Mimicking mother's milk

Stacy Kish

- The milk fat globule membrane (MFGM), which surrounds droplets of fat in breast milk, is a rich source of nutrients for infants, playing an integral role in brain and cognitive development. It also allows for the development of a robust immune system and healthy metabolism.
- Infant formula companies are exploring different techniques to enhance their product using components of MFGM to mimic the qualities and characteristics of breast milk. Clinical trial studies support the role enhanced formula play in an infant's growth and development.
- Companies are also exploring how the MFGM can improve the texture, composition and bioavailability of nutrients in foods, including butter and whipped cream.
- Future work may explore the role of MFGM in reducing frailty and improving muscle growth in older adults as well as reduce the harm from toxins produced by foodborne pathogens.

Food does more than deliver fat, protein, carbohydrates and vitamins to the body. The nutritional value of food is an interconnected web, a matrix. The food's structure affects how molecules interact and are absorbed. In fact, the food matrix is a more reliable way to evaluate a food's potential health benefits than simply considering each of the nutritional components alone.

"Molecules come embedded by nature in often complex, functional microstructures that we cannot see. Nutritional scientists aim to redesign some foods to protect nutrients and target them to perform specific functions in a way that may enhance human health," said José Miguel Aguilera, emeritus professor of chemical and food engineering at the Pontifical Catholic University of Chile in Santiago in an interview with BBC Food (https://www.bbc.co.uk/food/articles/food_matrix).

There may be no better example of this matrix effect than the milk fat globule membrane (MFGM), a tri-layer membrane that surrounds droplets of fat in breast milk.

CHALK FULL OF HEALTHY COMPONENTS

Milk fat globules range in diameter from 0.2 to 15 mM, far smaller than the width of a human hair. The MFGM that encloses this droplet of fat is even thinner. The membrane consists of a complex array of phospholipids and proteins arranged in three tiers (see image). The inner membrane is a monolayer of proteins and polar lipids obtained from the endoplasmic reticulum. The outer membrane is a double layer consisting of proteins and polar lipids originating from epithelial cells in the mammary gland. Sandwiched in between is a sheet of triglycerides (https://doi.org/10.1016/j.jnutbio.2020.108465).

While the MFGM accounts for less than 4% of total milk proteins, it contains a diverse collection of more than 500 different protein varieties. The MFGM is also rich in polar lipids, which provide the building blocks for cell membranes, the sheath (myelin) that covers nerves in the nervous system, and the production of lipoproteins, vitamin D and hormones. In addition, carbohydrates combine with the proteins or lipids to form glycoproteins or glycolipids that facilitate cellular recognition and signaling.

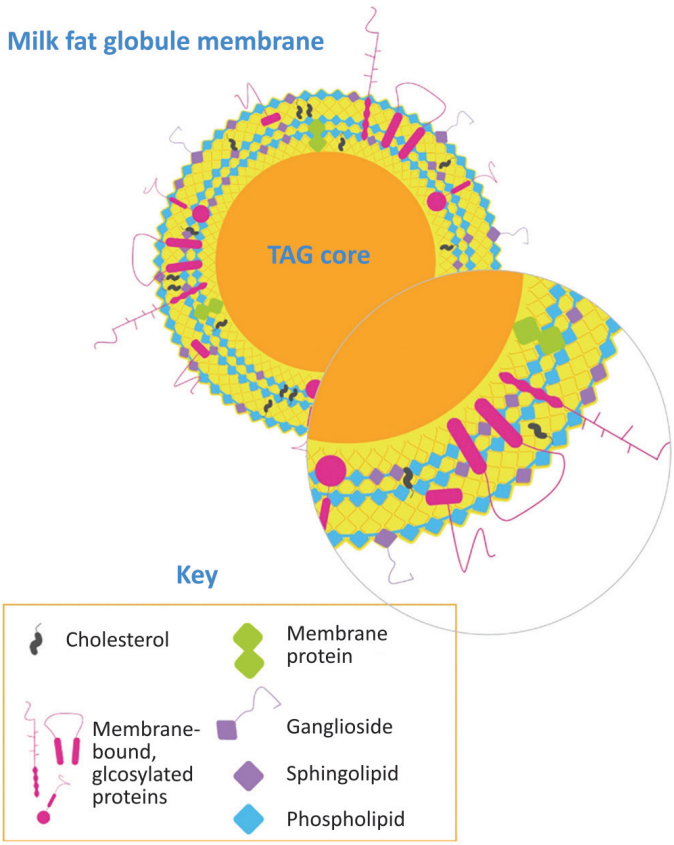
Breast milk is the gold standard for infant nutrition, offering the best path forward for an infant's growth and development. The MFGM perfectly encapsulates each milk fat droplet, preventing spoilage and aggregation. It also stabilizes the fat globule. The composition of the MFGM varies by lactation stage, season, fat globule size, maternal diet and even the collection method and time of day.

