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YEAR AT A GLANCE

A selection of content from the
Gut Microbiota for Health 2020

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EDITORIAL

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Year at a glance editorial head

Elena Verdú is a member of the Gut Microbiota for Health's Board of Experts. Dr Verdu's research has focused on the involvement of the gut microbiome in the pathophysiology of inflammatory and functional gastrointestinal disorders.

2020 – A year we will never forget

Is it any wonder 'coronavirus' is the word of 2020? It is the solitary issue that has changed our lives for most of this past year and provided us with lessons we would be wise not to forget, especially when it comes to the way the world does science. In 2020, the novel coronavirus, SARS-CoV-2, has shifted the priorities of many scientists worldwide. SARS-CoV-2 has emphasized the importance to better understand the central role of gut health in conditions that apparently are not connected to our gut, such as viral respiratory tract infections. SARS-CoV-2 can invade cells lining the gastrointestinal tract that are in close contact with the gut microbiota, thereby acting as a reservoir for the virus. Indeed, clinical studies indicate that gastrointestinal symptoms are common in COVID-19 and are associated with disease severity. As such, the activity of the gut microbiota, immune responses and nutrient intake may contribute to reducing the risk of respiratory infection due to the known gut-lung crosstalk.

Breakthrough scientific research and advances in 2020

While we are waiting for effective treatments against COVID-19 to be instituted, a nutritious and balanced diet that support people's immune systems may constitute a preventive approach. Good nutrition has a direct impact on the gut microbiome and immune system. These interactions are crucial to educate the immune system in a way that our bodies can fight infections, while avoiding dysregulated activation that can cause tissue destruction and inflammation, which also may result in a significant increase in the demand for energy and nutrients. Studies have described beneficial mechanisms through which probiotics could prevent respiratory tract infections and, others have shown that prebiotics enhance propagation of probiotic strains and indigenous beneficial microorganisms. The studies have encouraged scientists to begin exploring to what extent harnessing the gut microbiome with probiotics and prebiotics might be worth considering in COVID-19 patients.

Beyond the importance of nutrition and the gut microbiome in antiviral immunity, gut-dwelling bacteria are crucial for supporting proper gastrointestinal health, influencing health markers which are not obviously linked to the gut. Two large intervention studies have highlighted the importance of diet quality over the quantity of calories consumed and the participant's age, when striving for the following factors: a highly diverse microbiota, decreasing frailty markers and improved cognitive function. Beyond the gastrointestinal ecosystem, gut microbial signatures may also offer a novel paradigm for type 2 diabetes, as scientists have identified novel intestinal bioactive lipids that could aid in the development of new antidiabetic drugs. In addition, the link between the gut microbiota and an impaired metabolism of dietary tryptophan in celiac disease has also been elucidated.

Beyond the gut microbiome's role in modulating certain diseases, strategies shaping this commensal community are beginning to emerge as an important pillar of overall health and wellbeing. Current evidence-based strategies for modulating the gut microbiota include, a) probiotics (including certain micro-organisms of which the health-related benefits have only just been discovered, such as *Akkermansia muciniphila*; b) compounds produced by microorganisms, released from food components or microbial constituents (frequently called postbiotics) that have the potential to promote health and wellbeing; and c) prebiotic fibers . New names for key

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probiotic *Lactobacillus* species have been coined as scientists have reclassified this genus into 25 genera, including 23 novel genera. When it comes to synbiotics, a panel of experts under the auspices of the International Scientific Association for Probiotics and Prebiotics (ISAPP) has published a consensus statement on the definition and scope of a synbiotic. Human trials have reported the benefits of orally administered synbiotics for preventing infections, treating obesity, treating inflammation, as well as preventing and treating atopic dermatitis, among others.

Diet continues to gather interest, and specifically, fermented foods have undergone a surge in popularity over the last decade due to their proposed health benefits. Human studies in 2020 characterized the mechanisms of action of fermented foods that support their effects on both gastrointestinal and overall health in humans. The most widely investigated fermented foods are yogurt and kefir. While yogurt reduces symptoms related to lactose maldigestion and has also been reported to be beneficial for metabolic health, some kefirs may improve constipation, lactose malabsorption and aid in the eradication *Helicobacter pylori* infection.

Finally, it should also be acknowledged that not all diseases exhibit the same degree of gut microbiota alteration, and specific microbiota signatures are difficult to identify. A causal role for an altered gut microbiota composition or function in most diseases has yet to be established. For this, a combination of clinical longitudinal studies investigating pre disease phenotypes, as well as reverse translational approaches to test the role of defined microbial communities or their functions in relevant mice models, organoids and other research tools, should be employed.

GMFH ecosystem evolution

Aware of the important role of nutrition, the intestinal microbiome and the immune system, from GMFH we launched a social media education campaign with the hashtag **#GutToKnowYou,** around the World Digestive Health Day 2020 on May 29th and World Microbiome Day 2020 on June 27th.

Our digital community grew this year to exceed **111,100 members**, including scientists, healthcare professionals and the general public. In 2020, the GMFH website had more than **1,240,000 visits** and was, for the fourth year in a row, selected as one of the best gut health blogs by Healthline, a consumer health information website with over 65 million monthly readers.

With our 2020 platform redesign for a better user experience, and the new section called Food 4 Gut Health dedicated to promoting the role of food in gut well-being, GMFH is more engaged than ever in educating people about this popular topic. This year was also marked by the launch of the new Instagram @Food4Gut_Health, with the aim of sparking new conversations, sharing science in a colorful and fun way, as well as expanding our audience.

The 9th edition of the annual Gut Microbiota for Health World Summit, held in Madrid 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 the gut microbiota, we will continue promoting and participating in this conversation in 2021, while updating readers with the latest cutting-edge microbiome science and evidence-based dietary strategies that target the gut microbiome and its impact on gastrointestinal health and disease in humans.

As announced in 2020, we hope that the 10th edition of Gut Microbiota for Health World Summit can take place as planned in November 2021 and cover major advances in diet-gut microbiome relationships for better health. Our team at GMFH encourages you to keep in touch with our platforms, to receive updated information about the 2021 Summit and to find out more about the emerging science on the impact of the gut microbiome on health and wellbeing. Stay tuned to learn about evidence- and safety-based approaches that care for the community of microorganisms living in our gut.

Have a safe and gut-friendly 2021!

SELECTED CONTENT

How immune cells defend the mouse gut against infection like clockwork

Published on January 20th, 2020 by Megan Mouw

Circadian rhythms are also apparent within our gastrointestinal tract. Two new mice studies show that circadian rhythm and clock genes may also affect intestinal immune cells by boosting the secretion of cytokines that help maintain proper balance of the intestinal barrier.

Humans are creatures of habit – we tend to wake up, feel hungry, and fall asleep at the same time every day. We owe this tendency to our circadian rhythms – 24 hour cycles that are present in the biological processes of most living beings. These cycles are generated by "clock genes," which influence most of our organs and cells, including those of the digestive tract. This daily rhythm of the gastrointestinal system influences digestion, absorption, gastric motility, and the gut microbiota.

Recent studies suggest that circadian rhythm and clock genes may also affect intestinal immune cells, of which the circadian pathways are disrupted in inflammatory bowel disease. While the underlying reason behind this observation has remained to be seen, now Teng *et al.* and Wang *et al.* have identified for the first time that the development and functions of a group of immune cells in the gut are controlled by clock genes in mice.

The cells that researchers identified are called type 3 innate lymphoid cells (ILC3), which appear to help regulate the daily rhythm of the gut and help our GI tracts defend against pathogenic microorganisms. They do this by secreting cytokines that help maintain proper balance of the intestinal barrier and gut microbiota.

