GUT MICROBIOTA
RESEARCH & PRACTICE
edited by ESNM

YEAR AT A GLANCE

A selection of content from the
Gut Microbiota for Health 2019

January 2020

www.gutmicrobiotaforhealth.com

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EDITORIAL

Rene van den Wijngaard

GMFH Editorial Head
Rene van den Wijngaard is a scientific staff member in the Department of Gastroenterology and Hepatology at the Amsterdam UMC and carries out his research activities at the Tytgat Institute for Liver and Intestinal Research. His focus is on the role of mast cells and gut fungi/yeast in abdominal pain complaints of irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD).

Important progress has been made in 2019 in our understanding of the gut microbiome. Key developments include how host-microbe symbiosis is established in early life; translational advances of research into probiotics and prebiotics; gut microbiota-mediated mechanisms by which diet and cooking affect health; and metagenome-mining efforts to use the microbiome as a tool for precision diagnosis and personalized treatment strategies.

Gut microbial colonization starts early in life and may have an impact on the neonatal microbiome and health and disease in later life by programming immune and metabolic pathways. A particular focus of interest in 2019 has been the elucidation of how maternal and infant factors shape milk microbiota composition. For instance, in addition to other known factors such as maternal body mass index and mode of delivery, Moosavi and colleagues found that the method of breastfeeding also shapes milk microbiota diversity. Moreover, the finding that human milk oligosaccharides are also present in maternal serum suggests their systemic implications for both maternal and fetal health.

When it comes to tools for manipulating the gut microbiome, with the huge amount of scientific literature in the field, it's difficult to keep abreast of the clinical implications of studies into probiotics and prebiotics. Five of the world's leading scientists in the field have published a narrative review that summarizes the clinical application and use of prebiotics and probiotics (in terms of efficacy and safety) in humans, including their mechanisms of action and future goals. In addition to intestinal health, *Akkermansia muciniphila* has been shown to alleviate metabolic syndrome in a pioneering pilot study and *Bifidobacterium longum* 1714 has shown its modulatory role in brain function in response to social stress in healthy adults.

Diet has been the most widely studied modifiable factor for shaping the gut microbiome. But as nutrients are rarely consumed in isolation, scientists are moving toward examining the ability of dietary patterns to modulate the intestinal microbiota under both physiological and pathological conditions. Despite the popularity of some diets that are upheld as means of ensuring optimal gut health (e.g. the low-FODMAP diet),

the science-based long-term effects of such diets are unknown. As such, the gut microbiome might help provide a better understanding of the whole picture in terms of how these diets affect our health. Furthermore, in addition to nutrient composition, scientists have found the way we cook food also contributes inter-individual variation to the gut microbiome.

Studies integrating microbiome analyses with other 'omics' data sets and clinical data have also been published in 2019. Nowadays, accurate diagnosis and treatment of patients with gut-related diseases such as irritable bowel syndrome, inflammatory bowel diseases and colorectal cancer remain a challenge because approaches are based largely on clinical criteria. As such, integrating the personalized modulation of the gut microbiome into this scenario might help with precision disease prevention, diagnostics and response to treatment. However, it is still unclear whether gut microbiome imbalances precede or are a by-product of disease development.

Our digital community grew this year to exceed **80,000 members**, including scientists, healthcare professionals and the general public. In 2019, the GMFH website had more than **1,160,000 visits** and was, for the third year in a row, selected as one of the best gut health blogs by Healthline, a consumer health information website with over 65 million readers per month. Additionally, GMFH Twitter accounts (@GMFHx and @GutMicrobiotaWW) and Facebook page have been verified through the blue badge, which is a way to let people know that an account of public interest is authentic.

With the aim of keeping professionals updated with the main themes in gut microbiota science in 2019, GMFH arranged sessions on gut microbiota and nutrition at two international dietetics conferences this year: the 13th FENS European Nutrition Conference 2019 in Dublin (Ireland) and the 12th European Federation of the Associations of Dietitians (EFAD) conference in Berlin (Germany).

The 8th edition of the annual Gut Microbiota for Health World Summit, held in Miami in March, updated clinical researchers and healthcare professionals with the latest research on diet, nutrition and the gut microbiome.

As a platform devoted to sharing information about gut microbiota, we'll continue promoting the debate in 2020, while providing updates regarding the latest news about human-gut microbiome symbiosis and modulation of the gut microbiota as both a preventive strategy and a therapeutic option in different gastro-intestinal and systemic diseases. The 9th edition of Gut Summit, which will take place on March 7 and 8 2020 in Madrid (Spain), promises an equally illuminating overview of gut microbiota science, with topics ranging from dietary and non-dietary factors shaping the gut microbiome to its clinical applications. So be sure to stay in touch with GMFH to find out more about the latest studies and connect with the experts around the globe who are driving this field forward.

Last, but not least, on behalf of the rest of the GMFH team and myself I would like to acknowledge Prof. Paul Enck for his committed work and contributions as the editorial head since the launch of the project in 2012. Since the last October I have been occupying the position of the editorial head of GMFH publishing team.

> "Diet has been the most widely studied modifiable factor for shaping the gut microbiome. But as nutrients are rarely consumed in isolation, scientists are moving toward examining the ability of dietary patterns to modulate the intestinal microbiota under both physiological and pathological conditions."

When do bacteria first colonize the body? How host-microbe symbiosis is established in early life and its impact on neonatal health

Published on December, 9, 2019 by Joël Doré

The symbiotic relationship between host and microbes starts early in life and is important not only in terms of how the neonate microbiome ultimately develops, but also its potential impact on long-term infant health.

A current ongoing debate within the scientific community is whether gut colonization starts during pregnancy or at birth. Indeed, the crucial question of when bacteria first colonize the body has yet to be answered.

Microbial transfer at the feto-maternal interface

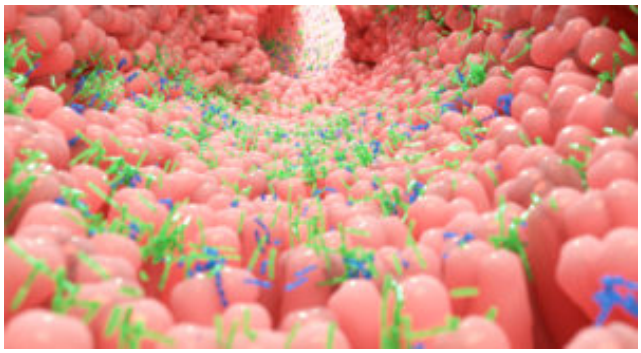
For long time, prevailing scientific dogma stated that neonates are born sterile and only upon delivery are they populated by microorganisms. For instance, in 1900, French pediatrician Henry Tissier declared: "The fetus lies in a sterile environment."

Things changed in 1982, however, when a study found bacteria in the placenta. That discovery prompted scientists to accurately corroborate these findings.

By using both conventional culturing techniques and 16S ribosomal RNA gene and/or metagenomic sequencing in animal studies and humans in the mid-2000s, bacteria were also detected in what had been presumed to be sterile tissue from healthy term neonates. These included the placenta, amniotic fluid and meconium.

Contrary to initial belief, therefore, the evidence of bacterial presence in fetal membranes and in newborns' first stool would not necessarily be a sign of infection. Furthermore, no distinction is made in this regard between premature infants and matched controls, which, in turn, might support the existence of a placenta microbiome in healthy pregnancies.

Other species such as clams, tsetse flies and turtles appear to inherit a mother's microbiome before birth. It is therefore no surprise that humans may also have microbes *in utero*.



Major caveats remain, however, making it difficult to prove the existence of a fetal-maternal microbiome. For instance, it is unclear which route microbes use to enter the intrauterine space, with their origin thought to be the mother. Furthermore, scientists leading this field remain uncertain about whether the organisms are viable or if free DNA is being detected, and it is unclear to what extent those bacteria are temporary passengers of the fetus or indeed residents in the fetal gut.

Contamination of the samples is also plausible. To tackle this issue, scientists have recently provided evidence of fetus exposure to bacterial DNA —it remains unclear whether this originates from viable or dead bacteria— and metabolites prior to birth beyond the level of background contamination.

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How the transfer of commensal organisms from the maternal gut to blood and systemic locations mechanistically occurs has been largely explored in mice, showing that maternal gut microorganisms migrate to various locations, including the mammary gland via an endogenous cellular route (called the bacterial entero-mammary pathway), taking place mainly during late pregnancy and lactation. These findings suggesting that transporting bacterial components from the gut to both blood and breast milk cells is possible, probably in the form of non-viable bacteria vectorized by immune cells, was formerly proposed from a study in mother-infant pairs. As such, this could program the neonatal immune system to better tackle the challenge of sorting out pathogens and commensal organisms.

