatal brain development (Mudd *et al.*, 2016). However, whether MFGM supplementation benefits result from the action of a single or a combination of bioactive components such as gangliosides, sphingomyelin, sialic acid, or cholesterol, is not known yet. Indeed, human neonates fed IF supplemented with gangliosides or sphingomyelin from milk displayed improved motor, neurobehavioural and cognitive development (Gurnida *et al.*, 2012; Tanaka *et al.*, 2013). In an animal study, supplementation with case in glycomacropeptide as a provider of sialic acid was associated with faster learning of difficult tasks and higher concentrations of protein-bound sialic acid in the frontal cortex and of learning-related genes in the hippocampus of piglets (Wang *et al.*, 2007). It has also been reported that cholesterol played an important role in synaptic plasticity, learning and memory since rats receiving a diet supplemented with cholesterol displayed better performances in learning and memory than rats receiving a normal diet (Ya *et al.*, 2013). Therefore, more studies have to be performed to unpack the mechanisms through which MFGM operates. Recent data in mice fed a diet mimicking more closely the lipid structure of breast milk (large lipid droplets coated with milk phospholipids) demonstrated improved performance in short-term memory tasks during adolescence and adulthood, suggesting that lipid structure would be also a relevant target to improve IF functionality (Schipper *et al.*, 2016).

3.2 MFGM prevents infection and improves gut barrier integrity in challenging conditions

Formula-fed infants are more prone to ear, respiratory and gastrointestinal infections than breastfed ones during the first year of life. The first study performed with young children consuming MFGM-enriched complementary food reported a decreased number of days with fever in young European children aged 2.5 to 6 years (4 month distribution), without any impact on diarrhea, constipation and cough (Veereman-Wauters *et al.*, 2012). Timby *et al.* (2015) corroborated this MFGM preventive effect on infections in younger Swedish children recruited before 2 months of age and fed with MFGM-supplemented IF until 6 months of age. Fewer episodes of acute otitis media and lower antipyretic use during the intervention were reported among infants fed the MGFM-supplemented IF compared with infants fed a non-supplemented IF. As proposed by the authors, MFGM-embedded glycoproteins (such as butyrophilin, lactadherin, mucins, lactoferrin) and lipids (gangliosides) may participate in the defense against infections by preventing pathogen adhesion to epithelium (Sprong *et al.*, 2012; Fuller *et al.*, 2013).

The benefit of MFGM in reducing the prevalence of diarrhea is far less well-documented. Indeed in Peruvian infants aged 6 to 11 months, 6 month distribution of complementary food with protein provided as whey protein enriched with the MFGM-enriched protein fraction *vs.* an equal amount of skim milk protein, reduced the global prevalence of acute diarrhea (3.84 % in the MFGM group *vs.* 4.37 % in the control group, $P < 0.05$) (Zavaleta *et al.*, 2011). In contrast, a prospective trial in which 8 to 24 month Indian infants received daily 2 g of complex milk lipids containing 10- to 20-fold higher phospholipids than standard commercial IF did not demonstrate a preventing effect on rotavirus diarrhea prevalence (Poppitt *et al.*, 2014). It is noticeable that the incidence of rotavirus infection was unexpectedly low in this trial, hampering the assessment of the supplementation efficacy. Similarly, MFGM-enriched milk was not associated with changes in diarrhea or abdominal discomfort scores in Belgian children (Veereman-Wauters *et al.*, 2012). Finally the safety evaluation of standard IF and IF enriched with a protein-rich MFGM fraction or a lipid-rich MGFM fraction in a multicenter trial with French and Italian full-term neonates age < 14 days did not reveal between-group differences in terms of diarrhea, intestinal discomfort, and ear, respiratory and gastrointestinal infections (Billeaud *et al.*, 2014). A higher rate of eczema was evidenced in the group receiving IF enriched with a protein-rich MFGM fraction, though this negative effect has not been described ever since in other trials using the same MFGM fraction (Timby *et al.*, 2014a, b). The few significant findings observed for prevention of diarrhea in human trials contrast with the beneficial impacts on gut epithelial barrier reported in animal studies. Indeed 10 day MFGM-supplemented formula feeding to rat pups from postnatal day 5 normalized delayed intestinal growth induced by standard IF feeding compared to suckling rats (Bhinder *et al.*, 2017). Specifically MFGM restored intestinal villus and crypt architecture and maintained crypt cell proliferation and the number of goblet cells and Paneth cells involved in protective and antimicrobial activities. But MFGM-supplementation did not change FITC-dextran

