



MÉXICO 2016

INTESTINAL MICROBIOME: Functional Aspects in Health & Disease

88th Nestlé Nutrition Institute Workshop
September 22-25, 2016 • Mexico



INTRODUCTION

Microbiota and human milk oligosaccharides are two of the fastest developing areas of research in pediatric nutrition today. Thus, with the theme “Intestinal Microbiome: Functional Aspects in Health & Disease”, the 88th Nestlé Nutrition Institute Workshop was held on September 22 to 25, 2016 in Mexico. The workshop convened international experts and key stakeholders to discuss the latest updates on these topics, and how these findings can contribute to disease prevention and healthier lifestyles, so as to benefit infants and children around the world.

The three-day workshop commenced with an opening speech by Natalia Wagemans, the Global Head of Nestlé Nutrition Institute. She welcomed delegates to the 88th workshop held by Nestlé Nutrition Institute (NNI) since 1981. The NNI is a non-profit organization based in Switzerland, but holds activities globally and its academic workshops are highly regarded in the field of nutrition. As the role of the microbiome in health and disease is increasingly recognized and studied, more research topics and questions have arisen, and this workshop aimed to address some of them.

The workshop program was led by three distinguished Chairs with special interests in microbiome, probiotics and prebiotics: Professor Allan Walker, Conrad Taff Professor of Nutrition and Professor of Pediatrics, Harvard Medical School; Professor Erika Isolauri, Professor of Pediatrics, Head of the Department of Clinical Medicine, University of Turku, Finland; and Professor Philip Sherman, Professor at the Hospital for Sick Children, University of Toronto, Canada.

SESSION I



Chair: Allan Walker

In the first session, speakers focused on the development of the human microbiota. In particular, they discussed the microbiome during pregnancy and in newborns, and how health and behavior is affected by epigenetics in the GI tract and the brain-gut axis.

OMRY KOREN (Faculty of Medicine, Bar-Ilan University, Israel) described microbiota changes during pregnancy. Microbiome composition alters in response to environment, diet, weight, hormones, and other factors. Unsurprisingly, pregnancy causes significant changes in the microbiome, as dramatic weight gain, metabolic and immunological changes occur. Several alterations in the gut microbiota have been associated with pregnancy progression. In general, pregnancy is characterized by an increase in the bacterial load and profound alterations in the composition of the gut microbiota. These dramatic changes are characterized by reduced individual richness, increased between-subject diversity, and alterations in abundance of certain species.

When starting to dissect the roles of the gut microbiota during pregnancy, the third trimester microbiota was shown to have greater impact on weight gain, insulin resistance and inflammatory response compared to that of the first-trimester. These findings demonstrate that the microbial components actively contribute to changes in host immunology as well as metabolism. Gut microbiota have also been suggested to play a role in host weight gain during pregnancy by leading to increased absorption of glucose and fatty acids, increased fasting-induced adipocyte factor secretion, induction of catabolic pathways, and stimulation of the immune system. Since the microbial communities are greatly affected by the host diet and initial weight, the microbiota of pregnant women differ accordingly. Overweight pregnant women exhibit significantly higher levels of gut *Bacteroides* and *Staphylococcus*,

as compared to pregnant women of normal-weight. In addition, antibiotics administered during pregnancy were shown to affect the microbiome composition for up to 6 months after treatment.

“Unlike certain disease states where dysbiosis is thought to contribute to negative effects, in pregnancy, microbial changes are welcome and even necessary for a healthy pregnancy.”

– Omry Koren –

SAMULI RAUTAVA (Department of Paediatrics, University of Turku, Turku University Hospital, Finland) gave an overview of the factors affecting microbial colonization of newborns. Prenatally, maternal exposure to farm environments may protect the child against asthma, whereas antibiotic exposure may increase asthma risk. Microbes in the amniotic fluid initiate gut colonization in the fetus. At birth, infants acquire microbiota predominantly from the mother. C-section infants are colonized with bacteria found on the mother’s skin, and have decreased gut microbiota diversity, delayed *Bacteroidetes* colonization and imbalanced immune responses compared to vaginally-delivered infants. The effects of the delivery mode on the infant gut bacteria have been observed to persist for up to 7 years. A pilot study demonstrated that vaginal microbial transfer can partially restore the microbiota of C-section born infants. After birth, neonatal gut colonization is guided by human milk factors, which selectively promote the growth of specific microbes, as well as by live microbes present in human milk. Antibiotic exposure in infancy increases a child’s risk of becoming overweight in the first 2 years of life. Dysbiosis in infants has been associated with increased risk of non-communicable disease in later life; for example, a recent study suggested that it may promote T-cell dysfunction associated with childhood atopy. Prudent antibiotic use, avoidance of unnecessary C-sections,

