

HMO: Supporting Infant Immunity and Beyond



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For more than two decades, Abbott has been researching human milk oligosaccharides (HMOs) to better understand how these prebiotics help support the infant immune system. A breakthrough occurred in 2010, when our team of scientists began to focus attention on the specific HMO, 2'-fucosyllactose (2'-FL). Since then, we have published more than 20 preclinical and clinical studies on 2'-FL to describe its role in the developing infant immune system; its anti-infective and prebiotic effects; and its potential role in cognitive development. We were the first company in the world to add an HMO to infant formula, and we will continue to expand our research with one overarching goal: to simulate the beneficial properties of breast milk in our formula in order to narrow the gaps between breast-fed and formula-fed infants – to give babies around the world the best start in life.

INNATE AND ADAPTIVE IMMUNITY: THE CRUCIAL FIRST YEAR

About 70% of the immune system's many biological structures and processes reside

in the gut, which is colonized by trillions of microbes. Although colonization begins during the birthing process, infants acquire more than a thousand different species before one year of age.

The principal roles of the immune system during infancy are to protect the host from pathogens and eliminate toxic substances that enter through mucosal surfaces lining the respiratory and intestinal tracts. Initially, maternal immunoglobulin G (IgG) from the placenta provides much of the infant's postnatal protection. This IgG declines rapidly after birth, however, which makes the first year of life an especially critical time for infants to grow the dense community of commensal bacteria that is needed to establish and maintain a healthy immune system.

All mammals, including humans, have two pathways for immune response—innate and acquired. Innate immunity refers to nonspecific defense mechanisms such as natural killer cells, a type of white blood cell, that immediately attack foreign cells. During the first months of life, the infant relies largely on its innate immune pathway for

general pathogen destruction.

Innate immunity not only is the first line of defense, but also induces acquired (or adaptive) immunity. After exposure to specific pathogens and toxins, an infant's acquired immune pathway matures and produces antibodies targeted to specific harmful invaders. In contrast to innate immune cells, adaptive immune cells respond in weeks instead of hours or days, and develop memories for removal of future threatening substances.

Optimal early development of both pathways is especially critical because innate immune cells do not reach adult levels until approximately 12 months of age. Furthermore, major adaptive immunity antibodies such as IgG and immunoglobulin M will only reach 80 and 75 percent of adult levels, respectively, at one year of age.

NUTRITION'S INTEGRAL ROLE IN IMMUNE DEVELOPMENT

The numerous protective compounds in breast milk serve multiple functions within the immune system. The most abundant antibody in human milk is secretory IgA, a key defensive

mechanism against invasion by inhaled and ingested pathogens at vulnerable mucosal surfaces. Other immune components in breast milk include:

- leukocytes, which ingest or kill pathogens;
- nucleotides, which support adaptive immunity by stimulating antibody production and lymphocyte maturation; and
- IgG antibodies, which identify and bind to harmful substances such as bacteria, viruses, and fungi to trigger an immune response.

A growing body of evidence now suggests that the HMOs found in breast milk play a critical role in the development of healthy immune systems.

HMOs AND 2'-FL: THE NEXT FRONTIER OF PEDIATRIC NUTRITION

HMOs are the third most abundant component in breast milk (after fat and lactose, a digestible carbohydrate), comprising about 10 percent of solids. Research suggests that HMOs serve as soluble decoy receptors that bind pathogens and prevent their attachment to infant mucosal surfaces, thus

lowering the risk for infection by these viruses or bacteria¹. HMOs are also thought to be involved in modulating epithelial and immune cell responses, including the reduction of excessive mucosal leukocyte infiltration and activation.

Of the more than 200 HMO structures reported², we became particularly interested in 2'-FL due to its unique properties. Although 2'-FL is quantitatively the most abundant oligosaccharide in breast milk, only 70-80% of women are genetically capable of producing it³. More importantly, however, recent research shows that 2'-FL might exert a variety of beneficial physiological effects. One study found that breast-fed infants whose mothers secreted 2'-FL could much more readily establish gut populations of beneficial bifidobacteria than could breast-fed infants of non-secreter mothers⁴. In another clinical study, the level of 2'-FL HMO in mother's milk was correlated to reduced risk of enteric infections in breast-fed infants⁵.

