Breast Milk Lipidomics: Insights to Infant Health Requirements and Targeted Strategies for the Vulnerable

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LIPIDS ARE A COMPLEX and structurally diverse group of compounds that are essential for optimal growth, health, and development. Long-chain polyunsaturated fatty acids are selectively transferred from maternal circulation to the developing fetus in the third trimester. The shortened gestation of preterm infants can result in altered postnatal levels of fatty acids, such as decreases in docosahexaenoic acid (DHA) and arachidonic acid (AA) and concomitant increases in linoleic acid.¹ These deficits in DHA and AA have been linked to late-onset sepsis and bronchopulmonary dysplasia (BPD), a type of chronic lung disease, in preterm infants. In a mouse model of BPD, treatment with downstream metabolites of DHA and AA that regulate inflammation and organogenesis was shown to reverse hyperoxia-induced lung injury, suggesting supplementation with these fatty acids or their metabolites may provide a novel therapeutic strategy for BPD.² These studies emphasize the pleiotropic effects of fatty acids and that the fetal/preterm period is a unique time allowing one to tease out this pleiotropy and to determine the role of bioactive molecules in health and disease.

Lipids are a major source of energy in breast milk, contributing 44% of the total energy intake in breastfed infants 1 month of age.³ Studies are starting to emerge about the lipid components of breast milk and how they relate to outcomes. A recent pilot study using liquid chromatography–mass spectrometry identified lipid biomarkers, such as medium-chain sphingomyelin, phospholipids containing dihomo- γ -linolenic acid (DGLA) and DHA, and DGLA-derived oxylipin, in breast milk that displayed a good ability to predict weight gain during the hospital stay in preterm infants.⁴ Plasmalogens, a type of glycerophospholipid, are also found in breast milk and have been linked to disease outcomes. Higher levels of plasmalogens and polyunsaturated fatty acids have been associated with reduced risk of BPD in preterm infants,⁵ and preliminary results from a current study

on the breast milk lipidome seem to support these findings. Plasmalogens are also one of the main classes of lipids present in the developing cerebrum, cerebellum, and brainstem, indicating that they are important for brain development.⁶ Of note, lower levels of plasmalogens have been reported in patients with Alzheimer's disease but not in patients with other neurodegenerative disorders, suggesting plasmalogen deficiency may be a specific biomarker for Alzheimer's disease.^{7,8}

Lipids in breast milk are contained within milk fat globules, which consist of a trilayer membrane of polar lipids, cholesterol, enzymes, and glycoproteins surrounding a triglyceride core.⁹ A study in rats demonstrated that formula supplemented with bovine milk fat globule membrane (MFGM) normalized intestinal development compared with control formula, with intestinal readouts similar to rats receiving mothers' milk.¹⁰ MFGM supplementation also altered the gut microbiota, resulting in a microbiome at the phylum level resembling that found in pups receiving mothers' milk. Microbial species richness and evenness were similar in pups receiving MFGM formula or mothers' milk; however, there were significant differences in diversity at lower taxonomic levels across all groups. Studies assessing the benefits of MFGM supplementation in infants and children have shown positive, but modest, effects on neurodevelopment and gut health.¹¹ A randomized controlled trial in healthy term infants reported higher cognitive scores at 12 months using the Bayley Scales of Infant and Toddler Development in infants fed a low-energy and low-protein formula supplemented with MFGM versus those fed a standard formula.¹² A separate randomized controlled trial comparing MFGM formula with standard formula in infants showed significant differences in the plasma and erythrocyte membrane lipidomes at 6 months and the serum lipidome at 4 months, suggesting changes in the lipidome may contribute to the beneficial effects reported in

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infants receiving MFGM.¹³ MFGM supplementation may also have beneficial effects in adult populations. Adults randomized to receive milk enriched with MFGM twice daily showed improved resistance to diarrheagenic *Escherichia coli* compared with controls, providing evidence that MFGM may affect resistance to infection.¹⁴

Although initial studies suggest MFGM supplementation may induce system-level changes, the effects are modest and further studies are needed to confirm long-term benefits. Understanding the structure and function of MFGM may offer insights into the optimal lipid composition and delivery system needed to support health and development across the life span. The unique properties of MFGM may also offer insights into natural drug delivery platforms for the targeted treatment of various disorders, such as cancer, mucosal injury, and neurodegenerative disorders.

Disclosure Statement

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