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promotion of breastfeeding and maternal supplementation of prebiotics and probiotics are possible interventions to support healthy, early microbial contact.

“Modulation of gut microbiota in the perinatal period may offer a means to reduce the risk of chronic disease.”

– Samuli Rautava –

ALLAN WALKER (Mucosal Immunology and Biology Research Center, Massachusetts General Hospital for Children, Boston, USA) emphasized the importance of normal colonization of the newborn in immune development and prevention of disease. Contrary to previous beliefs, the fetus does not reside in a sterile intrauterine environment, but is colonized prenatally by commensal bacteria from the maternal gut that passes into the amniotic fluid. This exposure to colonizing bacteria continues at birth and during the first year of life, and has a profound influence on lifelong health. Normal neonatal colonization results in symbiosis and immune homeostasis, which are essential for health. Prerequisites for a normal colonization are a healthy pregnancy, full-term vaginal delivery, no perinatal antibiotics and exclusive breastfeeding. Dysbiosis due to C-section delivery, perinatal antibiotics or premature delivery may adversely affect development of gut defense and predispose the infant to inflammation, leading to increased susceptibility to disease later in life. Prolonged empirical antibiotic exposure was also associated with increased risk of necrotizing enterocolitis (NEC) and death in very low birthweight infants. Clinical evidence suggests that babies born by C-section have a higher incidence of allergy, type 1 diabetes and obesity. Infants repeatedly administered with antibiotics are more likely to have asthma as adolescents. Probiotics may restore symbiosis and there is evidence indicating that prebiotics reduce the incidence and severity of NEC and reduce the risk of atopic dermatitis.

“Crosstalk with colonizing bacteria in the developing neonatal intestine helps in the initial adaptation of the infant to extrauterine life, particularly in acquiring immune homeostasis, and provides protection against disease expression later in life.”

– Allan Walker –

MATTHIAS ZILBAUER (Department of Paediatrics, University of Cambridge, Addenbrooke’s Hospital, Cambridge, United Kingdom) spoke on epigenetics in the gastrointestinal (GI) tract during health and inflammation. Epigenetics can be defined as stable, potentially heritable changes in cellular phenotype caused by mechanisms other than alterations in the DNA sequence, for example through DNA methylation. DNA methylation helps in regulating cellular differentiation, cell type-specific gene expression and genomic imprinting. Studies comparing germ-free mice and conventional mice showed that methylation levels were much lower in the absence of gut microbiota. This indicates that microbiota contributes to the maintenance of intestinal symbiosis via epigenetic modification of the host gene. The human intestinal tract represents a fascinating example for the capability of adapting to the environment. Following in-utero development, the intestinal mucosa is colonized postnatally by a vast number and variety of microbes while exposed to a multitude of increasingly complex

nutrients. It is well established that exposure to these environmental factors is critical for the physiological and functional development of the gastrointestinal (GI) tract. Conversely, alterations to these processes, possibly as a result of changes in our environment, are increasingly being recognized as major contributing factors to the development of GI-related diseases such as necrotizing enterocolitis and inflammatory bowel diseases (IBD). A comparison of IBD epithelium to that of healthy controls yielded clear differences in DNA methylation profiles. However, the changes in methylation profile during IBD development have substantial similarity with that seen in healthy development. The use of human intestinal epithelial organoids, generated from mucosal tissue from various gut segments and patient groups, provide a promising model to perform functional analysis.

“Given existing evidence of environmental factors (eg, diet, nutrition, infections) on human health, epigenetic mechanisms provide a plausible mechanistic framework for the development of many multifactorial diseases including inflammatory bowel diseases.”

