EXAMINING BREASTMILK FOR CLUES IN THE FIGHT AGAINST FOOD ALLERGIES

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There is growing interest in the role of breastmilk, in particular human milk oligosaccharides (HMOs), in preventing the development of food allergies.

Breastmilk is a dynamic, multi-faceted fluid that changes composition as the newborn feeds and grows. Many breastmilk components are unique to humans and collectively they provide the infant with the nourishment they need, while also helping to defend against infections and guide the development of the immature immune system. As such, the composition of a baby's first meals can have a profound influence on their lifelong health, particularly when it comes to food (and other) allergies. Research over recent decades is starting to clarify the picture. The Abbott Nutrition Health Institute recently launched a five-part on-demand video series featuring several experts discussing the latest contributions to this field. This is a summary of their presentations.

Early immune development and allergic responses

The world is charged with potential dangers, from viruses and bacteria to parasites and toxins. Before birth, a baby receives a boost of antibodies from its mother, which offers some degree of protection in the first weeks of life. But babies need to quickly develop their own immune system, and multiple factors influence this process, including mode of birth, nutrition, and early infections.

"When a baby is born, it has an immature immune system that is naturally skewed towards a certain type of immune response," says Christine Loscher, an immunologist at Dublin City University in Ireland.

The body's immune system recognises molecules, or antigens, that could be dangerous. Antigens are presented to naive T cells, which differentiate into various T helper (Th) cell populations, depending on the type of threat. These Th cells then prompt B cells to generate antibodies specific to each antigen. Broadly speaking, Th2 cells respond to threats including environmental allergens and parasites, whereas Th1 cells respond to viruses and bacteria.

A newborn's immune system has more Th2 than Th1 cells. "The infant's response to bacterial and viral infections is weak because it hasn't yet been exposed to the disparate pathogens we face daily," says Loscher.

As the developing immune system is exposed to more pathogens, it generates more Th1 cells and antibodies for viral and bacterial infections. Over time, this creates a balanced immune system. However, not all infants are able to boost their Th1 response in their first year, leaving their immune system weighted towards Th2.

A Th2 response involves the generation of Immunoglobulin E (IgE) antibodies, which activate histamine-releasing mast cells, causing allergic symptoms and inflammation. Another population of T cells, called Treg cells, can intervene before the allergic response, fostering tolerance. The immune system can therefore boost Treg populations and quell over-active Th2 responses to benign antigens (see 'T cell responses: a question of balance').

"Having a Th2-weighted immune system does not automatically mean you will have allergies, but it makes you more susceptible, even though this may not become apparent until later in life," explains Loscher. "A major influence is the types of infection you are exposed to early on, as these either help balance your immune system or exacerbate overactive Th2 responses. Similarly, food intake affects both microbiome composition and immunity."

Hence, early exposures for the naive immune system have a bearing on allergy development, and it is estimated that between 20 and 30% of children worldwide suffer from allergy-related disease[1]. Problems with an imbalanced immune system can be further exacerbated by lifestyle choices, such as eating processed foods and overuse of antibiotics.

COW'S MILK HAS HARDLY ANY OLIGOSACCHARIDES, AND NONE OF THEM MIRROR THE DIVERSE STRUCTURES AND FUNCTIONS OF HMOS.

Breastfeeding and allergy

Research shows that breastfed babies tend to have fewer, milder infections and fewer pro-inflammatory cytokines in circulation than formula-fed infants[2]. However, "the data on breastfeeding and allergy are not as clear as we would like," says allergy specialist and dietitian Carina Venter, from the University of Colorado in Denver. A 2019 clinical report from the American Academy of Pediatrics[3] referred to the limitations of available data when it comes to specific food allergies, but was able to say that breastfeeding beyond the first 3–4 months seems to lower the risk of asthma. "Breastmilk certainly doesn't cause food allergies," she adds, "but we cannot state that it alone prevents food allergy development."

Breastmilk is important as it nourishes not only the baby, but also feeds its growing gut microbiome. Understanding what is in breastmilk, and what these components do, is the key to solving this puzzle. Since the late 1990s, many research teams, including those at Abbott, have been focusing their attention on the third largest solid component of breastmilk after lactose and fat: complex carbohydrates called human milk oligosaccharides, or HMOs.

The diverse roles of HMOs

Perhaps surprisingly, given how plentiful they are in breastmilk, HMOs do not feed the infant. One of their many roles is to provide food for beneficial bacteria, such as Bifidobacterium in the gut, thereby shaping the developing microbiome and reducing the levels of pro-inflammatory cytokines released by gut tissues.

