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Editorial

What you have to know about Human Milk Oligosaccharides

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"… the sweetness of it sounds in me, yet."
Dante Alighieri, *The Divine Comedy. Purgatory, Canto II:79-114*

Keywords

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Introduction

The extraordinary properties of human Breast milk (BM) can mostly be attributed to several bioactive components provided to the breastfed neonate in addition to the fundamental nutritional compounds. Human Milk Oligosaccharides (HMOs), the third most important solid components of BM (the first and the second being lactose and lipids respectively), are a highly variable family of unconjugated glycans related to many pathophysiological

short- and long-term effects on infants [1-3] and, as recently demonstrated, even on the mother [4, 5].

The HMOs level appears to be higher in colostrum and decreases during lactation, especially regarding fucosylated compounds [5-7]. In addition, HMOs show a higher variability in samples collected from mothers who deliver preterm, especially in sialylated structures [4, 8].

Owing to HMOs' great abundance and inter-individual heterogeneity in BM samples, it would be very interesting to investigate the possible benefits of their presence in the mother-child dyad [8].

Among their functions are promotion and modulation of gut microbiota, effects on intestinal mucosa and its development, protection against intestinal or extra-intestinal infections, modulation of several immune responses and even extra-intestinal effects, such as brain development, as described in literature [4, 6, 9].

Infants' gut microbiota is mostly shaped by BM HMOs; in fact, different microbial patterns can be detected by comparing BM infants to those fed with formula milk (FM) [4, 6, 7].

HMOs are mostly processed in the gut and undergo fecal excretion (99%), but a very small percentage (1%) can be absorbed and reach many target organs through the circulation [1, 5, 8].

In the gut, HMOs act as prebiotics, representing a selective substrate and a carbon source for commensal bacteria such as *Bifidobacteria spp.*, *Bacteroidetes spp.*, and *Lactobacillus spp.* [4, 9, 10].

The metabolites produced by these beneficial species can also indirectly influence other microbial members (i.e. *B. fragilis* or *E. coli*). This interaction, as in a "cross-feeding" cascade, can exert several metabolic effects; it may promote an infant's growth and determine beneficial effects on many organs (such as liver, respiratory and urinary tract and brain, including an improvement in neurodevelopment and long-term intelligence quotients) [3, 4, 8, 9]. On the contrary, the growth of aggressive species, such as *Enterobacteriaceae* or, as recently demonstrated, *St. agalactiae*, is inhibited owing to the inability to metabolize HMOs [1, 8].

HMOs also show an effect on the reduction of the risk of developing allergies, asthma and other diseases, since they act directly and indirectly on the infant's gut mucosal and systemic innate and adaptive immunity [1, 10].

HMOs can modulate transcriptional responses and improve the barrier function [1, 6] of the intestinal epithelium.

As an additional mechanism, the presence in BM of extracellular vescicles (EVs) containing exosomes and mRNA has recently been proposed. This could promote some effects on gut microbiota modulation and also influence, immunity and growth through not fully clarified mechanisms [11].

Moreover, they can act as soluble decoys because of their homology to some intestinal receptors; this anti-adhesive antimicrobial activity can lead to the elimination of several pathogens, thus preventing severe viral, bacterial, protozoan and fungal infections [1, 3, 8]. Such an effect, mostly *in vitro* or in animal models, has been demonstrated against Norovirus, Rotavirus [1, 4], Calicivirus [5] and other pathogens causing diarrhea such as *C. jejuni* and enteropathogenic *E. coli*, *St. pneumoniae*, *P. aeruginosa*, or *H. influenzae* [4] and *E. histolytica* [5], Respiratory syncitial virus and Influenza virus [12] and a protective effect against postnatal HIV transmission may also occur [3].

Finally, since breastfed preterm newborns show a 6- to 10-fold lower risk of developing necrotizing enterocolitis if compared with FM fed neonates [4], HMOs, in particular 2'fucosyl-lactose (2'FL), have been shown to exert a beneficial effect on this outcome [8].