Researchers found that clock genes are highly active in ILC3 cells, and that the production of specific cytokines correspond with the activity of certain clock genes. If scientists eliminated the key clock gene *Nr1D1* (encoding REV-ERB) from the mice, ILC3 produced less IL-22 and more IL-17 cytokines compared to mice who still harbored the *Nr1D1* gene. A second group led by Teng *et al.* report similar results, finding that mice lacking the clock gene BMAL1 has a reduced number of intestinal ILC3s.

How immune cells defend the mouse gut against infection like clockwork

The *NR1D1* deficient mice were also less able to clear an infection caused by the dangerous pathogen *Clostridium difficile*. Previous reports have suggested that IL-17A is implicated in poorer disease outcomes for *C. difficile* infection. Authors suggest that hyperresponsive IL-17 secretion by the ILC3s of Nr1D1 deficient mice may contribute to more severe inflammation and bacterial burden.

Wang *et al*. wondered what would happen if they actively hindered the normal circadian rhythm of the mice, mimicking, for example, the schedule of a shift-worker. To achieve this, they disrupted the normal circadian rhythm of the mice by altering the conventional 12:12 (12 hours light: 12 hours dark) pattern to include an 8-hour phase advance every 2 days. **In altering the pattern of light and dark that the mice were exposed to, certain clock genes were also disrupted, as was the secretion of IL-17A and IL-22 by both NKp46+ and NKp46– ILC3s**. The researchers conclude that a disruption in the circadian rhythm might impair the ability of ILC3s to maintain normal interactions in the gut with nutrients and commensal bacteria, ultimately leading to malabsorption, changes in gut microbiota composition, and disease. *Teng et al*. also analyzed ILC3 cells isolated from inflamed and noninflamed intestinal regions of patients with inflammatory bowel disease (IBD). They found far less ILC3s in the inflamed intestinal regions of IBD patients compared to the noninflamed regions, and noticed that the inflamed intestinal regions exhibited altered expression of circadian-rhythm genes. The authors suspected that the altered gene expression is the result of chronic inflammation or microbial dysbiosis, leading them to suggest that circadian gene expression may be an important pathway for boosting ILC3 responses in the context of inflammation and dysbiosis.

Collectively, these studies highlight how the circadian rhythm affects crucial immune cells in the gut that are needed for proper interactions with nutrients and commensal bacteria. Future studies will specify which intestinal functions are affected by ILC3 daily fluctuations. Overall, these studies are the first evidence in mice showing that host circadian rhythms don't only affect the gut microbiota, but also have a drastic effect on gut immune cells.

Megan Mouw holds a Bachelor of Science in microbiology from McGill University (Canada). Driven by her experiences at UCSF medical center in San Francisco, Megan is passionate about the role that the gut microbiota plays in maintaining health and wellness. She is currently perusing graduate studies in Microbiology and Environmental Toxicology at the University of California Santa Cruz and hopes to share her love of science through writing.

References:

Teng F, Goc J, Zhou L, et al. A circadian clock is essential for homeostasis of group 3 innate lymphoid cells in the gut. *Sci Immunol*. 4(40):eaax1215. doi: 10.1126/sciimmunol.aax1215.

Wang Q, Robinette ML, Billon C, et al. Circadian rhythm-dependent and circadian rhythm-independent impacts of the molecular clock on type 3 innate lymphoid cells. *Sci Immunol*. 4(40):eaay7501. doi: 10.1126/sciimmunol.aay7501.

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Is gut microbiome-lung crosstalk worth considering during the current COVID-19 pandemic?

Published on May 11th, 2020 by Andreu Prados

While patients infected with SARS-CoV-2 typically present with a respiratory illness, certain patients also report gastrointestinal symptoms. The presence of virus receptors in gastrointestinal epithelial cells and an altered gut microbiota composition in some patients might have implications for managing COVID-19.

The intestinal microbiota influences the balance between pro-inflammatory and regulatory responses and shapes the host's immune system

Our immune system is a system of cells and tissue that protects the individual from invading pathogens, while at the same time providing tolerance to diet-based animal and plant materials, non-threatening organisms (i.e. our microbiota) and the self.

For the immune system to function properly, it needs to be exposed to antigens from food and microorganisms. The status of our defenses are also closely related to the host's nutritional status. In other words, an appropriate nutritional status means the organism's defenses work properly, while, conversely, certain physiological (e.g. aging and sports requiring low body weight, such as elite gymnastics) and pathological situations (e.g. obesity and eating disorders) may trigger immune function impairment.

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The immune system of the gut is one of the most extensive networks of immune cells in the body and the community of gut commensals within the gut lumen has a profound impact on its phenotype. Through direct contact with mucosa or soluble chemical mediators, several commensal species of *Lactobacillus* and *Bifidobacterium* have been found to regulate host immunity. However, the role of gut microorganisms in host immune responses is not straightforward. For instance, segmented filamentous bacteria colonizing the ileum influence protective immune responses, which can trigger autoimmunity in susceptible hosts.

In the current fight against the COVID-19, anti-viral host defense mechanisms may determine disease severity and evolution

While severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is generally mild, it sometimes progresses into severe pneumonia and causes death. This occurs especially in the elderly and individuals with co-morbidities, as host immune cells release more inflammatory cytokines than necessary (called a "cytokine storm"), which can cause widespread inflammation and a fatal outcome.

This overreactive immune system seems to indicate that immunosuppressive treatments that block cytokine production might help calm the "cytokine storm" and aid recovery in patients. In addition, preliminary data show that, as disease severity progresses in patients with COVID-19, a parallel rise in inflammatory cytokine levels may drive the reduction and functional exhaustion of CD8+ T cells, which could open a new target potential in fighting COVID-19.

In support of these findings, recent studies have revealed reduced levels of circulating CD8+ T cells in people infected with SARS-CoV-2, especially in severe cases. This has led scientists to argue that the circulating CD8+ T cells levels could be an independent predictor for COVID-19 severity and treatment efficacy.

In this context, one might argue that gut microbiome-immune system crosstalk could work as a team to normalize host immune responses, though further basic and clinical research is needed to better understand how SARS-CoV-2 affects the immune system.

How might the gut microbiome fare when fighting COVID-19?

While patients infected with SARS-CoV-2 typically present with fever and a respiratory illness, some patients also report gastrointestinal symptoms (even early on in the course of the disease) such as diarrhea, vomiting and abdominal pain.

These symptoms may have their roots not only in the use of antibiotics for managing bacterial pneumonia secondary to the viral respiratory infection, but also in the virus' capacity to infect and replicate in the gut, given that viral RNA has been recovered from the stools of infected patients. Moreover, the receptor that SARS-CoV-2 uses for infecting host cells can be expressed in the oral cavity, esophagus, stomach, intestine (and in gut-distal organs including the gall bladder, heart muscle, kidney and even the cerebellum).

The involvement of the gastrointestinal milieu in COVID-19 is also supported by small case series showing that some patients have an altered gut microbiota composition, with depleted *Lactobacillus* and *Bifidobacterium*. Undoubtedly, we will see larger cohort studies being published in the future.

Although the gut-lung axis is not new and has been proposed in the development of certain respiratory conditions, **the respiratory symptoms of COVID-19, the gastrointestinal tropism of SARS-CoV-2, and an altered gut microbiota in some cases make considering the gastrointestinal tract as a potential target in the disease's management and transmission worthwhile**.

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Could probiotics and prebiotics play a major role in defending against SARS-CoV-2?

