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ESPGHAN Satellite Symposium

Current insights in breast milk research – new reasons why breast is best

Friday, 12 May 2017
07:30 to 08:30 am
Prague Congress Centre
Panorama Hall

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Human Milk Oligosaccharides at the Interface of Maternal-Infant Health

Human milk oligosaccharides (HMO) are a family of structurally diverse unconjugated glycans that are highly abundant in and unique to human milk. After lactose and lipids, HMOs are the third most abundant component of human milk. One liter of mature human milk contains 5 to 20 g of these complex sugars, which often exceeds the concentration of all human milk proteins combined. HMO concentrations in colostrum are even higher. HMOs consist of the five monosaccharide building blocks glucose (Glc), Galactose (Gal), N-acetylglucosamine (GlcNAc), fucose (Fuc) and the sialic acid N-acetyl-neuraminic acid (Neu5Ac). The combination of these building blocks in defined glycosidic linkages yields several dozen if not hundred structurally distinct HMOs, but it is important to note that total amount and composition are highly variable between different women. Which maternal genetic, epigenetic as well as environmental factors like diet, physical activity or drug exposures determine HMO composition is not well understood and at the focus of current research.

Once ingested, HMOs resist the low pH in the infant's stomach as well as digestion by pancreatic and brush border enzymes. Thus, HMOs reach the distal small intestine and colon in an intact form where they are available to help shape microbial communities and host-microbe interactions. Originally, HMOs were discovered as a prebiotic "bifidus factor" that serves as a metabolic substrate for desired bacteria and shapes an intestinal microbiota composition with health benefits for the breast-fed neonate. Today, HMOs are known to be more than just "food for bugs". An accumulating body of evidence suggests that HMO are antiadhesive antimicrobials that serve as soluble decoy receptors, prevent pathogen attachment to infant mucosal surfaces and lower the risk for viral, bacterial and protozoan parasite infections. HMOs also directly impact bacterial growth in the infant's intestine and urinary tract, where they act as bacteriostatics and reduce the risk for infections. Moreover, HMOs may modulate epithelial and immune cell responses and reduce excessive mucosal leukocyte infiltration and activation.

In addition to influencing microbial communities and host-microbe interactions in the infant gut, HMOs may already have an effect on microbes in the oral cavity and upper respiratory tract, potentially even the skin, at least around the mouth. Furthermore, HMOs are absorbed in the infant gut, reach the systemic circulation, and are eventually excreted in an intact form with the infant's urine. Although the concentrations of HMOs that reach the urinary tract are much lower than the concentrations of HMOs in the infant's gut, it is possible that HMOs also impact microbial communities in the infant's urinary and genital tract with potential effects of health outcomes, e.g. reducing urinary tract infections. The microbiota-shaping effects of HMOs might occur even earlier, before they reach the infant. Human milk itself is not sterile and contains bacterial communities that live within the milk matrix while still in the mammary gland, waiting to be expressed. Milk microbiota and HMOs co-localize in the mammary gland between feeding or pumping episodes, potentially influencing each other through similar mechanisms that have been described for the infant gut.

Individual HMOs like 2'-fucosyllactose (2'FL) or Lacto-N-neo-tetraose (LNnT) are now available at large-scale to be used in products not only for infants, but also for adults with the goal to treat or even prevent diseases that are associated with dysbiosis. Future research needs to investigate whether or not the use of individual HMO is harmful when fed alone and not in concert with dozens and potentially hundreds of other oligosaccharides as they naturally occur in human milk.

Despite the many new advances and discoveries in the field of HMO research, many unanswered questions remain. How does the HMO composition relate to other human milk components like lipids, proteins or the human milk microbiome? Which genetic and environmental factors influence HMO composition? Is there a preferred HMO composition in a specific infant health or disease context? Are individual HMOs alone beneficial or potentially harmful? Do we need to provide HMOs in a mixture of different structures? Are there specific HMO composition profiles that are less desirable because they might increase the risk for certain undesirable short- or long term outcomes like HIV-transmission through breastfeeding? What are the long-term effects of HMO exposure, e.g. in the context of allergies, asthma obesity, cardiovascular risk, cognitive development? And are those effects mediated through or independent of the infant gut microbiome? Do HMOs provide potential benefits to the breastfeeding mother?

It is clear that we are only at the very beginning of understanding the value of HMOs as they take center stage at the interface of maternal and infant health.