In this perspective, HMOs may also act by stabilizing the intestinal microbial community, modulating epithelial and immune cell responses, dealing with leukocyte infiltration and activation [13, 14] and improving intestinal blood flow [15].

In addition, there are also several effects on the oligosaccharidic fractions caused by the microbiota. Intestinal microbes, through diverse interactions both among different species and with host-derived metabolites and HMOs, contribute to correct gut development. Locally, these signaling and inflammatory pathways potentially influence the gut, as well as distant organs [7, 16].

Utilization of HMOs in the gut, the effects on microbiota, the interactions among the host and microbial communities (cross feeding) and the effects promoted by HMOs on several organs and systems are represented in **Fig. 1**.

Microbiota acts on the HMOs metabolism through specific enzymes such as glycosidases, transporters and other molecules [1, 4, 8].

Recently, it has been demonstrated that microbial community maturation and its stabilization over time act differently on HMOs, whose profile in stools changes over time in the same patient [5, 8, 17].

Regarding HMOs composition, it appears that maternal genetic factors play the major role in

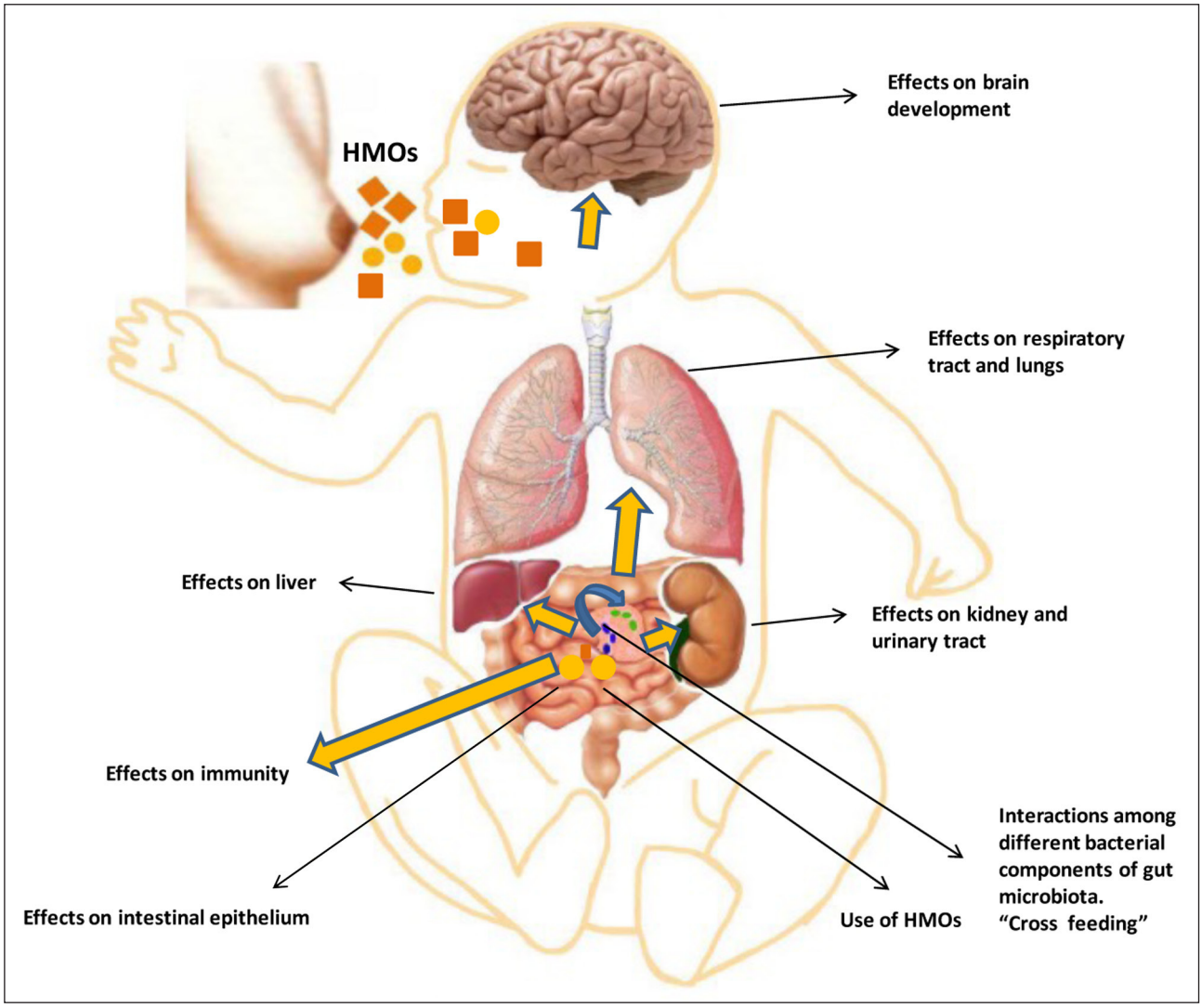

Figure 1. Utilization of Human Milk Oligosaccharides (HMOs) in the gut. Effects on microbiota and interactions among the host and microbial communities (cross feeding). Effects promoted by HMOs on several organs and systems.

conferring its high and peculiar inter- and intra-individual variability to BM [18, 19].

HMOs greatly depend on four maternal phenotypes, defined depending on the expression of two specific genes and maternal blood group. The α-1-2-fucosyltransferase (FUT2) gene, expressed in more than 70% of Caucasian women, is codified by the Se gene and allows classification of secretor (Se+) and non-secretor (Se-) mothers. In addition, the α-1-3-4-fucosyltransferase (FUT3) gene indicates positivity or negativity for the Lewis Group (Le+ or Le-) [1, 4, 19-21].