Although at first sight, the role of gut bacteria in improving respiratory outcomes might seem like science fiction, previous research in mice and humans has highlighted the benefits of food fibers and probiotics in ameliorating some symptoms and health outcomes in respiratory diseases.

More relevant to the current COVID-19 pandemic, two meta-analyses reported the efficacy of probiotics in reducing the incidence and duration of viral respiratory infections. Recently, China's National Health Commission and National Administration of Traditional Chinese Medicine recommended probiotics in the treatment of patients with severe COVID-19 infection as a means of preventing secondary bacterial infection.

However, in the light of these preliminary findings, it is too early to recommend probiotics for preventing pneumonia or reducing intensive care unit mortality in patients with COVID-19, concluded correspondence in *The Lancet Gastroenterology & Hepatology.*

When it comes to prebiotics, a previous study has revealed that a diet supplemented with the fermentable fiber inulin for 8 weeks led to increased levels of CD8+ T cells in the lungs of mice infected with the influenza A virus. Mice supplemented with inulin showed a 10-fold reduction in the influenza A viral load and increased survival. To what extent increasing soluble fiber-rich foods as means for improving recovery and survival in people infected with SARS-CoV-2 remains to be seen.

Even though the potential of fecal microbiota transplants in the transmission of COVID-19 is not known, an international expert panel recommends screening all FMT donors for SARS-CoV-2 and quarantining frozen samples for 30 days and releasing them only if the donor has not developed symptoms.
On the whole, available data until now has revealed that the SARS-CoV-2 infection goes beyond the lungs and may affect not only the immune system but also the gastrointestinal tract. Although more evidence in humans is needed before recommending probiotics and prebiotics in patients with COVID-19, considering the gastrointestinal tract and gut microbiome in managing the virus could offer a valuable approach in the clinical setting.

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Is gut microbiome-lung crosstalk worth considering during the current COVID-19 pandemic?

References:

Calder PC. Feeding the immune system. *Proc Nutr Soc*. 2013; 72(3):299-309. doi: 10.1017/S0029665113001286.

Calder PC & Yaqoob P (2012). Nutrient regulation of the immune response. In: Present Knowledge in Nutrition, 10th ed., pp. 688-708 [JW Erdman, IA Macdonald and SHH Zeisel, editors]. Ames: ILSI.

Ahern PP, Maloy KJ. Understanding immune-microbiota interactions in the intestine. *Immunology*. 2020; 159(1):4-14. doi: 10.1111/imm.13150.

Yang Y, Shen C, Li J, et al. Exuberant elevation of IP-10, MCP-3 and IL-1ra during SARS-CoV-2 infection is associated with disease severity and fatal outcome. doi: 10.1101/2020.03.02.20029975 [Preprint]. 2020 [cited 2020 April 30]. Available from: https://www.medrxiv.org/content/10.1101/2020.03.02.20029975v1

Moon C. Fighting COVID-19 exhausts T cells. *Nat Rev Immunol*. 2020; 1. doi: 10.1038/s41577-020-0304-7.

Zheng M, Gao Y, Wang G, et al. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. *Cell Mol Immunol*. 2020; 17:533-5. doi: 10.1038/s41423-020-0402-2.

Wang F, Nie J, Wang H, et al. Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia. *J Infect Dis*. 2020; jiaa150. doi: 10.1093/infdis/jiaa150.

Wong SH, Lui RNS, Sung JJY. COVID-19 and the digestive system. *J Gastroenterol Hepatol*. 2020. doi: 10.1111/jgh.15047.

Xu H, Zhong L, Deng J, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int J Oral Sci*. 2020; 12(1):8. doi: 10.1038/s41368-020-0074-x.

Mak JWY, Chan FKL, Ng SC. Probiotics and COVID-19: one size does not fit all. *Lancet Gastroenterol Hepatol*. 2020. doi: 10.1016/S2468-1253(20)30122-9.

Enaud R, Prevel R, Ciarlo E, et al. The gut-lung axis in health and respiratory diseases: a place for inter-organ and inter-kingdom crosstalks. *Front Cell Infect Microbiol*. 2020; 10:9. doi: 10.3389/fcimb.2020.00009.

King S, Glanville J, Sanders ME, et al. Effectiveness of probiotics on the duration of illness in healthy children and adults who develop common acute respiratory infectious conditions: a systematic review and meta-analysis. *Br J Nutr*. 2014; 112(1):41-54. doi: 10.1017/S0007114514000075.

Hao Q, Dong BR, Wu T. Probiotics for preventing acute upper respiratory tract infections. *Cochrane Database Syst Rev*. 2015; (2):CD006895. doi: 10.1002/14651858.CD006895.pub3.

Gao QY, Chen YX, Fang JY. 2019 Novel coronavirus infection and gastrointestinal tract. *J Dig Dis*. 2020. doi: 10.1111/1751-2980.12851.

Ianiro G, Mullish BH, Kelly CR, et al. Screening of faecal microbiota transplant donors during the COVID-19 outbreak: suggestions for urgent updates from an international expert panel. *Lancet Gastroenterol Hepatol*. 2020; 5(5):430-2. doi: 10.1016/S2468-1253(20)30082-0.

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Health benefits linked to yogurt consumption could be explained as a result of improvements in gut barrier function

August 24th, 2020 by GMFH Editing Team

The mechanisms underlying associations between yogurt consumption and a reduced risk of negative health outcomes have not been widely studied. A cross-sectional study now suggests that maintaining normal gut barrier function is a new mechanism that supports the benefits of consuming yogurt.

Although the health benefits of fermented foods have been acknowledged for centuries, an emerging interest in understanding the science supporting that understanding has witnessed a huge rise over the last decade.

Within fermented foods, the health properties of fermented dairy products such as yogurt have mainly been studied in large populations. As such, epidemiological data has linked yogurt consumption with greater adherence to the Mediterranean Diet and protection against the risk factors of type 2 diabetes.

However, the mechanisms of action that explain yogurt's health benefits are multiple and presumably driven by different components (e.g. probiotic bacteria, nutrients, and the beneficial byproducts derived from fermentation).

A new cross-sectional study, led by Xuehong Zhang from the Harvard T.H. Chan School of Public Health, shows that the consumption of 2 cups of yogurt a week may confer a benefit on gut barrier function, as suggested by reduced plasma soluble CD14 concentrations.

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Health benefits linked to yogurt consumption could be explained as a result of improvements in gut barrier function

Diet is a major factor that shapes gut barrier structure and function. When it comes to the effects of fermented milks on immune-related markers, for instance, previous research has shown the effects of fermented dairy milks on modulating the number of lymphocytes and CD56 cells in students under examination stress.

The consumption of 2 cups of yogurt a week may confer a benefit on gut barrier function, as suggested by reduced plasma soluble CD14 concentrations.

In the new study, the authors explored the impact of yogurt consumption on plasma soluble CD14 concentrations – a surrogate marker of gut barrier dysfunction. Specifically, plasma sCD14 is a receptor molecule released by macrophages and hepatocytes as part of the innate immune response to lipopolysaccharide and has been used as a marker of gut hyperpermeability.

The authors conducted a cross-sectional study in 1,076 men and women using datasets from two prospective US cohorts (i.e. the Nurses' Health Study and Health Professionals Follow-up Study). After adjusting for potential confounding demographic, lifestyle and medical factors, **higher yogurt consumption (at least 2 cups/week) was associated with lower plasma sCD14 concentrations compared to non-consumers, especially in men.**

On the whole, this is the first study showing the effect of high levels of yogurt consumption on improving gut barrier function, which separates the intestinal lumen and the underlying lamina propria. In the light of current findings, strengthening the gut barrier could mediate the health benefits of yogurt in adults, thus warranting further research in order to elucidate which yogurt-based components are involved.