Despite the fact that breast milk promotes healthy growth and development, only a fraction of children worldwide receive this nutritional support throughout infancy. In the United States, less than a quarter of infants are breastfed after six months of age. Pre-term infants are at an even greater disadvantage, having also lost out on the growth and brain and lung development that occurs during the third trimester. Infant formulas provide an option for the sole or partial nutritional support for most infants during the first year of life, but infant formula is not a one-to-one replacement for breast milk.

Infant formula companies are working to address this nutrition gap and the market for this product is growing. The Global Infant Formula Oil and Fat Ingredients market size was valued at $5,309 million in 2020 (https://tinyurl.com/58kvm265). It is projected to increase to $5,650 million by 2027. The infant formula industry has been exploring how the different components of the MFGM can be used to create new lipid-based products that have similar properties as breast milk to ensure all children have the best start to their young lives.

REAPING THE BENEFITS OF THE MFGM

Infancy is a critical period for brain growth and development and early nutrition plays a key role in optimizing brain structure and function. While breast milk provides the most convenient form of nutrients to meet this need, infant formula enriched with bioactive nutrients provide a healthful and effective alternative. A recent study published in the journal *Frontiers in Nutrition* provides the first evaluation of the long-term impact of this early nutritional intervention (https://doi.org/10.3389/



The complex, multi-layer structure of the MFGM, including key polar lipids and proteins. Source: Brink, L.R. and Lönnerdal, B., *J. Nutr. Biochem., 85*, 2020.

fnut.2022.820224). The study enrolled infants and toddlers during the first 18-months of life. The children were then followed for six years to evaluate changes in their brain structures.

The study found infants fed formula enriched with MFGM, long-chain polyunsaturated fatty acids (LC-PUFA) and synbiotics (a mixture of prebiotics and probiotics) had neurocognitive outcomes and brain development that were similar to breastfed children at six years of age. The children fed the enriched infant formula scored higher in terms of IQ, vocabulary, and attention compared to their breastfed peers.

In addition, the children who received the enriched formula had greater brain volume and higher cortical thickness compared to children fed the standard infant formula. The researchers noted these changes in brain structure are related to improved cognitive development.

This study was unable to identify which of the three components (MFGM, LC-PUFAs and synbiotics) in the study were responsible for the observed improvements or if it was the result of a synergistic combination of all three.

