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Human Milk Oligosaccharides (HMOs): a window of opportunity or a strong weapon in strengthening immunity

Friday June 5th, 2020
15:00 to 16:45

Human Milk Oligosaccharides (HMOs): a window of opportunity or a strong weapon in strengthening immunity

Chaired by Prof. Hania Szajewska
Poland

The science of HMOs: What they are and what they do

Prof. Lars Bode, USA

Lactation for Infant Feeding Expertise (LIFE) – focus on HMOs

Dr. Sagar Thakkar, Singapore

Learnings from the last decade of clinical evidence on HMOs

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Prof. Yvan Vandenplas, Belgium

The science of HMOs: What they are and what they do

Prof. Lars Bode

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Key message

Human milk oligosaccharides (HMOs) are a group of complex carbohydrates that are highly abundant in human milk and contribute to shaping the infant's gut microbiome and immune system for immediate and long-term health benefits.

Abstract:

Human milk is unique when it comes to the high concentration and structural diversity of oligosaccharides - a group of complex carbohydrates. In fact, human milk oligosaccharides (HMOs) are the third most abundant solid component of human milk after lactose and lipids, often exceeding the total amount of human milk proteins. HMOs are composed of up to five different building blocks: glucose, galactose, N-acetylglucosamine, fucose and sialic acid. More than 150 different HMOs have been identified and characterized so far, and, most intriguingly, the composition varies between women and changes over the course of lactation. Single-nucleotide-polymorphisms (SNPs) in genes that encode specific fucosyltransferase enzymes are known to dramatically affect HMO composition. However, how other enzymes, transporters, etc. are involved in HMO biosynthesis remains largely unknown. The combination of genome-wide association

studies, human milk transcriptomics, in vitro gene editing, and in silico pathway modeling allows us to reconstruct the HMO biosynthetic pathway and lays the foundation to modulate and optimize it once we fully understand the effects of HMOs on infant and maternal health and development. Once ingested, HMOs resist degradation through the infant, a small percentage is absorbed and reaches the systemic circulation, and the rest reaches the colon where it gets metabolized by the infant gut microbiota or is excreted intact with the feces. HMOs are known to be prebiotics, but also serve as antimicrobials, antiadhesives or immune cells modulators – both locally in the gut as well as systemically after absorption. Using new data-mining approaches and leveraging samples and metadata from large mother-infant cohorts allows us to identify associations between individual HMOs or HMO composition profiles with infant and maternal health outcomes. Suitable preclinical models and clinical intervention studies allow us to corroborate the established associations for causal relationships and test for in vivo efficacy in humans. In some cases, individual HMOs alone are effective and the effects are highly structure-specific and dose-dependent, suggesting mediation through specific receptors – either on a host cell or on microbes. For example, we discovered that a specific HMO named disialyllacto-N-tetraose (DSLNT) improves survival and reduces pathology scores in an animal model of necrotizing enterocolitis (NEC). In human cohort studies, preterm infants that receive human milk with low levels of the same HMO are at higher risk to develop NEC. This example highlights the power of combining data generated from suitable preclinical models with data obtained from mother-infant cohorts. In other cases, the mixture and relative abundance of different HMOs to each other is what makes them most effective, suggesting mediation through complex interactions of multiple different HMOs on different molecular targets that shape the composition

of gut microbial communities or complex multi-cell immune responses. Overall, the knowledge generated from combining suitable preclinical models, mother-infant cohort association studies, as well as randomized clinical trials will help us establish true structure-function relationships and provide the rigorous evidence required to improve infant health and development.

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Lactation for Infant Feeding Expertise (LIFE) – Focus on HMOs

Dr. Sagar Thakkar

Research & Development Center
Nestlé Singapore, Singapore

Key message

Nestle Research has been investigating human milk since 1960s. Our human milk research initiative called LIFE (Lactation for Infant Feeding Expertise) is one of the biggest efforts on characterization of HM and association of its components to infant and maternal variables.

Human milk oligosaccharides (HMOs) are the third most abundant component of human milk excluding water. Its concentration ranges from 5 to 15 g/L in mothers' milk and has implications in wide-ranging health outcomes of the new-born.

Our data from 8 cohorts executed in 15 countries and employing approximately 3,600 human milk samples indicate that maternal genetics, BMI, stage of lactation, preterm birth and mode of delivery are important drivers of oligosaccharide concentration in mothers' milk.