> “This is the first study showing the effect of high levels of yogurt consumption on improving gut barrier function”

Reference:
Luo X, Sui J, Birmann BM, et al. Association between yogurt consumption and plasma soluble CD14 in two prospective cohorts of US adults. *Eur J Nutr*. 2020. doi: 10.1007/s00394-020-02303-3.

Read the original post online at:
https://www.gutmicrobiotaforhealth.com/health-benefits-linked-to-yogurt-consumption-could-be-explained-as-a-result-of-improvements-in-gut-barrier-function/

Lactic acid bacteria in fermented foods can be transferred to the human gut

Published on June 8th, 2020 by GMFH Editing Team

Fermented foods are a known source of lactic acid bacteria. A high-throughput sequencing analysis of food and human metagenomes proves that fermented foods are a source of lactic acid bacteria for the gut microbiome, and that abundance is shaped by both age and lifestyle.

Lactic acid bacteria (LAB) have long been used for the production of fermented foods. These bacteria, which are also commensal members of the human microbiome, are known for improving lactose digestion and have been regarded as safe when ingested in cheese and yogurt.

More interestingly, some LAB present in fermented foods may contribute to human health in a manner similar to probiotics. That is, the notion that fermented food microorganisms have probiotic features is supported, as many of the species found in fermented foods are either identical to or share physiological traits with species that play a role in improving gut health. Whether the LAB we usually ingest within fermented foods become members of the gut microbiome (measured with stool samples), however, is not yet known.

Some lactic acid bacteria present in fermented foods may contribute to human health in a manner similar to probiotics

A new genome-wide analysis led by Dr. Danilo Ercolini from University of Naples Federico II (Italy) proves that **the LAB found in the human gut resemble the ones typically found in fermented foods and beverages, with some patterns shared within global populations.**

The analysis considered around 303 publicly available and new food metagenomes, corresponding to a wide range of fermented foods and beverages including cheese, yogurt and milk kefir, among others. While some bacteria grouped together in human and food genomes, the reconstruction of previously underexplored microbial genomes from food sources

allowed for the disentangling of lactobacilli found in food that did not overlap with human lactobacilli, and they require further characterization. A strain-level analysis of 9445 human metagenomes from public datasets, including multiple body sites, was performed to provide a comparison.

“Some lactic acid bacteria present in fermented foods may contribute to human health in a manner similar to probiotics”

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Lactic acid bacteria in fermented foods can be transferred to the human gut

LAB species occurred with variable prevalence and generally low abundance in the human gut, with *Streptococcus thermophilus* and *Lactococcus lactis* being the most abundant (31.2% and 16.3%, respectively). Continuous consumption of these bacteria through diet (mainly dairy products) might explain these findings, suggesting that it could be worth exploring their potential as probiotics. On the other hand, a broad range of *Lactobacillus* species of food origin were detected at lower prevalence, suggesting that they were unlikely to be long-term gut commensals.

The authors also stratified 9445 publicly available human metagenomes according to host conditions such as body site, age, westernized lifestyle and continent. It turned out that **age, lifestyle**—intended as consumption of fermented foods that vary geographically and culturally— **and geographical origin were the factors that most affected the abundance of LAB in human microbiomes**.

For instance, LAB abundance tended to increase from childhood to adulthood, which may be due to the increased consumption of fermented foods such as yogurt and cheese. As for geography, food-related LAB were most abundant in westernized populations. By contrast, China and non-westernized cohorts harbored *Leuconostoc and Weissella* from the microbiota of fermented vegetables and cereal-based fermented foods, while showing a very low abundance of *S. thermophilus* and *L. lactis*. That reflected these populations' lower consumption of dairy products.

A comparative analysis of the DNA sequences of 2859 LAB genomes showed a high level of similarity of LAB from fermented foods with those of LAB from the human gut. This noteworthy finding suggests that consuming foods rich in LAB may enrich the gut with potentially probiotic microorganisms, acknowledges Ercolini in an article in TheCork.ie.

The lack of health-related metadata from the human cohorts under consideration did not provide any clues about how LAB in stool samples were related to health.

On the whole, the analysis provides an idea of which LAB occur in the human gut. Human metagenomes also allowed for the reconstruction of LAB genomes of human origin that were not previously available, and that in itself is a step forward in the field. These findings highlight that fermented foods are a valuable source of viable LAB that can be transferred to the human gut. Last but not least, it seems that the stool detection of LAB could be used as an indicator of fermented food and probiotics consumption.

> "Lactic acid bacteria found in the human gut resemble the ones typically found in fermented foods and beverages, with some patterns shared within global populations"

Marco ML, Heeney D, Binda S, et al. Health benefits of fermented foods: microbiota and beyond. *Curr Opin Biotechnol.* 2017; 44:94-102. doi: 10.1016/j.copbio.2016.11.010.

Pasolli E, De Filippis F, Mauriello IE, et al. Large-scale genome-wide analysis links lactic acid bacteria from food with the gut microbiome. *Nat Commun*. 2020; 11:2610. doi: 10.1038/s41467-020-16438-8.

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A fermented milk product with a probiotic bacterium may improve the tolerance of a flatulogenic diet in healthy subjects

Published on March 2nd, 2020 by GMFH Editing Team

Meal residues entering the colon are metabolized by the gut microbiota and may lead to functional digestive symptoms in the general population. New research shows that probiotics may help improve the tolerance of a plant-based flatulogenic diet.

Although under physiologic conditions meal ingestion has a pleasurable dimension, a large proportion of the general population presents functional digestive symptoms including abdominal bloating, distension and discomfort. And gastrointestinal discomfort usually appears in the context of a plant-based diet rich in fermentable residues for our gut microbiota.

A new exploratory intervention study, led by Dr. Fernando Azpiroz from the Digestive System Research Unit at University Hospital Vall d'Hebron (Barcelona), **shows the potential role of a fermented milk product with a probiotic bacterium in improving digestive comfort in response to a plant-based diet in healthy individuals**.

Briefly, 63 healthy adult subjects received a 3-day high-residue diet—including foods such as legumes, vegetables, whole grain cereals and fruit—before and after 28 days' consumption of a fermented milk product with lactic acid bacteria and the probiotic bacterium *Bifidobacterium animalis* subsp. lactis CNCM I-2494. In an initial phase, participants received their habitual diet followed by a 3-day flatulogenic diet. Those subjects with at least 50% daily adherence to the flatulogenic diet and an increase in flatulence score equal to or higher than 2 then entered the 28-day administration phase consisting of 2 daily pots of a fermented milk product with *B. lactis* CNCM I-2494 and lactic acid bacteria.

The 3-day flatulogenic diet induced gas-related symptoms, increased the daily number of anal gas evacuations and dampened digestive well-being, compared with the habitual diet. These findings were in agreement with a previous study that found patients omplaining of flatulence had an increased number of gas evacuations related with abdominal symptoms, which was tied to instability in the gut microbial ecosystem.

> The 3-day flatulogenic diet induced gas-related symptoms, increased the daily number of anal gas evacuations and dampened digestive well-being

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A fermented milk product with a probiotic bacterium may improve the tolerance of a flatulogenic diet in healthy subjects

Consuming the fermented milk product for 28 days reduced the subjective flatulence sensation and improved digestive well-being, which was accompanied by a reduction in the number of daily anal gas evacuations.

