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It's in the Milk: Feeding the Microbiome to Promote Infant Growth

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Malnutrition is a global health burden affecting the development of millions of children worldwide, but the effects of current treatment strategies are modest. In this issue of *Cell Metabolism*, Charbonneau et al. (2016) identify sialylated oligosaccharides in breast milk as microbiota-dependent growth-promoting metabolites, paving the way for a new rational treatment of severe infant stunting.

Malnutrition represents a global health problem associated with almost half of all deaths in children under the age of 5, resulting in about 3 million cases of childhood death per year (Prendergast and Humphrey, 2014). Growth stunting caused by undernutrition affects about 165 million children under the age of 5 (Prendergast and Humphrey, 2014). The "first 1,000 days" from a child's conception until its second birthday are considered a crucial period during which nutritional nourishment is critical to prevent long-lasting adverse effects. Malnutrition during this period results in irreversibly stunted growth and impaired cognitive ability (Black et al., 2013). In addition, it was recently found that infant malnutrition impairs the normal pattern of gut microbiota assembly (Subramanian et al., 2014).

The severe health burden associated with child malnutrition has motivated the development of nutrient formulations to compensate for nutrient deprivation during early childhood (Ahmed et al., 1999). Based on the widely recognized benefits of breast feeding on infant development, health organizations recommend exclusive breast feeding for the first 6 months of a baby's life (Haroon et al., 2013). However, it remains unknown how variations in the composition of breast milk contributes to infant stunting and how such variations can potentially be exploited for the development of more effective nutritional interventions. In a recent article in *Cell*, Charbonneau et al. (2016) use gnotobiotic and metabolomic approaches to delineate a pathway linking breast milk composition, gut microbiota, and infant growth (Figure 1).

Charbonneau et al. (2016) compared the composition of breast milk from Malawian mothers of healthy children with those whose children exhibited severe growth retardation. They found a significant enrichment of sialylated oligosaccharides in the breast milk received by healthy infants. Sialylated oligosaccharides are an abundant component of human breast milk involved in a diverse spectrum of functions that include the compositional development of gut microbiota, prevention of intestinal infections, and brain development (Bode, 2012). To test whether these metabolites are causally involved in fostering growth in newborns, Charbonneau et al. (2016) colonized gnotobiotic mice and piglets with around 20 commensal strains obtained from a Malawian infant with stunted growth. The animals were then fed a chow containing eight ingredients that are representative of Malawian diet, with or without isocaloric addition of sialylated bovine milk oligosaccharides (S-BMOs). This dietary supplementation altered anabolic lipid homeostasis in the recipients and accelerated weight gain as well as maturation of bone morphology. Notably, these effects were not achieved when the S-BMO-enriched diet was fed to germ-free mice. These observations yield two interesting insights: first, the milk oligosaccharides seem to exert their growth-promoting effect not through direct alteration of host metabolism, but rather through modulation of microbiota activity. Second, the "immature" microbiome of Malawian infants with stunted growth does not appear to be refractory to growth-promoting intervention, but it does support infant growth when the right nutrients are provided.

Charbonneau et al. (2016) further explored potential mechanisms by which S-BMOs alter the microbiota in order to foster infant growth. Interestingly, rather than changing the composition of the gut microbial community, the dietary intervention changed gene expression in a limited number of commensals, most prominently in the polysaccharide utilization loci of *Bacteroides fragilis*. Based on results obtained from in vitro experiments, the authors suggest that S-BMO degradation by *B. fragilis* could "cross-feed" other members of the defined community, as demonstrated for *E. coli*. Of note, a gnotobiotic mouse model colonized with a minimal community consisting of only *B. fragilis* and *E. coli*, which in principal is capable of S-BMO-induced cross-feeding, did not feature improved growth when supplemented with milk oligosaccharides, indicating that a more complex network of microbial community interactions may be required to induce these physiological effects. Thus, the full scope by which the microbiota derived from Malawian infants metabolizes sialylated milk oligosaccharides to promote growth, and the in vivo extent of the "cross-feeding" mechanism, merit future studies.