Abstract:

Human milk (HM) is ideal food for infants and ensures optimal growth and development[1]. The composition of human milk is very dynamic and complex and varies

with multitude of factors[2]. We, at Nestle Research, have been investigating human milk since 1960s[3]. Our human milk research initiative called LIFE (Lactation for Infant Feeding Expertise) is one of the biggest efforts on characterization of HM and association of its components to infant and maternal variables. Human milk oligosaccharides (HMOs) are the third most abundant component of human milk by dry mass. Its concentration ranges from 5 to 15 g/L in mothers' milk and has implications in wide-ranging health outcomes of the neonate. To date approximately 200 HMOs have been detected, approximately 160 identified and around 30 quantified. LIFE team have characterized HMOs from 8 cohorts, executed in 15 countries and using approximately 3,600 human milk samples. The most abundant HMOs are 2'fucosyllactose (2'FL) and lacto-N-tetraose (LNT). Even though there are many HMOs identified, a combination of 2'FL, LNT, DFL, 3'SL, 6'SL constitutes approximately 50% of HMOs by weight. Exploratively, our data also indicates that maternal genetics, BMI, stage of lactation, preterm birth and mode of delivery are important drivers of oligosaccharide concentration in mothers' milk[4,5]. While we have done many studies on characterization of HMOs and their association to developmental outcomes of the infants, we plan to continue our exploration of human milk oligosaccharides.

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Learnings from the last decade of clinical evidence on HMOs

Prof. Ryan Carvalho

Chief Medical Officer
Nestlé Nutrition, Switzerland

Key message

> 2'FL and LNnT are among the most studied HMOs with clinical evidence to support immunity and the developing microbiome. Latest research on additional HMOs in human milk & beyond show promise in expanded benefits on gut, immune, brain and bone health.

Abstract

Breast milk is recognized as the gold standard to provide the best nutrition to an infant from the start of life. It is well established that human milk influences the establishment of the gut microbiota, intestinal development and maturation of the gut mucosal and systemic immune systems. Among the bioactive components in breast milk modulating these processes are human milk oligosaccharides (HMOs), with their composition, structure and function unique to human milk. Recent decades of human milk research and advances in glycobiology and technologies, made it possible to include some of the key HMOs in infant formulae. 2FL is the most studied HMO to date. 2FL and LNnT were assessed in a clinical study and demonstrated support for immune health by reducing antibiotic use and lowering respiratory tract illnesses, as well shifting gut microbiota towards that seen in breastfed infants in the first months of life[1,2].

Another clinical study, performed recently has shown that higher levels of 2´FL in infant formula, as found in breast milk, is associated with a lower abundance of pathogenic bacteria such Clostridium difficile and Klebsiella pneumonia at certain periods during early infancy[3].
Latest Nestlé research contributes to enrich the knowledge beyond 2'FL and LNnT to other members of the HMO's families, including LNT, DFL, and two sialylated HMOs 3'SL and 6'SL, which shows expanded benefits on gut, immune health and new benefits on brain and bone health[4]. Pre-clinical data indicate that these HMOs may help to protect and support healthy development of a child during the critical first stages of life
These findings warrant confirmation through a clinical study, which is currently ongoing. This clinical trial aims to evaluate in infants and toddlers the safety, growth and tolerance of a unique HMO complex added to infant formula, as well as its efficacy on the developing microbiome, immunity, brain and bone health.

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HMOs and allergic sensitization: current evidence

Dr. Carine Blanchard

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Key message

Currently there is scientific evidence linking HMOs and more particularly 2 FL and LNnT with the prevention of allergic sensitization. The results both from preclinical and clinical observational data, from the LIFE Child Cohort, demonstrates a positive effect of 2FL and LNnT in reduction of allergic sensitization.

Abstract

Background: Human Milk Oligosaccharides (HMOs) represent a family of approximately 200 complex carbohydrates present in human milk. They are the third-largest solid component in breast milk after fat and lactose. HMOs have been shown to strengthen the gut barrier function and to block pathogens. They are also known for their prebiotic effect and for promoting beneficial intestinal microbiota growth and stimulating the immune system.
Aim: Here we aimed at understanding the effect of a HMO on allergy prevention in preclinic and human.
Methods: The role of specific HMO (2'FL and LNnT) on allergic sensitization prevention and tolerance induction was investigated in preclinical experiments (epicutaneous sensitization and mucosal sensitization models). The nutritional intervention was performed

