



GUT MICROBIOTA
RESEARCH & PRACTICE
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GUT MICROBIOTA & EARLY LIFE

A selection of content from the
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TABLE OF CONTENT

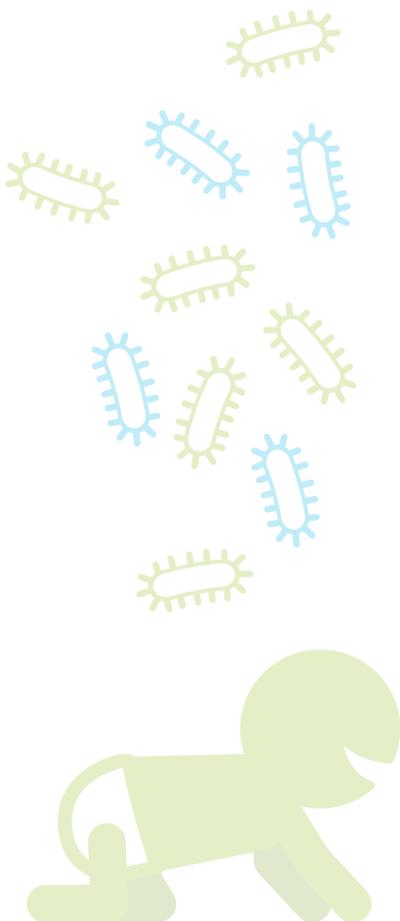
EDITORIAL	3
SELECTED CONTENT FROM GUTMICROBIOTAFORHEALTH.COM	
• Study adds new insights regarding when and how infant microbiome develops in the first six weeks of life	6
• Role of gut microbiota diversity in protection from asthma and allergy development	8
• Mouse study shows maternal microbiota shapes offspring's immune system	11
• Benefits of breast milk go beyond infant nutrition	13
• Clinical implications of recent study exploring 'microbial restoration procedure' for caesarean-born infants	16
• How the transition to family foods may influence infant gut microbiota development	18
• Long-term follow-up shows safety of perinatal probiotic administration	20

Of babies and microbes



Prof. Marie-Claire Arrieta

Marie-Claire Arrieta is Assistant Professor in the Department of Physiology & Pharmacology and the Department of Paediatrics at the Cumming School of Medicine at the University of Calgary (Canada). Trained in mucosal immunology, physiology, and intestinal microbiology, she currently uses multi-omic techniques, including microbiome high-throughput 16S, 18S, and ITS sequencing, metabolomics, and transcriptomics in large-scale pediatric population-based studies, and combines them with mechanistic studies in animal models in order to evaluate the role of the intestinal microbiota in the development of asthma.



The birth of an infant kick-starts a plethora of physiological adaptations to extra-uterine life, including changes in respiratory, cardiac, thermoregulatory, neurological, digestive, and immune functions. The neonatal gut undergoes drastic adaptations in order to successfully carry out its dual role of absorbing nutrients and hosting a biomass of foreign life forms—the gut microbiota—which colonize this organ rapidly and permanently.

An ever-expanding number of studies point to microbial colonization early in life as an important source of biochemical signals that trigger and drive important aspects of immune, metabolic, and neurological development. Given the degree of an infant's physiologic reliance on microbe-derived signals and metabolites in the first months of life, it has come as little surprise that alterations to the gut microbiome during the first few weeks and months can lead to changes in immune and metabolic development

and, under certain conditions, to the chronic immune-mediated diseases that continue to increase in incidence around the world. Asthma, the most common chronic pediatric disease, is the focus of my research.

Influences on early gut microbial colonization

The eventual ability to manipulate the gut microbiome for the benefit of health depends on knowledge of the factors that influence gut microbial colonization and development. Several factors are emerging as important influencers.

- **In utero environment:** Very weak support exists for colonization in utero (Lauder *et al.*, 2016; Perez-Muñoz *et al.*, 2017), as researchers have not been able to distinguish between placental samples and contamination controls. However, an elegant recent study in mice recently demonstrated that maternal microbe-derived signals strongly

EDITORIAL

influence immune development of the fetus (Gomez de Agüero *et al.*, 2016).

- **Birth:** Mode of birth plays an important role in shaping gut microbiota composition (Dominguez-Bello *et al.*, 2010; Bäckhed *et al.*, 2015; Yasuda *et al.*, 2015; Yassour *et al.*, 2016), although it is unclear for how long infants born by caesarean section display differences from their vaginally delivered counterparts. Nonetheless, these differences occur in a period of immune permissiveness, during which crucial immune functions, such as the proliferation of peripheral regulatory T cells (Tregs), are most responsive to microbiome interactions (Arpaia *et al.*, 2013; Furusawa *et al.*, 2013; Smith *et al.*, 2013).

- **Host biology:** A recent study performed in pre-term babies in a neonatal intensive care unit showed that although mode of birth and nutrition are important drivers of sequential changes in the gut microbiome, genetic and physiologic characteristics of the pre-term infant gut drive a conserved pattern of succession (La Rosa *et al.*, 2014).

- **Infant nutrition:** The intestinal microbiome differs between breastfed and formula fed infants (Palmer *et al.*, 2007; Yatsunenکو *et al.*, 2012). Breastmilk contains an array of immune effectors (IgA, lysozyme, lactoferrin, immune cells) that protect the infant from infection, help in infant immune maturation, and also shape the infant's gut microbiome. Recently, a glycan component in breastmilk has caught the attention of many

research groups: human milk oligosaccharides (HMOs) are only digested by bacterial metabolism and have a strong bifidogenic effect (Barile & Rastall 2013; Oozeer *et al.*, 2013). HMOs are the first prebiotics ingested by babies.

