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The term “oligosaccharide” (derived from the Greek oligos, meaning little or few, and sakkhar, meaning sugar) is generally used to describe a group of complex carbohydrates made of 3 to 6 simple sugars, such as glucose and fructose. Interestingly, breastmilk contains a diverse and unique set of oligosaccharides – collectively referred to as human milk oligosaccharides (HMO). HMO profiles and amounts differ among women living in different regions of the world. For instance, whereas almost all women living in Peru produce milk that contains the HMO 2'-fucosyllactose (2'FL), only about 70% of Ghanaian women do. Although some of this variation due to genetics, other factors might also be important. For instance, environmental pathogen exposure might support variation in HMO profiles to best protect infants from diseases they are most at risk of contracting. There is also evidence that variation in HMO profiles are related to those of bacterial profiles found inherently in human milk. This relationship between HMO and the milk microbes might have important implications for establishment of the breastfed infant’s gastrointestinal tract microbes. Concentration of certain HMO have also been linked to variation in the amount and profiles of maternally-derived immune cells in milk. However, nothing is known about whether HMO variation drives that of immune cells, vice versa, or the possibility that this relationship is coincidental and due to a confounding factor. To fill this knowledge gap, relationships between HMO and milk immune cells will need to be repeatedly measured and evaluated over time. Maternal diet might also impact HMO. For instance, some research suggests that concentrations of certain fatty acids found in milk (mostly derived from the diet) are correlated with both total and individual HMO concentrations.

An example is a reported inverse association between higher levels of stearic acid and lower 2'FL concentration. Foods rich in stearic acid include beef, dairy products, and tropical foods such as coconuts. However, controlled dietary intervention studies are needed to determine if these associations are causal or coincidental. In addition, longitudinal studies are needed to evaluate whether variation in HMO profiles seen across populations are related to health and wellbeing, and if so whether the relationships depend on the environment in which infants live. In summary, there are convincing data that HMO vary globally and their concentrations are related to other milk components. However, substantial research is needed to understand the importance (if any) of this variation and these relationships.

Supporting literature
Human milk oligosaccharides (HMOs) are complex sugars (carbohydrates) that represent the third most abundant component of human milk after lactose and lipids. More than 150 different and structurally distinct HMOs have been identified so far and accumulating evidence indicates strong structure-function relationships — in other words: different HMOs have different functions. HMO composition varies tremendously between different women and to a lesser extent over the course of lactation.

Recent research focuses on how fixed and modifiable maternal factors influence HMO variation. So far, maternal genetics appear to be the strongest predictor of HMO composition. Single nucleotide polymorphisms (SNPs) in genes that encode specific glycosylation enzymes involved in HMO biosynthesis can alter HMO composition to an extent that entire groups of HMOs are missing from the milk. Other maternal factors have more subtle effects on HMO composition, increasing or decreasing the absolute concentration and/or relative abundance of individual HMOs on a continuous scale. While it is important to understand which maternal factors drive the variation in HMO composition and how, most research focuses on whether and how HMOs impact infant health and development.

Once ingested, HMOs resist degradation and reach the distal parts of the gastrointestinal tract. HMOs serve as natural prebiotics and help shape the infant gut microbiome with immediate and potential long-term consequences for health and development, including infant growth, body composition and potential risk of childhood obesity. However, HMOs are more than just “food for bugs”. HMOs serve as antimicrobials and antiadhesives that keep potential pathogens in check. HMOs also have direct effects on epithelial cells as well as on immune cells, both locally in the gastrointestinal tract as well as systemically. Some of the effects of HMOs are highly structure-specific and dose-dependent, suggesting that they interact with specific host and/or microbial receptors. Specific HMOs are required to exert these effects while other, structurally distinct HMOs cannot mimic these effects. Other HMO effects require a specific “mixture” of HMOs with specific ratios of different HMOs to each other.

One HMO alone is ineffective; instead a group of different HMOs is required to act together in modulating the composition and activity of microbial communities and/or a complex immune system response. HMOs were first discovered in the mid 1950s and HMO research has come a long way since and has been greatly accelerated over the past few years due to advances in analytical technologies as well as in methods to generate individual HMOs at large scale for research and application. However, we are still at the very beginning of uncovering the complexity of HMOs and understanding the full potential of how HMOs influence the immediate and long-term health and development of infants and mothers.
Physiological significance of HMO: Why are they in mother’s milk?
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Presented at NNI Satellite Symposium – ESPGHAN 2018

Human milk oligosaccharides (HMO) have no nutritive value, yet mothers spend significant energy for their synthesis. So what do they do? Clinical observational studies together with basic research position HMO as multifunctional innate breastmilk component. They shape the establishing gut microbiota and supposedly help the development of appropriate immune competence.

