Child health

Commensal bacteria share life with humans from the prenatal state until death. Trillions of microbes are found in the mature human gastrointestinal tract, mostly bacteria but also archaea, viruses and protozoa, that undertake multiple functions to promote human health, but also can cause diseases. Maturation of the gut microbiome commences in utero but continues after birth, only becoming fully developed several years later. The development of the fetal gut microbiome is suggested to begin when the fetus swallows amniotic fluid (Chong et al., 2018). The amniotic fluid and placenta contain bacteria, as well as free bacterial DNA and bacterial metabolites, so the amniotic fluid may provide the initial inoculum for microbial colonization (Collado et al., 2016). During and after birth, the infant is exposed to maternal intestinal bacteria that are translocated to peripheral tissues and to the mammary gland by cells of the immune system in the systemic circulation. Therefore, in addition to contact with the maternal intestinal and vaginal microbiome during birth, the consumption of breast milk contributes to the further gastrointestinal inoculation of the newborn. The bacteria found in human milk may play a fundamental role in modulating and influencing the neonatal immune system (Toscano et al., 2017). With the beginning of life, the composition of the developing gut microbiome is mostly influenced by the diet of the baby.

Breastfeeding for longer periods is correlated with multifold beneficial effects for the infant, including lower infection rates, and a lower risk of asthma, allergies, inflammatory diseases and even obesity. In addition to nutrients, human breastmilk contains hormones, vitamins, growth factors, immunoglobulins and cytokines that help to mature the infant immune system. After lipids and lactose, human milk oligosaccharides (HMOs) are the third most abundant component of human breastmilk. HMOs are diverse, unconjugated short-chain and long-chain glycans (3–15 monosaccharide units) found at concentrations of 20–25 g/L in the colostrum, the first milk, to 5–20 g/L in mature milk. The diversity, complexity and concentration of HMOs are unique to humans, and cannot be provided by the milk of domestic animals such as cows, sheep or goats. The concentration and composition of HMOs is individual and varies during the period of lactation, complementing the needs of the feeding infant. Furthermore, the HMO profile in human breastmilk depends on the nursing mother’s genetic factors. The FUT2 gene is particularly important: 80% of mothers possess an active copy and are known as ‘secretors’ because they produce an enzyme that allows the synthesis of HMOs with alpha-1,2-linked fucose units (such as 2’-fucosyllactose and the

Human milk oligosaccharides enhance the neonatal immune system

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more complex lacto-N-fucopentaose I) whereas 20% of mothers are non-secretors. The milk of secretor mothers contains up to 2.4 g/L 2′-fucosyllactose, which is the most abundant HMO (Sprenger et al., 2017).

Whereas lactose in breastmilk is a source of energy for the infant, HMOs are not digested. They are resistant to low gastric pH and are absorbed by only 1%. HMOs act primarily as prebiotics in the infant gut. They promote the growth of beneficial microbes such as bifidobacteria, bacteroides and lactobacteria, but not pathogens such as enterobacteria. Specific strains of bifidobacteria are capable to break down and ferment HMOs, especially Bifidobacterium longum ssp. infantis, others consume the simpler sugars released from HMOs by bacterial enzymatic hydrolysis. The growth of these commensal bacteria is therefore supported by HMOs and has a direct effect on the developing microbiome, with life-long consequences for the host.

These beneficial bacteria shape their environment by secreting antimicrobial factors, by competing with pathogens for nutrients and host receptors, by changing the local redox status and pH, and by producing beneficial metabolites. Bifidobacteria are enriched in the intestine of healthy breastfed infants compared to those fed on formula milk (Lee et al., 2015), and the consumption of milk containing high concentrations of 2′-fucosyllactose in particular promotes the dominance of B. longum ssp. infantis in the gut microbiome (Lewis et al., 2015).

The beneficial bacteria secrete a wide range of metabolites into the gut lumen that influence the physiology of the human host. Metabolites and bacterial cell wall structures influence the expression and differentiation of T-cells by inhibiting the enzyme histone deacetylase, thus modulating the secretion of cytokines to inhibit inflammation (Yang and Duan, 2017). The optimal relative abundance of different immune system cells correlates with homeostasis in the gut immune system, which can enable an adequate immune response to defend against pathogens and to prevent local or systematic autoimmune and inflammatory diseases such as irritable bowel disease,
asthma and rheumatoid arthritis (Yang and Duan, 2017). Beneficial bacteria also secrete proteins that enhance the mucosal barrier and prevent inflammation by modulating the immune system (Sánchez et al., 2010), and short-chain fatty acids (SCFAs) such as acetate, propionate and butyrate, which help to main homeostasis in the gut and the immune system (Underwood et al., 2014). For example, butyrate is a key energy source for epithelial cells and helps to maintain the integrity of mucosal layers and the epithelial barrier, whereas acetate can influence the appetite by acting on the hypothalamus and modulating hepatic glucose homeostasis.