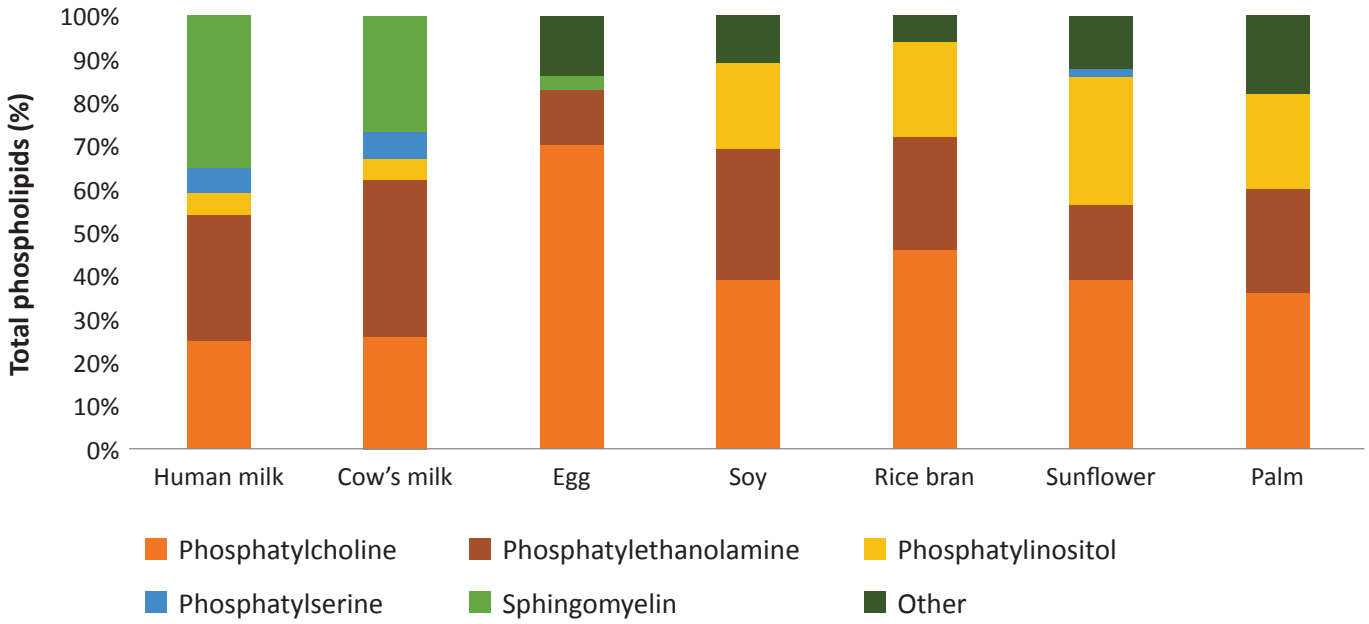
Beyond the brain, the MFGM supports gut health. The intestinal tract of infants is a blank slate that is colonized through environmental exposure. These bacterial colonies play a significant role in the immune system to protect the infant from infection. Breast milk has evolved to help colonize the gut of infants with beneficial bacteria. Animal studies show how the MFGM modulates immune activities, offering protection from foodborne pathogens. Further, these studies have shown that gangliosides, molecules within the MFGM, inhibit production of *E. coli* enterotoxin, as well as cholera toxin by strengthening the barrier properties along the intestinal tract.

The MFGM also contributes to a healthy metabolism. Unlike standard infant formula, the MFGM in breast milk is high in cholesterol, and breastfed infants have a higher concentration of cholesterol that levels off throughout childhood. Over time, breastfed children have lower incidence of cardiovascular risk, which points to the important role MFGM may play in cholesterol metabolism. Clinical trial studies point to the impact of MFGM-enhanced formula on higher serum cholesterol (HDL cholesterol and homocysteine) and higher serum choline compared to infants fed the standard formula. These results are more in line with levels found in breastfed infants. The study points to how these differences affect infant metabolism and long-term health.

ENHANCING FORMULA

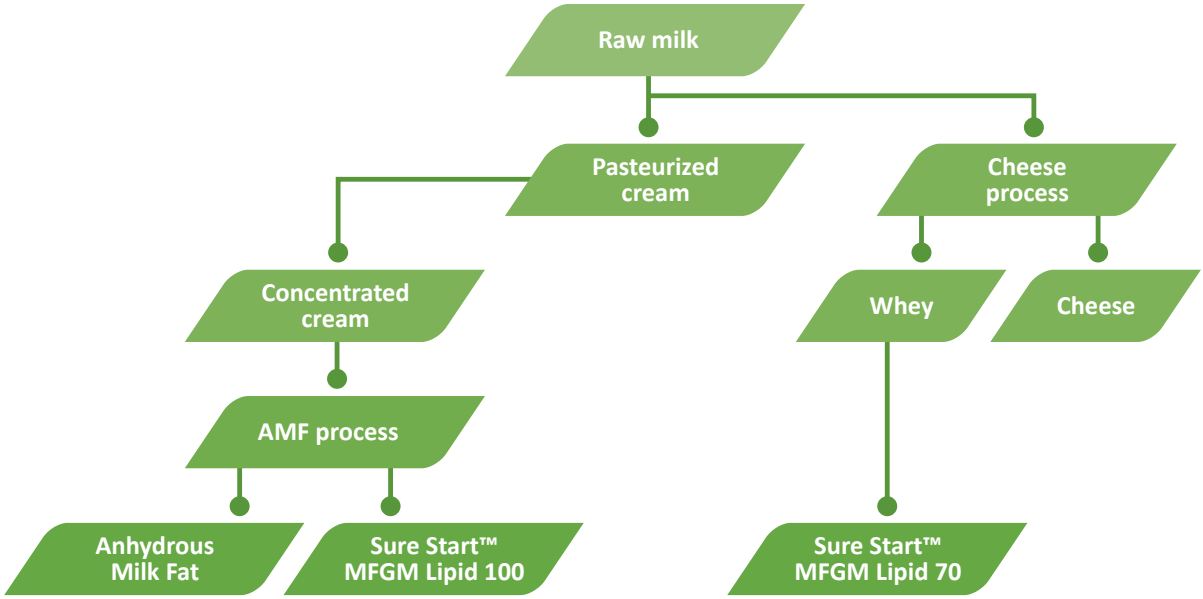
In recent decades, researchers have made progress creating better nutritional quality infant formula, and MFGM have played an integral role in these innovations. According to a 2017 study in the journal *Nutrients*, infant formula that incorporates the bioactive compounds found in MFGM may optimize the long-term health of the immune system and cognitive functioning of infants into childhood (https://doi.org/10.3390/nu9080817). Animal studies and human clinical trials support the role that MFGM play in cognitive and brain development.