The early-life gut microbiome establishes and matures sequentially during infancy and early childhood from an aerobic to anaerobic milk-oriented early life microbiome towards an adult like microbiome. Different phases of this maturation process can be characterized by a progression of microbiota communities, starting from Enterobacteriaceae, Streptococcaceae dominated aerobic communities over anaerobic Bifidobacteriaceae dominated communities to increasingly diverse Bifidobacteriaceae and Lachnospiraceae dominated communities. The age-appropriate microbiome maturation is considered important for normal digestive, immune competence and metabolic development (Blanton et al. Science 2016;22:713). Mode of delivery, antibiotic use and diet are probably most influential to this end. (Chart 1).

Breastfeeding is associated with a lower risk of gastrointestinal and respiratory infections, and possibly lower risk of diabetes and obesity, while the effect on allergies is less clear (Victora et al. Lancet 2016; 387:475). This suggests that breastmilk-specific components may contribute.

Among such breastmilk specific components are the non-digestible human milk oligosaccharides (HMO), the third largest solid breastmilk component. Chemically, HMOs are elongations of the milk sugar lactose by galactose, N-acetyl-glucosamine, fucose and sialic acid. Most HMOs such as the fucosyl-oligosaccharides are not present in farmed-animal milks and therefore absent from animal milk based nutrition products. In structure and composition the HMO resemble and have identical epitopes like mucosal surface glycans that are at the interface between the mucosal cells and the intestinal microbiome.
In contrast to HMOs, generic prebiotics like Fructooligosaccharides (FOS, inulin) are elongations of the table sugar sucrose by fructose units. These are typical plant storage glycans usually consumed from weaning with the introduction of solid plant based complementary food.

Mothers spend a considerable amount of energy to form HMOs in milk at an estimated 5 to 15 g/L. The HMO composition varies primarily due to the maternal genotype for the Secretor and Lewis gene encoded fucosyltransferases as well as stage of lactation. While most HMOs decrease in concentration with time of lactation, some increase. This means with age-dependent growing milk intake infants consume relatively constant amounts of most HMOs per day and increasing amounts for some. Generally, HMOs are non-digestible and hence have no nutritive value per se. Small amounts of HMOs can go systemic and are mostly excreted in urine, while the bulk of HMOs remains in the gut lumen (Chart 2).

Generally, we base our hypothesis on possible roles of HMOs for healthy infant growth and development on observational clinical association studies. In a first step towards the establishment of causality, we investigate the formulated hypothesis using basic research mode of action models. In a second step, we run randomized clinical intervention trials (Chart 3).

In cohorts of breastfed infant-mother dyads, specific HMOs correspond with infant gut microbiota, allergies, morbidity, infectious diarrhea and respiratory infection (Chart 4). In the gut lumen, HMOs modulate the establishing gut microbiome through the promotion of a bifidobacteria-dominated microbiome. Basic research studies identified different bifidobacteria strains that can use HMOs for growth, either after internalization or after extracellular breakdown. Interestingly, specific HMOs also boost the metabolic activity of specific bifidobacteria seen primarily as higher formation of the short chain fatty acid (scfa) acetate that is not necessarily seen with prebiotics that lead to similar growth. Metabolites from the HMO stimulated bifidobacteria provide immune protection from inflammation and pathogen invasion in preclinical models. The bifidobacteria-dominated early life microbiome, likely through its metabolites and acidification of the gut lumen, leads to colonization resistance against the intrusion of new and potentially harmful microbes and thus represents a major intestinal barrier.