There is also evidence of the impact on offspring development of symbiotic interactions between the mother and gut microbiome. In this regard, Elaine Hsiao and colleagues showed that injecting pregnant dams with a mock virus yielded offspring that exhibited autism-like symptoms. Such behavioral abnormalities in the offspring of maternal immune activation in mice were accompanied by defects in intestinal integrity and alterations in gut microbiota composition.

From an evolutionary perspective, it has been hypothesized that microbes may have influenced host sociability and behavior through the known microbiota-gut-brain axis as a way to propagate their own genetic material.

Other host-related and environmental factors such as maternal obesity and weight gain and exposure to environmental factors such as a high-fat diet and non-nutritive sweeteners may also affect infant microbial colonization and health programming later in life.

Thus, gut colonization during the perinatal period, especially during the first 2 to 3 years of life, is influenced by multiple biological and environmental factors and provides a window of opportunity to potentially reduce the risk of chronic diseases in childhood and later life.

Birth as the major microbial encounter

Although data exists regarding gut colonization before birth, some scientists remain skeptical and argue that the presence of bacterial DNA in presumably sterile fetal tissues such as the placenta does not lead to the establishment of the seed of the human microbiome before birth.

It is widely accepted that humans' first exposure to microbes occurs in the birth canal. After delivery, maternal peripheral blood mononuclear cells and human breast milk cells contain the genetic material of a wide range of gut microbes, some of which are also found in infant feces.

At birth, newborn babies experience rapid colonization by microbes from their mothers and the surrounding environment. Delivery type is a critical factor involved in establishing the infant gut microbiota. Epidemiological studies indicated that cesarean section birth may come with a slightly increased risk of developing allergies and later obesity. Recent research has revealed that, compared with vaginal delivery, cesarean sections may predispose individuals to opportunistic infections.

Scientists have found no differences in the bacterial DNA recovered from placenta samples (of preterm infants and those of babies born at term) from that found on commercial reagents. Therefore, given that the placenta has a low bacterial biomass, it is also plausible that the bacterial DNA identified may derive from contamination through dust or commercial reagents.

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More recently, an analysis of placental samples from more than 537 women, with either complicated or uncomplicated pregnancies, showed that the placenta was unlikely to be the major source of the infant microbiota. An experimental approach consisting of the use of two different kits for DNA extraction and different molecular methods to detect bacterial DNA allowed to reduce the chance of false-positive results due to contamination. The fact that almost 5% of placenta samples collected before labour contained group B Streptococci, a major cause of sepsis in newborns, also reveals that bacterial infection of the placenta is not a frequent cause of adverse pregnancy outcome.

Meanwhile, the observation of a handful of microbes in the placenta, umbilical cord blood, amniotic fluid and meconium does not necessarily support the existence of a complex microbiome, like the ones found in other niches such as the gut or saliva. As with the study of the breast milk microbiome, characterizing microorganisms colonizing the fetus prior to birth requires sophisticated methodologies that distinguish resident microbes from those that temporarily colonize the sample.

On the whole, it is clear that host interaction with intestinal microbes either during pregnancy or during the immediate postnatal period may have a profound impact on the neonatal microbiome and health and disease in later life by programming immune and metabolic pathways. Compensating for the lack of exposure to maternal microbes upon cesarean section delivery by a simple gesture might prove beneficial. Targeting the development of host-microbes symbiosis in early life might also be considered as a means of preventing the uncontrolled rise in incidence of chronic diseases that current medicine is not able to cure.

Research Director at the Research Institute for Agriculture, Food and Environment, INRAE. Dr. Joël Doré is currently President of the Executive Committee of the Pre-Industrial Demonstrator MetaGenoPolis, a platform of excellence dedicated to quantitative and functional metagenomics, funded by the French government Futures Investments. He is Deputy Head of the MICALIS institute "Food and Gut Microbiology for Human Health" and scientific board member of Microbiology Pole of the Doctoral School "Therapeutic Innovations" at Paris-XI University. Joël Doré received his PhD from the University of Illinois at Urbana-Champaign, USA, in 1988. His main research interest is the molecular assessment of the human intestinal microbiota in health and disease and metagenomic investigation of the molecular cross-talk between intestinal bacteria and human cells. Dr. Doré has published >120 publications in peer reviewed scientific journals. His goal is to provide a better understanding of the intestinal ecosystem in order to support therapeutic choices in the medical area, as well as health claims for functional foods.

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Read the original post online at:
https://www.gutmicrobiotaforhealth.com/en/when-do-bacteria-first-colonize-the-body-how-host-microbe-symbiosis-is-established-in-early-life-and-its-impact-on-neonatal-health/

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A new study sheds light on maternal and infant factors that shape breast milk microbiome

Published on February, 25, 2019 by GMFH Editing Team

Just like other body parts and fluids in contact with the external environment, breast milk has its own microbiome that plays a key role in infant health by helping to establish a baby's gut microbiota. Over the past decade, new genomic techniques have increased our understanding of the human milk microbiome and the factors influencing its composition and activity. However, an in-depth study of maternal and early-life factors that affect the milk microbial community is lacking.

A new study, led by Dr. Meghan B. Azad from the Department of Pediatrics and Child Health at the University of Manitoba (Winnipeg, Canada), **explores how maternal and infant factors are associated with milk microbiota composition in nearly 400 mothers.**

The researchers used 16S ribosomal ribonucleic acid (rRNA) gene sequencing to profile the milk microbiota in 393 breastfeeding mothers and their infants from the CHILD birth cohort, which represents one of the largest studies of the human milk microbiota to date. The **women's milk microbiota profiles were highly variable and a core milk microbiota** —dominated by *Proteobacteria* and *Firmicutes* and consisting of four discrete clusters that might reflect different sources of exogenous milk bacteria— **was identified in all milk samples**.

On the other hand, the researchers explored the relationship between maternal and infant factors and milk microbiota diversity and composition, after adjusting for confounding factors relating to both mother and infant.

Milk microbiota diversity and composition were associated with maternal factors, including body mass index (BMI), parity, mode of delivery, mode of breastfeeding and several milk components.

Among the early-life and infant factors analyzed, having siblings and the sex of infants showed significant associations with milk microbiota composition. Maternal BMI and parity were associated with milk microbiota composition in a sex-specific manner,

whereas maternal atopy and smoking were associated with milk microbiota diversity in a phylum-specific manner.

In addition, milk components including human milk oligosaccharides' compositional profile and the profile of fatty acids found in milk were also relevant in determining milk microbiota composition. These non-bacterial milk components were found to be affected by maternal diet.

From the many factors examined, **the method of breastfeeding** in the two weeks preceding the collection of a breast milk sample for the study (indirect as at least one serving of pumped and stored milk versus exclusive direct breastfeeding) **was the most consistent factor related to milk microbiota composition when using different statistical analysis methods.**

The authors found that indirect breastfeeding was associated with a lower abundance of beneficial

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Bifidobacterium **and increased abundance of** ***Enterobacteriaceae*** **and potential opportunistic pathogens** ***Stenotrophomonas*** **and** ***Pseudomonadaceae*** (possibly pump-associated). In contrast, members of the Actinobacteria phylum and *Veillonellaceae* (a family member representative of the oral microbiota) were enriched with direct breastfeeding.

In addition, indirect breastfeeding was associated with lower overall milk microbiota richness and diversity when compared with direct breastfeeding.

The researchers suspect that pumping may prevent the transfer of oral bacteria from the infant to the breast milk microbiota, thus introducing other bacteria from the pump. **These findings show that milk bacteria may have its origins in the infant oral cavity.** This is in agreement with scientists who have previously shown the infant oral cavity as the origin of breast milk bacteria, while others believe breast milk bacteria originate in the mother's gut.

The same research group had previously found that modes of infant feeding other than direct breastfeeding —including breastfeeding with some pumped breastmilk— were less beneficial than direct breastfeeding in terms of the increased risk of asthma at 3 years of age.

In conclusion, this study has revealed maternal and infant factors involved in shaping milk microbiota composition. Of all the factors examined, the breast-feeding method was the most consistent factor associated with milk microbiota composition, which highlights the importance of considering this variable in future milk microbiome research.

These findings also highlight the importance of the infant's mouth as a source of bacteria in breast milk and this, together with maternal gut microbiota, contributes to explaining the origins of milk microbiota. Research monitoring and analyzing the long-term impact on infant health of factors affecting the milk microbiota will provide useful insights for the clinical setting.

> Milk microbiota diversity and composition were associated with maternal factors, including body mass index (BMI), parity, mode of delivery, mode of breastfeeding and several milk components.