These open questions notwithstanding, Charbonneau et al. (2016) uncover an interesting and important connection between breast milk metabolites, defined gut commensal interactions, and host metabolism that could potentially be exploited for the design of rational dietary formulations used against infant growth retardation. In light of potential future clinical trials of growth-promoting diets for

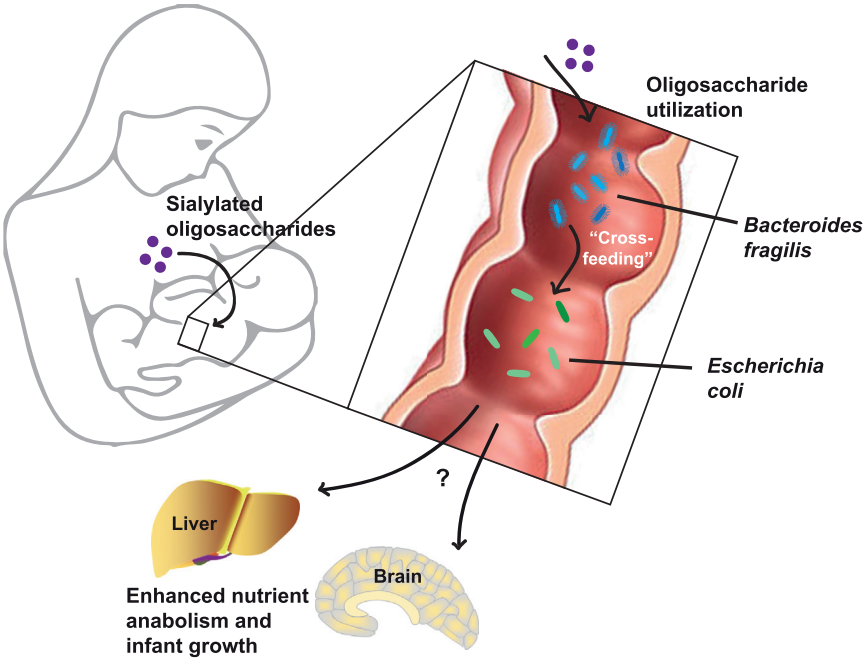

Figure 1. Feeding the Microbiome with Sialylated Milk Oligosaccharides to Promote Infant Growth

Sialylated breast milk oligosaccharides induce transcriptional responses in certain members of the gut microbial community. This metabolite utilization sets forth a "cross-feeding" cascade affecting other members of the microbiota. Together, these metabolic changes enhance the ability of the host to utilize dietary nutrients, leading to alterations in metabolic states and metabolite composition in major metabolic organs.

malnourished human infants, it is important to note that the authors used bacterial species obtained from only a single Malawian child, and that both gnotobiotic mice and piglets were fed a synthetic diet consisting of only eight carefully selected ingredients. Given the enormous inter-individual variability in intestinal microbial community composition across geographical regions and the impact of local diets in shaping the gut microbiome (De Filippo et al., 2010; Yatsunenko et al., 2012), it will be critical to determine whether the described pathway is effective in a larger variety of microbial communities beyond the selected cultured strains and beyond a defined eight-component diet. Potentially, in order to reach maximum efficiency, dietary supplements to counteract undernutrition might have to be adapted to regional diets and microbiota compositions across populations of malnourished children and their mothers (Zmora et al., 2016). The combinatorial usage of personalized microbiota cultures, gnotobiotic models and metabolomics described by Charbonneau et al. (2016) for the case of a Malawian child might thus serve as a blueprint for defining metabolite-based therapies applicable for a regional diet-microbiota context. In the quest for finding such ideally suited nutritional formulations, this study therefore provides an innovative example and a valuable resource for implementing more effective interventions to fight the global health problems associated with malnutrition.

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