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Should Infants Cry Over Spilled Milk? Fecal Glycomics as an Indicator of a Healthy Infant Gut Microbiome

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The gut microbiome is rapidly assembled after birth with profound implications for human health and development. Recent research suggests the infant gut microbiome is strongly shaped by microbial exposures at birth followed by a range of other environmental factors, most notably mother's milk, the one food shared by all humans (1–4). Human milk is an incredibly complex assemblage of nutrients and bioactive factors that evolved under diverse selective pressures to both nourish and protect the infant while simultaneously shaping the infant gut microbiome. Amazingly, the more that is revealed as to the nature of the tripartite relationship between mother's milk, the infant, and the infant gut microbiome, the more complex the story becomes. For example, one of the most abundant components of milk, the complex assembly of sugars called glycans, are completely indigestible to the infant itself (5). Numerous *in vitro* studies have shown that these glycan structures are consumed by a relatively small group of early colonizers in the infant gut, primarily of the genera *Bifidobacterium* (6). However it was unclear if glycan consumption truly takes place inside the infant gut. Is a more saccharolytic microbiota (i.e. high in bifidobacteria) associated with a reduction in milk glycans in feces? Since infants colonized by bifidobacteria show a wealth of favorable health outcomes (7), is there a correlation between their presence and the disappearance of glycans in the feces? Moreover when infants are not colonized by bifidobacteria they often possess a host of other taxa, some of which are less than desirable for infant health (1, 8). Do these latter assemblages consume less milk glycans?

In this issue of JGPN, Wang et al (1) helps resolve this issue by showing associations between the milk glycans emerging in the infant feces and various microbial populations in the infant gut. They show that a host of these milk glycans are negatively correlated in abundance with the presence of a suite of microbial taxa such as *Bifidobacterium* and *Bacteroides*, known to consume these glycans *in vitro*. In contrast, microbial populations with less favorable relationships with infant health such as *Escherichia* and *Klebsiella*, are not negatively correlated with these human milk glycans, suggesting that they are unable to consume these sugars. However, Wang et al suggest potential cross-feeding among the glycan degraders and these taxa that are not known to consume milk glycans *in vitro*,

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DAM is a co-founder of Evolve Biosystems, a company focused on diet-based manipulation of the gut microbiota.

pointing to associations between keystone taxa that may be contributing to these populations (1).

This work is timely, considering a prior study by De Leoz et al (8) which showed that *Bifidobacterium* colonization was associated with a concomitant decrease in the presence of milk glycans in the feces of a breast-fed infant while in another infant (not colonized by *Bifidobacterium),* these structures do not decrease in abundance.

These two studies together provide a powerful example of the potential utility of fecal glycomics for assessing the "health" of the developing breast fed infant gut microbiome. If beneficial microbial populations are linked with the presence of specific breast milk glycans and health outcomes, then measurements of these structures could provide a diagnostic readout on infant gut health. Thus the relative absence of these complex milk sugars in the feces would be a measure of a healthy gut microbiome. In contrast, an abundance of 'spilled milk' glycans could be a measure of a dysbiotic system. Future work investigating these relationships in larger infant populations is necessary to confirm these trends, but these complementary studies provide great promise in understanding how milk glycans shape the gut microbiome.

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