– Matthias Zilbauer –

EMERAN MAYER (Division of Digestive Diseases, David Geffen School of Medicine, UCLA, California, USA) presented on the link between the brain-gut-axis and behavior. Brain-gut interactions are complex. The brain-gut axis plays a crucial role in the homeostasis of the organism during perturbations such as food intake, stress and changes in emotion. Microbes exist in large quantities in our bodies; in the gut, microbes convert luminal compounds to secondary metabolites. As such, diet can have a major impact on gut microbial composition and function, which in turn influences gut and brain functions. Besides the brain and GI tract, microbial signals also affect the immune system, cardiovascular system, hypothalamic–pituitary–adrenal axis and host metabolism. Research has shown that the gut microbiota regulates host serotonin biosynthesis, which may modulate GI motility and platelet function. In mice, alterations in gut microbial composition induced by antibiotics, prebiotics or fecal microbial transplantation are linked to significant changes in behaviors. Host-microbe interactions in rodents impact affective, social, nociceptive and ingestive behavior. There is insufficient data to conclude if gut microbiota has a similar effect on humans, although studies found that regular probiotic intake affects brain networks, ie, specific metabolic pathways involved in polysaccharide degradation and changes in the connections between the brain regions were observed. Data also indicate a growing list of disorders attributed to the brain-gut-microbiome, including hepatic encephalopathy, obesity, Parkinson’s disease, depression and IBD. Interventions in early life have the potential for greatest impact because the brain is still developing during this stage.

“A crucial role of the gut microbiota in these bidirectional brain-gut interactions has been identified. Due to their immediate vicinity to the gut epithelium, the gut microbiota is in a unique position to respond to autonomic brain signals during stress and different emotional states, and to send signals back to the host.”

– Emeran Mayer –

SESSION 2



Chair: **Erika Isolauri**

In the second session, experts presented the clinical practices and environmental exposures interfering with the development of normal gut microbiota, as well as clinical conditions associated with dysbiosis.

JOSEF NEU (Department of Pediatrics, Division of Neonatology, University of Florida, USA) spoke about dysbiosis in the neonatal period, particularly on the role of preterm birth and C-section deliveries. Microbiome-host interactions are at play during gestation. A higher number of bacterial rDNA in the amniotic fluid seems to correlate with earlier gestational age at delivery. Over 50% of the microbes in meconium are the same as those in the amniotic fluid, suggesting fetal swallowing of amniotic fluid. Moreover, the meconium microbe pattern of preterm babies is different from that of full-term babies. It is thus postulated that swallowing of infected amniotic fluid may produce an inflammatory response in the fetal intestines, possibly leading to preterm labor and morbidity. Compared with vaginally-delivered babies, C-section babies have increased risk of developing immunologic and metabolic diseases. C-section babies have lower total microbiota diversity and lower colonization with *Bacteroidetes*. Provision of vaginal bacteria using a mouth swab may partially restore infant microbiota; however, the safety and efficacy of this approach needs to be evaluated. Some studies indicate that breastfeeding could normalize the microbial profile of C-section babies. The profiles of breast milk microbes vary between lactating women, but remains stable over time within each individual lactating woman, suggesting a personalization of microbiota. The risks of routine antibiotic usage in preterm infants very likely outweigh the benefits, especially when usage is prolonged. Studies should be conducted to evaluate the metabolic, immunologic and epigenetic effects of manipulating the microbiome in the maternal-fetal unit and the newborn.

“There is a strong signal that the infants delivered by elective C-section develop microbiota that differs from those of babies born by vaginal delivery. Epidemiologic studies show increased odds ratios for the development of immunologic disorders and metabolic diseases in those babies born by C-section.”

