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

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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.

References:

1. Bode L, Raman AS, Murch SH, Rollins NC, Gordon JI (2020) Understanding the mother-breastmilk-infant "triad". Science. 367(6482):1070-1072.
2. Jantscher-Krenn E, Zherebtsov M, Nissan C, Goth K, Guner YS, Naidu N, Choudhury BP, Grishin AV, Ford HR, Bode L (2011) The Human Milk Oligosaccharide Disialyllacto-N-tetraose prevents Necrotizing Enterocolitis in neonatal rats. GUT. 61(10):1417-25
3. Autran CA, Kellman BP, Kim JH, Asztalos E, Blood AB, Hamilton Spence EC, Patel AL, Hou J, Lewis NE, Bode L (2018) Human milk oligosaccharide composition predicts risk of necrotizing enterocolitis in preterm infants. Gut. 67(6):1064-1070.