Reference:
Moossavi S, Sepehri S, Robertson B, *et al.* Composition and variation of the human milk microbiota are influenced by maternal and early-life factors. Cell Host Microbe. 2019; 25:324-35. doi: 10.1016/j.chom.2019.01.011.

Read the original post online at:
https://www.gutmicrobiotaforhealth.com/en/a-new-study-sheds-light-on-maternal-and-infant-factors-that-shape-breast-milk-microbiome/

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An overview of prebiotics and probiotics' effects on health and their mechanisms of action

Published on September, 2, 2019 by GMFH Editing Team

With the huge amount of press coverage of the effectiveness of probiotics and prebiotics as a way to improve human health and wellbeing, it's difficult to keep abreast of everything that's going on in the field.

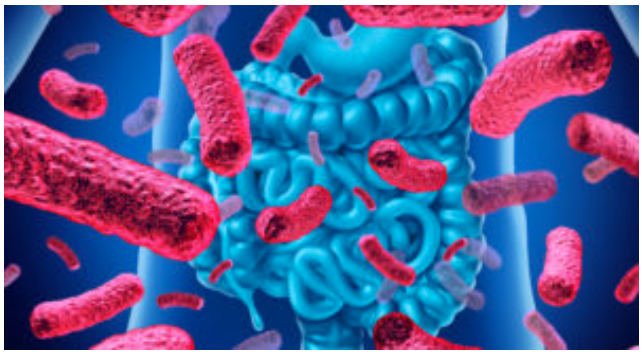
A recent narrative review, authored by five of the world's leading scientists in the field, summarizes the clinical application and use in humans of prebiotics and probiotics, including the mechanisms that drive their benefits for host health and future goals.

In terms of diet and their effect on health, prebiotics and probiotics are the most closely studied gut microbiota-targeted tools. Strains of *Lactobacillus*, *Bifidobacterium* and *Saccharomyces* have a long history of safe and effective use as probiotics. And the clinical benefits of probiotics in pediatric and adult populations can be seen in the following conditions:

- Necrotizing enterocolitis;
- Infantile colic;
- Neonatal sepsis;
- *Helicobacter pylori* infection;
- Defecation frequency and abdominal discomfort;
- Mild to moderate ulcerative colitis;
- Irritable bowel syndrome;
- Antibiotic-associated diarrhea;
- Acute diarrhea;
- *Clostridium difficile*-associated diarrhea.

The prophylactic and therapeutic effects of probiotics on these conditions can be mediated by modifying the gut microbiota composition or its function. This is done by involving antimicrobial production and cross-feeding and substrate transformation for other commensal microorganisms, which has been one of the most widely studied means by which probiotic microorganisms act.

Other probiotics mechanisms of action are also plausible and include interaction with host cells (e.g. modulating the immune system and improving intestinal barrier integrity), colonization resistance, and the formation of enzymes and neurochemicals.



In fact, probiotics may act through a wide range of mechanisms that are not necessarily related to a direct effect on the resident microbiota. This means that if a probiotic doesn't colonize the human digestive tract, that doesn't mean it is ineffective.

So what does the future hold? On the horizon lies the promise of newly constructed recombinant strains and next-generation candidate probiotics, which include *Roseburia, Akkermansia, Propionibacterium* and *Faecalibacterium* species.

As for prebiotics —defined as substrates that are selectively utilized by host microorganisms, conferring a health benefit— both glucans and fructans have shown their health benefits.

Nevertheless, the evidence for prebiotic intervention is weaker than that reported for probiotics. **Two of the most closely studied prebiotic indications include the**

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protection of formula-fed infants against infections when administered in infant formulas and improved bowel function in healthy adults.

The mechanisms of action by which prebiotics might confer health benefits have been tested via *in vitro* and animal models and include: defense against pathogens, immune modulation, increased mineral absorption, improved bowel function, metabolic effects and effects on satiety.

Other substrates such as polyphenols and polyunsaturated fatty acids might exert prebiotic effects and therefore show promise for the future. Promising outcomes of prebiotic application also include increased satiety, reduced energy intake and body fat mass, and improved post-prandial glucose responses.

In addition, the authors mention prebiotics and probiotics' applications beyond their gut-derived effects, including in the oral cavity, the vaginal tract and on skin. And consumption of vegetables rich in inulin-type fructans is associated with increased satiety and fewer cravings for sweet and salty foods in healthy adults.

A key take-home message from the authors is that the use of prebiotics and prebiotics by healthcare professionals and consumers should be evidence-based—preferably from randomized trials. As not all products have been validated and gut microbiota differences don't imply that modification will lead to improved health, it is important to keep updated on their clinical application and use, with any decisions supported by reliable research.

In addition, the authors highlight that research in the field should move from traditional probiotics to new targets (e.g. anti-adhesive molecules) and beneficial gut bacteria that aren't used nowadays as probiotics (e.g. butyrate-producers). Although the increased use of high-throughput sequencing technologies is widely used, considering the overall functional potential of the microbiome assessed by transcriptomic, metabolomic and proteomic analysis will also optimize clinical translation of the role of targeting gut microbiota for improving health.

> "In terms of diet and their effect on health, prebiotics and probiotics are the most closely studied gut microbiota-targeted tools."

Reference:
Sanders ME, Merenstein DJ, Reid G, *et al.* Probiotics and prebiotics in intestinal health and disease: from biology to the clinic. Nat Rev Gastroenterol Hepatol. 2019. doi: 10.1038/s41575-019-0199-6.

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Akkermansia muciniphila helps improve features of metabolic syndrome in overweight and obese subjects

Published on July, 15, 2019 by Patrice D. Cani

The gut microbiota has become a new player in the onset and development of metabolic syndrome and its associated pathologies. One gut bacterium that has been positively associated with leanness in mice and humans is *Akkermansia muciniphila*, which is naturally present in the gut microbiota of healthy people.

In 2017, our research team at UCLouvain (Belgium) found that a pasteurized form of *A. muciniphila* led to a stronger reduction in fat mass development, insulin resistance and dyslipidemia in mice when compared with the live bacterium. However, its effects on alleviating metabolic syndrome in humans are unknown.

A new randomized, double-blind, placebo-controlled pilot study, which I led with a team of researchers from UCLouvain and the Cliniques universitaires Saint-Luc, in collaboration with Wageningen University, University of Helsinki and the VIB-KU Leuven Center for Microbiology, reveals that **heat-inactivated *A. muciniphila* helps to limit the increase of different cardiovascular risk factors in subjects who are overweight and obese.**

We administered *A. muciniphila* for a 3-month period in 32 overweight or obese insulin-resistant subjects who were asked not to change their dietary habits or their physical activity. The subjects were given equal doses (10^{10} bacteria per day) of either live *A. muciniphila* or a pasteurized form of the bacterium obtained after exposure to mild heat inactivation. In a previous mice study, we showed that a protein (called Amuc_1100), isolated from the outer membrane of *A. muciniphila*, recapitulated the metabolic benefits reported after administration of pasteurized *A. muciniphila*.

Participants treated with the pasteurized —not the live— form of *A. muciniphila* had lower circulating insulin levels, reduced insulin resistance indices, lower total blood cholesterol and lower circulating

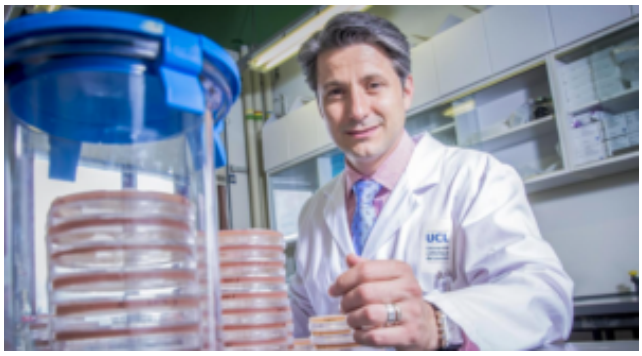

Image source: UCLouvain

dipeptidyl peptidase IV (DPP-IV) when compared with the placebo group. The enzyme DPP-IV has been involved in modulating glucose homeostasis, satiety and emotional-affective behavior.

Furthermore, **pasteurized but not live *A. muciniphila* reduced white blood cell counts** —their levels are elevated in obesity and have been associated with glucose intolerance— **and lowered the number of proinflammatory bacterial lipopolysaccharides**-involved in metabolic endotoxemia-circulating in the blood.

When compared with placebo, *A. muciniphila* also led to reduced levels of the liver inflammatory markers gamma-glutamyl transferase and aspartate amino-transferase and decreased levels of serum lactate dehydrogenase and creatine kinase, which are markers of tissue-damage and muscle injury.