Data from preclinical studies also hint at additional uses for 2'-FL HMO. Experiments using *ex vivo* murine colonic segments demonstrate that 2'-FL modulates gut motility⁶, suggesting that it might potentially be useful for reducing abdominal discomfort caused by colic or irritable bowel syndrome, or for improving feeding tolerance in preterm infants. Similarly, another study using a mouse model suggests that 2'-FL HMO may be protective against necrotizing enterocolitis⁷ (NEC), a potentially devastating and fatal intestinal disease in premature infants.

CLINICAL STUDY OF 2'-FL IN INFANT FORMULA

A recent clinical trial compared term infants fed an experimental infant formula containing 2'-FL with breast-fed infants as well as those in a control group who were fed formula without 2'-FL⁸. The study found that the 2'-FL-fortified formulas were well-tolerated and that growth was no different from that of breast-fed infants. Interestingly, reports of eczema were lower in the 2'-FL groups than the control group, and were no different from breast-fed infants. The study also investigated the effects of feeding formulas supplemented with 2'-FL on biomarkers of immune function⁹. Following six weeks of feeding, researchers discovered that five immune markers were significantly lower in infants who were fed the formulas containing 2'-FL compared to control formula, and they were nearly identical to those of breast-fed infants. The results showed that 2'-FL:

- reduced production of plasma pro-inflammatory cytokines to levels similar to breast-fed infants;
- closed plasma cytokine gaps between breast-fed and formula-fed infants; and
- narrowed respiratory syncytial virus *ex vivo* cytokine gaps between breast-fed and formula-fed infants.

With respect to adaptive immunity, the study noted that 2'-FL also narrowed the differences in proportions of total T lymphocytes (including helper T cells and cytotoxic T cells) between breast-fed and control formula-fed infants. Based on these findings, the investigators concluded that 2'-FL fortification supports aspects of immune

development and regulation similar to that in a breast-fed reference group of infants.

INFANT NUTRITION AND THE GUT-BRAIN-MICROBIOTA AXIS

Nutrition plays an important role in supporting the rapidly growing brain during the first year of life. While some nutrients such as docosahexaenoic acid, lutein, and vitamin E appear to act directly in the brain, new research indicates that others influence the brain through the action of trillions of microbes that reside within the gut. Some of these gut microbes generate metabolites that are identical to the neurotransmitters found in the human brain, thus implying bidirectional host-microbe communication via a gut-brain-microbiota axis¹⁰.

In addition to supporting the developing immune system, both sialylated and fucosylated HMOs are likely involved in shaping the developing nervous system. Both sialylated¹¹ and fucosylated¹² molecules have been shown to participate in synaptic signaling. Furthermore, sialylated HMOs may also serve as a source of sialic acid, a key nutrient for central nervous system/brain development and function¹³. Indeed, a study in pigs found that sialylated HMOs serve dual functions as: a source of sialic acid that modulates brain composition, and a prebiotic to promote the growth of beneficial bacteria¹⁴. Likewise, experiments in rodents show that oral 2'-FL enhances hippocampal long-term potentiation, a measurement that coincided with improved performance on various types of learning behavioral tests¹². Follow-up studies revealed

that the effect of 2'-FL on CNS function was likely mediated through the vagus nerve¹⁵.

A FOUNDATION FOR GOOD HEALTH

Research shows us that the development of the immune system is closely associated with the intestinal microbiota, highlighting the important connecting roles of HMOs as prebiotics and immunomodulators. As awareness grows of the importance of early nutrition on life-long health, Abbott will continue to partner with experts worldwide in exploring the myriad of connections between infant nutrition, gut microbiota, immune development and brain health to ensure we're doing all we can to give babies around the world the best start in life.

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