Although fermented milk product consumption did not lead to changes in fecal microbiota diversity, some associations were found between the product and both clinical parameters and the relative abundance of some gut bacteria.

For instance, the reduction in the number of anal gas evacuations correlated with a decrease in the relative abundance of *Mogibacterium* and *Parvimonas* and an increase in *Desulfobibrionaceae*. Furthermore, the reduced flatulence sensation was associated with a depletion in the relative abundance of *Methanobrevibacter* species and an increase in *Succinivibrio*.

On the whole, these findings show that the inclusion of a fermented milk product with a probiotic bacterium in the diet of healthy subjects may help improve the tolerance of a plant-based flatulogenic diet. The authors suggested that the improvement of digestive symptoms through intake of a fermented milk product could be related to both the gut microbiota metabolism of plant substrates and an effect probiotics have on gut sensitivity. Due to the high prevalence of functional digestive symptoms among the general population, exploring the role of probiotics for managing them might be worthwhile.

This review article belongs to the special issue "Food and Diet for Gut Function and Dysfunction" in the peer reviewed open access journal *Nutrients*. This issue was instigated by the European Society of Neurogastroenterology and Motility, guest edited by Profs Fernando Azpiroz and Paul Enck, and made possible through an unrestricted educational grant from Danone.

> "Due to the high prevalence of functional digestive symptoms, exploring the role of probiotics for managing them might be worthwhile"

References:
Le Nevé B, Martinez de la Torre A, Tap J, et al. A fermented milk product with *B. lactis* CNCM I-2494 and lactic acid bacteria improves gastrointestinal comfort in response to a challenge diet rich in fermentable residues in healthy subjects. *Nutrients*. 2020; 12(2), 320. doi: 10.3390/nu12020320.

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Why the gut microbiome is behind the health effects of the Mediterranean diet

April 14th, 2020 by GMFH Editing Team

The Mediterranean dietary pattern has been largely associated with improved health outcomes. Two new randomized controlled trials reveal the contribution of gut microbiome composition and functions to explaining the potential beneficial effects of the Mediterranean diet.

People following a Mediterranean diet (MedDiet) — characterized by low intake of refined cereal products, dairy and meat products and higher amounts of vegetables, fruits, legumes, whole grains, fish and a daily serving of nuts—show the best overall health and appear to be protected from metabolic-related diseases, cancer and even mental health-related disorders.

Two new human intervention studies have recently made progress towards understanding the gut microbiome's involvement in the protective effects of the MedDiet.

In the first randomized controlled study, sedentary subjects who were overweight or obese were assigned to follow either a MedDiet (n = 43) or their regular diet (n = 39), characterized by low amounts of fruits and vegetables, for a period 8 weeks. It should be acknowledged that participants in the MedDiet group were instructed to improve the quality of their diet without changing their habitual energy intake, macronutrient intake or physical activity.

In the MedDiet subjects, a reduction in total plasma cholesterol was reported as early as 4 weeks after the beginning of the diet. In addition, lower total high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol was observed at the end of the intervention, which was proportional to MedDiet adherence rates.

Metabolomic analyses of feces, urine and blood showed that the MedDiet was characterized by higher levels of the biomarkers of whole grains,

legumes—commonly used as biomarkers of plant food intake—**vegetables and nuts, together with reduced concentrations of the biomarkers of meat and protein degradation products**.

Specific changes in the gut microbiota's composition and functions were also found, including an abundance of butyrate-producing bacteria *Faecalibacterium prausnitzii* and *Roseburia*; a lower abundance of the potentially proinflammatory *Ruminococcus gnavus* and *R. torques*; and increased urinary levels of urolithin glucuronides produced by urolithin-producing gut bacteria. Although MedDiet consumption was related to a reduction in fecal levels of bile acids and branched-chain fatty acids when compared with the conventional diet group, the high fiber intake did not affect fecal levels of short-chain fatty acids.

Baseline gut microbiota is known to be a major factor that influences how people respond to dietary intervention. The authors found that the participants with higher baseline levels of *Bacteroides uniformis* and

Why the gut microbiome is behind the health effects of the Mediterranean diet

B. vulgatus and lower levels of *Prevotella copri* reduced their Homeostatic Model Assessment for Insulin Resistance. Furthermore, subjects showing increased gene richness displayed lower levels of C-reactive protein after dietary intervention.

In the second randomized controlled trial, elderly non-frail and pre-frail subjects across five European countries followed either a MedDiet (n = 323) or a control diet (n = 289) for 1 year.

Regardless of body mass index and age, **adherence to a MedDiet led to a higher abundance of different taxa that were positively linked to markers of lower frailty and better cognitive function and negatively associated with inflammatory markers such as C-reactive protein and interleukin-17**.

Although diet and gut microbiome profiles differed between countries at baseline, gut microbiome diversity remained almost unaffected by the MedDiet across different countries. Interestingly, **high levels of adherence to the MedDiet attenuated the loss of gut microbiome diversity across the study, with 75 operational taxonomic units (OTUs) predicting the microbiome's response to the diet**. On the other hand, machine learning methods allowed for diet-responsive taxa to be identified. While 44 OTUs showed a positive association with adherence to the diet, 45 OTUs were negatively associated.

A prediction of fecal microbial metabolites based on gut microbiota species suggested that the MedDiet promoted short-chain fatty acid production while decreasing detrimental metabolites, including bile acids and cresols.

On the whole, these studies show that one of the ways by which the MedDiet is linked to better metabolic health and healthy ageing in older adults is through positive changes in the gut microbiome at both the composition and functional level. Further studies will need to focus on what key nutrients and food staples in a MedDiet are responsible for these positive gut microbiome changes and who will benefit the most.

> These studies show that one of the ways by which the MedDiet is linked to better metabolic health and healthy ageing is through positive changes in the gut microbiome

Reference:
Meslier V, Laiola M, Roager HM, et al. Mediterranean diet intervention in overweight and obese subjects lowers plasma cholesterol and causes changes in the gut microbiome and metabolome independently of energy intake. *Gut* Epub ahead of print: 2 April 2020. doi: 10.1136/gutjnl-2019-320438.

Ghosh TS, Rampelli S, Jeffery IB, et al. Mediterranean diet intervention alters the gut microbiome in older people reducing frailty and improving health status: the NU-AGE 1-year dietary intervention across five European countries. *Gut* Epub ahead of print: 2 April 2020. doi: 10.1136/gutjnl-2019-319654.

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New research shows the keto diet, used to treat neurological and metabolic diseases, suppresses bifidobacteria and Th17 cells

Published on June 15th, 2020 by Andreu Prados

Could the keto diet's therapeutic benefits be linked to changes in the gut microbiota? New work in mice and 17 men who are overweight or obese reveals ketone bodies exert suppression of bifidobacteria and intestinal pro-inflammatory Th17 cells.

Although the ketogenic (or keto) diet was initially used for treating childhood refractory epilepsy in the 1920s, fasting has been used to treat epilepsy since 500 BC. Later on, variations of the ketogenic diet (such as the Atkins diet) have appeared and its use has extended into adults for purposes other than reducing seizure frequency. They include treating weight loss, metabolic syndrome, certain cancers and psychiatric disorders such as Alzheimer's disease.

This high-fat diet resembles the physiological effects of fasting by restricting carbohydrate intake to between 20g and 50g non-fiber carbohydrate per day (an average person in an industrialized country consumes 200g carbohydrate per day). This means replacing grains, fruit, starchy vegetables, legumes and sweets with carb-free or very low-carb foods such as non-starchy vegetables, cheese, avocados, nuts and seeds, eggs, meat, seafood and olive or coconut oil for cooking and dressing. That fat is then turned into ketone bodies in the liver, which can be taken up and used to fuel the body's cells.