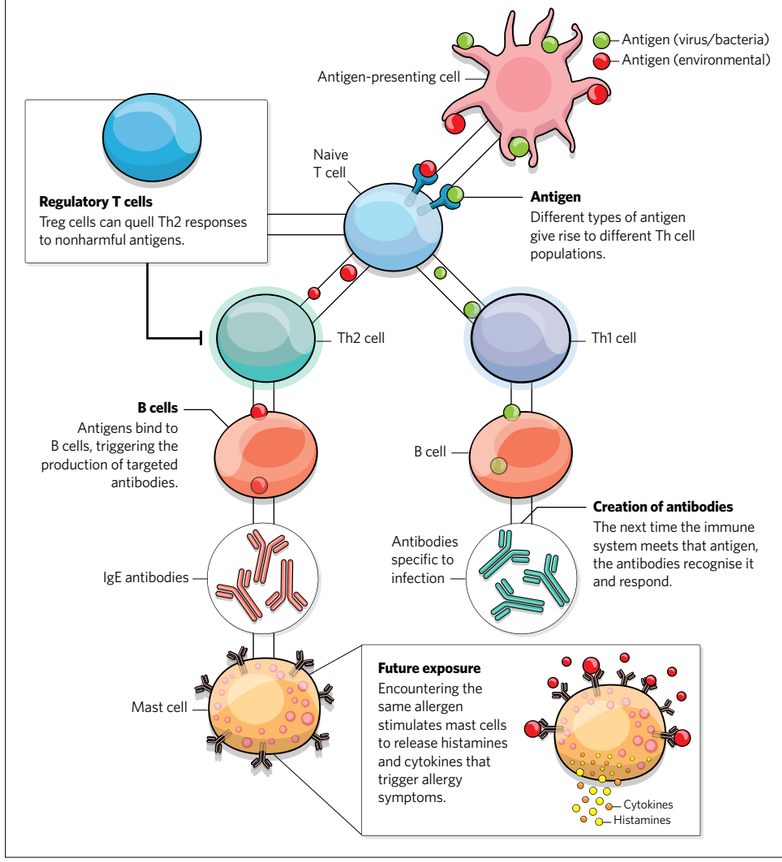
"HMOs are specific to humans," says Evelyn Jantscher-Krenn, researcher in obstetrics and gynaecology at the Medical University Graz, Austria. "Cow's milk — the basis of most formula milks — has hardly any oligosaccharides, and none of them mirror the diverse structures and functions of HMOs[4]."

As well as feeding the gut microbiota, some HMOs act as decoy receptors for pathogens and prevent pathogens from adhering to host cells, thus helping maintain the healthy structure and function of the developing gut tissues[4]. Animal models have shown[5] that HMOs can prevent necrotizing enterocolitis, a serious illness where gut tissues become inflamed and start to die, explains Jantscher-Krenn. HMOs are built from only five basic monosaccharide building blocks. Yet, more than 200 structurally different HMOs have been identified, which seem to serve specific purposes.

The most abundant HMO, present in around 80% of mothers' breastmilk, is 2'-fucosyllactose (2'-FL), which can prevent pathogens like diarrhoea-causing Campylobacter jejuni from

T CELL RESPONSES: A QUESTION OF BALANCE

The immune system responds in a different way depending on the type of antigen it faces. The challenge is to develop a balanced immune system where no T helper (Th) cell response is stronger than another. The immune system can learn to regulate overactive Th2 responses, reducing the likelihood of allergic reactions.