Although we do not know why the pasteurized form of *A. muciniphila* seem to be more effective in alleviating metabolic syndrome when compared with the

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live bacterium, it seems plausible that mild heat inactivation allows cell-wall components or membrane proteins of bacteria to promote metabolic benefits in the host.

Our findings also demonstrated that *A. muciniphila* was safe and well tolerated across the study period of 3 months. These results are in agreement with previous findings from our research group.

This is the first exploratory study that shows how a bacterium naturally present in the human gut may alleviate metabolic syndrome. Although diet and physical activity are the major cornerstones for managing cardiovascular disease, our findings pave the way for using next-generation beneficial microbes such as *Akkermansia* and/or specific bacterial components to play a role in improving metabolic health in obese and overweight human subjects.

Our next steps include planning larger-scale tests and commercializing the bacteria in the form of food supplements.

See here a video from UCLouvain that summarizes main findings from our study.

> “Heat-inactivated *Akkermansia muciniphila* helps to limit the increase of different cardiovascular risk factors in subjects who are overweight and obese.”

Prof. Patrice D. Cani is group leader in the Metabolism and Nutrition lab at the Louvain Drug Research Institute (LDRI) at the Université catholique de Louvain (UCL) in Brussels, Belgium. He is investigator for the WELBIO (Walloon Excellence in Lifesciences and BIOtechnology). He is the author or co-author of more than 200 scientific publications, and has been elected associated member of the Royal Academy of Medicine of Belgium.

Reference:
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Read the original post online at:
https://www.gutmicrobiotaforhealth.com/en/akkermansia-muciniphila-helps-improve-features-of-metabolic-syndrome-in-overweight-and-obese-subjects/

SELECTED CONTENT

An expert panel helps end users identify high quality probiotics

Published on June, 10, 2019 by Mary Ellen Sanders

Many consumers and healthcare providers are aware that certain probiotics may be beneficial for health. But they sometimes have difficulty identifying high quality products in the marketplace.

What is a high quality probiotic product? It contains microbial strains that are properly identified, characterized and quantified, it meets specifications for purity, it is safe for its intended use, and it is manufactured in compliance with Good Manufacturing Practices appropriate for the category of the product. Further, to be called 'probiotic', the product must have been shown in controlled human trials to confer a health benefit.

A panel I chair under the auspices of the United States Pharmacopeia, recently collaborated on an expert opinion paper that **summarizes recommendations to companies producing probiotics, outlining proper standards in quality manufacturing processes and ways to communicate quality to end users.**

We recommend that probiotic producers undergo third-party evaluations to certify both probiotic quality and label accuracy. This use of a third party provides unbiased confirmation of product quality to end-users. Our paper describes the steps necessary for setting up the third-party certification of a probiotic product, in a process that is followed by established certification bodies:

- Submission of an application to the certification body.
- Submission of documents regarding facility statistics, a standard operating procedures index, an analytical methods index, a quality manual index, a hazard analysis, a critical control point plan and an allergen control plan.
- Quality management systems audit.
- Documentation review.
- Verification of all testing methods.
- Corrective or preventative actions.
- Formal issuance of the certification for the product.

These steps will assure the consumer about quality in manufacturing. To improve transparency to the end-user, some organizations offering third-party certification services authorize the use of a logo or seal that makes it clear that the specific probiotic has been manufactured following stringent conditions.

It should be noted that this process is separate from assessments of the strength of evidence supporting any health claims for a probiotic product.

The panel also calls for publicly available quality standards and methods for identifying the probiotic strain, quantifying viable probiotic cells throughout production and distribution, and ensuring purity. The definition of a probiotic implies that it must be a defined entity to allow for appropriate identification to the strain level, so the panel recommends quantifying specific strains in multi-strain probiotic products. Some of the emerging methodologies that may be useful for quality assessment thus include whole genome sequencing of the bacteria to confirm the probiotic identity.

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As both consumers and healthcare providers struggle to know which probiotics are backed by evidence, we recommend that the probiotic products available on the market conform to labeling standards advanced by the World Health Organization and the World Gastroenterology Organization:

- Genus, species and strain names.
- Statement of quantity (using colony forming units or another validated measure) of live/active micro--organisms through the use-by date. (Levels of live probiotics should be provided through the 'best by' or 'use by' date and not time of manufacture).
- Use by date.
- Statement of benefit: although it is not required, when present, it must be supported by a human study showing the benefit at the dose delivered in the product.
- Proper storage conditions.
- Company contact information.

Information can be found at these links on how to read a label on a probiotic food supplement sold in the European Union and the United States.

Overall, this new expert panel document aims to provide ways of showing probiotic quality standards to consumers so they can recognize high-quality products. Currently, this goes beyond regulatory requirements in many jurisdictions. But undergoing unbiased third-party certification is a straightforward way for probiotic companies to improve transparency when it comes to probiotic product quality.

> What is a high quality probiotic product? It contains microbial strains that are properly identified, characterized and quantified. Further, to be called 'probiotic', the product must have been shown in controlled human trials to confer a health benefit.

Mary Ellen Sanders is a consultant in the area of probiotic microbiology, with special expertise on paths to scientific substantiation of probiotic product label claims. Dr. Sanders served as the founding president of the International Scientific Association for Probiotics and Prebiotics (www.isappscience.org) and is currently the organization's Director of Scientific Affairs/ Executive Officer.

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Jackson SA, Schoeni JL, Vegge C, *et al*. Improving end-user trust in the quality of commercial probiotic products. Front Microbiol. 2019; 10:739. doi: 10.3389/fmicb.2019.00739.

Read the original post online at:
https://www.gutmicrobiotaforhealth.com/en/an-expert-panel-helps-end-users-identify-high-quality-probiotics/

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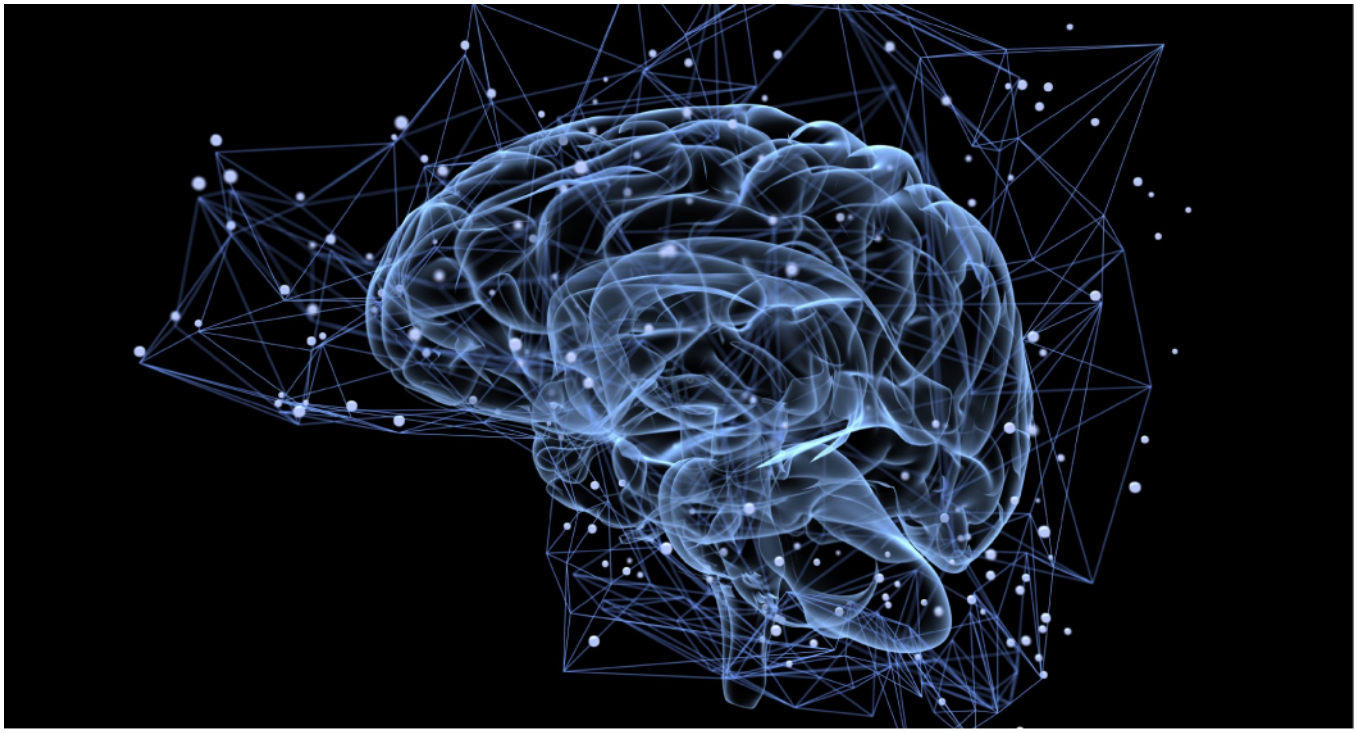
Bifidobacterium longum 1714 may modulate brain function in response to social stress in healthy adults

Published on May, 2, 2019 by Paul Enck

Modulating the gut microbiota has emerged as a means of affecting the central nervous system function and, thus, human behavior, especially in the context of stress, mood and anxiety disorders and even neurocognitive disorders. Clinical studies with probiotics using neuroimaging methods have started exploring the benefits of probiotics in the human brain. Among them, the probiotic *Bifidobacterium longum* 1714 has been shown to reduce stress-related behaviors and improve stress responses and cognitive function in mice and healthy volunteers, respectively. However, the mechanisms by which this probiotic influences brain function and human behavior are unclear.