– **Joseph Neu** –

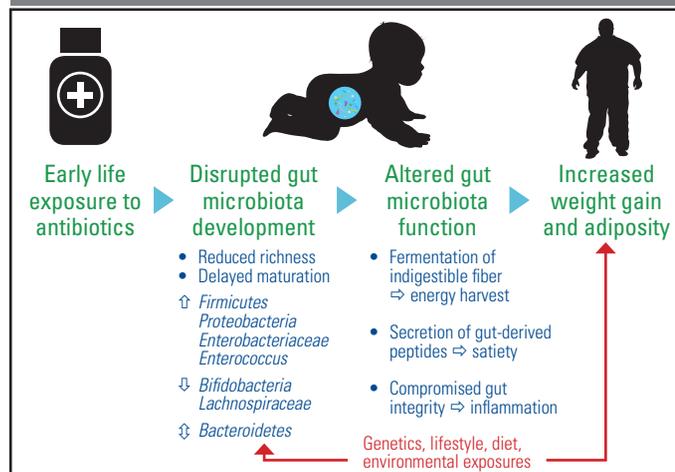
MEGHAN AZAD (Children’s Hospital Research Institute of Manitoba, Canada) continued the theme with a lecture on the effects of antibiotic use in early life on the gut microbiome. Early-life antibiotic exposure is very common, with one-third of prescriptions being inappropriate. This has potentially adverse effects on the developing gut microbiota and related metabolic processes (Figure 1). Data from 13 epidemiologic studies showed a correlation between antibiotic exposure during critical periods of early development and the development of obesity. Infants who had earlier exposure (eg, in the first 6 months), more exposure and had broader spectrum antibiotics were more likely to gain weight and develop obesity. A study also found that the associations persist long term and is more

pronounced in boys. *In utero* antibiotic exposure was also associated with obesity. She shared findings from her own research, suggesting that intrapartum use of antibiotics was associated with infant gut microbiota dysbiosis, and breastfeeding appeared to modify some of these effects. Complementary research in both humans and rodents indicates that gut microbiota play a key role in this process, although further research is needed to confirm and characterize the causal mechanisms involved. For example, longer breastfeeding is associated with lower BMI at 2-6 years, except if exposed to early-life antibiotics, suggesting that the benefits of breastfeeding are conveyed by microbiota. Obesity is a complex and multifactorial condition; however, evidence to date suggests that strategies to curb obesity should include the judicious use of antibiotics, especially in early life when the developing gut microbiota is particularly susceptible to perturbations with long-lasting implications for metabolic programming and obesity risk.

“Studies show a correlation between antibiotic exposure during critical periods of early infancy and the development of obesity.”

– **Meghan Azad** –

FIGURE 1. The impact of antibiotics on microbiota & obesity



SANJAY PATOLE (Department of Neonatal Paediatrics, King Edward Memorial Hospital for Women, Perth, Australia) spoke on the association between necrotizing enterocolitis (NEC) and microbiota. NEC is an acquired gastrointestinal inflammatory condition with significant mortality and morbidity in preterm very low birthweight infants. The interplay between toll-like receptors, bacterial endotoxins, excessive proinflammatory response of the immature innate immune system, hypoxia, ischemia, reperfusion, free radicals, presence of substrate, and bacterial endotoxins, is thought to play an important role in the pathogenesis of NEC. The association of various microbes with NEC has intrigued researchers for many years. Recent studies show that in contrast to the healthy adult gut microbiota, the microbiota in preterm infants is simple,

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varies greatly among individuals, dynamic, and plays an important role in the development of NEC. Despite general agreement that gut microbes play a vital role in NEC pathogenesis, no specific pathogen has been consistently linked to NEC. Newer molecular methods (eg, 16S rRNA gene specific primers, pyrosequencing of fecal DNA) have been used in an attempt to elucidate the role of gut microbiota in the pathogenesis of NEC. Studies showed that development of NEC was positively correlated with Gammaproteobacteria and negatively correlated with anaerobic bacteria (eg, Negativicutes). Decreased bacterial diversity was also observed in the period preceding development of NEC. Assessing the reproducibility of previous findings in large prospective studies with standardized methodology (eg, sample processing, PCR primer, DNA extraction) is important.

“Emerging evidence suggest that microbial colonization may alter epigenetic signature of the immature gut establishing inflammatory changes and compromising barrier properties predisposing to NEC.”
– Sanjay Patole –