Because HMOs modulate the maturation of the early life microbiome and because the microbiome presumably affects food efficiency and energy harvest, variation in HMO composition might affect infant growth and body composition. We did not observe growth differences through 4 months of age in a cohort of 25 boys and 25 girls in relation to 2’Fucosyl-HMOs (Sprenger et al. PlosONE. 2017; 12:e0171814). However, another group observed lower fat mass related with higher breastmilk content of one specific 2’Fucosyllactose (2’FL) in a cohort of 25 infants (Alderete et al. AJCN. 2017; doi: 10.3945/ajcn.115.115451). It will be interesting to further study HMO relations to body composition in larger cohorts. Numerous environmental, including microbiome and nutrition, and genetic factors affect allergies. Among them are breastmilk bioactives, and possibly HMOs. In a cohort of 266 mother infant dyads with hereditary allergy risk, 2’Fucosyllactose (2’FL) concentrations in breastmilk related to lower risk to manifest IgE-eczema through 2 years of age in the C-section born infants only (Sprenger N, et al. Eur J Nutr 2017;56:1293–1301). This indicates that 2’FL might have an immune effect via the promotion of
specific bifidobacteria that were at lower prevalence in the C-section born infants up to 6 months in this cohort (Kuitunen et al. JACI 2009;123:335). Noteworthy, specific Bifidobacterium breve were related to lower eczema risk and 2’FL related to abundance of specific B. breve strains and their metabolic activity (Pediatric Allergy and Immunology 2016; 27:838. Matsu ki et al. Nature Comm 2016; 7:11939). Further, HMOs like 2’FL and another larger fucosyl-HMO (LNFP III) interact with the dendritic cell lectin DC-SIGN, which might modulate immune development. Another group found LNFP III related to cow milk allergy (CMA) at 18 months of age in a cohort of 39 mothers with CMA infants and 41 mothers with healthy infants (Seppo et al. (2017) JACI 139:708). They speculated that LNFP III might have acted via DC-SIGN. In a mouse model on food allergy, 2’FL and the sialyllactose 6’S L were tested and both reduced symptoms via the modulation of mast cell response (Castillo-Courtade L et al. (2015) Allergy. 70:1091).

DC-SIGN, which might modulate immune development. Another group found LNFP III related to cow milk allergy (CMA) at 18 months of age in a cohort of 39 mothers with CMA infants and 41 mothers with healthy infants (Seppo et al. (2017) JACI 139:708). They speculated that LNFP III might have acted via DC-SIGN. In a mouse model on food allergy, 2’FL and the sialyllactose 6’S L were tested and both reduced symptoms via the modulation of mast cell response (Castillo-Courtade L et al. (2015) Allergy. 70:1091).
Because HMOs resemble mucosal glycans and largely escape complete fermentation, they can act as soluble decoys preventing pathogen adhesion to mucosal cells. Besides glycans the mucosa and immune cells are also rich in lectins (glycan binding proteins) and some were shown to bind specific HMOs. Examples are DC-SIGN, galectins and Siglecs. Whether observed changes in epithelia and immune cells upon treatment with specific HMOs is mediated via such lectins remains to be shown. Together, such proposed mechanisms including the aforementioned colonization resistance and importance of the microbiome for immune development suggest that HMOs contribute to protection from infections in the gastrointestinal tract and likely at other mucosal sites such as the respiratory tract.

Chart 5: Why are HMOs in mother’s milk?

Possibly
To help the development of appropriate immune competency likely in part through the support of age-appropriate microbiome maturation

Outlook
We defined observational studies for confirmation and further hypothesis generation including metabolic and nervous system development
Randomized controlled intervention trials to establish causality and evidence based nutrition

In a cohort of Mexican mothers and infants (n=93), higher 2’Fucosyl-HMOs in breastmilk related to lower incidence rate of infectious diarrhea through 9 months of age primarily caused by Campylobacter jejuni, but also by Calicivirus (Morrow AL, et al J Pediatr 2004;145:297–303). In a smaller cohort of 33 infant mother pairs 2’Fucosyl-HMOs related to lower morbidity in the first 4 months of age (Davis JC, et al. Sci Rep 2017;7:40466). These observations are corroborated by findings from different preclinical models, where 2’FL (i) prevented adhesion and reduced disease index by Campylobacter jejuni (Ruiz-Palacios et al., JBC 2003; 278:14112; Yu et al. J Nutr 2016: 146:1980) and (ii) helped from pathogenic E. coli by strengthening barrier function (He et al., Gut 2016; 65:33; Angeloni et al. Glycobiology 2005; 15:31-41).