intestinal permeability, although it improved expression of tight junction proteins. Using neonatal piglets, we also evidenced MFGM-induced mucosal growth without any impact on epithelial permeability as measured in Ussing chambers (Le Huërou-Luron *et al.*, 2018). Moreover, in challenging conditions against pathogenic bacteria such as *Clostridium difficile* or *Listeria monocytogenes*, MFGM were described as conferring protection, probably by stimulating mucin secretion and preventing adherence of pathogens to the intestinal mucosa in rats (Sprong *et al.*, 2012; Bhinder *et al.*, 2017). In weaned mice, providing a membrane-rich milk fat feed decreased the inflammatory response to a systemic LPS challenge and was associated with decreased gut permeability (Snow *et al.*, 2011). These effects may be partly related to gangliosides that inhibited degradation of tight junction occludin during LPS-induced acute inflammation (Park *et al.*, 2010). Therefore, a role of MFGM and its components in protecting the integrity of the intestinal barrier is only demonstrated using disease models, suggesting a protection of the gut barrier mainly in acute inflammatory conditions.

3.3 MFGM and metabolic health

No effect on infant growth (Timby *et al.*, 2014a, b; Billeaud *et al.*, 2014) and very few effects on metabolic parameters such as a higher cholesterol serum level (Timby *et al.*, 2014a, b) or no difference in cholesterol level but a higher LDL concentration (Lukoyanova *et al.*, 2017) were reported with MFGM supplementation. An IF containing large, phospholipid-coated lipid droplets was also found to support adequate growth in healthy Asian infants during the first 4 months of life as with a standard IF (Shek *et al.*, 2017). Besides, recent animal studies highlight the importance of the structure of MFG on later adiposity and metabolism without any effect on growth. Indeed providing to mice pups IF with large vegetable fat droplets covered by milk phospholipids of MFGM origin (concept IF Nuturis®), resulting in particle size distribution and interfacial composition close to HBM (Gallier *et al.*, 2015), reduced fat accumulation as well as fasting leptin, resistin, glucose and lipids in adults fed a western diet (Oosting *et al.*, 2012). Both large droplet size and MFGM coating contributed to the observed protective effect against obesity in later life (Baars *et al.*, 2016). The programming effect of MFG size would involve key regulators of metabolic activity such as decreased expression of PPARγ, CCAAT/enhancer binding protein and RXR in white adipose tissue in adulthood, and a reduced adipocyte hypertrophy (Oosting *et al.*, 2014). The digestive behavior of these specific MFG is still questioned (Bourlieu *et al.*, 2017).

Overall, the complexity of MFGM composition and structure, impacts many functions. However, not all MFGM protein and lipid components are commercially available. The reintroduction of bovine milk fat, which resembles that of HBM such as the presence of MFGM, similar ω3 PUFA concentration, close TG content and a high percentage of esterification of palmitate at the sn-2 position, would be an alternative way to better mimic HBM-induced health benefits in infants and adulthood (Delplanque *et al.*, 2015; Lonnerdal, 2016; Bourlieu *et al.*, 2017).

