Human milk oligosaccharide-utilizing bifidobacteria produce immunomodulatory aromatic lactic acids in the infant gut

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Abstract

Breastfeeding protects against infectious and immune-related diseases although mechanisms are not fully understood. Breastfeeding is also a key factor that shapes the infant gut microbiota, which in turn is critical for early life immune development. Indeed, the gut microbiota can impact host physiology in various ways, such as through the production of metabolites. However, few breastmilk-dependent microbial metabolites mediating host-microbiota interactions are currently known. We recently demonstrated that breastmilk-promoted *Bifidobacterium* species convert aromatic amino acids (tryptophan, phenylalanine and tyrosine) into their respective aromatic lactic acids (indolelactic acid, phenyllactic acid and 4-hydroxyphenyllactic acid) via a previously unrecognised aromatic lactate dehydrogenase (ALDH), *in vitro* and further *in vivo*, using gnotobiotic mice. Profiling of the faecal microbiota composition and metabolome in two separate cohorts of Danish infants showed that faecal concentrations of aromatic lactic acids are correlated positively with the abundance of human milk oligosaccharide-degrading *Bifidobacterium* species containing the aromatic lactate dehydrogenase, including *Bifidobacterium longum*, *Bifidobacterium breve* and *Bifidobacterium bifidum*. We further demonstrated that faecal concentrations of *Bifidobacterium*-derived indolelactic acid are associated with the capacity of these samples to activate *in vitro* the aryl hydrocarbon receptor (AhR), a receptor important for controlling intestinal homeostasis and immune responses. Finally, we showed that indolelactic acid modulates *ex vivo* immune responses of human CD4+ T-cells and monocytes in a dose-dependent manner by acting as an agonist of both the AhR and hydroxycarboxylic acid receptor 3 (HCA_3). Our findings reveal that breastmilk-promoted, HMO-consuming *Bifidobacterium* species produce aromatic lactic acids in the infant gut and suggest that these microbial metabolites are impacting immune function in early life.