- **Solid foods:** Several studies have shown an increase in diversity upon the introduction of solid foods, due to the sudden availability of additional nutrient sources for bacterial growth and to the effect of weaning (Koenig *et al.*, 2011; Fallani *et al.*, 2011; Bäckhed *et al.*, 2015).

Early life critical window for influencing health

The developing gut microbiome is not very resilient compared with the established microbiome after 3 years of age. This lack of community resilience makes the gut ecological community more prone to permanent alterations in structure and composition, at a time when the host immune system is more responsive to microbial signals. Antibiotic treatment early in life leads to or accelerates disease in experimental models of asthma (Russell *et al.*, 2012), inflammatory bowel disease (Scheer *et al.*, 2016), obesity (Cho *et al.*, 2012; Cox *et al.*, 2014), and autoimmune diabetes (Livanos *et al.*, 2016). We and others recently showed that microbiome alterations occur during the first 100 days of human life in babies at a high risk of atopy and asthma (Arrieta *et al.*, 2015; Fujimura *et al.*, 2016). Early life dysbiosis has also been observed in babies that later develop autoimmune diabetes (Vatanen *et al.*, 2016).

Studying more than bacteria

Traditionally not included in microbiome studies, fungi are important members of the gut microbiome, especially in the first months of life, when fungal species are present at a much higher diversity than later in life. A recent study in babies at risk of atopy measured the fecal fungal community and found several fungal taxa (in addition to bacterial taxa) involved in the gut dysbiosis associated with asthma (Fujimura *et al.*, 2016). Moreover, recent work from our group in collaboration with colleagues (currently under review) found marked fungal dysbiosis in babies that later develop asthma, suggesting that fungal species may play a role during this immune developmental stage. Further studies may bring mechanistic insights.

Summary

Gut microbial colonization during early life influences human development by triggering age-dependent immune mechanisms. Although considerable research effort has been made to understand microbial influences on health in early life, many of the processes through which microbial exposures facilitate immune system development remain to be identified. Future studies in human longitudinal cohorts, especially those focused around the events that lead to shifts in microbial compositions, hold great potential to improve our understanding of the dynamics at play and to yield early-life health interventions that target the gut microbiota.

EDITORIAL

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SELECTED CONTENT

Study adds new insights regarding when and how infant microbiome develops in the first six weeks of life

Published on February, 27, 2017 by Andreu Prados



Andreu Prados holds a Bachelor of Science Degree in Pharmacy & Human Nutrition and Dietetics. Science writer specialised in gut microbiota and probiotics, working also as lecturer and consultant in nutrition and healthcare.

Maternal microbiota, mode of delivery, type of infant feeding and other factors can influence the infant microbiota in the perinatal period. Microbiota composition in the neonatal period and beyond seems to have a relevant role in health, but researchers still have much to learn about the microbiota assembly process in healthy term infants and which aspects could have a causal relationship with future disease.

A recent study, led by Dr. Kjersti Marie Aagaard from the Department of Obstetrics and Gynecology at Baylor College of Medicine in Houston (Texas, USA), has found that the microbiome of infants greatly expands between birth and 4 to 6 weeks of age, and – contrary to current thinking – caesarean delivery (C-section) does not appear to affect maturation and diversity of the infant microbiome.

The researchers enrolled a cohort of 81 pregnant women in their early third trimester for longitudinal sampling at 4-6 weeks after delivery. To better explore the effects of mode of delivery, a second matched cross-sectional cohort of 81 pregnant women was enrolled for sampling once at the time of delivery. For each maternal-infant pair, microbiota samples from the skin, oral cavity, nares, stool and vagina were collected. Composition and function

of both the neonatal and maternal microbiota were analysed using both 16S ribosomal ribonucleic acid (rRNA) gene and whole-genome shotgun sequencing. Researchers applied general linear models to control for confounders like the reason for the caesarean delivery and other factors related to the mother, such as maternal diet, breast milk feeding, antibiotic use and diabetes.

At the time of delivery, neonatal microbiota and its associated functional pathways were relatively homogeneous across all body sites, except that the microbiota in the neonatal meconium diverged as compared with those of the skin, nares and oral cavity. However, by 4 to 6 weeks of age, the infant microbiome started to show body niche separation and its structure and function had notably expanded and diversified.

C-section does not appear to affect maturation and diversity of the microbiome.

SELECTED CONTENT

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C-section does not appear to affect maturation and diversity of the microbiome.

The microbiota structure in the neonatal meconium was not linked to the caesarean mode of delivery, whereas in infants born by C-section, minor variations in the neonatal microbiota community structure were found in the oral cavity, nares and skin. Besides this, there were no differences in community function at the time of birth, regardless of delivery mode. At 6 weeks of age, neither community structure nor function was different between infants delivered vaginally and those born by caesarean surgery.

In conclusion, within the first 4 to 6 weeks of life the infant microbiome undergoes a significant expansion and maturation that is primarily driven by body site and not by mode of delivery.



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Within the first 4 to 6 weeks of life the infant microbiome undergoes a significant expansion and maturation that is primarily driven by body site and not by mode of delivery.