The CLIMB (Complex Lipids In Mothers and Babies) study evaluated the outcomes of infants born to mothers who received complex milk lipids during pregnancy compared to those who received a standard maternal milk formulation (https://doi.org/10.1136/bmjopen-2017-016637). The researchers found prenatal maternal supplementation of gangliosides may improve brain development in the fetus. The CLING clinical trial assessed whether an enriched infant formula supports brain development as the children grow compared to infants fed a standard formula (https://tinyurl.com/y336eura). The study found that MFGM supplementation in early life improves some measures of normal cognitive development in infants, including higher cognitive, language, motor, social emotional, and general adaptive scores.



Human and cow (bovine) milk have a similar phospholipid composition. Both human and cow milk are more similar to composition of the human brain than other sources, like soy, egg or palm. The graph was developed using the work of Antonio Cilla and others in an article.

Source: Einerhand Science & Innovation



Fonterra manufactures MFGM-rich dairy streams from both the whey and cream components of cow's milk using two different processing routes. Source: Fonterra.

"This is one of the biggest revolutions in infant formula over the last several years," said Sandra Einerhand, founder and head of Einerhand Science & Innovation, a Dutch consultancy company that advises businesses on nutrition- and health-related questions (https://esi4u.nl/about/). "The MFGM market has not yet reached its full potential," she says.

Most MFGM found in infant formula is obtained from either the whey or cream concentrates from cow milk, which has a similar nutritional profile to human breast milk; however, different separation techniques affect the overall MFGM concentration gathered. While more research is needed to confirm the best approach and source material for new products, many companies are now exploring how to incorporate whey or cream MFGM into enhanced infant formulas that more closely resemble the nutritional profile and properties of human breast milk.

The New Zealand infant formula company, Fonterra, is a pioneer in the MFGM market (https://www.fonterra.com). It has created a MFGM lipid supplement, called Surestart™ Lipid, from the whey and cream components of cow milk. Using MFGM from both components provides the company greater flexibility in the formulation of their products. The company has focused on the role of complex milk lipids, especially on milk gangliosides, which play an integral role in the cognitive development of infants. Surestart Lipid has been shown to support fetal brain composition and infant cognitive development in several clinical trials.

Arla Foods, another pioneer in MFGM products, has created an array of food products, including Lacprodan® (https://www.arlafoodsingredients.com). This series of infant formulas use a dry blend protein, which contains a unique protein and lipid profile, including lactoferrin, IgG, sialic acid, phospholipids, and gangliosides. The product has been shown to have antiviral and antibacterial mechanisms that support the colonization of the gut with healthy bacteria. Infants that are fed the enhanced formula have lower gut infections and reduced incidence of diarrhea episodes, which is particularly important for premature infants. Clinical studies have found that infants that have been fed formula supplemented with Lacprodan® MFGM-10 demonstrated improved neurodevelopment, improved behavior performance, and reduced stress-induced sensitivity (https://doi.org/ 10.3390/nu12061607). These infants showed changes in brain structure and higher serum cholesterol. This study was unable to determine the precise mechanism that leads to these benefits.

In the infant formula market space, Danone has created the product Nuturis® (https://doi.org/10.1017/S0007114518001988). The enhanced formula contains large phospholipid-coated lipid droplets isolated from buttermilk and butter serums through micro and ultrafiltration. The droplets in Nuturis® are larger (3–5 mm) than typical fat droplets in infant formula (0.4 mm) and mimic the structure of lipids in human milk. The larger droplet size has been shown to promote fat digestion.