In the BM collected from Se+/Le+ mothers, all the fucosylated oligosaccharides can be detected (2'FL, lactodifucotetraose LDFT, lacto-N-fucopentaose I LNFPI, lactodifucoesaose I LNDFHI). On the contrary, the Se-/Le+ mothers' phenotype determines the presence of HMOs with (α1-3)- and (α1-4)-linked fucose residues [1, 4, 6, 19].

Even other environmental and maternal factors, represented by age, diet, health status, medication and drugs appear to play a role in HMOs composition [l].

Moreover, we previously underlined briefly the importance of a metabolomic approach in defining HMOs; our preliminary data would suggest that the human milk metabolome does not depend on infant gender, delivery mode and/or birth weight [19].

Finally, although on a small sample of patients, Smith-Brown et al. [22] demonstrated that the beneficial influence of maternal secretor status on gut microbiota composition can also persist after 2-3 years from suspension of breastfeeding.

In conclusion, since BM oligosaccharide composition varies in each mother, it can exert a different influence on microbiota, thus modulating the short- and long-term outcome of the infant in several ways [1].

In addition to intestinal microbes, HMOs may also influence extra-intestinal microbial communities; therefore, the maternal "lactobiome" may cause different systemic effects both in the newborn and on the lactating mother [5].

Improved knowledge of all these aspects will help in developing more suitable dietary foods for infant nutrition with the closest similarity to BM, both in terms of composition and functions [14]. Up to now, supplementation with key human milk glycans appears very promising and 2'FL is considered a safe additive for human nutrition.

The introduction of sialylated oligosaccharides has recently been proposed as an efficacious strategy against undernutrition and growth impairment [9, 23].

However, more studies are needed to clarify the complexity of the HMOs structure and interactions and also to evaluate the reliability of the potential benefits related to their supplementation in the infant diet [14].

Declaration of interest

The Authors declare that there is no conflict of interest regarding the publication of this paper.

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