While scientists still struggle with figuring out which mechanisms underlie the keto diet's therapeutic benefits, the gut microbiota, epigenetic changes and metabolic reprogramming appear to be involved in the response to diet.

Elaine Hsiao and her colleagues found that the microbiome is required for the anti-seizure effects of the keto diet. When germ-free mice received stool from mice on a keto diet, seizures were reduced, with *Akkermansia muciniphila* and *Parabacteroides* being involved in reducing electrical activity in the brain.

This has led scientists to explore whether the keto diet might be worth considering in gastrointestinal disease.

A new study in mice and humans, led by Peter J. Turnbaugh from UC San Francisco, **breaks down the effects of the keto diet on the gut microbiome involving a reduction in bifidobacteria levels and pro-inflammatory Th17 immune cells**.

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New research shows the keto diet, used to treat neurological and metabolic diseases, suppresses bifidobacteria and Th17 cells

First, Ang and colleagues assigned 17 men who were overweight or obese (but non-diabetic) to a control diet for 4 weeks, followed by the keto diet for 4 weeks. **Metagenomic sequencing revealed bifidobacteria species**—in particular ***Bifidobacterium adolescentis***—**decreased the most on the keto diet**.

The authors were also interested in exploring whether these changes were specific to the keto diet or were also observed in the high-fat and high-carbohydrate diet that is known to promote metabolic disease in mice by inducing shifts in the gut microbiome. To this end, Ang and colleagues fed groups of mice with high-fat diets formulated with graded levels of carbohydrates. It turned out that ***Bifidobacterium*** **levels decreased with increasing carbohydrate restriction, thus highlighting that carbohydrate restriction, rather than high-fat intake, is the main contributor to the keto diet's impact on the gut microbiome**.

The mucus layer was maintained in the absence of dietary carbohydrates and bile acid metabolism was not affected. This led the authors to test whether ketone bodies themselves could be directly responsible for the progressive decreasing of *Bifidobacterium* as carbohydrates decreased.

Feeding mice with the high-fat diet and high-carbohydrate diet or the keto diet supplemented with a synthetic ketone ester—developed for mimicking ketosis without modifying diet—led to increased levels of beta-hydroxybutyrate ketone bodies in the intestinal lumen and less adiposity. That can be explained by the fact that, beyond the liver, intestinal epithelial cells are also a source of ketone bodies.

Interestingly, *in vitro* experiments in human stool samples and work in rodents showed that **ketone bodies selectively inhibited bifidobacterial growth in a dose- and pH-dependent mechanism**. While other members of the gut microbiota were also affected to a lesser extent, the selective inhibitory effects of ketone bodies on *Bifidobacterium* may involve changes at the gut ecosystem's ecological level and warrants further research.

Finally, both mono-colonization of germ-free mice with *B. adolescentis*—the most abundant species in the baseline diet that experienced the most marked decrease after going on the keto diet—and human microbiome transplantations into germ-free mice showed that **the keto diet mediates the lack of intestinal pro-inflammatory Th17 induction by reducing colonization levels of *B. adolescentis***. The observed differences in the gut were also detected on Th17 cells in the visceral adipose tissue.

To sum up, this study shows that the keto diet induces changes in the gut microbiome characterized by marked suppression of bifidobacteria coupled with a decrease in intestinal Th17. Said reduction would be worth considering in the context of improving obesity and immune-related diseases with increased Th17 activation.

The results reported here regarding changes in beneficial bifidobacteria, together with gut-related side effects and the nutritional safety of the keto diet due to the exclusion of major food groups, warrants caution on the use of this diet for managing gut symptoms or gastrointestinal disease progression.

New research shows the keto diet, used to treat neurological and metabolic diseases, suppresses bifidobacteria and Th17 cells

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. Follow Andreu on Twitter @andreuprados

References:

Kossoff EH, Zupec-Kania BA, Auvin S, et al. Optimal clinical management of children receiving dietary therapies for epilepsy: updated recommendations of the international ketogenic diet study group. *Epilepsia Open*. 2018; 3(2):175-92. doi: 10.1002/epi4.12225.

Wheless JW. History of the ketogenic diet. *Epilepsia*. 2008; 49(Suppl. 8):3-5. doi: 10.1111/j.1528-1167.2008.01821.x.

Tuck CJ, Staudacher HM. The keto diet and the gut: cause for concern? *Lancet Gastroenterol Hepatol.* 2019; 4(12):908-9. doi: 10.1016/S2468-1253(19)30353-X.

Cabrera-Mulero A, Tinahones A, Bandera B, et al. Keto microbiota: a powerful contributor to host disease recovery. *Rev Endocr Metab Disord*. 2019; 20(4):415-25. doi: 10.1007/s11154-019-09518-8.

Olson CA, Vuong HE, Yano JM, et al. The gut microbiota mediates the anti-seizure effects of the ketogenic diet. *Cell*. 2018; 173(7):1728-41. doi: 10.1016/j.cell.2018.04.027.

Ang QY, Alexander M, Newman JC, et al. Ketogenic diets alter the gut microbiome resulting in decreased intestinal Th17 cells. *Cell*. 2020. doi: 10.1016/j.cell.2020.04.027.

Turnbaugh PJ, Backhed F, Fulton L, et al. Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. *Cell Host Microbe*. 2008; 3:213-23. doi: 10.1016/j.chom.2008.02.015.

Newport MT, VanItallie TB, Kashiwaya Y, et al. A new way to produce hyperketonemia: use of ketone ester in a case of Alzheimer's disease. *Alzheimers Dement*. 2015; 11(1):99-103. doi: 10.1016/j.jalz.2014.01.006.

Reddel S, Putignani L, Del Chierico F. The impact of low-FODMAPs, gluten-free, and ketogenic diets on gut microbiota modulation in pathological conditions. *Nutrients*. 2019; 11(2):373. doi: 10.3390/nu11020373.

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SELECTED CONTENT

The inflammatory potential of diet is tied to Crohn's disease risk but not to ulcerative colitis, suggests a new observational study

Published on November 2nd, 2020 by Rene van den Wijngaard

Despite the fact that current guidelines for managing inflammatory bowel diseases do not devote attention to diet as a central element of treatment, there is an increasing amount of evidence that supports the role of diet in patients with IBD. A new nationwide cohort study shows the association between the level of inflammatory potential in diet and risk of Crohn's disease.

Environmental factors involving diet may play an important role in the onset and development of inflammatory bowel diseases (IBDs), especially in their early stages. That is because of the involvement of dietary patterns and nutrients in shaping inflammatory responses that become detrimental if they persist over the long term.

A new nationwide cohort study **shows the association between the inflammatory potential of diet and risk of Crohn's disease**.

The authors used an empirical dietary inflammatory score, derived by weighting food groups based on their relationship with plasma inflammatory markers (i.e., C-reactive protein, interleukin-6 and tumor necrosis factor a receptor 2), to explore the link between dietary inflammatory potential and risk of incident IBD.

The index assesses the inflammatory potential of diet and is the weighted sum of 18 food groups based on food frequency questionnaire data, with higher scores indicating proinflammatory diets (e.g., processed and red meat, some fish, refined grains and high-energy beverages) and lower scores indicating anti-inflammatory diets (e.g., dark yellow and green leafy vegetables, tea, coffee, beer and wine).

The sample under study consisted of 328 cases of incident Crohn's disease and 428 cases of incident ulcerative colitis from 3 large prospective cohorts in the United States.