4 Benefits of bovine milk fat in IFs

The addition of dairy lipids in IF modifies the structure of the fat emulsion and its composition in polar and apolar lipid fractions. Introducing fat from CM in IFs may also have consequences on the presence of potentially bioactive proteins (Li *et al.*, 2014). An IF containing a mix of CM lipids and plant oils enabled a normal growth of healthy Italian newborns from inclusion (at < 3 weeks of age) to the 4 subsequent months compared to control IF containing only plant oils as lipid sources, without any significant impact on gastrointestinal symptoms or infant behavior (Gianni *et al.*, 2018). Benefits of the introduction of dairy lipids in IFs were observed in animal models. In a murine model with an early life LPS-induced brain inflammation, the partial replacement of vegetable lipids with dairy lipids had a protective effect on the adverse consequences of LPS exposure on neurogenesis and adult spatial memory (Dinel *et al.*, 2016). In a neonatal piglet model fed IF from birth, the presence of dairy lipids in combination with MGFM changed the dynamic of dairy protein digestion compared to IF containing only vegetable lipids or vegetable lipids plus MFGM, with a higher resistance of casein and β-lactoglobulin to digestion (Le Huërou-Luron *et al.*, 2018). This effect may be related to differences in emulsion interface composition between IFs (Macierzanka *et al.*, 2009). Introduction of dairy lipids also resulted in modified luminal contents in the intestine, increasing β-casein peptides while decreasing lipids in jejunal digesta of pigs fed dairy lipids and MFGM-supplemented IF, compared to the ones fed exclusive vegetable lipid IF. In addition, intestinal contents of piglets fed dairy lipids and MFGM-supplemented IF displayed higher amounts of medium-chain saturated fatty acids, phosphatidylcholine and sphingomyelin. The addition of dairy lipids also accelerated the maturation of the intestinal immune system that was closer to the one observed in mother-fed piglets (Le Huërou-Luron *et al.*, 2016). A follow-up of this study was recently performed by investigating long-term impacts of dairy lipids in IF on adult gut physiology. IF supplemented with dairy lipids had a beneficial impact on intestinal immune function. Indeed in adult pigs fed a dairy lipid-supplemented IF in infancy, pro-inflammatory cytokine (TNFα and IL-8) secretions of ileal explants in response to a LPS challenge was decreased compared to adult pigs early fed IF containing vegetable lipids (Lemaire *et al.*, 2017). Therefore, the introduction of bovine fat in IFs may reduce the gap between breast-fed and IF-fed infant physiology and health, with a higher efficacy than the introduction of solely MFGM, as demonstrated in animal studies. It is noticeable that bovine fat contains a low fraction of MFGM that may account for 2–6% of the fat mass (Zheng *et al.*, 2013).

More recently, the interaction between the lipid matrix and gut microbiota was questioned. Formula-feeding is usually associated with a higher bacterial richness and diversity and different taxonomic composition compared with breastfeeding. Supplementation of IF with MFGM-did not change oral microbiota species richness compared to standard IF fed infants and both formula-fed infants display higher species richness than breastfed infants at 4 months of age. However, differences still occurred at taxonomic levels (Timby *et al.*, 2017a, b). Similarly, the composition of fecal microbiota

differed between piglets fed IF containing dairy lipids and MFGM or IF containing vegetable lipids or mother-reared (Le Huërou-Luron *et al.*, 2018).

5 Conclusion

Overall, numerous human studies have reported beneficial effects of MFGM supplementation on neurocognitive development and protection against infectious agents without deleterious impact on growth. Based on animal studies, benefits of introducing bovine MFGM and dairy lipids in IFs on gut digestion, physiology and protection against pathogens and inflammatory challenges have also been highlighted.

Lipids in breast milk are extremely complex and diverse, and their synergistic roles on health outcomes are not yet fully understood. Introducing dairy lipids including MFGM may be an important way to improve quality of IFs. However, more randomized controlled trials testing lipid functions must be performed to increase scientific-based knowledge and address safety concerns (Delplanque *et al.*, 2015; Timby *et al.*, 2017a, b). Another issue of using IFs supplemented with dairy lipids concerns the programming of adult health. Recent animal studies report promising effects but better understanding of underlying mechanisms must be achieved to reach optimal use of dairy lipids.

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