Human Milk Oligosaccharides: Next-Generation Functions and Questions

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The past decade has experienced an immense increase in research on human milk oligosaccharides (HMOs), mostly driven by (a) advances in high-throughput glycan analysis and (b) large-scale glycan synthesis as well as (c) the advent of modern microbiome research.

Advances in high-throughput glycan analysis have enabled the research community to analyze HMO composition in hundreds and sometimes thousands of milk samples from large mother-infant cohorts to investigate associations between maternal factors and HMO composition as well as between HMO composition and infant outcomes. However, the identified associations cannot prove cause-and-effect relationships. Cohesive and consistent results from suitable preclinical in vitro, tissue culture and animal models, human cohort associations, as well as randomized controlled trials (RCTs) will be required to make conclusive claims about specific HMO functions. As an example from our own work, we identified a specific HMO called disialyllacto-N-tetraose (DSLNT) that reduces incidence and severity of necrotizing enterocolitis (NEC) in a rodent model [1]. While the results are encouraging, the validity of data from available preclinical NEC models in rodents or piglets is limited [2]. Animals are exposed to external hypoxic and/or hypothermic insults that are rather artificial, and the use of animals itself is a limitation due to interspecies differences in gastrointestinal development, anatomy, and physiology. Thus, advancing a potential therapeutic like DSLNT from controversial preclinical models to clinical treatment trials carries a tremendous risk of failure. However, in parallel, we conducted a multicenter clinical cohort study on 200 mothers and their preterm, very low-birthweight infants that were predominantly human milk-fed and showed that infants who developed NEC received less DSLNT with the milk than infants who did not develop NEC [3]. The latter results do not prove cause-and-effect, but the combination of preclinical testing and human cohort associations raises the confidence towards clinical application. Future studies in the preclinical model as well as in tissue culture...
are going to help us elucidate the underlying mechanism, and a carefully designed RCT is going to be needed to ultimately prove the use of DSLNT in NEC prevention.

Advances in glycan synthesis have made individual HMOs available for research as well as commercial application. Chemoenzymatic synthesis is extending our repertoire of available HMOs at smaller scale for in vitro and preclinical research [4]. The help of bioengineered microbes allows the synthesis of individual HMOs at large scale for commercial application [5]. However, knowledge about specific functions and potential adverse effects of individual HMOs remains very limited at best. Human milk contains a personalized mixture of hundred or more different and structurally distinct HMOs, which raises questions whether the application of single individual HMOs instead of complex mixtures causes imbalances in infant gut microbial communities or in the infant immune system with potential short- and long-term health consequences.

Advances in microbiome research and the associated analytical and bioinformatics tools further sparked an interest in HMOs. The composition of microbial communities in the gut and other organs and their metabolic and functional capabilities have been associated with numerous conditions, including obesity, inflammatory bowel disease, autism, asthma, and allergies – to only name a few. The concept that HMOs help shape microbial communities early on in life and affect short- and long-term health is indeed striking. Future research is going to apply a combination of preclinical and clinical studies to systematically elucidate HMO structure-function relationships and identify whether individual HMOs like DSLNT or mixtures of HMOs (the way they naturally occur in human milk) provide short- or long-term benefits to infants and potentially adults.

References