with a blend of 2 HMO (2'FL and LNnT) added to the diet at 0.2, 1, 5 and 10% . In the LIFE Child cohort in Leipzig, Germany, allergic sensitization and allergic symptoms were recorded in the infants up to 1 year old. Milk samples were collected from lactating mothers participating in the LIFE Child cohort in Leipzig, Germany. A total of 25 HMOs were analyzed in 156 breast milk samples, collected at 3 months after birth. **Results:** In preclinical models, oral administration of the blend of 2'FL and LNnT at 1 or 5% supplementation in the diet consistently decreased allergic sensitization in the epicutaneous or mucosal sensitization models respectively. The HMO blend administration also induced modulation of the gut microbiota and SCFA production as well as an increase in regulatory T cell numbers in the mesenteric lymph nodes. From the observational human study, levels of 2'FL ranging from 0.8 to 2.5g/L in the mother breast milk were positively associated with a decreased risk of sensitization in the infants. **Conclusion:** Altogether, these data suggest that specific doses of 2'FL and LNnt are associated with decreased allergic sensitization.

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HMOs boost the immune system

Prof. Yvan Vandenplas

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Key message

> HMOs stimulate the development of a bifidogenic microbiome, which is boosting a maturation of the immune system into a balanced TH1/TH2 development resulting in a reduced risk of allergic disease.

Abstract

Breast milk is the natural and ideal food for infants, providing the energy and nutrients that every infant needs during the first four to six months of life in the correct quality and amount. Breast feeding is shown to influence immune responses through the bioactive, immune-modulating properties of breast milk and through the impact of breast milk on intestinal microbiota. Observational studies have shown stool bacterial composition differs between breastfed and formula-fed infants and both breastfeeding and the resulting gut microbiota are linked to the better health of the breastfed infants. Human milk oligosaccharides (HMOs) are non-digestible carbohydrates with unique structures. They are the third largest solid component in breast milk. The amount of HMOs in mother's milk is a dynamic process as it changes over time. Many factors such as duration of lactation, environmental and genetic factors influence the amount of HMOs. Breastfed infants

have a microbiome which is richer in bifidobacteria than cow's milk based formula fed infants not supplemented with prebiotic oligosaccharides. Dysbiosis induces qualitative and quantitative changes in the microbiota which can directly affect immunological mechanisms leading to allergic diseases. HMOs support the infants' immune system through four potential mechanisms: supporting the growth of beneficial bacteria in the gut and eliminating pathogens, as well strengthening the gut barrier function and guiding a maturation on the immune system towards a balanced Th1/Th2 response[1]. HMOs provide protection against allergy and infectious diseases directly through the interaction of the gut epithelial cells or indirectly through the modulation of the gut microbiota, including the stimulation of the bifidobacteria. Human milk observational studies found that some HMOs in human milk, specifically 2'FL and LNnT, were associated with lower incidence of IgE-associated eczema, and lower prevalence of allergic sensitization and skin problems[2]. Clinical data suggest that the addition of HMOs to infant formula is safe and well tolerated, inducing a normal growth and suggesting a trend towards a health benefit. New clinical data show that the supplementation of infant formula with 2´FL + LNnT (2:1) promotes the development of a high level bifidobacteria dominated gut microbiota community close to that observed in breastfed infants[3]. It is known since many years that babies who developed an allergy have fewer bifidobacteria in their early life gut microbiota prior to the development of symptoms, than those who do not develop allergy. The addition of two HMOs supports a bifidobacteria predominant gut microbiota which will decrease the incidence of allergic disease. In a clinical study in infants fed a formula with 0.2 or

1 g 2'FL/L, there was a lower percentage of subjects with reported eczema than in the control group[4].
There were also 2 studies performed in infants with cow's milk allergy (CMA). The first ever study with an extensively hydrolysed formula (eHF) supplemented with the two HMOs (2´FL + LNnT), confirmed their safety and hypo-allergenicity for infants with CMA[5]. Another recent study in infants with CMA was performed with the objective to assess growth and tolerance of the same formula, and showed normal growth and good tolerance in infants with CMPA. Moreover, the per protocol analysis suggests a reduced risk of lower respiratory tract and ear infections, as well as lower antibiotic and antipyretic use[6].
HMOs positively influence host epithelial and immune cell responses with documented clinical benefits for breast- and formula-fed infants. The addition of HMOs in infant feeding could be a new promising scientific concept in allergy prevention and management.

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