Recently, we observed an association between 2’Fucosyl-HMO positive milk and a 1.4 times reduced risk of acute respiratory infections during the predominant breastfeeding period through 6 months of age in a cohort of 220 mother infant pairs in Bangladesh (Sakwinska and Binia et al. NRC, unpublished results). We currently further investigate etiology. From preclinical models there is data indicating that specific HMOs might block adhesion of respiratory pathogens and that HMOs, among them 2’FL, modulate immune response to influenza virus infection and immunization (Sprenger, et al. NRC, unpublished results; Xiao, et al. Frontiers in Immunology 2018. 9:452). Whether the connection between the gut and the lung is mediated by specific microbial metabolites like the scfa or trafficking immune cells as proposed from studies in mouse models has to be established still for HMOs.

Conclusion
Together, such clinical observations corroborated by experimental basic research data suggest that HMO act in a multifunctional way, affecting the (i) establishment of the early-life microbiota dominated by bifidobacteria, (ii) resistance to pathogens and (iii) mucosal barrier and immunity. Interestingly, several basic research models indicate that specific HMO may not only modulate the gut-lung axis, but also modulate brain and cognitive development, via the gut-brain axis.
HMO are the third most important component in human milk, more important as solid than protein fraction. And that is a big difference with infant formula and cow’s milk, in which this part is not present.

The oligosaccharides are very complex, very abundant and the proportion is not similar during the whole period of lactation.

More than 150 different HMOs have been identified. To more simplify the 150 we can according to the different monosaccharides present them in three categories. (Chart 1) Two of those are more abundant: 2’FL and LNnT. And from in vitro studies we know that there is accumulating evidence suggesting that they may support gastrointestinal and immune functions of breastfed infants. The mechanisms that have been put forward are the effect of the microbiota growth, function and establishment, protection from infection and effects on allergy and immune competence. One of the ways why people think that they might help against infections and bacterial infections is that they have similarities with some receptors of certain gastrointestinal bacteria and they could interact or prevent the adherence of those microbes to the receptors in our gut.

We performed in two centers in Palermo, Italy, and in Hasselt, Belgium, this randomized controlled trial with infant formula supplemented with 2 synthetic human milk oligosaccharides (Alliet et al JPN 2017; 64: 624–631). The overall objective of that safety study was the effect of this formula supplemented with these 2 synthetic human milk oligosaccharides on growth, digestive tolerance and morbidity in healthy infants. For the microbiota related objectives we compare microbiota profile and metabolic signature among the infants given the test formula (EF) and the control formula (CF) and there was also a non-randomized exclusively breastfed infants group (BF).

The hypothesis was that microbiota profile and metabolic signature in the infants fed EF (vs. CF) will be closer to that of BF infants. Infants were enrolled before the age of 2 weeks. After informed consent they got a medical examination and anthropometry. Then they were randomized towards the test or the control formula. (Chart 2)

They were seen at 1, 2, 3, 4 and 6 months, which was the end of the treatment. All infants received a standard follow-up formula from 6-12 months and were seen again at the end of the treatment. All infants received a standard follow-up formula from 6-12 months and were seen again at 12 months. Complementary food was only started at 4 months of age, digestive tolerance and adverse effect were recorded in a parent’s diary. (Chart 3)
**Baseline characteristics**

175 infants were included, most of them were followed up at 6 and 12 months. Baseline characteristics were comparable between EF and CF groups. Mean difference in weight gain (EF vs. CF) was -0.30 g/day (95% CI -1.94–1.34, \( p = 0.72 \)), within the non-inferiority margin. Infants receiving EF (vs. CF) did not differ in weight, length, head circumference, BMI, or corresponding z-scores through 12 months. Digestive Tolerance Measures of digestive tolerance were generally similar between groups:

- no difference in stool consistency, except at 2 mo (softer in EF vs. CF)
- no difference in stool frequency between EF and CF groups
- GI symptoms and behavioral patterns were similar between groups

**The bacterial composition**

There was a big distinction between EF and CF groups.

- 2’FL and LNnT-containing formula shifted the global gut microbiota composition closer to that of breastfed infants. (Chart 4)
- Formula with 2’FL and LNnT promoted the colonisation of potentially beneficial Bifidobacterium and reduced taxa with potentially pathogenic members.
- Stool metabolic signature of EF was closer to BF, consistent with the findings in bacterial composition and diversity.
- Altered bacterial composition may result in reduced protein fermentation in EF vs. CF.