ERIKA ISOLAURI (Department of Pediatrics and Adolescent Medicine; Turku University Hospital, Finland) elaborated on how changes in microbiota affects obesity. The microbiota is a new target for interventions aiming to halt the progression of neonatal adiposity to adulthood obesity. An aberrant gut microbiota induces immune and metabolic disturbances and may lead to low-grade systemic inflammation, causally linked to insulin resistance. Current evidence indicates that C-section delivery, antibiotic use and lack of breastfeeding interfere with the host-microbe interactions, and may increase the risk of obesity. Compared with that of normal-weight mothers, the breast milk of overweight mothers was observed to contain higher *Staphylococcus* levels, lower *Bifidobacterium* levels, and lower TGF- β 2 and sCD14 levels. A randomized controlled trial showed that nutrition counselling and use of probiotics (*Lactobacillus rhamnosus* GG and *Bifidobacterium lactis*) during pregnancy and breastfeeding reduced the risk of gestational diabetes and large birth size, and prevented early excessive weight gain in the offspring. In a follow-up study 10-years later, children of mothers who received probiotics had significantly lower incidence of allergy and fewer cases of obesity, compared with those in the placebo group. The idea that the gut microbiota can be re-programmed with probiotics and synbiotics is an attractive proposition. However, it must be noted that the gut microbiota composition is only one piece of the puzzle. The bidirectional communication between microbes and host through endocrine, immune and neural signals and their targets in metabolic, immune humoral and neural pathways must be considered.

“Being highly sensitive to environmental impacts, particularly to early feeding, the compositional development of the gut microbiota may prove to be the target of choice in efforts to reduce the risk of obesity.”
– Erika Isolauri –

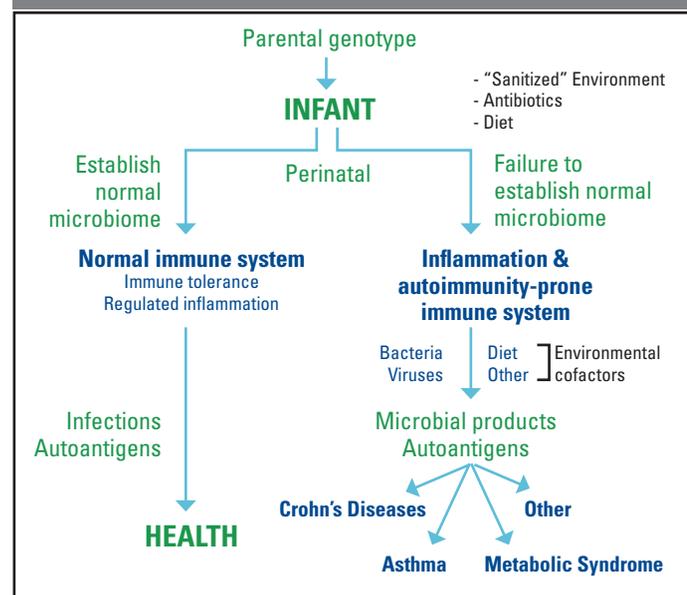
PHILIP SHERMAN (Research Institute, Hospital for Sick Children, University of Toronto, Canada) presented on the relationship between microbiota and functional GI disorders in infants and children. Dysbiosis is increasingly recognized as having

an etiologic role in a variety of conditions, including functional gastrointestinal disorders, such as colic in infants and irritable bowel syndrome in older children. Infants with colic have decreased gut microbial diversity compared to controls. Various methods have been proposed to increase microbial diversity, such as fecal transplants or using a consortium of organisms, single strains and bioactive compounds (molecule produced by a strain). Several double-blinded placebo controlled trials showed that the strain *L. reuteri* DSM 17838 effectively reduced crying time in breastfed infants with infantile colic. This finding was also confirmed in a meta-analysis, though the precise component of the probiotic agent mediating observed effects is the subject of current research. Children with IBS have similar gut microbiome profiles as healthy children, except for a greater abundance of γ -proteobacteria. Randomized controlled trials suggest that IBS may be treated effectively by probiotics such as *Lactobacillus plantarum* 299v and *Bifidobacterium logum* subsp *infantis* 35624. Many issues remain unresolved, including those related to optimal dosages, timing of ingestion, single versus combination formulations, maintenance of viability in storage, and the merits of employing probiotic-derived products.