> A new nationwide cohort study shows the association between the inflammatory potential of diet and risk of Crohn's disease

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The inflammatory potential of diet is tied to Crohn's disease risk but not to ulcerative colitis, suggests a new observational study

Dietary patterns with high inflammatory potential were associated with increased risk of Crohn's disease, compared with participants who showed a high intake of foods with lower inflammatory potential.

The authors also examined whether change in dietary inflammatory potential could affect the risk of IBD. Participants who shifted from a low to a high inflammatory potential diet and those who usually consumed a proinflammatory diet showed a greater risk of Crohn's disease, compared with participants who persistently consumed a diet with low inflammatory potential.

In contrast, different levels of dietary inflammatory potential were not linked to risk of ulcerative colitis.

On the whole, the current study highlights the importance of diet in the development of Crohn's disease by modulating inflammatory mechanisms. Although more mechanistic data and intervention controlled studies are needed, the findings show that what you eat is an important modifiable factor in IBD prevention.

> "Dietary patterns with high inflammatory potential were associated with increased risk of Crohn's disease"

Editorial Head – Netherland Dr van den Wijngaard's research 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). He undertook his PhD training at Amsterdam UMC where he next became a scientific staff member in the Department of Gastroenterology and Hepatology. He carries out his research activities in the Gut Research group at the Tytgat Institute for Liver and Intestinal Research.

References:
Lo CH, Lochhead P, Khalili H, et al. Dietary inflammatory potential and risk of Crohn's disease and ulcerative colitis. *Gastroenterology*. 2020;159(3):873-883. doi: 10.1053/j.gastro.2020.05.011.

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SELECTED CONTENT

Gut microbes in celiac disease show impaired metabolism of dietary tryptophan, according to researchers at McMaster University

Published on October 27th, 2020 by Heather Galipeau

Evidence over the past few years suggests that metabolites produced from microbes in the gut play a crucial role in maintaining gut health.

Evidence over the past few years suggests that metabolites produced from microbes in the gut play a crucial role in maintaining gut health. Tryptophan is an essential amino acid that can be metabolized by certain gut microbes or host cells to produce a variety of derivatives. The products of the microbial metabolism of tryptophan are known ligands of the aryl hydrocarbon receptor (AhR), and activation of this pathway can modulate immune cell populations and barrier function in the gastrointestinal (GI) tract. Alterations in this diet-microbiota-host pathway are thought to contribute to chronic inflammation.

In 2019, Dinallo *et al* showed lower expression of AhR in the small intestine of patients with celiac disease, an immune-mediated enteropathy that occurs in genetically predisposed individuals who consume gluten in wheat, barley, and rye. The only treatment for celiac disease is strict adherence to a gluten-free diet, which is difficult to follow, has high non-adherence rates and does not always lead to complete mucosal recovery. Altered gut microbiota composition and function has been reported in patients with celiac disease. Those alterations include a decreased proportion of lactobacilli, which have a high tryptophan metabolizing capacity.

A study led by Dr. Elena Verdu in collaboration with Dr. Harry Sokol, recently published in *Science Translational Medicine*, set out to investigate the microbial link between celiac disease dysbiosis and the altered AhR pathway in celiac disease.

Using mice that express a celiac disease susceptibility gene, the authors showed that, compared to a low tryptophan diet, a high tryptophan diet shifted gut microbiota composition, leading to a higher abundance of *Lactobacillus* and *Ruminococcus gnavus*, which are known AhR ligand producers. That change was accompanied by higher levels of AhR ligands in the feces and increased AhR pathway activation in the small intestine. On the other hand, lower levels of kynurenine, a tryptophan metabolite produced mainly by host cells and implicated in chronic inflammation, was found in mice fed the low tryptophan diet. Importantly, intestinal contents from mice fed the high tryptophan diet had an increased ability to activate AhR, and they were protected from gluten-induced inflammation. Mice fed the high tryptophan diet showed a lower degree of enteropathy and lower number of intraepithelial lymphocyte counts, which are key measurements for diagnosing celiac disease.

The authors then used two different strategies to confirm that AhR signaling could modulate gluten-induced inflammation in mice. First, the authors supplemented mice with two strains of lactobacillus with a high capacity for producing AhR ligands (Lamas *et al*, 2016, Natividad *et al*, 2018). Similar to previous studies, lactobacillus supplementation increased the capacity of the small intestinal microbiota to activate AhR, even in the context of a low tryptophan diet, while reducing gluten-induced inflammation. To exclude

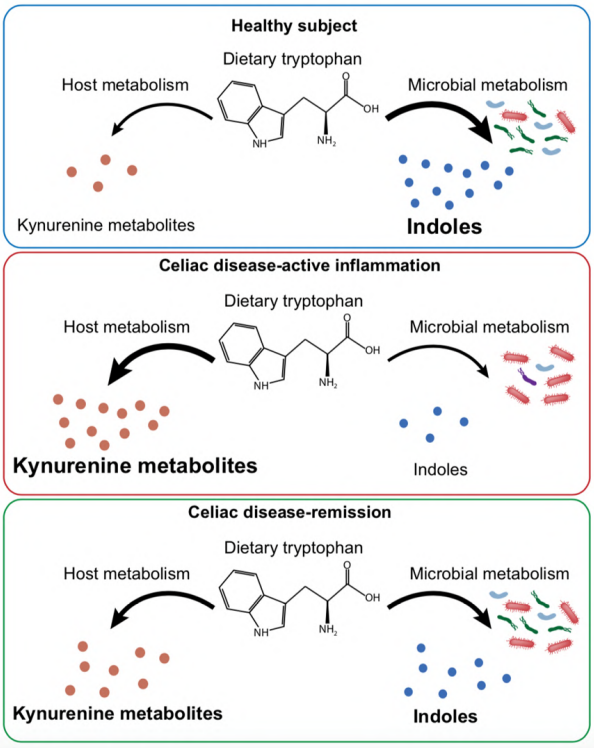
Gut microbes in celiac disease show impaired metabolism of dietary tryptophan, according to researchers at McMaster University

the possibility that the lactobacillus strains could have independent anti-inflammatory effects, the authors next used a pharmacological approach and treated mice with an AhR agonist, which also reduced the degree of gluten-induced inflammation.

Finally, the authors studied a cohort of patients with active celiac disease, patients after 2 years on a gluten-free diet (in remission), and non-celiac controls. Microbial metabolites known to activate AhR were lower in the feces of active celiacs compared to controls. In line with those findings, the microbiota of active celiacs had a reduced capacity to activate AhR and reduced expression of AhR pathway genes such as IL-22, a cytokine that is important in host defense at mucosal surfaces and in tissue repair. Notably, AhR activation by the microbiota and IL-22 expression were rescued in patients treated with the gluten-free diet.

Together, the findings suggest that the microbiota in active celiac disease shows an impaired metabolism of tryptophan, leading to reduced AhR ligand production and reduced expression of the barrier-promoting cytokine IL-22. At the same time, tryptophan metabolism by host cells leading to proinflammatory kynurenine metabolites increased in active celiac disease, potentially contributing to inflammation. The gluten-free diet partly corrected the impaired tryptophan metabolism by reducing kynurenine production and increasing AhR agonist production, leading to AhR activation and IL-22 expression.

