Bioactive milk proteins and their impact on infant health and development

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Breast-feeding confers many benefits to the newborn and developing infant. There is substantial support from meta-analyses for better long-term outcomes, such as less obesity, diabetes and cardiovascular disease, in breast-fed as compared to formula-fed infants. More short-term outcomes such as incidence and duration of illness, nutrient status and cognitive development during the first year of life also demonstrate benefits of breast-feeding. Several proteins in breast milk have been shown to have bioactivities, which range from being involved in the protection against infection and cognitive development to the acquisition of nutrients from breast milk. In some cases, bovine counterparts of such proteins can exert similar bioactivities and it is thus possible by dairy technology to add protein fractions highly enriched in these proteins to infant formula.
Lactoferrin, α-lactalbumin, milk fat globule membrane (MFGM) proteins and osteopontin are examples of such bioactive proteins. Since clinical trials with human milk proteins are difficult to perform due to a limited supply of these proteins, studies with bovine milk protein counterparts showing beneficial outcomes provide proof-ofconcept that these proteins in human milk provide valuable bioactivities.

Lactoferrin is the major iron-binding protein in breast milk and has been shown to bind to a specific lactoferrin receptor in the small intestine. In the gut lumen, lactoferrin has bacteriostatic and bactericidal activities and the lactoferrin receptor will facilitate the uptake of both lactoferrin and iron into the intestinal cell. Internalized lactoferrin can bind to the nucleus and affect the expression of genes involved in cell growth and proliferation as well as in immune function. Clinical studies have shown that bovine lactoferrin can reduce respiratory disease in term infants and sepsis and NEC in preterm infants.

Alpha-lactalbumin is a major protein in human milk. During its digestion in the gastrointestinal tract of breastfed infants, peptides are released that, in turn, have been shown to have biological activity. Among these peptides are an immune-stimulating peptide, peptides enhancing the absorption of essential micronutrients like iron and zinc, and peptides that have prebiotic activity, i.e. they stimulate the development of a beneficial gut microflora. When the protein content of infant formula is reduced, increasing the proportion of alphalactalbumin improves the amino acid pattern of the formula and may improve the gut microflora.

Milk fat globule membrane (MFGM) proteins. These proteins surround the lipid droplets in human milk together with phospholipids, gangliosides, cholesterol, sialic acid, etc. Although a minor protein fraction, proteomics analyses have shown many proteins with anti-infective properties and the capacity to affect signaling pathways. We have conducted a clinical trial on Swedish infants who were fed regular formula or formula supplanted with bovine MFGM from 6 weeks to 6 months of age. A breast-fed reference group was also included. We found that infants fed the MFGM-supplemented formula had significantly better cognitive development at 12 months of age (as assessed by the Bailey III test) than those fed regular formula and that there was no difference between them and the breast-fed infants. We also found that infections were lower in the MFGM-supplemented group as compared to those fed regular formula and again not different from the breast-fed infants. This was especially pronounced for acute otitis media.

Osteopontin is a complex protein being phosphorylated and glycosylated at multiple sites. It is present at a relatively high concentration in breast milk as compared to cow's milk. This protein is involved in immune function and possibly also in brain development. Osteopontin has a specific domain that allows it to bind to integrin, a protein in the intestinal mucosa. By this docking mechanism, osteopontin can trigger signaling events in the cells, thereby affecting the immune system. Our recent clinical trial on bovine osteopontin added to infant formula resulted in an improved cytokine profile and immune parameters as well as less illness, making these infants different from infants fed regular formula and more similar to breast-fed infants.

In conclusion, human milk contains many bioactive proteins that are likely to be involved in the better outcomes of breast-fed infants as compared to those fed infant formula. Bovine milk proteins or protein fractions may be able to provide some of these benefits and may therefore soon be added to infant formula.