

# What is all the fuss about the gut microbiome and 2'-FL?

## The microbiome and beyond



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### Key points:

- A healthy microbiome is essential for appropriate development of body's immune responses, preventing infections and absorption of nutrients.
- Infant microbiome develops from the time of birth and is very variable, influenced by factors like mode of delivery, type of feeding, use of antibiotics and maternal genetics.
- Human milk oligosaccharides, including 2'-fucosyllactose, promote the development of a healthy microbiome by promoting proliferation of beneficial bacteria and suppressing growth of pathogenic organisms.

### Introduction

The gastrointestinal tract is colonised by large numbers of microorganisms, including bacteria, fungi, viruses and protozoa, commonly referred to as the microbiota. *Lactobacillus* and *Proteobacteria* are the predominant organisms in small bowel because of its abundance in disaccharides. *Bacteroidales* and *Clostridiales* are predominant in large intestine which is rich in undigested carbohydrates and act as their food substrate. In infants, *Lactobacillus*, *Prevotella*, or *Sneathia* spp. dominate the gut flora at birth, with proliferation of *Bifidobacterium* and *Bacteroides*<sup>1</sup> within the next few months. The diversity of infant gut microbiome is affected by a multitude of factors, including: gestational age, mode of delivery, feeding method and pharmaceutical exposure.<sup>2</sup> The gut microbiome has a significant impact on our physiology and plays a role in developing the body's immune responses, preventing

proliferation of pathogenic organisms and aiding digestion and absorption of nutrients.<sup>3</sup> The gut microbiome plays an important role in the development of immune system. It protects against invasion by pathogens through direct colonisation resistance inhibiting the growth of pathogenic bacteria by competing for nutrients; stimulating the host to form a protective mucous layer on the intestinal lining<sup>4</sup> and making the host environment unfavourable for the growth of pathogens - e.g. *Lactobacilli* lowers the pH within the gut.<sup>5</sup> Beneficial bacteria stimulate the body's immune system through low level leakage in the blood stream and increased signalling within the gut. This educates the host to respond to pathogens and regulates the immune system, reducing the risk of infections and autoimmunity.<sup>6</sup> Reduced microbiome diversity and dysbiosis increase the risk of developing autoimmune disorders like inflammatory bowel disease.<sup>7</sup>

There is increasing evidence that promoting the growth of beneficial bacteria through use of pro and prebiotics can reduce the risk of necrotising enterocolitis in preterm infants.<sup>8,9</sup> The gut microbiome also influenced the metabolic response within the host. Depleted microbial diversity has been associated with a lifelong risk of elevated adiposity, insulin resistance and dyslipidaemia.<sup>10</sup> A healthy microbiome is therefore associated with improved health. The majority of microbes are established within the first year of life and there is little variation of the healthy microflora after 3 years of age. Breast feeding plays a vital role and the microbiome of a breast-fed baby born by caesarean section becomes similar to that of the vaginally delivered baby by 6 months of age.<sup>2</sup> The infant microbiome is closely related to the microbiota in mother's breast milk and the composition of human milk oligosaccharides (HMO) in milk. Breast milk bacteria are largely comprised of *Staphylococcus*, *Streptococcus*, *Acinetobacter*, and *Enterobacter* primarily derived from maternal areolar skin and infant oral sites in breastfeeding pairs.<sup>11</sup>

Carbohydrates in breast milk are mainly in the form of lactose, with other significant carbohydrates being human milk oligosaccharides (HMO), a group of complex and diverse glycans. HMOs are non-nutritive bioactive factors resistant to gastrointestinal digestion and reach the infant colon as the first prebiotics.<sup>12</sup> They are composed of units of glucose, galactose, N-acetylglucosamine, L-fucose and N-acetylneuraminic acid conjugated via glycosidic linkages. Each HMO structure starts with a lactose unit 'Gal ( $\beta$ 1-4) Glc', which results from formation of a  $\beta$ 1-4 glycosidic linkage between galactose and glucose catalysed by the lactose synthase protein complex.<sup>13</sup>

The three major types of HMOs in breast milk are fucosylated, non fucosylated and sialylated HMOs. 2'-fucosyllactose (2'FL), a type of fucosylated HMO, is the most abundant HMO, constituting up to 30% of the total HMOs. HMOs being the third most abundant biomolecule found in human milk after lactose and lipids reaching between 5-20 g/L.<sup>13</sup>

The composition and amounts of HMOs vary based on the stage of lactation, maternal nutrition and genetics. The concentration of HMOs are highest in colostrum and the amount decreases within the first three months of lactation. HMOs are prebiotics that play a key role in the development of the immune system by promoting the growth of beneficial bacteria, inhibiting the growth of pathogenic organisms and inducing maturation of intestinal mucosa and by the modulation of immune cells. HMOs, especially 2'-FL in the colon encourage the proliferation of beneficial bacteria and alters gut microbiota shifting the balance of bacteria towards *B adolescentis*.<sup>14</sup> They prevent infections by inhibiting the attachment of pathogenic bacteria to the mucosal surface by stimulating mucin production,<sup>15</sup> and the use of HMOs as a substrate produce organic acids as a by-product which inhibits the growth of pathogenic bacteria.<sup>16</sup>

Additionally, HMOs have been shown to have an immunomodulatory effect, though the exact mechanism is not known, they are believed to modulate intrinsic expression of inflammatory cytokines and signalling pathways.<sup>16</sup>

The infant gut microbiome develops from the time of birth with diversity dependent on multiple genetic and environmental factors. A healthy microbiome positively impacts health outcomes throughout the life span and practices that promote a diverse microflora should be encouraged.

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