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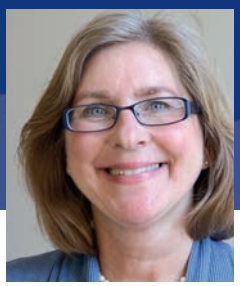

The Human Milk Microbiome — A Paradigm Shift in Infant Nutrition

Human Milk — The Only Food Designed for Humans Human milk is inarguably the only food „designed" by Mother Nature to be consumed exclusively by humans - providing all the essential nutrients (and other bioactive compounds and constituents) needed for growth and development of the human infant. As such, understanding human milk composition and variation, therein, is critical to optimizing human health during this vulnerable time, particularly in the most at-risk infants. In addition, documentation of human milk composition has direct links to being able to make better recommendations about nutrient intakes in infancy and optimizing nutrient composition of infant formulae. More complete characterization of human milk composition (and in particular to this talk, as it relates to the microbiome) may also lend important insight as to what constitutes optimal nutrition in other phases of the lifecycle, not only for the human host but also for the myriad commensal, mutualistic, and sometimes pathologic microbes with which we coexist. However, our understanding of human milk composition and its impact on host and microbial health is far from complete.

Paradigm Shift — Human Milk Isn't Sterile Until recent advances in instrumentation allowing the detection and identification of difficult-to-culture bacteria, common dogma was that human milk was sterile unless produced by an infected mammary gland or contaminated after expression (as reviewed by McGuire and McGuire, 2017). As such, although it has long been known that gastrointestinal (GI) microbial communities are different in breastfed vs. formula-fed infants, explanations for this difference have focused on roles played by nonliving milk constituents, such as the complex (an indigestible) human milk oligosaccharides (HMO). We now know, however, that human milk (like bovine milk) contains a diverse population of bacteria. As such, we and others postulate that, in addition to HMO and other "prebiotic" milk constituents, milk microbes themselves may impact the infant's GI microbiome in a "probiotic" fashion. In addition, it is likely that these mammary communities are important for maternal health as well.

What We Know, Don't Know, and Need to Know Here we will briefly describe what is currently known about variation in the human milk microbiome as well as relationships among perinatal variables (e.g., delivery mode), maternal diet and nutritional status, milk nutrient content, maternal health and disease, childcare patterns, and the milk microbiome around the globe. For instance, there is growing evidence that microbial profiles in milk are relatively stable within a woman but are different among women (Hunt et al., 2011) and populations (e.g., Dave et al., 2016; Cabrera-Rubio et al., 2012; Jost et al., 2015; Kumar et al., 2016). However, results from next-generation sequencing approaches suggest that human milk, regardless of location, is typically dominated by Staphylococcus, Streptococcus, and Pseudomonas. Differences in milk collection, DNA extraction and amplification, DNA sequencing, and bioinformatics may explain some of the differences in other bacteria reported thus far. Alternatively, genuine differences may exist in the bacterial communities of milk produced around the globe, and it is not known whether these differences are shaped by genetics, environment, lifestyle, or a combination of these factors. In addition, maternal diseases such as mastitis and breast cancer are also associated with variation in the milk/mammary microbiome (Jiménez et al., 2015; Urbaniak et al., 2014; Xuan et al., 2014; Hieken et al., 2016; Chan et al., 2016); and maternal micro- and macronutrient intakes and chronic energy balance appear to be related to variation in milk microbial community structure (Williams et al., unpublished data; Cabrera-Rubio et al., 2012).

We will discuss emerging data from an ongoing cross-cutting study funded by the Integrated National Science Foundation Support Promoting Interdisciplinary Research and Education (INSPIRE) funding mechanism designed to help us better understand what is "normal" in terms of milk microbes (and other milk constituents) in various locations worldwide, and why this is important. The possible origins of the milk microbiome will also be presented. The importance of cooperation and interdisciplinary discussion around methods and vocabulary will be emphasized as will some of the challenges faced in terms of sample collection, storage, and transport; microbiome analyses; and data analysis. Finally, a framework for considering what work is needed to link variation in the human milk microbiome to human health and disease will be presented.

Selected References

Cabrera-Rubio R, et al. Am J Clin Nutr. 96(3):544-51, 2012; Chan AA, et al. Sci Rep. 2016 Jun 21;6:28061; Davé V, et al. Pediatr Res. 79(6):846-54, 2016; Hieken TJ, et al. Sci Rep. 6:30751, 2016; Hunt KM, et al. PLoS One. 6(6):e21313, 2011; Jiménez E, et al. J Hum Lact. 31(3):406-15, 2015; Jost T, et al. Nutr Rev. 73(7):426-37, 2015; Kumar H, et al. Front Microbiol. 13;7:1619, 2016; McGuire MK and McGuire MA. Prebiotics and Probiotics in Human Milk. McGuire, McGuire, and Bode, eds. Elsevier Inc., 2017; Urbaniak C, et al. Appl Environ Microbiol. 80(10):3007-14, 2014; Xuan C, et al. PLoS One. 9(1):e83744, 2014.

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