A new randomized, double-blinded, placebo- controlled trial, which I led with a team of researchers from the University of Tübingen (Germany), reveals that ***B. longum* 1714 may reduce stress responses in healthy volunteers by modulating the brain regions involved in emotional regulation.**

The researchers tested the effects of *B. longum* 1714 at a dose of 1 x 10^9 colony forming units/day for 4 weeks on neural responses to social stress in a sample of 20 healthy adult volunteers (intervention group) compared with 20 controls (placebo group). Social stress was induced by social exclusion through a computerized ball game called "Cyberball game". Magnetoencephalography (MEG) was used for measuring brain activity under social stress, whereas health status was measured with a 36-item short-form health survey.

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Changes in neural activities during the resting state were observed after the intervention for participants in the probiotic group vs placebo. In addition, participants in the probiotic group showed unique correlations between the alteration in resting brain activity and increased subjective vitality. Considering previous findings that mental fatigue causes enhancement of the right prefrontal cortex, the current findings suggest that the role of *B. longum* 1714 in managing stress might be related to enhanced vitality and reduced mental fatigue.

Both groups reported increased changes in subjective stress scores after the 4-week intervention, which might be due to the low sample size.

However, **only *B. longum* 1714 led to a difference in the changes in neural activity in brain areas that might be involved in the counterregulation of negative emotions in response to a social stressor.** Furthermore, changes in neural activity under social stress induced by *B. longum* 1714 were correlated with changes in distress levels reported by questionnaire. Changes in participants' neurophysiology due to the probiotic is a new finding, because previous research has only shown its role in improving stress responses and behavior.

In conclusion, for the first time, this study shows the role of *B. longum* 1714 in modulating brain function in response to social stress.

Next steps with this novel probiotic include exploring its role in other central nervous system functions in both healthy controls and patients with psychiatric, neurological and gastrointestinal disorders. Using standardized neuroimaging methods and correlating the brain data with changes in the gut microbiota at composition and functional level will help elucidate the contribution of *B. longum* 1714 and other probiotics to mental health.

Prof. Dr. Paul Enck, Director of Research, Dept. of Psychosomatic Medicine and Psychotherapy, University Hospital Tübingen, Germany. His main interests are gut functions in health and disease, including functional and inflammatory bowel disorders, the role of the gut microbiota, regulation of eating and food intake and its disorders, of nausea, vomiting and motion sickness, and the psychophysiology and neurobiology of the placebo response, with specific emphasis on age and gender contributions.

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Wang H, Braun C, Murphy EF, Enck P. *Bifidobacterium longum* 1714™ strain modulates brain activity of healthy volunteers during social stress. Am J Gastroenterol. 2019. doi: 10.14309/ajg.0000000000000203.

Read the original post online at:
https://www.gutmicrobiotaforhealth.com/en/bifidobacterium-longum-1714-may-modulate-brain-function-in-response-to-social-stress-in-healthy-adults/

SELECTED CONTENT

An update of the scientific evidence behind the microbiota-specific effects of common dietary patterns

Published on March, 21, 2019 by Andreu Prados

Diet is the most widely studied modifiable factor for shaping gut microbiota composition and function and we are beginning to understand how isolated macronutrients and micronutrients modify the gut microbiome. As nutrients are rarely consumed in isolation, scientists are moving toward examining the ability of dietary patterns to modulate the intestinal microbiota under both physiological and pathological conditions.

Two recent reviews update what we know based on different levels of evidence about the impact of common dietary patterns on gut microbiota composition and function.

Complex carbohydrates have the greatest influence on the human gut microbiota. As not all dietary fibers can be digested by gut microbes, the term "microbiota-accessible carbohydrate" (MAC) has been proposed for complex carbohydrates that cannot be digested by humans but which are metabolically available to gut microbes.

The amount of carbohydrates accessible to gut microbes is affected by common dietary patterns that either increase, reduce or exclude specific nutrients.

The **Western diet** (high in animal protein and fat, low in MACs) leads to a decreased richness and diversity of total bacteria —with a marked decrease in numbers of

An update of the scientific evidence behind the microbiota-specific effects of common dietary patterns

beneficial *Bifidobacterium*, *Lactobacillus* and *Eubacterium* species and an increase in *Bacteroides* and *Enterobacteria*— as compared with a plant-based diet. The use of intestinal mucus as the main source of energy by gut microbes due to compromised gut barrier integrity and reduced production of short chain fatty acids (SCFAs) is a known consequence of MAC restriction.

Beyond complex carbohydrates, proteins are an important nitrogen and carbon source for gut microbes and a diet high in protein is frequently used for weight loss in Western societies. The microbiota-specific effects of **dietary patterns high in proteins and low in carbohydrates**—frequently encompassed under the term Paleolithic diet—have been studied through comparison of hunter-gatherer societies and industrialized populations. Both lifestyle and the high consumption of plant-derived MACs found in tubers and the roots of plants in pre-agricultural societies hinder translation of the health benefits of this kind of diet when followed in Western societies. It should also be acknowledged that high protein consumption may generate some toxic metabolites related to diseases such as colorectal cancer.

On the other hand, the **ketogenic diet** (KD), with carbohydrate consumption of less than 10% of total caloric intake, is being studied for neurological disorders, weight loss, cancer, and extending longevity. The preclinical effects of KD on beneficial gut microbes such as *Akkermansia muciniphila* and SCFA-producing bacteria in the gut are contradictory, with an overall reduction in gut microbiota diversity. On the other hand, small studies with follow-up periods covering from 1 week to 6 months in patients with refractory epilepsy and multiple sclerosis have found that KD may restore some microbiota functions impaired by the inherent disease, but with a negative impact on the intestinal environment. These findings highlight the need for further studies exploring the diet's long-term safety.

Regarding dietary management of functional gastrointestinal disorders, the **diet low in short-chain fermentable carbohydrates and polyalcohols** (known as the low-FODMAPs diet), pioneered by Peter Gibson and colleagues, is a frequent treatment for irritable bowel syndrome (IBS). The short-term reduction of FODMAPs in patients with IBS leads to gut symptom relief, which subsequently persists for between 6 and 18 months after high-FODMAP foods are reintroduced to individual tolerance.

These findings highlight that the low-FODMAP diet is not a diet for life, as it may decrease beneficial bacteria including *Bifidobacterium*, *Faecalibacterium prausnitzii* and *Clostridium* Cluster IV levels due to decreasing the availability of fermentable carbohydrates. FODMAP restriction should therefore be implemented in the short term, followed by reintroduction and personalization, preferably with the support of registered dietitian nutritionists.

Despite this dietary restriction approach, alternative dietary approaches for IBS are also in the pipeline. In a recent pilot proof-of-concept study, scientists showed that certain prebiotics may lead to symptom improvement maintained in the short term when compared with the low-FODMAP diet. This is likely attributable to changes in the gut microbiota. Unlike long-term dietary restrictions, following the regular Mediterranean-like diet along with a prebiotic supplement may emerge as a potential dietary approach for improving abdominal pain and bloating.

Similar regimes to the low-FODMAPs diet have also arisen and they include the specific carbohydrate diet (SCD) and the gut and psychology syndrome (GAPS) diet. However, the scientific evidence supporting their effectiveness is scarce as little is known about their ability to modify the gut microbiota and confer host health benefits.

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An update of the scientific evidence behind the microbiota-specific effects of common dietary patterns

When it comes to specific dietary components, the **gluten-free diet** (GFD) is a special diet followed not only by patients with celiac disease (CD) but also by individuals with gastrointestinal complaints. In the short-term, the GFD has been shown to affect the composition and activity of the gut microbiota in healthy adults (here; here). Moreover, in CD patients, the GFD over two years may also lead to shifts in the gut microbiota profile, with a decrease in *Bifidobacterium* and *Lactobacillus* and an increase in potential pathobionts from the *Enterobacteriaceae* family. Indeed, the GFD cannot fully restore the gut microbiota imbalances typical of CD patients, with the three-year follow-up highlighting a close relationship between gut microbiota profile and persistence of symptoms. The explanation for these findings includes the absence of fructans and a lack of a prebiotic function for gluten in the GFD.