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Read the original post online at:

<http://www.gutmicrobiotaforhealth.com/en/study-adds-new-insights-regarding-infant-microbiome-develops-first-six-weeks-life/>

SELECTED CONTENT

Role of gut microbiota diversity in protection from asthma and allergy development

Published on December, 23, 2016 by Andreu Prados



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A recent study led by Dr. Alex Mira (FISABIO, Spain) and Dr. Maria C. Jenmalm (Linköping University, Sweden) and researchers at IATA-CSIC (Spain) has presented an analysis of a total of 192 faecal samples from 28 healthy children and 20 children developing allergic symptoms at age seven, from when the children were 1 and 12 months of age. It has found that children who develop asthma or allergies later in life have altered immune responses to intestinal bacteria in the gut mucosal environment at an early age. The results also suggest that the mother's immune system may play a role in the development of asthma and allergies in children.

Majda Dzidic, first author of the study, corresponded with GMFH editors about the significance of the work.

What is already known and what have you already found about the role of gut microbiota in allergic diseases? Why do the first 2-3 years of life appear to represent the most critical period for microbiota modulation to reduce children's risk of asthma and allergic disease?

We believe that the first years of life are crucial when it comes to the maturation of a healthy gut. This early period of childhood is also known as a "critical window of opportunity" [when] the infant's immune system is being instructed on how to react against (and tolerate) the symbiotic microbiota. Mucous membranes are present in the airways and gastrointestinal tract and here they come into contact with large amounts of bacteria and viruses. IgA antibodies,

[principal] primary [mediators] of humoral mucosal immunity, are present in mucous membranes. Here they bind to microorganisms that they recognize and act as a barrier, preventing them from entering the mucosal tissue and creating immune responses that might damage the surrounding tissue. [Besides] the fact that the microbial recognition by maternal and infant IgA antibodies must be appropriately orchestrated for an optimal maturation of the mucosal immune system, the microbiota itself plays a central role in this early immune modulation. So we believe that diversity and composition [of] the bacteria are major drivers for the normal maturation of a healthy mucous membrane. Thus, perturbations in this symbiotic relationship between the immune system and intestinal microbiota, during the early period of life, seem to be highly correlated with the child's risk of asthma and allergic disease development.

SELECTED CONTENT

Role of gut microbiota diversity in protection from asthma and allergy development



What are the most relevant new findings in your research group regarding the effects of gut microbiota on asthma and allergy development during the first years of life? What does your newest study add?

This is the first study where the role of mucosal immune responses towards the gut microbiota, in relation to childhood allergy development, has been addressed. By investigating the bacterial taxa that were targeted or not by IgA antibodies, we could confirm the importance of early life intestinal microbiota for later allergy

development. We saw that the children who subsequently developed allergies had a lower fraction of IgA antibodies bound to their intestinal bacteria at one year of age compared to those children who stayed healthy. This was particularly manifested in children who developed asthma during the first seven years of life. We could also detect the differences in the types of bacteria that were targeted by the immune system of these two groups of children, as early [as] one month of age. These interesting results are suggesting that the barrier function of the mucous membranes is less effective

in children who develop allergies later in life and that this can be monitored already during the first year after birth.

What is the role of the mother's immune system and breastfeeding in childhood allergy development?

Studies and clinical reports suggest that secretory IgA that [originates] from the mother's breast milk is important for immune regulation and protection against many infections in suckling infants. In this study we were interested to note that the differences in intestinal microbiota IgA responses were

SELECTED CONTENT

Role of gut microbiota diversity in protection from asthma and allergy development

obvious in infants as young as one month. This was surprising since the IgA antibodies in children that young come largely from the mother, through breast milk. Moreover, all the infants included in the study were exclusively breastfed until at least one month of age. So it seems that the immune response of the mother and the antibodies that the child receives in breast milk are connected with the development of allergies. This is something we want to look at in more detail in future work.

Based on your study, what kind of potential interventions do you suggest to combat the current asthma and allergy epidemic?

We are still far from understanding what is defining a healthy gut microbiome that promotes tolerance and prevents allergy development. I would say that the interventions enhancing infant mucosal barrier function, such as prebiotic/probiotic supplementation

and [encouraging] exclusive breastfeeding during the first months of life (6 months according to the WHO guidelines), may represent efficacious preventive strategies required to combat the asthma and allergy epidemic. Also, we should work on reducing the use of antibiotics and encourage children to play outside, thus increasing the microbial exposure important for healthy immune system development.

What further steps are you planning to take in the way of using gut microbiota as a biomarker for identifying infants with increased risk of asthma and allergic disease?

We think that the early characterization of IgA coating patterns of intestinal microbiota may represent a possible way to identify infants with increased risk to develop asthma and allergic disease later in life. Although this needs to be confirmed in larger

cohorts, it paves the way to develop diagnostic kits to identify children with high risk so preventive strategies, including those aiming to enhance gut diversity, can be directed towards that population group. Also, it would be of great interest to detect what factors in breast milk, reflecting the immune response of the mother, are connected with the development of allergies. This is something we are planning to investigate in more detail.

We should work on reducing the use of antibiotics and encourage children to play outside, thus increasing the microbial exposure important for healthy immune system development.