A randomized clinical study examined the benefits of the larger fat droplet size on infant development. The study examined the outcomes of breastfed infants compared to infants fed Nuturis® or standard infant formula (https://clinicaltrials.gov/ct2/show/NCT01609634). It found the enhanced lipid structure in Nuturis® improved infant nutrition to support growth and body composition, which is more in line with the outcomes in breastfed infants.

THE FUTURE OF FOOD AND BEYOND

While the infant formula market may have the corner on MFGM, other industries are not far behind. Because MFGM

Techniques to harvest the MFGM

In 2015, Australian researchers developed a new, faster technique to separate milk fat globules for industrial applications. The system uses two fully submersible plate transducers contained within a large rectangular reaction vessel that can hold up to two liters of milk. The separation process begins when one plate emits a one- or two-megahertz ultrasonic wave that passes through the milk and reflects off the second plate. As the sound wave moves through the milk, it separates and concentrates the fat portion into the cream that floats to the top of the tank, while the remaining skim sinks to the bottom of the tank. The process takes only 20 minutes and is faster than traditional methods like natural fat sedimentation and buoyancy processing, which typically take six hours.

In an article for *Food Processing* magazine, the study author Thomas Leong, an ultrasound engineer and a postdoctoral researcher from the Faculty of Science, Engineering and Technology at the Swinburne University of Technology, in Melbourne, Australia stated, "These streams can be further fractionated to obtain smaller and larger sized fat globules, which can be used to produce novel dairy products with enhanced properties." Leong believes this process can create fat globules that can enhance the taste and texture of many products (https://tinyurl.com/ypx5bwwt).

contain both hydrophilic and hydrophobic components, it makes an excellent emulsifier to improve and texturize foods. Studies have found MFGM- and MFGM protein-based emulsions produced smaller droplets creating a liquid with a greater viscosity and improved stability. This approach offers the food industry a new way to enhance and transmit nutrients. For example, the bioavailability of beta carotene is low when it is found in an aqueous solution, but the bioavailability increases when beta carotene is contained in an emulsion.

Bhesh Bhandari, professor at The University of Queensland's School of Agriculture and Food Sciences, in St. Lucia, Australia is pioneering techniques to create innovative dairy products by focusing on fat globule size. According to Bhandari, adjusting the size of fat globules in milk can produce different structures and textures in food.

Bhandari and his team are using existing dairy equipment with only minor modifications to prepare nano-emulsions, a technique developed by the pharmaceutical industry. The new process can manufacture functional cream powder to make whippable low fat cream that can be recombined with liquid milk, cheese, yogurt, and butter to make low fat butter and fat spreads.

"By tuning system parameters according to acoustic fundamentals, the technique can be used to specifically select milk fat globules of different sizes in the collected fractions, achieving fractionation outcomes desired for a particular dairy product," said Bhandari, in a 2017 press release (https://tinyurl.com/2p8mar6m). "Our latest findings reveal that small fat globules impart an amazing stability to cream and give cold butter softer texture and improved spreadability."

The MFGM also offer opportunities in the medical nutrition space as a medical food or as an oral nutritional supplement. Studies in healthy older adults suggest this product could strengthen muscle to prevent frailty. According to Einerhand, MFGM supplementation combined with regular exercise has been shown to improve skeletal muscle strength. Taking the data together, MFGM administration in combatting muscle loss and function at older age provides an interesting avenue for future studies. Einerhand says, the research completed to date have been small and used low doses of MFGM. In addition, the studies have produced conflicting and inconsistent results.

The role of MFGM in strengthening the barrier properties along the intestinal tract has also piqued research interest. The protective nature of MFGM against pathogens is particularly interesting after two long years of the pandemic. The protective property offered by MFGM provides an enticing path of study not only against viral agents, but also common bacterial pathogens, like *Clostridium difficile* and *E. coli.* MFGM research provides a ripe area of exploration for new products to reduce the incidence of respiratory or diarrhea-related illnesses in older adults or during extended hospital stays.

"MFGM lipid-containing products may have beneficial effects in adults, but clinical evidence is still quite preliminary," said Einerhand. "The science needs to continue to evolve."

Stacy Kish is a freelance science writer. She has worked for 15 years to bring engaging stories about an array of science topics to a general audience. She can be contacted at earthspin.science@gmail.com.