Breastfeeding is known to correlate inversely with the risk of developing type-1 diabetes resulting from the autoimmune destruction of insulin-producing pancreatic beta cells. As stated above, the development of a healthy gut microbiome early in human life influences the innate immune system and reduces the risk of autoimmune diseases. HMOs can also alter the gut microbiome in animal models to promote the growth of bacteria that secrete SCFAs, particular butyrate. Luminal SCFAs enhance the epithelial barrier function by promoting mucin synthesis. Additionally, the direct effect of HMOs alone and in combination with SCFAs on particular types of immune system cells supports the hypothesis that HMOs administered in early life may protect against type-1 diabetes and autoimmune diseases in general (Xiao et al., 2018).

The diversity of HMOs also has the potential to directly modulate both the innate and adaptive neonatal immune systems. By binding to carbohydrate-recognizing receptors, HMOs can trigger signaling in immune system cells to control cell proliferation and function. Fucosylated HMOs such as 2′-fucosyllactose and 3-fucosyllactose bind to glycan-binding lectins on dendritic cells at the physiological concentrations of these HMOs in the human gut (Noll et al., 2016). HMOs also influence cytokine expression in vitro to reduce inflammatory reactions. Exposure to HMOs stimulates the maturation of intestinal cells and strengthens the gut barrier function. A clinical study involving healthy term infants revealed that the cytokine profile of infants fed exclusively on formula containing 2′-fucosyllactose and galacto-oligosaccharides (GOS) was identical to that of breastfed children, but differed significantly from that of infants fed exclusively on formula containing only GOS (Goehring et al., 2016).

In addition to their prebiotic effects on beneficial bacteria, HMOs also directly deter colonization by pathogens (not only bacteria but also viruses) by acting as anti-adhesive antimicrobials. Many cell-surface glycans function as pathogen receptors or co-receptors. The structure of some HMOs is so similar to these receptors that they can act as decoys – pathogens or virulence factors such as toxins bind to the soluble HMOs instead of the cellular receptors, and are therefore carried through the gut harmlessly rather than triggering an infection. This protective mechanism has been reported for several diarrhea-causing pathogens such as Campylobacter jejuni and Salmonella typhimurium, but also against pathogenic Escherichia coli, Pseudomonas aeruginosa and Streptococcus pneumoniae. Fucosylated HMOs such as 2′-fucosyllactose and 3-fucosyllactose are particularly adept at reducing the risk of norovirus infections, which are among the most common intestinal infections in infants worldwide. HMOs even show antimicrobial activity against pathogenic Staphylococcus aureus and Acinetobacter baumannii, the major source of nosocomial infections, suggesting HMOs could be used therapeutically or prophylactically as well as nutritionally (Craft and Townsend, 2017). In a clinical trial, infants fed on formula supplemented with 2′-fucosyllactose and lacto-N-neotetraose suffered significantly lower rates of respiratory tract infections than infants in the control group receiving formula without HMOs (Puccio et al., 2016).

Until recently, the advantages of HMOs were limited to breastfed babies because it was not possible to source HMOs elsewhere for inclusion in formula milk. In 2016 however, the first infant formula containing 2′-fucosyllactose reached the US market, followed in 2017 by a product supple-
mented with 2′-fucosyllactose and lacto-N-neotetraose in Spain. Nowadays, 2′-fucosyllactose can be produced at the multi-ton scale and is provided as a supplement for infant formula, medical nutrition and general nutrition. Jennewein Biotechnologie GmbH, located in Germany, has developed a unique HMO production process based on bacterial fermentation, which allows the industrial-scale synthesis of various HMOs including 2′-fucosyllactose. The family-founded company is a pioneer in HMO production, and the biotech-derived 2′-fucosyllactose product was awarded US Food and Drug Administration (FDA) generally regarded as safe (GRAS) status in 2015. Authorization under the Novel Food legislation, Regulation (EC) No 258/97, was granted by the European Food Safety Authority (EFSA) in 2017. Jennewein 2′-fucosyllactose is manufactured under ISO22000 and it conforms to kosher and halal standards.

References
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