Read the original post online at:

<http://www.gutmicrobiotaforhealth.com/en/role-gut-microbiota-diversity-protection-asthma-allergy-development/>

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Mouse study shows maternal microbiota shapes offspring's immune system

Published on May 18, 2016 by Andreu Prados



Andreu Prados holds a Bachelor of Science Degree in Pharmacy & Human Nutrition and Dietetics. Science writer specialised in gut microbiota and probiotics, working also as lecturer and consultant in nutrition and healthcare.

A recent study, led by Prof. Andrew Macpherson from the University of Bern (Switzerland), has found in mice that maternal microbiota and immunity strengthen the immune system of the newborn.

Although it is a well-known fact that a newborn's gut microbiota can affect its own immune system, little is known about the impact of the maternal microbiota on her offspring's immune development. By transiently colonizing pregnant female mice with gut bacteria, Gomez de Agüero *et al.* studied whether the maternal microbiota in pregnancy affects the early postnatal immune system of the offspring. The researchers used a system in which pregnant females were transiently colonized with genetically engineered *Escherichia coli* HA107, a strain that dwindles over time in the intestine and thus allows pregnant dams to become germ-free again before they give birth.

Compared to offspring born to germ-free female mice, the pups born to colonized mothers showed increased numbers of certain innate leukocytes and different patterns of gene expression in their guts. Maternal microbial exposure during pregnancy increased small intestinal innate lymphoid cell (ILC) and intestinal mononuclear cell (iMNC) proportions and total numbers compared with germ-free controls. This increase reached a

maximum at 14 and 21 days after birth and persisted until at least 8 weeks of age in the colon.

Similar effects on early postnatal innate leukocytes were seen when pregnant dams were temporarily colonized with a cocktail of eight other microbes. After gestation-only colonization, B and T cell relative or absolute populations were not affected. Interestingly, maternal gestational colonization caused increased expression of several genes, including those that influence epithelial cell division and differentiation, mucus and ion channels, epithelial immunoglobulin transport, and metabolism of dietary xenobiotics and bile acids, complex lipids, and sugars. These results suggest that the changes in mucosal transcriptional and metabolic signatures after maternal gestational colonization were part of a wide range of adaptations triggered by maternal exposure to intestinal microbes.

By transferring serum from bacteria-colonized pregnant mice to germ-free pregnant mice, the researchers found that maternal antibodies were required for gestational colonization effects.

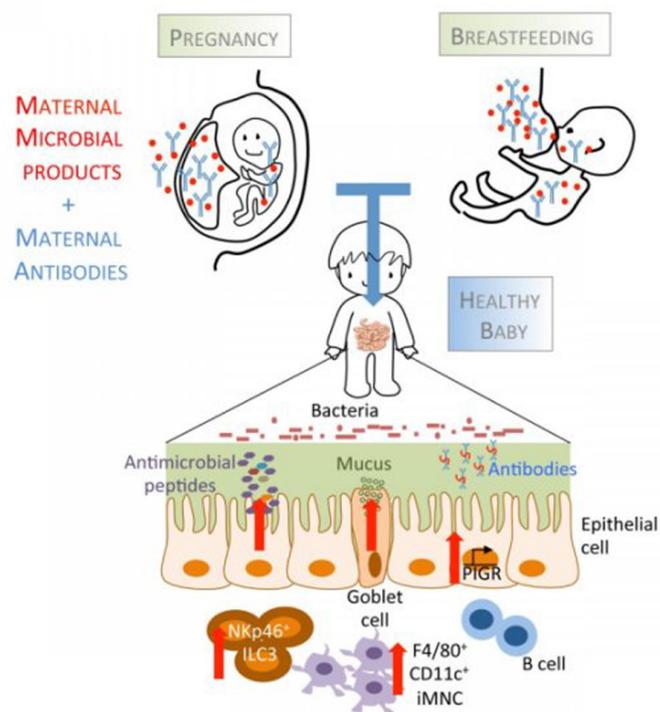
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Maternal microbiota-derived compounds were transferred to maternal tissues and subsequently to the offspring and this process was increased in the presence of maternal antibodies. In addition, the researchers demonstrated that maternal antibodies enhanced the retention and transmission of microbial molecules. Maternal microbial molecules were bound to maternal IgG after intestinal exposure and therefore transferred to offspring across the placenta and through intestinal uptake from the milk. Maternal microbial molecules reached neonatal tissues such as the small intestine, liver, and spleen, and functionally protected them by limiting inflammatory responses to microbial molecules and penetration of intestinal microbes.

To sum up, during gestation, the maternal microbiota shaped the offspring's immune system and prepared it for participating in a host-microbial mutual relationship. Maternal antibody-mediated transfer of bacterial products was required for gestational colonization effects.

Shaping of the immune system starts with the MATERNAL microbiota



A graphical abstract of our findings. This material relates to a paper that appeared in the March 18, 2016 issue of *Science*, published by AAAS. The paper, by M. Gómez de Agüero at University of Bern in Bern, Switzerland, and colleagues was titled, "The maternal microbiota drives early postnatal innate immune development."

CREDITS: MERCEDES GÓMEZ DE AGÜERO, STEPAHNIE GANAL-VONARBURG, KATHY D. MCCOY AND ANDREW J. MACPHERSON



Reference:

Gomez de Agüero M, Ganal-Vonarburg SC, Fuhrer T, *et al.* **The maternal microbiota drives early postnatal innate immune development.** *Science*. 2016;351(6279):1296-302.