Until now the most adequate dietary pattern for preserving the diversity of gut microbes has been shown to be the **Mediterranean diet,** which is generally characterized by greater intake of vegetable over animal protein. Greater adherence to the Mediterranean diet has been related with increased levels of fecal short-chain fatty acids and *Lactobacillus, Bifidobacterium, Eubacteria, Bacteroides*, and *Prevotella* along with decreases in *Clostridium*. Meanwhile, the diet's beneficial impact on the gut microbiota could be explained by its capacity to improve lipid profile and inflammation.

On the whole, sufficient inclusion of a variety of plant-based foods, rather than restrictive diets that exclude entire food groups, is the key to shaping high microbiota diversity. This assumption is also supported by genus and species changes driven by vegetarian and vegan diets. Although modest differences have been found in the gut microbiome of vegan versus omnivorous subjects at diversity and richness levels, a plant-based diet allows a higher availability of MAC substrates for the gut microbiota, while also providing a high bioavailability of phytochemicals that may benefit gut health.

Andreu Prados holds a Bachelor of Science Degree in Pharmacy & Human Nutrition and Dietetics. Science writer specialized in gut microbiota, nutrition and gastroenterology, working also as a health communication consultant and lecturer in health communication.

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Read the original post online at:
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SELECTED CONTENT

Gut microbiota response to red meat associated carbohydrates may affect human health

Published on October, 28, 2019 by Allison Clark

Diet is known to be a major modulator of the gut microbiota composition. Dietary compounds such as protein, fat, fiber and polyphenols from our foods can affect the gut microbiota composition and microbial metabolites that can influence human health. For example, diets high in animal protein may lead to the production of harmful bacterial metabolites and high red meat consumption has been linked to negative alterations of the gut microbiota and various diseases such as heart disease and colorectal cancer; however, little is known about the effect red meat associated carbohydrates have on the gut microbiota and host health.

Red meat is enriched in N-glycolylneuraminic acid (Neu5Gc), which is a type of sialic acid that is a type of acid sugar composed of a nine-carbon backbone that is typically found at the outermost end of glycan chains found in all cell types of most non-human mammals. Sialic acids are involved in various physiological and pathological processes. In human, red meat consumption can cause Neu5Gc incorporation into cell surface glycans, which are a type of polysaccharide, especially in carcinomas. **It has been hypothesized that chronic inflammation can be triggered when Neu5Gc -containing glycans encounter circulating anti-Neu5Gc antibodies, which has been termed "xenosialitis".**

Humans cannot synthesize Neu5Gc due to an evolutionary loss of the enzyme CMP-Neu5Ac hydroxylase (CMAH). On the other hand, bacteria can use free sialic acids as a nutrient and carbon source, but it is unknown if the gut microbiota triggers the release of Neu5Gc from food or how bound Neu5Gc is metabolized in the intestines.

To investigate the host-microbe interaction as it relates to sialic acid, **Zaramela and colleagues from University of California San Diego investigated if a Neu5Gc rich diet could affect the bacterial metabolism and gut microbiota composition in mice and humans**. Through 16S rRNA gene amplification, they identified and compared the fecal microbiome from human like transgenic *Cmah*$^{-/-}$ mice, which were bred to not contain the gene that encodes the CMAH enzyme like humans, and wild type mice that were both fed either

a sialic acid-free (soy) diet, a Neu5Gc-rich porcine submaxillary mucin (PSM) diet, or a Neu5Ac-rich edible bird's nest (EBN) diet.

The authors discovered a significant difference in the bacteria present in *Cmah*$^{-/-}$ versus wild type mice which were diet dependent. A diet rich in Neu5Gc altered the gut microbiota, especially among Bacteroidales and Clostridiales. Independent of genotype, the microbiome of PSM-fed mice was significantly less diverse compared to the microbiome of those fed soy and EBN diets. Additionally, by computationally simulating 773 metabolic models of the human gut microbiome, the researchers found that members of *Bacteroidetes*, including *Bacteroides fragilis, Bacteroides cacae* and *Bacteroides thetaiotaomicron*, were some of the most efficient microorganisms using sialic acids as a carbon source.

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In order to study the sialidase genes present in the microbiome, combined metagenomes were co-assembled and 51 genome bins, which group contigs and assign them to operational taxonomic units (OTUs), containing 21 sialidase genes were identified. Bin13, which contained five sialidases whose closest relative was *B. thetaiotaomicron*, was the most abundant in PSM compared to EBN diets suggesting it plays an important role in intestinal Neu5Gc metabolism.

To test their findings in humans, the scientists re-analyzed fecal shotgun sequences from the Tanzanian hunter gather group the Hadza. During dry season, when their diet is enriched with meat, bin 13 was more abundant in microbiome samples compared to wet seasons. Of the 24 genome bins discovered, binHz19 which contained sialidaseHz136, had the greatest sequence similarity to sialidase26 which was previously identified in the mouse study. **The researchers also discovered that both sialidase26 and sialidaseHz136 release Neu5Gc from food sources (beef, pork and PSM chow) indicating that sialidases exhibiting Neu5Gc preference may be widespread in the mammalian intestine.**

In summary, Zaramela and colleagues identified several sialidases that have a preference for Neu5Gc, which are enriched in the gut microbiota of both mice and humans upon consuming a Neu5Gc-rich diet. **The authors conclude that although more *in vivo* studies are needed, a gut microbiome that harbors less bacteria with Neu5Gc-preferring sialidases could result in increased xenosialitis (xeno-autoantibody response to glycan incorporated Neu5Gc) which might promote inflammatory diseases such as colorectal cancer and atherosclerosis.**

> Dietary compounds such as protein, fat, fiber and polyphenols from our foods can affect the gut microbiota composition and microbial metabolites that can influence human health.

Allison Clark has a master in nutrition and health from Open University in Barcelona and a master in journalism. She is a freelance writer and nutritionist and has written various peer review papers about the role the gut microbiota plays in health, disease and endurance exercise performance. Allison is passionate about the role diet and the gut microbiota play in health and disease. Follow her on Twitter @Heal_your_Gut

Reference:
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Read the original post online at:
https://www.gutmicrobiotaforhealth.com/en/gut-microbiota-response-to-red-meat-associated-carbohydrates-may-affect-human-health/

SELECTED CONTENT

Beyond nutrients and bioactive compounds in food: cooking also matters for the gut microbiome

Published on October, 10, 2019 by Andreu Prados

Macronutrients, micronutrients and non-nutritive compounds are major drivers of the composition and metabolic functions of gut microbial communities. However, nutrient composition alone cannot explain the way people's gut microbiomes are so different to each other.

One feature that distinguishes humans from other species is our ability to heat-treat our meals. This process alters nutrients and makes foods more digestible, while also developing flavors and tastes not present in raw versions.

But can cooking affect the gut microbiome and should it therefore be considered as a new covariable in microbiome studies?

This seems to be the case, according to a new study from Dr. Rachel Carmody at Harvard University (USA), Dr. Peter Turnbaugh at University of California San Francisco (USA) and colleagues, which shows that **raw and cooked diets have a distinct effect on the structure and metabolic activities of the gut microbiome in mice and humans.**

For instance, raw and cooked versions of the same foods affected the gut microbiome differently in mice. **While raw and cooked lean beef had a similar impact on the gut microbiome, the mice gut microbiome responded differently when the animals were fed raw and cooked sweet potatoes.** Consuming raw sweet potatoes led to lower within-subject diversity, a higher expression of genes and enzymes for metabolizing starch, sugar and xenobiotics, and altered metabolic byproducts when compared with cooked-fed mice.

By feeding the mice controlled diets with different raw and cooked low- and high-starch foods —including sweet potato, white potato, corn, peas, carrots, and beets— the authors confirmed that **gut microorganisms were sensitive to starch digestibility.**

Thus, starchy foods with a high amount of low-digestibility starch when raw (sweet potato and white potato) led to the most profound changes in gut microbial community structure. However, low-starch foods (carrot and beet) or foods with a high amount of high-digestibility starch when raw (corn and peas) led to almost undetectable changes in gut microbes.