“Strain-specific effects on colonization resistance, epithelial barrier integrity, modulation of signal transduction, impacts on innate and adaptive immune responses, and effects on visceral hyperalgesia likely explain observed variability of various probiotic strains.”
– Philip Sherman –

DAVID SHEN (Division of Gastroenterology, Perelman School of Medicine, University of Pennsylvania, USA) gave an overview of the role of diet and microbiota on health and disease. The development of a stable and diverse gut microbiota is essential to various host physiologic functions such as immunoregulation, pathogen prevention and metabolism, and leads to good health, whereas a dysbiotic gut microbiota is altered in structure and

FIGURE 2. Host gene-microbial Interactions in the pathogenesis of immune-mediated diseases in modern society



function, and predisposes an individual to disease states (Figure 2). Sialylated milk oligosaccharides found in breast milk promote healthy growth of infants; conversely, infants were malnourished when they consumed breast milk with low levels of oligosaccharides, and interestingly, these effects were microbiota-dependent. As infants mature, they develop a more diverse microbiome. Notably, the cessation of breastfeeding, rather than the introduction of new foods, is the impetus for the development of a more adult-like microbiome. Diet is intricately linked with the gut microbiome and has been shown to modulate disease states. For example, the mechanism by which dietary fiber improves glucose metabolism may be attributed to increased abundance of *Prevotella*, as *Prevotella* protects against *Bacteroides*-induced glucose intolerance and promotes increased hepatic glycogen storage. In disorders related to

mucosal immune dysregulation such as inflammatory bowel disease, the dysbiotic gut microbiota and diet contribute to its pathogenesis. Reversal of dysbiosis through fecal microbiota transplantation may provide benefit in the treatment of ulcerative colitis. These interventions represent important strategies to modify the gut microbiota and its metabolite production for health maintenance as well as disease prevention and management.

“As a shared substrate between the host and the gut microbiota, diet significantly impacts the health and disease states of the host both directly and through gut microbial metabolite production.”

– David Shen –

SESSION 3



Chairperson: **Philip Sherman**

In the third session, key opinion leaders covered various aspects of human milk oligosaccharides (HMO), including evolution in human milk, basic science, compositional analysis, functional outcomes and future role in infant nutrition.

BRUCE GERMAN (Foods for Health Institute, University of California-Davis, California, USA) spoke on the evolution of the mammalian lactation system, with a focus on the role of human milk oligosaccharides (HMO). Milk proteins evolved to provide nourishment, and act as carriers of encrypted functional sequences that must be released by selective proteolytic action by an array of native milk proteases and infant-produced enzymes. Animal research has been performed to understand milk composition and its changes in tandem with the developmental needs of infants. A study on Tammar wallabies has demonstrated how feeding milk meant for 60-day-old young to 110-day-old young accelerated their growth and development in a comprehensive and coordinated fashion. Based on this principle, Sydney researchers use marsupial milk components to accelerate lung development in premature infants. HMOs are the third most abundant class of biomolecule in human milk, yet they cannot be digested by humans. HMOs are structurally diverse and they act as substrate that shape the microbiota composition. In addition, HMOs assist in pathogen deflection as well as immune and neural development. Contrary to popular belief, HMOs are not digestible by most types of microbiota. In summary, milk has a complex, yet controlled active proteolytic system that begins to degrade specific milk proteins within the mammary gland and assists in protein digestion in the infant stomach and intestine. Milk components, HMOs in particular, are abundant, diverse and multifunctional. The study of milk provides a ‘Rosetta stone’ for glycan and microbiota research.

“Evidence suggests that certain human milk peptides have antimicrobial, immunomodulatory and other functions that protect the infant from pathogens, guide development and contribute in diverse ways to the infant’s competitive success.”