Read the original post online at:

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Benefits of breast milk go beyond infant nutrition

Published on June 15, 2016 by Andreu Prados



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It is well-known that breastfeeding is the gold standard of infant nutrition, as breast milk contains protective nutrients for the growth and development of infants and may have a protective effect against long-term diseases including obesity, asthma, celiac disease, and allergies. A recent review, published by Dr. Thierry Hennet and Dr. Lubor Borsig from the Department of Physiology and Centre for Integrative Human Physiology at University of Zürich (Switzerland), describes the up-to-date data regarding the unique biology of human breast milk as a multifunctional fluid.

Humans may have the most complex breast milk of all mammals. It comprises close to 200 different oligosaccharides, far above the average 30-50 found in other mammals. Not only do human milk oligosaccharides act as prebiotics, but they also exert antimicrobial functions by acting as soluble receptors for harmful bacteria and viruses, which inhibit them to infect the host. Researchers still don't know the role of each of these sugars and the reason why their composition changes during breastfeeding, but authors of the review suggest that oligosaccharides are likely linked to the development of the gut microbiota and the training of the mucosal immune system.

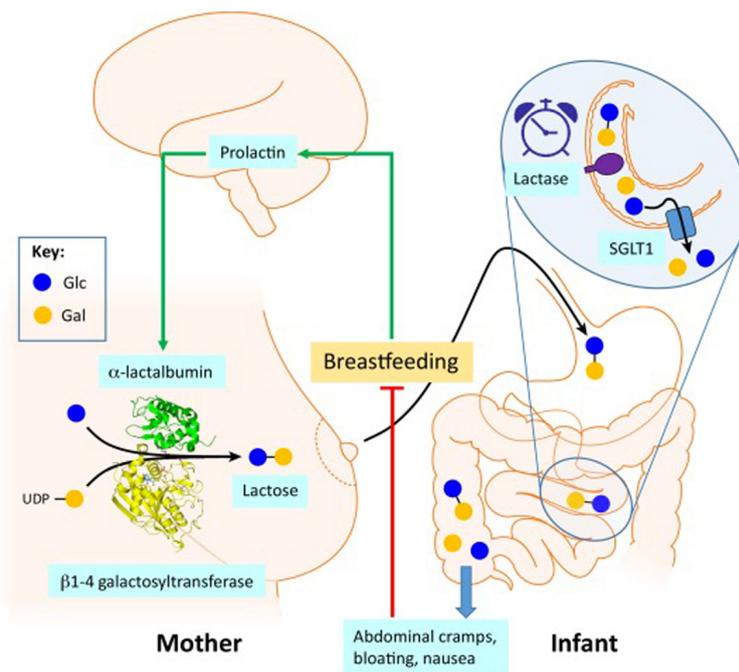
Breast milk acts as a fertilizer for bacteria, favouring the colonization of the newborn gut by specific bacterial groups that can digest breast milk oligosaccharides. In fact, complex milk oligosaccharides -which are higher in colostrum than in mature milk- cannot be digested

by the suckling infant and reach the large intestine, where they are assimilated by selected bacterial taxa including *Bifidobacterium* spp. and *Bacteroides* spp. Gut bacteria have preferences for specific milk oligosaccharides and, therefore, interindividual variability in maternal milk oligosaccharides may affect the pattern of bacterial colonization in the neonatal gut.

A recent study, led by Prof. David A. Mills from the Department of Food Science and Technology at the University of California at Davis, has found that oligosaccharide structures released from mother's milk and cow's milk can serve as a sole source for the selective growth of *Bifidobacterium* species. The researchers have demonstrated previously that glycoproteins from human milk (i.e. compounds with both protein and oligosaccharides) may be a source of nourishment for the beneficial microbes in the infant gut. They have also showed that *Bifidobacterium longum subsp. infantis* (*B. infantis*) expressed

SELECTED CONTENT

Benefits of breast milk go beyond infant nutrition



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constitutively an enzyme called EndoBI-1 (a kind of *N-acetylglucosaminidase*) that could split the *oligosaccharides* away from the glycoproteins. However, there was no definitive answer as to which component of the glycoproteins (either protein or sugar molecules) was supporting growth of *B. infantis*, which is a key infant gut microbe. In the new study, the researchers showed that *B. infantis*-produced EndoBI-1 enzyme is able to harvest specific sugar compounds that are obtained from human breast milk and bovine colostrum. These sugar molecules, named EndoBI-1-released N-glycans, supported the rapid growth of

Bifidobacterium longum subsp. longum, *B. infantis*, *B. breve* and *B. bifidum*, which consumes these released N-glycans as a sole carbon source. However, the oligosaccharides from the cow's milk did not support growth of *Bifidobacterium animalis subsp. lactis*, which is found in the human gut. Noticeably, released N-glycans enable more rapid bifidobacteria growth than the conjugated form. Prof. Mills noted that *B. infantis* has many genes involved in breaking down glycoproteins in mother's milk in order to release the oligosaccharides. The study also showed that *B. infantis* does not grow on the deglycosylated milk

protein fraction, clearly indicating that the oligosaccharides provide the key substrate for growth. On the whole, this study points out that oligosaccharides from milk may serve as selective substrate for the enrichment of infant bifidobacteria. Also, the findings suggest that N-glycans released from bovine milk glycoproteins may serve as a novel prebiotic substrate for infants.