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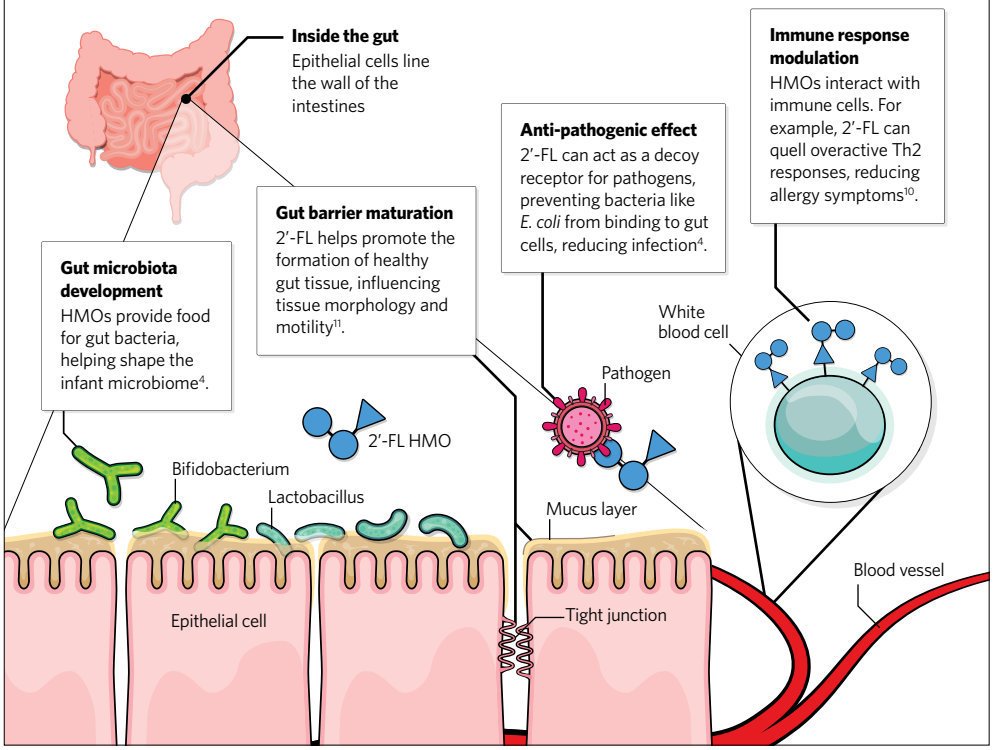
binding to host cells[6]. It also has strong health signals (see 'What do HMOs do?'). Breastfed infants of mothers with high 2'-FL in their milk have significantly lower incidence of diarrhea[7], and consuming milk with higher levels of 2'-FL lowered the risk of allergy-related eczema[8]. However, over time, and even between mothers, the composition of breastmilk varies.

Based on knowledge gained from these studies, many companies have started adding HMOs to their infant formulas. "Abbott has contributed extensively to HMO research since the 1990s, and we were the first to introduce 2'-FL to formula-fed infants," says Barbara Marriage, researcher and nutrition scientist at Abbott. For example, Abbott's research has shown that children fed formula milk supplemented with 2'-FL have levels of pro-inflammatory cytokines that are closer to those seen in breastfed infants, and lower than those seen in infants fed traditional formula[9]. "We believe that 2'-FL may be beneficial to food-allergic infants," she adds.

WHAT DO HMOS DO?

Human milk oligosaccharides (HMOs), including 2'-FL, support the infant's developing immune system in a variety of ways. Research is ongoing to uncover more about their diverse roles.



HMOs and allergy

There is growing interest in the idea that HMOs could be used more widely, not just in infant formulas, but to manipulate immune responses to improve allergy management. It may one day be possible to incorporate HMOs into food supplements or allergy therapies for all ages.

The underlying mechanism by which 2'-FL modulates the allergic response is the focus of research by Paul Forsythe, a biochemist at McMaster University in Hamilton, Canada.

WE'RE ALSO EXPLORING HOW THE GUT-BRAIN AXIS IS INFLUENCED BY 2'-FL.

In studies using a mouse model of food allergy, Forsythe and his team demonstrated that giving a boost of 2'-FL decreased the number of activated mast cells in the mouse intestines[10]. Further, 2'-FL stabilized remaining mast cells, significantly reducing their degranulation and associated release of histamines.

Rather than interacting directly with the mast cells, the team found that 2'-FL was actively increasing the animal's Treg cell population, which fostered allergen tolerance in the intestinal tissue. The mouse models retained healthy Treg levels following 2'-FL treatment, suggesting that their immune system resilience was boosted.

"We're also exploring how the gut-brain axis is influenced by 2'-FL," says Forsythe. "Mental stress affects our gut and bowels. It appears that 2'-FL can quell contractions in the intestines of mice exposed to stress[11]." This suggests there is considerable interaction between HMOs and the nervous system, which Forsythe is keen to explore further.

"It's also crucial that we ascertain which of the beneficial effects of HMOs are direct, and which are indirect via their influence on the microbiome," adds Forsythe.

Considerable progress has been made in understanding the unique components of mother's milk, but Marriage still has many questions to investigate. "How do HMOs collaborate with and complement one another?" she asks. "Since the gut and brain communicate, is there a possible role for HMOs in cognition? And do they have a role in allergy management in older children and adults?" There are many more insights to be uncovered in this growing area of research, and Abbott will continue contributing to this field. ■

Full talks from all the speakers can be viewed at ANHI.org

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