– Bruce German –

CLEMENS KUNZ (Institute of Nutritional Science, Justus-Liebig University Giessen, Germany) discussed HMO composition analysis and metabolism in infants. Since around 1900, concomitant with the discovery of lactobacilli and bifidobacteria and their relevance for health and disease, pediatricians have already realized that the microbial composition of stool samples from breast-fed and bottle-fed infants differed. Observations indicated that this difference is particularly linked to the milk carbohydrate fraction. This was the starting point of research on human milk carbohydrates – HMOs. There are around 150-200 types of HMOs identified so far. Nowadays, through biotechnological advances, single HMOs can be produced in large amounts and purified for use in metabolic and functional studies in humans. HMOs have also been shown to provide benefits to formula-fed infants by influencing the establishment of the gut microbiota. A randomized controlled trial showed that infants fed formulas fortified with a type of HMO, 2'-fucosyllactose (2'FL), had similar growth as breastfed infants. Another randomized controlled trial showed that use of term infant formula supplemented with two HMOs, 2'FL and lacto-N-neotetraose (LNnT), shifts stool microbiota and metabolic signatures closer to that of breastfed infants. Studies conducted by Kunz's research team found no difference in the concentration of HMOs in term and preterm milk, but there were differences in HMO pattern and quantities based on secretor status (Table 1). A secretor is a person who secretes their blood type antigens into body fluids (eg, saliva, mucus), whereas a non-secretor does not. Secretor milk also had significantly higher amounts of HMOs than non-secretors milk. In the feces of breastfed infants, the variability in HMO excretion was high, which may be caused by variations in the infants' intestinal microbial composition. HMO excretion in urine generally followed the HMO pattern of milk, with a notable exception: even though LNFP I is one of the main HMOs in secretor milk, LNFP I was not found in the urine of infants who consumed this milk. HMO excretion does not decrease gradually over time, as even after seven months of exclusive breastfeeding, intact HMOs can be detected. In addition, whenever oligosaccharides were detected in feces, LNnT, the major core structure of HMO was present. Hence, the data do not support speculations that LNnT is a preferable source for the microbiota.

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TABLE 1: Presence of HMO structures in dependence of the Lewis blood group and secretor status.

HMO structure		Blood group (% of the population)			
Name	Structure	Lewis b secretor (70)	Lewis a non-secretor (20)	Lewis O secretor (5-10)	Lewis O non-secretor (0.1-1)
2'FL	Fuc α 1-2 Gal β 1-4 Glc	+	-	+	-
LDFT	Fuc α 1-2 Gal β 1-4 (Fuc α 1-3) Glc	+	-	+	-
LNFP I	Fuc α 1-2 Gal β 1-3 GlcNAc β 1-3 Gal β 1-4 Glc	+	-	+	-
LNFP II	Gal β 1-3 (Fuc α 1-4) GlcNAc β 1-3 Gal β 1-4 Glc	-*	+	-*	-
LNDFH II	Gal β 1-3 (Fuc α 1-4) GlcNAc β 1-3 Gal β 1-4 (Fuc α 1-3) Glc	-*	+	-*	-

2'FL: 2'-fucosyllactose; LDFT: lacto-difuco-tetrose; LNFP: lacto-N-fuco-pentaose; LNDFH: lacto-N-difuco-hexaose

*traces may be present

“The short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides found in infant formula are very different structurally from human milk oligosaccharides (HMOs).”

– Clemens Kunz –

DAVID MILLS (Department of Food Science and Technology, University of California-Davis, California, USA) presented the functional roles of HMOs. In terms of its prebiotic function, HMOs act as a food substrate for certain species of bifidobacteria, eg. *B. longum* subsp *infantis*. Bifidobacteria play a major role in structuring the gut microbiome of breastfed infants due to their ability to consume HMOs. However, recent studies have revealed that bifidobacteria are often missing from the gut microbiome of many breastfed infants in some locations. Low rates/duration of breastfeeding, milk glycan composition, and antimicrobial use may act against bifidobacteria. Gut bacteria consume HMO in different ways. *B. longum* subsp *infantis* consume HMO by importing it into its cell and allowing its intracellular glycolytic enzymes to deconstruct the oligosaccharides, making it an “inside eater”. In contrast, “outside eaters” such as *B. bifidum* or *Bacteroides* cause the degradation of HMOs outside the cell and absorbing selected components. *B. longum* subsp *infantis* thrive on HMOs and can outcompete *Bacteroides*; therefore, when it colonizes the gut, the diversity of the microbiota is lower. However, when an outside eater colonizes the gut, undigested components allow cross-feeding of other types of bacteria. For instance, HMO consumption of *Bacteroides* spp cross-feed proteobacteria, such as *E. coli*. Data drawn from studies in preterm infants who develop NEC supports this cross-feeding model; preteobacteria isolated from NEC patients grew on fucose, a breakdown product of HMOs, but not on conjugated HMOs. This knowledge can be used for translation of specifically chosen probiotics that consume all milk-related sugars.