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**Chart 3: Reporting of AE (morbidity)**

- Parent kept a diary to record infant’s illness, fever, symptoms, and medication use
- This information was reviewed and confirmed by study physicians at each study visit before being recorded as an AE
- AEs were then coded and categorized by a single physician (not involved in study conduct) using SOC categories and PTs
- Several AE PTs were identified a priori of interest, i.e., upper respiratory infection, bronchitis, otitis media, and gastroenteritis
- Three AE clusters were identified: upper respiratory infection, lower respiratory tract infection, and otitis/ear infection
- Medication use were categorized into groups as appropriate, including antibiotics, antipyretics, and GERD medications

AE: adverse event; SOC: system, organ and class; PTs: preferred terms; GERD: gastrolesophageal reflux disease.

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**Chart 4: Bacterial diversity at 3 months**

- Diversity of BF significantly lower than formula groups \( \text{p}<0.01 \). Diversity of Enterobacteriaceae/Lachnospiraceae \( \text{p}=0.05 \) and therefore closer to BF.
- 2’FL and LNnT-containing formula shifted the global gut microbiota composition closer to that of breastfed infants.

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**Chart 5: Distribution of fecal community types**

- Formula with 2’FL+LNnT decreased the number of infants with FCT C and increased those with FCT B, which was the majority in the BF group.

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Clinical results

The only way we could look at the clinical results in this study was by using the reported adverse events, identified a priori, and medication use.

- Infants receiving EF (vs. CF) were less likely to experience bronchitis through 4 months (OR 0.16, 95% CI 0.02–0.78, p=0.010), 6 months (p=0.005) and 12 months (p=0.004), and lower respiratory tract infection through 12 months (OR 0.45, 95% CI 0.21–0.95, p=0.027).
- Infants receiving EF were also less likely to receive antipyretics through 4 months (OR 0.44, 95% CI 0.20–0.98, p=0.032), and antibiotics through 6 months (OR 0.53, 95% CI 0.27–1.02, p=0.047) and 12 months (p=0.016).

Of course we have to be careful with the interpretation of these results since they were secondary endpoints of the study.

Fecal community types in infants at 3 months

If you put all data of the enrolled infants together you can find 3 types of fecal community type (FCT), namely

- FCT A: low bifidobacteria, high enterobacteriaceae/lachnospiraceae
- FCT B: high bifidobacteria and low others
- FCT C: medium bifidobacteria and also the others

When we now looked in the three groups in our study (EF, CF, BF) we see again a big difference between the breastfed and formula fed. But it seems that in the test group (EF) the FCT B was higher and the FCT C was lower than in the control group (CF). (Chart 5)

And if we compare that to the antibiotic use it looked that especially the FCT C was more prominent in the group that was receiving the antibiotics. All those data seem to go into the same direction and are concordant to the in vitro data.

But this of course need further research in order to confirm these results.

Conclusion

- First clinical data demonstrate that synthetic HMOs are safe and well tolerated (structurally identical to those found in human milk)
- First clinical data show that formula with 2’FL + LNnT promotes the Fecal Community Type B seen in breastfed infants
- The reported reduced likelihood of antibiotic use with 2’FL + LNnT may be linked to the Fecal Community Types
- After these first promising health outcomes, further studies are needed to establish efficacy
Human milk oligosaccharides (HMO) are abundant in human milk (5–20 g/L) (1) and exert numerous beneficial effects (2–4). The two predominant HMO are lacto-N-tetraose (LNT) and 2′-fucosyllactose (2′-FL), although 2′-FL presence depends upon maternal secretor type (1). Bovine milk oligosaccharide content and composition are lower and less complex (5), thus infant formulae are nearly devoid of oligosaccharides (6). Most contain prebiotics, but large scale production has enabled the recent addition of 2′-FL and LNnT to formula (6). Note that LNT type 1 and LNnT type 2 cores differ, which affects their recognition (7) and utilization (8), thus their functionality is likely not identical.

Two randomized clinical trials have investigated adding HMO to formula (9, 10). In the first, infants were fed control formula (CF) or formula containing 0.2 or 1.0 g/L 2′-FL for the first 4 months of life and were compared to a breast-fed (BF) reference (9). All formulae also contained galactooligosaccharides, which was reduced in the 2′-FL formulae to maintain a total oligosaccharide content of 2.4 g/L. Growth, stool consistency or adverse events were similar across treatments (9). Immune outcomes were assessed in these infants using blood samples collected on day of life 42 (11).