Human breast milk also delivers immune-active compounds (such as immunoglobulins, cytokines, defensins, and lactoferrin, among others) to the infant gut. These bioactive proteins help establish the baby's immune system by contributing to innate immune protection and maturation of mucosal immunity, preventing pathogenic bacterial overgrowth and inducing tolerogenic responses towards structurally related mucosal glycans. As an infant's immune system matures further, there is a decrease in the levels of maternal antibodies of up to 90%, and a decrease in the diversity of breast milk sugars, whereas mature milk has proportionally high levels of lipids and caseins.

Several hormones in breast milk (e.g., leptin, adiponectin) affect metabolic pathways and support the growth and development of the suckling infant. Beyond providing protective compounds as discussed above, breast milk also may transmit environmental lipophilic contaminants and a few pathogens,

SELECTED CONTENT

Benefits of breast milk go beyond infant nutrition

such as human immunodeficiency virus (HIV) and cytomegalovirus (CMV), to the suckling infant. Newborns from CMV-positive mothers are protected prenatally, whereas in the case of HIV, transmission of the virus has been reported in up to 40% of mother-infant pairs.

Regarding the role of the newborn's immune system in tolerating gut microbes, until now it has been thought that IgA antibodies supplied by breast milk are primarily responsible for it in early life. A recent study, led by Dr. Gregory Barton from the Department of Molecular and Cell Biology at University of California, Berkeley (USA), has demonstrated in mice that IgG antibodies acquired from breast milk help limit immune responses to newly encountered microbes early in life to a greater extent than do IgA antibodies. Maternal transmission of microbiota-specific IgG antibodies starts as early as 2 weeks of age and they are acquired from mothers after birth. Besides this, maternal transmission of IgG coordinates with IgA to limit mucosal T cell

responses against commensals and reinforce intestinal immunity in neonates. As abnormal immune responses against beneficial gut microbes may lead to disease, the researchers mention that characterizing the immune response to gut microbes may offer new insights for assessing an individual's risk for inflammatory intestinal disorders and implementing early therapeutic interventions.

Additional health benefits of breast milk are often overlooked: those that extend to the nursing mother. Recent data presented in the Hennet, *et al.* review demonstrate the functional complexity of breast milk bioactive components, including immunoglobulins, cytokines, antimicrobial proteins, hormones, and oligosaccharides, which work together to fortify mucosal immunity, shape the gut microbiota, stimulate body growth, and even regulate birth spacing in mothers.

Researchers are careful to note that these findings do not translate directly into specific breastfeeding

recommendations. "Despite the many functions of breast milk, children can grow up healthy with limited supplies or without ever being exposed, raising controversial questions about what is normal when it comes to the length of breastfeeding," stated a press release related to the study by Hennet, *et al.* "Breast milk is the product of millions of years of evolution and certainly possesses the optimal nutrients for a newborn, but the question is how long does the newborn really need this supply? We feel families should make that decision, and not scientists," said study co-author Lubor Borsig.

In conclusion, human breast milk comprises a complex composition of protective compounds for the infant. Although a few of them have been characterized and well studied, further research is needed to depict a clear picture of the role of protective factors provided by breast milk in influencing the mucosal immune system and the intestinal microbiota.



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SELECTED CONTENT

Clinical implications of recent study exploring ‘microbial restoration procedure’ for caesarean-born infants

Published on April 20, 2016 by Kristina Campbell.



Science writer Kristina Campbell (M.Sc.), from British Columbia (Canada), specializes in communicating about the gut microbiota, digestive health, and nutrition. Author of the best selling Well-Fed Microbiome Cookbook, her freelance work has appeared in publications around the world. Kristina joined the Gut Microbiota for Health publishing team in 2014.

Mode of delivery is known to influence the microbiota composition of newborns. Vaginally-born infants develop a microbiota that resembles the mother’s vaginal bacterial community, while those born by caesarean section (C-section) have a microbiota that more closely resembles adult skin. C-section delivery—increasingly prevalent in many countries—is associated with a greater risk of obesity, asthma, allergies, and immune disorders, but it’s not known whether microbiota differences account for the increased risk.

A group of researchers from the USA and Puerto Rico recently conducted a pilot study on a technique aimed at ‘restoring’ the microbiota of caesarean-born infants. They studied eighteen infant-mother pairs: seven of the babies were delivered vaginally, and eleven by scheduled C-section. Of the C-section babies, four underwent the “microbial restoration procedure” and the others did not. The procedure involved incubation of sterile gauze in the vagina of the mother prior to the C-section; within the first two minutes of birth, each baby’s mouth, face, and body were swabbed with the gauze. Researchers sampled the anal, oral, and skin microbiota of the babies at six time points within the first month. Results were reported in *Nature Medicine*.

No adverse events were observed in this small cohort of C-section infants. Researchers found the bacterial communities in the gut, mouth, and skin of newborns who received the intervention were

enriched in vaginal bacteria that were underrepresented in the infants who hadn’t received the intervention. For the infants who underwent microbial restoration, the similarity of their microbiomes to those of vaginally delivered infants was high in the oral and skin samples and lower in the anal samples. Since all the women breastfed, diet was not considered a confounding factor.

Authors concluded that the complement of vaginal microbes was partially restored at birth in infants who received this intervention. They speculated that full restoration of the vaginal microbiota was not achieved because of the antibiotics that accompany C-section procedures, or because of suboptimal bacterial transfer from vagina to gauze and from gauze to baby. They also noted that this preliminary data is not enough to justify implementation of the microbial restoration procedure on a large scale.

