

# Human Milk: Role of Indigenous Prebiotics and Probiotics

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The goals of this presentation are to summarize the recent findings on the pre and probiotic components present in human milk and to present on-going investigations in my laboratory on the bioactivity of human milk, infant formula, HMO and prebiotics in the human infant and piglet model.

Development of the gastrointestinal (GI) microbiome begins soon after birth and is influenced by environmental factors (e.g. route of delivery, early nutrition, antibiotic use) interacting with genetic factors innate to the infant. Normal GI development and function depends on the presence of complex microbiota, which perform numerous metabolic, growth-promoting, and protective roles. Facultative anaerobes, such as streptococci, staphylococci, enterococci, lactobacilli or enterobacteria, together with some strictly anaerobic ones, especially bifidobacteria, are among the first colonizers. The intestinal ecosystem of breast-fed infants is characterized by a strong prevalence of *Lactobacilli* and *Bifidobacteria*, with predominant species *B. longum*, *B. infantis* and *B. breve*. In contrast, the microbiota of formula-fed infants is more diverse and prone to changes and contains higher counts of *Bacteroides*, *Clostridium*, and *Enterobacteriaceae*. Oligosaccharides (HMO) are the 3<sup>rd</sup> most abundant component of human milk, averaging 10 g/L. HMO are resistant to digestion, so reach the colon, where they prevent attachment of enteropathogens and serve as prebiotics. *In vitro* fermentation studies demonstrated that LNT, the most predominant HMO, is preferentially fermented by *B. infantis*. Recent reports support prebiotic actions of other human milk components, including alpha-lactalbumin, lactoferrin and nucleotides. The prebiotic potential of these substances has not yet been clearly defined, however, the prebiotic potential of human milk likely represents an interaction of these components with HMO. On-going work in my lab is assessing how mother's milk impacts the intestinal transcriptome, microbiome and metagenome compared to infant formula.

Culture-dependent and independent (DGGE and qPCR) analysis of aseptically collected human milk samples revealed live bacteria, including streptococci, staphylococci, enterococci, lactobacilli and enterobacteria. Importantly, *B. longum*, *B. bifidum*, *B. adolescentis* and *B. breve* were detected in 22 milk samples with ~40-10,000 16S rRNA gene copies/ml milk. Application of pyrosequencing has further elucidated the complexity of the human milk microbiome of milk samples collected from 16 healthy women over a 5-week period. Bar-coded 454 pyrosequencing of 16S rRNA genes produced an average of 4,000 reads/sample, with *Streptococcus*, *Staphylococcus*, and *Corynebacterium* identified as the dominant phylotypes at the genus level when evaluated using the Ribosomal Database Project classifier. The ACE richness metric estimated from 180 to 1,700 distinct phylotypes (97% similarity) in each sample. The community composition of milk collected from each woman was relatively consistent over time, although dramatic changes in composition could be observed at some time points, perhaps due to environmental characteristics in the mammary gland related to diet, milk composition, or immune factors.

In summary, human milk is a complex biological fluid containing both bifidogenic prebiotics as well as live probiotics. These synbiotics likely facilitate the successful postnatal adaptation of the newborn by stimulating cellular growth and digestive maturation, the establishment of symbiotic microflora, and the development of gut-associated lymphoid tissues. Supported by the National Institutes of Health (HD061929) and an unrestricted 'Freedom to Discover' award from the Bristol Myers-Squibb Foundation.