Cooked foods were mainly digested and absorbed in the small intestine (thus, processed by host enzymes), **whereas raw foods reached the colon, where they had detrimental effects on microbes, attributable to antimicrobial compounds.**

By quantifying microbial cell damage in gut samples, Carmody and colleagues found that the mice fed raw tubers had the same extent of microbial cell damage as the mice group treated with the oral antibiotic ampicillin.

A metabolomic analysis of the six plant foods used in the experiments revealed multiple compounds that were both sensitive to cooking and showed antimicrobial

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Beyond nutrients and bioactive compounds in food: cooking also matters for the gut microbiome

activity, thus supporting the high xenobiotic gene expression found in mice that were fed raw food.

The author Rachel Carmody had previously found that poorly processed foods led to rapid weight loss in mice when compared with cooked foods. In this study, researchers wanted to explore to what extent shifts in the gut microbiota induced by cooking might affect host energy balance.

As such, germ-free mice receiving the gut microbiome of raw-fed mice rapidly lost weight. However, transplanting this altered gut microbiome into mice on a regular diet led to weight gain and increased body fat, which was associated with increased calorie intake. This shows that changes in gut microbes are not the underlying cause of the weight loss associated with a raw diet.

The relevance of raw versus cooked diets in shaping the gut microbiome was also assessed in humans. With the help of co-author and chef Vayu Main Rekdal, the researchers showed that **raw and cooked menus altered the gut microbiome when fed in a random order to a small group of healthy participants for three days.**

Altogether, this new research highlights that beyond nutrient intake and drugs, cooking also matters in shaping the gut microbiome. In the light of these findings, we may be able to suggest that cooking has exerted a relevant effect on changes to the composition of the microbiome during hominid evolution. Consequently, Peter Turnbaugh is planning new research to better elucidate cooking's contribution to modulating host-microbiome interactions.

> “Raw and cooked diets have a distinct effect on the structure and metabolic activities of the gut microbiome.”

Andreu Prados holds a Bachelor of Science Degree in Pharmacy & Human Nutrition and Dietetics. Science writer specialized in gut microbiota, nutrition and gastroenterology, working also as a health communication consultant and lecturer in health communication.

Reference:
Carmody RN, Bisanz JE, Bowen BP, *et al.* Cooking shapes the structure and function of the gut microbiome. Nat Microbiol. 2019. doi: 10.1038/s41564-019-0569-4.

Read the original post online at:
https://www.gutmicrobiotaforhealth.com/en/beyond-nutrients-and-bioactive-compounds-in-food-cooking-also-matters-for-the-gut-microbiome/

Gut microbiome data may enable precision diagnostics of children with irritable bowel syndrome

Published on November, 21, 2019 by Dr. Numan Oezguen and Dr. James Versalovic

Previous research has shown that differences in the gut microbiomes of adult patients with irritable bowel syndrome (IBS) -both in structure and in the levels of metabolites produced or modified by gut microbes- often accompany abdominal pain. An association between gastrointestinal microbes and IBS in children has been also reported and is characterized by shifts in the abundances of members of the phyla Bacteroidetes, Proteobacteria, and Firmicutes.

However, in the clinical setting, an accurate diagnosis of patients with IBS remains a challenge because it is based largely on clinical criteria. Microbiome data could help in this regard.

In collaboration with other scientists from Baylor College of Medicine, Texas Children's Hospital, Diversigen, and the University of Washington, we have developed an improved disease classification technique that enables personalized diagnosis of pediatric patients with IBS based on their gut microbiome.

We sought to explore the associations between abdominal pain and the gut microbiome by using a multiomics approach in 23 preadolescent children with IBS—diagnosed according to the validated Rome III questionnaire and daily pain and stool diaries for 2 weeks—and 22 healthy controls.

A battery of tests meant children with IBS could be distinguished from healthy children in terms of bacterial species composition, bacterial genes, and fecal metabolite abundances. The stool communities of children with IBS were enriched in *Gammaproteobacteria*, unclassified *Clostridiales*, metabolic pathways related to amino acid metabolism and phospholipid synthesis, together with higher levels of sterols, steroids (sulfated steroids), bile acids, and phenylalanine and tyrosine metabolites.

Moreover, correlations were found between abdominal pain and the relative abundances of different bacterial species, metagenomic functions and metabolites. Pain frequency and severity assessed by a validated numerical rating scale showed positive correlations with the relative abundances of *Flavonifractor plautii*, *Lachnospiraceae bacterium* and unclassified *Eggerthella*, fucose and rhamnose degradation and phospholipid biosynthesis, and protein-degradation products, among others.

The clinical relevance of the gut microbiome in IBS was also supported by a previous study led by Professor Magnus Simrén that found that IBS symptom severity in adults is linked to a specific fecal microbiota signature characterized by low microbial richness, low CH_4 exhaled, an enriched *Bacteroides* enterotype and the absence of *Methanobacteriales*.

> Through non-invasive gut microbiome-related data, we are closer to delivering tailored diagnoses for individuals with IBS, which may help identify the subset of patients more likely to benefit from nutritional interventions.

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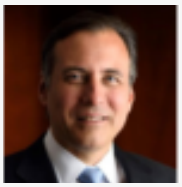
Gut microbiome data may enable precision diagnostics of children with irritable bowel syndrome

By using a set of only 10 bacterial features (species, functional pathways and metabolites) that differed the most between IBS cases and healthy controls, we generated a disease classifier that helped distinguish cases from healthy controls with an area under the curve of 0.93 and an accuracy around 80%. As such, **our microbiome-based classifier could pave the way towards more effective and personalized diagnosis and treatment of children with IBS based not only on microbial features, but on biochemical and molecular characteristics as well.** This study also provides a foundation for future improvements in building disease classifier models for the diagnosis and monitoring of chronic gastrointestinal diseases.

Our study is the first to combine deep microbiome analysis with developing new diagnostic strategies to tailor the diagnosis of children with IBS. Through non-invasive gut microbiome-related data, we are closer to delivering tailored diagnoses for individuals with IBS, which may help identify the subset of patients more likely to benefit from nutritional interventions.

Dr. Oezguen received a Diploma in Physics (1994), and a PhD in Polymer Physics (1999) from the Rheinisch Westfaelische Teschnische Hochschule in Aachen, Germany. In 2012, he joined Baylor College of Medicine and Texas Children's Microbiome Center as instructor. Dr. Oezguen authored 41 peer reviewed articles and one US patent. Current h-index for his publications is 25.



Dr. Versalovic currently serves as Pathologist-In-Chief at Texas Children's Hospital. He also serves as Vice Chair of Pathology & Immunology at Baylor College of Medicine (BCM), and Director of the Texas Children's Microbiome Center. He holds the Milton J. Finegold endowed chair as Professor of Pathology & Immunology, and is Professor of Pediatrics, Molecular and Human Genetics, and Molecular Virology & Microbiology at BCM. In 2019, Dr. Versalovic was elected as a Fellow of the American Academy of Microbiology (AAM).

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SELECTED CONTENT

New data on the Human Microbiome Project reveal multi-omic host-gut microbiome interactions in inflammatory bowel diseases and prediabetes

Published on September, 16, 2019 by Andreu Prados

The second phase of the 10-year National Institutes of Health-funded Human Microbiome Project, the Integrative Human Microbiome Project, has recently been completed and provides a useful repository of microbiome-related data, tools and protocols for the research community.

The two studies featured in this post have characterized host-microbiome interactions through longitudinal sampling in inflammatory bowel diseases (IBDs) and prediabetes. Although some of reported shifts in the composition and function of the microbiome were reported in previous studies, the use of multi-omic technologies has allowed for the discovery of new host-microbiome interactions.

The multi-omic profiling of 2,965 stool, biopsy, and blood specimens from 132 pediatric and adult individuals followed with either Crohn's disease, ulcerative colitis or who did not have IBD identified taxa, expressed functions, IBD-linked metabolites and host gene expression disrupted in the gut during increased disease activity over the space of a year.

At the taxonomic level, an unclassified *Subdoligranulum* species was markedly reduced in participants with IBD and may contribute, alongside a reduction in butyrate producers, to the carnitine and bile acid dysregulation observed. Other metabolites such as nicotinuric acid were present in participants with IBD and distinguished them from controls.

The involvement of the host and gut microbiome in IBD activity was also supported by an increase in facultative anaerobes, alterations in transcription for several microbial species such as clostridia, and increased levels of antibodies in host serum.

Among them, changes in the metabolome —mainly methylimidazole acetic acid and urate— explained the more frequent and extreme temporal shifts in the gut microbiome in participants with IBD compared with controls that did not have IBD.

On the other hand, the study of 106 healthy individuals and individuals with prediabetes explored host (plasma proteomics and metabolomics, exomes and transcriptomes in peripheral blood mononuclear cells, glucose dysregulation tests and weight) and microbial (16S sequencing and metagenomics) features over 4 years and during periods of health and perturbations, including respiratory viral infections and directed weight gain and weight loss.