SELECTED CONTENT

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In a published comment on the paper, Alexander Khoruts wrote that the technique, “although clever in its simplicity, does seem to require optimization.”

GMFH editors reached for comment Dr. Allan Walker of Harvard Medical School (USA), who was not involved in the study. Says Walker, “This is a very preliminary publication... [that has found] the ability to transiently demonstrate the presence of vaginal bacteria in C-section babies exposed to maternal vaginal microbiota. No long term affects are provided, there is no evidence whatsoever that this does in fact affect the incidence of either immune mediated or metabolic disease.”

Walker also notes that vaginal birth is complex, as infants born in this way are exposed to their mothers’ intestinal microbiota as well as their mothers’ vaginal microbiota. The gut microbial communities of the mothers were not tracked in the recent study.

A news article from Imperial College London (UK) reported that patient requests for this ‘vaginal seeding’ procedure are growing, despite expert opinion that the technique is not ready for widespread use. In a recent BMJ editorial, Dr. Aubrey Cunnington and colleagues warned against implementing the procedure, arguing the small risk of harm is not justified unless there is clear evidence of benefit to the infant. The authors highlighted the possible risk of infant infection from exposure to vaginal bacteria such as group *B streptococcus*—a particular concern in countries where pregnant women are not routinely screened.

Researcher Rob Knight, who has publicly discussed carrying out this technique surreptitiously with his own daughter after her C-section birth, defended vaginal seeding in a recent opinion article in *The Scientist*, noting “the challenge of evidence-based parenting.”

Indeed, in Cunnington’s BMJ article he and co-authors acknowledge the vaginal seeding procedure is transparent and parents may decide to carry it out themselves. In these cases, they say, “we should respect their autonomy but ensure that they are fully informed about the theoretical risks.” They advise keeping lines of communication open: if an infant becomes unwell, health professionals should not hesitate to ask about vaginal seeding and parents should not hesitate to mention they performed it.

Walker says there is much work to do before justifying the procedure clinically. He says, “At this point the only thing that could be suggested [is] further studies in larger numbers over a long period of time and that this should not be at the moment recommended routinely for C-section delivered infants.”



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How the transition to family foods may influence infant gut microbiota development

Published on April 18, 2016 by Andreu Prados



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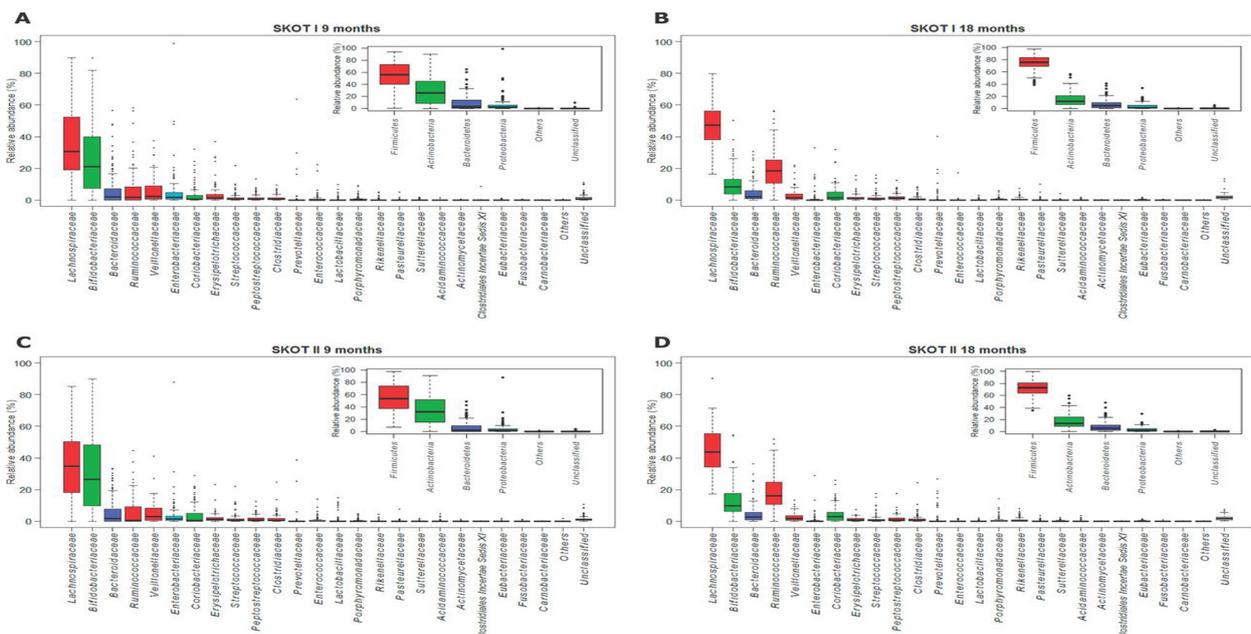
A recent study, led by Dr. Tine Rask Licht, head of the Research Group for Microbiology and Immunology from the National Food Institute at Technical University of Denmark, found that the development and establishment of the infant gut microbiota at 9 months of age is primarily driven by the transition to family foods, independently of maternal obesity.

