Transport proteins provide key to improve infant formula

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Sugar compounds in breast milk play a crucial role in the development of a healthy gut bacterial community and contribute to the maturation of the immune system in infants. In a new study professors from DTU and Kyoto University, Japan, have established a framework to identify and describe the function of key transport proteins that mediate the uptake of nutrients from the mother's breastmilk to an important group of bacteria in the child's intestines.

These proteins transport human milk oligosaccharides or HMOs, which are complex sugars produced by the mother, to nourish important bifidobacteria associated with the development of good health.

"Our work allows us to establish a clear link between the type of sugars in the mother's milk and the health-promoting bacteria in the infant's gut. More importantly, our work allows mapping the best sugar from mothers milk on the menu of infant health-beneficial gut bacteria based on the transport proteins" says Professor Maher Abou Hachem from DTU Bioengineering, who conducted the study in collaboration with Professor Takane Katayama from Kyoto University.

Maher Abou Hachem believes that this new line of research will guide milk formula producers to synthesize new sugar additives in a rational manner, thereby ensuring that children who drink milk formula receive similarly beneficial sugars as children who are breast-fed do.

The research on human milk sugars has been published in *Science Advances* and has been conducted in a broad collaboration between researchers with expertise in microbiology, protein and carbohydrate chemistry as well as bioinformatics. A part of the study involving analyses of fecal bacteria and mother's milk from mother-infant pairs and a control group of human adults has been conducted in Japan, while the molecular description of the transport proteins and their HMO preferences has been conducted in Denmark.

The establishment of the gut microbiota begins at birth and this bacterial community develops until the age of 2-3 years. During this critical window, before maturation of the immune system, large changes can occur in the gut microbiota. After weaning, the immune system is programmed for a specific structure of the gut community, which persists throughout adulthood.

Maher Abou Hachem emphasizes that it is well documented that bifidobacteria play a major role in the development of healthy gut microbiota in children. A well-developed infant bacterial community reduces the risk factors for immune and metabolic disorders such as allergy, asthma, diabetes, obesity and a variety of other diseases.

"It is crucial to establish the right gut microbiota early in the child's life. Conversely, factors that interfere with the development of the "right"

microbiota are associated with life-long health disorders. If we get the wrong organisms from early life and we get used to them and they are accepted as part of the microbiota, it will be very difficult to re-select the normal and beneficial bacteria afterwards," says Maher Abou Hachem.

In the publication "Evolutionary adaptation in fucosyllactose uptake systems support bifidobacteria-infant symbiosis," the scientists reveal and comprehensively analyze two functionally distinct but overlapping human milk sugar (oligosaccharides), HMO, transporters of *Bifidobacterium longum subsp. infantis*.

The research establishes a methodological platform to investigate and map the correlations between occurrence and the function of specific transport proteins and genes, HMO consumption, and the establishment of a bifidobacteria-rich microbiota in the breast-fed infant guts.

Mother's milk and milk formula

Mother's milk contains the essential nutrients for neonates, including fats proteins and carbohydrates (lactose or milk sugar). Notably, the third most abundant component in milk comprises a complex mixture of oligosaccharides termed human milk oligosaccharides (HMOs). These HMOs are not digestible by infants but are exclusively synthesized as "nutrient sugars" to attract a healthy gut microbiota, dominated by members of Bifidobacterium.

HMOs, play a crucial role in the development of healthy gut microbiota and a strong immune system in infants, which has life-long consequences on their health as adults. Strikingly, HMOs from mother's milk contains more than 100 different sugar structures that differ in size and complexity. To date, the specific impact of distinct sugars on the composition of the gut microbiota, and thereby on the health trajectory of the infant remains unclear.

Since many infants are raised on milk formula, intense research is ongoing in academia and industry to create an infant formula that compensates for the lack of HMOs in bovine milk (human HMOs are unique and are not present in animal milk).

The first generation of infant formula contained oligosaccharides from plants, e.g. galacto-oligosaccharides, which had little resemblance to HMOs, but currently, different companies are endeavoring to add synthetic sugars identical to authentic HMOs. The synthesized HMOs are chosen based on how easy they are to produce or how abundant they are in human milk, but there is no insight into how different types of HMOs influence the assembly of a healthy infant gut microbiota.

More information: Mikiyasu Sakanaka et al. Evolutionary adaptation in fucosyllactose uptake systems supports bifidobacteria-infant symbiosis, *Science Advances* (2019). DOI: 10.1126/sciadv.aaw7696

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