Infants fed the 2′-FL formulae did not differ from BF, but had 29 to 83% lower plasma proinflammatory cytokine concentrations than CF-fed infants. In terms of immune cells, BF infants had higher total T-cell and cytotoxic (CD8+) T-cells than CF-fed infants. Total T-cells in infants fed 2′-FL were intermediate between BF and CF, and CD8+ T cells in infants fed 1.0 g/L 2′-FL were intermediate between BF and CF (11).

In the second study, infants received a CF or a formula with 1.0 g/L 2′-FL and 0.5 g/L LNnT for 6 months, after which all were fed the CF until 12 months of age (10). Weight gain and digestive symptoms were similar in both groups, except infants fed HMO had softer stool and fewer nighttime wake-ups at 2 months. Secondary outcomes showed that consuming HMO-supplemented formula reduced parent-reported morbidity (particularly bronchitis) and antiyptics and antibiotics use (10). In addition, the HMO formula shifted the microbiome composition to be more similar to that of BF and increased Bifidobacterium abundance (12). Taken together, supplementing formula with 2′-FL or 2′-FL+LNnT affected infant immunity, reduced infection and medication use, and increased bifidobacteria abundance, thus narrowing the gap between breast- and formula-fed infants.

References
A number of benefits of breastfeeding, particularly protection against child infections, may be, at least partially, related to the presence of human milk oligosaccharides (HMOs). Among others, the postulated effects of HMOs include prebiotic and antiadhesive/antimicrobial effects, modulation of intestinal epithelial cells, and immune modulation. Progress in biotechnology nowadays allows the production of at least some HMOs. Two HMOs, 2-fucosyllactose (2′-FL) and lacto-N-neo-tetraose (LNnT), have recently been added to infant formula, either alone or in combination. We are at the beginning of a new era in infant nutrition which poses a number of clinical questions, the answers to which should be evidence-based.

Evidence-based medicine (EBM) relies on finding and critically appraising the relevant scientific literature with regard to the trustworthiness of the data reported and with the purpose of determining the merits of an intervention. This knowledge is then implemented in clinical care. The key elements of practicing EBM are formulation of an answerable question, finding the evidence, critical appraisal of the evidence, and applying the evidence. The extent to which one can draw conclusions from published clinical research depends on whether the data and results of the study are free of biases. If there are biases, the task is to consider how they might affect the results.

In the context of EBM, potential benefits, along with safety, should be considered when adding a new ingredient, such as an HMO, to formulas. Major databases were searched up to January 2019 for randomized controlled trials to review current evidence on HMO-supplemented formulas. The administration of currently evaluated HMO-supplemented formulas to healthy infants does not raise safety concerns with regard to growth and adverse effects. Some favorable clinical effects are possible; however, further high-quality randomized clinical trials are needed. These trials should assess outcomes over a longer period of time and use validated outcomes that are agreed on by experts in the field of infant nutrition. Future research should also examine the optimal composition and dosage for HMO interventions and consider effectiveness in different settings/populations. Stay tuned for future publications.
HUMAN MILK
OLIGOSACCHARIDES (HMOs)

HMOs are the third most abundant solid component of human milk, after lactose and fat.

**Categories of HMOs (% total)**
- Fucosylated (35 - 50%)
- Sialylated (12 - 14%)
- Non-fucosylated neutral (42 - 55%)

**Macro and micro nutrients, and HMO (5-15g/L)**
- Water (93g/L)
- Lactose (70g/L)
- Protein (8g/L)
- Lipids (40g/L)

**2’FL is the most predominant HMO in human milk, accounting for more than 30% of total HMOs**

**6’S is the predominant sialylactose in human milk in beginning of lactation**

**LNnT is one of the 10 most abundant HMOs in human milk**

**HMOs AND OTHER PREBIOTIC OLIGOSACCHARIDES (PBOS)**

Prebiotic Oligosaccharides (PBOs) have complete different structures which impact on their functions.

**HMOs promotes the growth of beneficial bacteria, shaping the establishment of a protective intestinal microbiota.**

**Reducing adhesion of pathogens**

HMOs act as a decoy, avoiding adhesion of pathogens to the gut barrier.
HMOs also directly affect intestinal epithelial cells and modulate their gene expression, which lead to changes in cell surface glycans and other cell responses.

**Immune modulator effect**

HMOs modulate lymphocyte cytokine production, potentially leading to a more balanced Th1/Th2 response.

**References:**
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