Although baseline measurements tended to maintain stable within individuals, **clinical laboratory measurements, cytokine profiles and low abundance microbial taxa were highly variable between participants.**

> Molecular and microbial profiles tend to be personalized and differ between insulin-resistant individuals and insulinsensitive. participants

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New data on the Human Microbiome Project reveal multi-omic host-gut microbiome interactions in inflammatory bowel diseases and prediabetes

Specifically, **participants who developed insulin resistance had distinguishable molecular and microbial patterns at baseline compared with participants who were insulin-sensitive.** This was accompanied by differential responses to respiratory viral infections and weight loss depending on whether a participant was insulin sensitive or insulin resistant.

While insulin-resistant participants showed a reduced response to respiratory viral infections, more chronic inflammation and altered lipid metabolism, insulin-sensitive participants were responsive to respiratory viral infections through a proper activation of acute phase response pathways.

As different clinical and biochemical parameters together with gut microbial changes shaped glucose dysregulation over the study period, such results suggest the need for taking into account different measurements for better managing patients' health.

On the whole, these findings reveal that **molecular and microbial profiles tend to be personalized and differ between insulin-resistant individuals and insulin-sensitive participants both at baseline and in response to periods of respiratory viral infections and weight loss.**

These results provide an in-depth description of the host and microbial activities involved in inflammatory bowel diseases and prediabetes and help create databases with resources for researchers and even for use in the clinical setting. Moving from descriptive microbiome sequencing studies to multi-omics approaches that integrate both host and microbial responses gives a better understanding of overall host-microbiome dynamics that may pave the way to predicting disease events.

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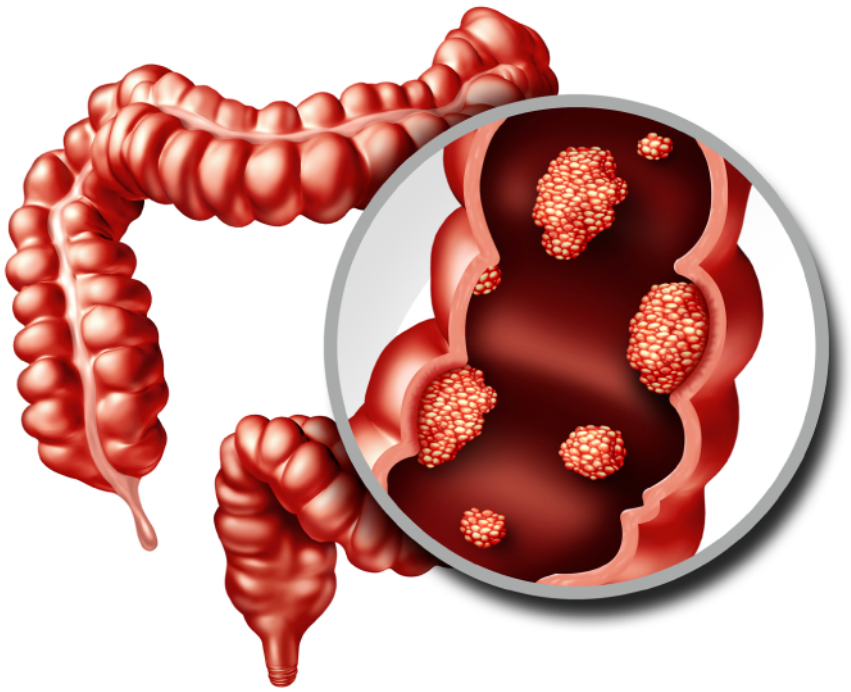
Read the original post online at:
https://www.gutmicrobiotaforhealth.com/en/new-data-on-the-human-microbiome-project-reveal-multi-omic-host-gut-microbiome-interactions-in-inflammatory-bowel-diseases-and-prediabetes/

Two new studies reveal universal gut microbiome signatures in colorectal cancer

Published on April, 22, 2019 by Andreu Prados

Genes alone cannot explain the current rise in colorectal cancer (CRC) and scientists are now trying to elucidate the gut microbiota's contribution as an important player. Previous human research has shown mechanisms by which the bacteria might affect tumorigenesis, especially in the early stages. However, gut microbiome signatures of CRC in association studies have not always been validated across different populations and are subject to biological and technical confounders.



Two articles on the involvement of gut microbiome in CRC were recently published in *Nature Medicine*.

The first study, led by researchers from the European Molecular Biology Laboratory in Heidelberg (Germany), the University of Copenhagen (Denmark) and the University of Trento (Italy), **has identified a set of 29 species indicative of colorectal cancer across populations from seven countries.**

By comparing fecal metagenomic data from case-control studies and using newly generated data, the researchers sought to establish robust gut microbiome signatures of CRC across seven cohorts from France, Austria, Italy, Germany, the United States, China and Japan.

Despite differences in geography, dietary patterns and lifestyles, the authors found a set of 29 species

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indicative of CRC that seem to be universal, rather than only disease-specific. Most of these core gut microbial markers were previously associated with CRC and were more driven by geographical and technical study differences than the disease itself, whereas 11 *Clostridiales* species were unknown until now.

Interestingly, metagenomic analyses among the core set of 29 species enriched in the CRC gut microbiome revealed 4 species clusters with different gut microbiota composition, which were also related to tumor location and patient sex. They were, however, in general, independent of tumor stage:

- Cluster 1: exclusively comprised *Porphyromonas* species and was enriched in rectal tumors.
- Cluster 2: contained species with intermediate prevalence in CRC cases and was more abundant in female CRC patients.
- Cluster 3: comprised species with higher prevalence in CRC cases.
- Cluster 4: only contained members of the *Clostridiales*

At a functional level across studies, **the gut microbiome from CRC patients was enriched in metabolic pathways involved in the degradation of amino acids, mucins and organic acids.** That is indicative of a metabolic shift towards amino acid metabolism secondary to a fat- and meat-rich diet. In contrast, genes for carbohydrate metabolism were depleted.

Moreover, some gut microbial virulence and toxicity mechanisms were found to be enriched in CRC patients, which suggests their role in colorectal carcinogenesis. They included the adhesion protein A by *Fusobacterium nucleatum*, the enterotoxin of *Bacteroides fragilis*, colibactin by *Escherichia coli* and conversion of primary to secondary bile acids by *Clostridium* species. The enrichment of genes that encoded for these virulence factors was validated across all study populations.

Wirbel and colleagues also succeeded in establishing CRC-specific microbiome signatures and separated them for other conditions such as type 2 diabetes, Parkinson's disease and inflammatory bowel disease, with similar effects on the gut microbiome, based on previous research showing gut microbiome signatures driven by specific diseases.

On the other hand, a related study from the University of Trento has revealed **higher gut microbiome richness and altered potential for microbiome choline metabolism in patients with CRC.**

The researchers used five available datasets and two new cohorts to explore the reproducibility of previous links between the gut microbiome and CRC. The findings were also validated in two additional cohorts.

The gut microbiome of CRC cases showed higher richness than controls, which was explained by the translocation of microbes from the oral cavity into the colon.

> Both studies show the potential of gut microbial signatures for predicting colorectal cancer.

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At a functional level, Maltez Thomas and colleagues showed **an enrichment of gluconeogenesis and amino acid putrefaction and fermentation pathways associated with CRC**. In contrast, complex carbohydrates, stachyose and galactose metabolism pathways were enriched in controls.

It is worth mentioning that the capacity of certain gut bacteria to degrade choline —found in meat and other foods— into trimethylamine (TMA) metabolite —previously involved in atherosclerosis— was more abundant in CRC. This was explained by a higher expression of genes related to TMA synthesis in the CRC-associated metagenomes. The close relationship between gut microbiome and choline metabolism adds to mechanisms described by Wirbel and colleagues in confirming potentially carcinogenic gut microbiota virulence in CRC.

On the whole, both studies show the potential of gut microbial signatures for predicting CRC. This is based on the availability of whole-metagenome shotgun datasets of CRC cohorts, with an accuracy similar to the fecal occult blood test used for CRC screening.

As the specific gut microbiome signatures were validated in early CRC stages and in different studies, these data suggest potential for use as candidate for developing non-invasive CRC screening. However, it should be acknowledged that stool microbiome could help with predicting CRC when pooled datasets, rather than using independent cohorts, are used. This may be explained by the heterogeneity of studies and population characteristics.

“In the future we hope we can use these signatures as biomarkers and as a diagnostic tool for colorectal cancer,” says author Manimozhiyan Arumugam in a press release from the University of Copenhagen.

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