“Bifidobacteria play a major role in structuring the gut microbiome of breastfed infants due to their ability to consume HMOs. However, recent studies have revealed that bifidobacteria are often missing from the gut microbiome of many breastfed infants in some locations.”

– David Mills –

“HMOs that have been approved by the EU as novel foods include lacto-N-neotetraose and 2'-O-fucosyllactose. In the US, GRAS (Generally Recognized as Safe) notifications have also been granted by the United States Food and Drug Administration (US FDA) for both of these HMOs.”

– Seppo Salminen –

SEPPO SALMINEN (Functional Foods Forum, Faculty of Medicine, University of Turku, Finland) covered the regulatory aspects of HMOs. Human milk oligosaccharides (HMOs) are a group of sugars, which are structurally diverse unconjugated glycans. They are found in human milk with a composition unique to each lactating mother. They have not been used in any other foods previously and therefore the application of human milk oligosaccharides to our food supply requires both safety assessment and most likely also assessment of potential health benefits. While HMOs have been shown to have an impact on the development of infant gut microbiota, it is not well known if HMOs similarly affect human milk microbiota composition or microbiota in oral, nasopharyngeal, gastrointestinal and urinary tract areas. However, they do have a role in the early colonization and modification of the infant gut and possibly an immuno-protective role specific to the mother and infant during pregnancy and breastfeeding. HMOs are currently regarded as new ingredients for infant formula as well as other foods and food supplements, and as such, come under the purview of the novel food regulation (EU 2015/2283). The European Food Safety Authority (EFSA) is an advisory body that conducts independent risk assessment and risk communication regarding food safety, and advises the European Commission, EU Parliament and member states. Under EU 2015/2283, member states can decide whether a type of food falls within the scope, and grant market authorization based on safety of the product; functionality is not assessed nor is it a basis for approval. Nutrition and health claims are covered under regulation (EC) 1924/2006. Health claims are approved based on scientific substantiation that apply to normal EU population. HMOs that have been approved by the EU as novel foods include lacto-N-neotetraose and 2'-O-fucosyllactose. In the US, GRAS (Generally Recognized as Safe) notifications have also been granted by the United States Food and Drug Administration (US FDA) for both of these HMOs.



CONCLUSION

The 88th Nestlé Nutrition Institute Workshop, aptly titled “Intestinal Microbiome: Functional Aspects in Health & Disease”, focused on research on the microbiome and human milk oligosaccharides (HMO). Microbiome research has revealed multiple essential roles of the microbiota on host metabolism, immunity and overall health. Numerous physiological and disease states, such as atopy and obesity, have been correlated with altered microbiota, also known as dysbiosis. However, pregnancy is an exception, as alterations in the microbiome occur even during healthy pregnancies. Crosstalk with colonizing bacteria in the developing neonatal intestine helps the infant to adapt to extrauterine life, particularly in acquiring immune homeostasis, and provides protection against disease expression later in life. Perinatal events such as Caesarean-section delivery, preterm birth, antibiotic administration or type of feeding may disrupt intestinal microecology, and dysbiosis in infants has been linked with the development of immunological and metabolic diseases in later life. Research indicates that microbiota modify the epigenetic expression of the host gene through DNA methylation; this has implications for cellular development and immunological disease. In addition, research on connections between the brain, gut and microbiome reveal that microbial signals may affect host behavior and a range of targets throughout the body, including the immune system, cardiovascular system, hypothalamic–pituitary–adrenal axis and host metabolism. Human milk oligosaccharides (HMOs) are abundant in human milk and are diverse in profile between lactating mothers. HMOs has functions as bifidus factors in the development of a healthy gut microbiome, prevention of infection, and modulation of the immune system. HMOs represent novel tools to modulate the gut microbiome, and to potentially improve health outcomes. HMO is an area of active research, and large-scale production of HMOs have recently become possible. From the regulatory perspective, HMOs are considered novel foods and require safety assessments before they can be made available to the public, as well as efficacy evaluations if any health claims are to be made. Two HMOs that have been approved by the EU as novel foods are lacto-N-neotetraose and 2'-O-fucosyllactose. In the US, GRAS (Generally Recognized as Safe) notifications have also been granted by the United States Food and Drug Administration (US FDA) for both of these HMOs.

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