The first 3-5 years of life represent the most critical period for dietary interventions to improve child growth and development, as during this period the intestinal microbiota is established. To shed light on the impact of maternal obesity and dietary factors such as breastfeeding and complementary diet composition on infant gut microbiota development, the researchers compared the gut microbiota of two different cohorts of Danish infants: those born to normal-weight healthy mothers (n = 114) and those born to obese mothers (n = 113). Faecal samples were obtained at 9 and 18 months of age. Infants' anthropometry and body composition were also measured. Infant diet was recorded by parents at the age of 9 months using validated 7-day food records. Furthermore, information on sex, socioeconomic, prevalence of C-section, gestational age at birth, prior use of antibiotics and other medications, duration of exclusive and total breastfeeding, and age of introduction to complementary feeding were also collected from parental background interviews at the 9 and 18-month-old visits.

Within-sample and between-sample diversity of the gut microbiota in the two cohorts changed over time, while maternal obesity per se did not impact gut microbiota development. The mode of delivery, gestational age at birth, and the use of oral antibiotics during the 2 weeks before sampling had limited influence on gut microbial diversity at 9 or 18 months. Infants from normal-weight healthy mothers were breastfed significantly longer than infants from obese mothers. Interestingly, the duration of exclusive breastfeeding (0 to 6 months) was associated with increased abundance of specific bacterial taxa at 9 months of age, and this was more noticeable in infants born to healthy mothers. In both cohorts, bacterial species that are involved in degrading plant-derived fibres and resistant starch in solid foods were negatively affected by the duration of exclusive breastfeeding. However, positive correlations with exclusive breastfeeding were observed in both cohorts for *Bifidobacteriaceae* (which utilize both lactose and oligosaccharides found in breast

SELECTED CONTENT

How the transition to family foods may influence infant gut microbiota development



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milk) and *Veillonellaceae* (which are considered lactate-degrading bacteria). Besides this, the effects of breastfeeding on microbial composition were limited at 18 months of age. On the other hand, the timing of introduction of complementary (solid) foods (3 to 6 months) did not correlate with gut microbial composition during late infancy.

Based on the infant diet recorded by parents at the age of 9 months, the transition from early infant

foods to foods introduced in late infancy with higher protein and fibre content correlated with increased gut microbiota diversity, thus suggesting that this progression to more nutritionally diverse family foods is a major driver of gut microbial changes during late infancy.

Although these results show that gut microbiota composition is correlated with the dietary patterns during late infancy, the researchers could not link microbiota composition to any

health differences in the infants. Thus, it does not yet have clinical implications.

In conclusion, introduction of family foods with higher protein and fibre content may be considered the main driver of infant gut microbiota development at 9 months of age. "Until now nobody has addressed the effect of diet at his age. We found that the food determines the diversity and the composition of the microbiota, and this is very important," says Professor Licht.



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Long-term follow-up shows safety of perinatal probiotic administration

Published on April 24, 2017 by Andreu Prados



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The prevalence of non-communicable diseases, also known as chronic diseases, is increasing worldwide and altered gut microbiota has been related to their early onset. Probiotic intervention during the perinatal period has been proposed as a way to reduce the risk of some of these diseases, but long-term efficacy and safety studies are lacking.

A recent study, led by Dr. Erika Isolauri, a professor of paediatrics at the University of Turku and chief physician at the Department of Paediatrics at Turku University Hospital in Finland, has found that perinatal probiotic administration is safe and may have the long-term effect of decreasing allergy prevalence.

The researchers combined data from four double-blind, randomized, placebo-controlled trials conducted in a single tertiary centre in Turku, Finland, between 1997-2012 (with 10-15 years of follow-up). Studies I (here) and IV (here) used *Lactobacillus rhamnosus* strain GG alone in the probiotic group (LGG and LGG ATCC 53103, respectively). Study II (here) used both *Lactobacillus rhamnosus* strain GG ATCC 53103 and *Bifidobacterium lactis* Bb12 in the probiotic group, whereas the study III (here) used two kind of probiotic combinations: *Lactobacillus rhamnosus* LPR + *Bifidobacterium longum* BL999 and *Lactobacillus paracasei* ST11 + *Bifidobacterium longum* BL999.

Outcome measures included diagnosis of asthma, allergic rhinitis, or atopy based on ISAAC criteria, and overweight or obesity defined by international age- and sex-specific body mass index cutoffs. Included children had a heightened allergy risk (atopic disease in a first-degree relative) or preterm birth and were seen at baseline and at a 2-year follow-up visit.

Altogether 303 mother-infant pairs (placebo group: n = 140; probiotic group: n = 163) were included in the analysis. Children receiving perinatal combined probiotics (combined probiotic group) showed no differences in allergic disease (atopic eczema, allergic rhinitis, food allergy, or asthma) prevalence compared to placebo. However, a subgroup of the probiotic group consisting of 133 children receiving LGG as a single strain or LGG mixed with other probiotics (the LGG group) had a significantly ($p=0.048$) decreased prevalence of allergic disease (59 of 133, 44.4%), as compared to placebo

Children who regularly consumed probiotic-containing products showed a tendency to a decreased risk of overweight.

SELECTED CONTENT

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(79 of 140, 56.4%). The perinatal probiotic intervention proved safe in long-term follow-up.

The prevalence of asthma, food allergy, allergic rhinitis and atopic eczema in the children receiving probiotics perinatally was not statistically different from that

in children given placebo. Breastfeeding for 6 months or longer was related to a decreased risk of overweight. Besides this, children who regularly consumed probiotic-containing products showed a tendency to a decreased risk of overweight.

In conclusion, perinatal probiotic administration is safe in long-term follow-up. LGG administered alone or in combination with other defined probiotics may lead to a lower risk of developing allergic disease.



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