The findings are in line with previous studies in metabolic syndrome and colitis, and suggest that the products of the microbial metabolism of tryptophan could be used as biomarkers for dysbiosis. Importantly, the findings extend the potential therapeutic value of targeting tryptophan catabolites from microbial metabolism to celiac disease. The gluten-free diet is very challenging for patients to follow. *"A proportion of patients with celiac disease will not respond to a gluten-free diet, either initially, or will re-experience symptoms. Also, healing of inflammation in the intestine can take years, despite compliance with the diet*," says Verdu. Future clinical studies should examine therapeutic strategies, such as tryptophan supplementation in combination with next generation probiotics that produce AhR ligands from the diet, in celiac patients who do not respond to a gluten-free diet.



Graphical abstract created by Heather Galipeau and published in Science Translational Medicine.

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Gut microbes in celiac disease show impaired metabolism of dietary tryptophan, according to researchers at McMaster University

Heather Galipeau is a Research Associate at McMaster University (Canada) where she is researching dietary and microbial interactions in celiac disease and inflammatory bowel disease. She obtained her PhD in 2015 from McMaster University in Elena Verdu's lab, during which she found that the small intestinal microbial background influences the degree of immuno-pathology triggered by dietary antigens, such as gluten.

References:

Lamas B, Natividad JM, Sokol H. Aryl hydrocarbon receptor and intestinal immunity. *Mucosal Immunol*. 2018; 11(4):1024-38. doi: 10.1038/s41385-018-0019-2.

Dinallo V, Marafini I, Di Fusco D, et al. Protective effects of aryl hydrocarbon receptor signaling in celiac disease mucosa and in poly I:C-induced small intestinal atrophy mouse model. *Front Immunol*. 2019; 10:91. doi: 10.3389/fimmu.2019.00091.

Verdu EF, Galipeau HJ, Jabri B. Novel players in coeliac disease pathogenesis: role of the gut microbiota. *Nat Rev Gastroenterol Hepatol*. 2015; 12(9):497-506. doi: 10.1038/nrgastro.2015.90.

Lamas B, Richard ML, Leducq V, et al. CARD9 impacts colitis by altering gut microbiota metabolism of tryptophan into aryl hydrocarbon receptor ligands. *Nat Med*. 2016; 22(6):598-605. doi: 10.1038/nm.4102.

Natividad JM, Agus A, Planchais J, et al. Impaired aryl hydrocarbon receptor ligand production by the gut microbiota is a key factor in metabolic syndrome. *Cell Metab*. 2018; 28(5):737-49. doi: 10.1016/j.cmet.2018.07.001.

Lamas B, Hernandez-Galan L, Galipeau HJ, et al. Aryl hydrocarbon receptor ligand production by the gut microbiota: a new therapeutic target in celiac disease. *Sci Transl Med*. 2020.

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SELECTED CONTENT

Could targeting the gut help treat type 2 diabetes? Intestinal bioactive compounds offer clues for developing new antidiabetics

Published on October 22nd, 2020 By Patrice D. Cani

Enteric neurons have recently emerged as a new target in the management of type 2 diabetes. The findings in mice and humans identify new intestinal bioactive compounds released after prebiotic administration, with potential for improving glucose metabolism.

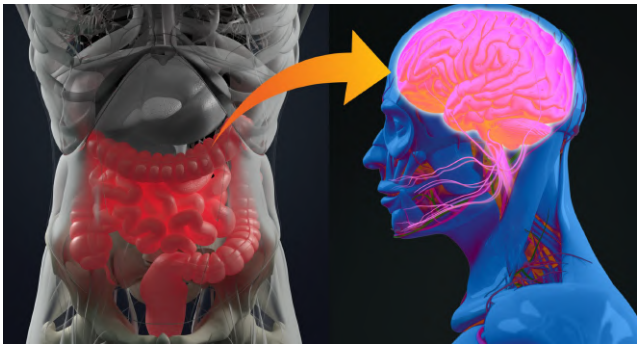
The connection between gut microbiome, brain unction and glucose metabolism is currently a hot area of research. As a result, the enteric nervous system (ENS) has emerged as a new target in the management of type 2 diabetes (T2D), while the underlying mechanisms remain unknown.

Together with professor Claude Knauf and our teams, we previously showed that bioactive peptides present in the gut of mice can modulate duodenal contractility via the hypothalamus, thus controlling peripheral glucose utilization. This discovery led us to the identification of bioactive molecules originating in the gut and that we called 'enterosynes'. These molecules target the ENS to improve insulin sensitivity.

Even though strategies that modulate the gut microbiome, such as probiotics, prebiotics and fecal transplants, have been shown to alleviate features of metabolic syndrome, a characterization of intestinal actors with potential antidiabetic properties is lacking.

In a new study published in Gut, with Dr Anne Abot and Eve Wemelle we sought to identify novel gut molecules and receptors involved in glucose metabolism by exploring the action of prebiotics within the gut microbiota in diabetic versus normal mice.

The administration of the prebiotic oligofructose decreased duodenal contraction frequency by modulating enteric neurons activity, which, in



turn, led to attenuated hyperglycemia and decreased inflammatory markers in the diabetic mice's white adipose tissue. By using lipidomic analysis, we discovered that the modulation of the microbiota observed upon prebiotic feeding was associated with a selective increase in the colonic levels of 12-hydroxyeicosatetraenoic acid (12-HETE)—an intestinal bioactive lipid derived from arachidonic acid. Then, when we decided to test whether this 12-HETE was acting, we found that it improved glucose metabolism by eliciting gut-to-brain to peripheral organ signals that resulted in an increased glucose uptake and eventually lower blood glucose in the mice's.

We confirmed ex vivo the effects of the identified intestinal lipid on duodenal contractility, which were dependent on the presence of mu-opioid receptors (MOR)—activated by enkephalin—and eventually signal through the nuclear receptor proliferator-activated receptor gamma (PPAR-g). Altogether, the signaling pathway known as

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Could targeting the gut help treat type 2 diabetes? Intestinal bioactive compounds offer clues for developing new antidiabetics

12-hydroxyeicosatetraenoic acid/ENK-MOR/PPAR-g can transmit the signal originated within the colon to the brain, highlighting how prebiotic effects within the gut act systemically. As a result, the final outcome was an improvement in the diabetic mice's inflammatory state and glucose utilization compared to control mice.

The aforementioned preclinical findings were supported by human data showing a reduction in the levels of 12-hydroxyeicosatetraenoic acid and a decreased expression of the proenkephalin and MOR messenger ribonucleic acids in the duodenum of patients with T2D.

Overall, in the study, we identified novel intestinal bioactive compounds that could aid in the development of new antidiabetic drugs. In the light of the findings, enkephalin and 12-hydroxyeicosatetraenoic acid emerge as new targets with a potential role in treating T2D. As the new bioactive lipid discovered in the study can also be produced by certain gut bacteria beyond production by the body, we argue that both approaches could serve as a therapeutic target.

Professor Patrice D. Cani is a researcher from the Belgian Fund for Scientific Research (FRS-FNRS-WELBIO). He is leading a team at the Louvain Drug Research Institute (LDRI) from the University of Louvain (UCLouvain), Brussels, Belgium. His main research interests are the investigation of interactions between the gut microbiota and the host in the context of obesity, type 2 diabetes, cardiometabolic disorders and cancer. He is author and co-author of more than 260 scientific research publications, reviews and book chapters. His motto is: "In Gut We Trust".

References:

Fournel A, Drougard A, Duparc T, et al. Apelin targets gut contraction to control glucose metabolism via the brain. *Gut*. 2017; 66(2):258-269. doi: 10.1136/gutjnl-2015-310230.

Abot A, Wemelle E, Laurens C, et al. Identification of new enterosynes using prebiotics: roles of bioactive lipids and mu-opioid receptor signalling in humans and mice. *Gut*. 2020. doi: 10.1136/gutjnl-2019-320230.

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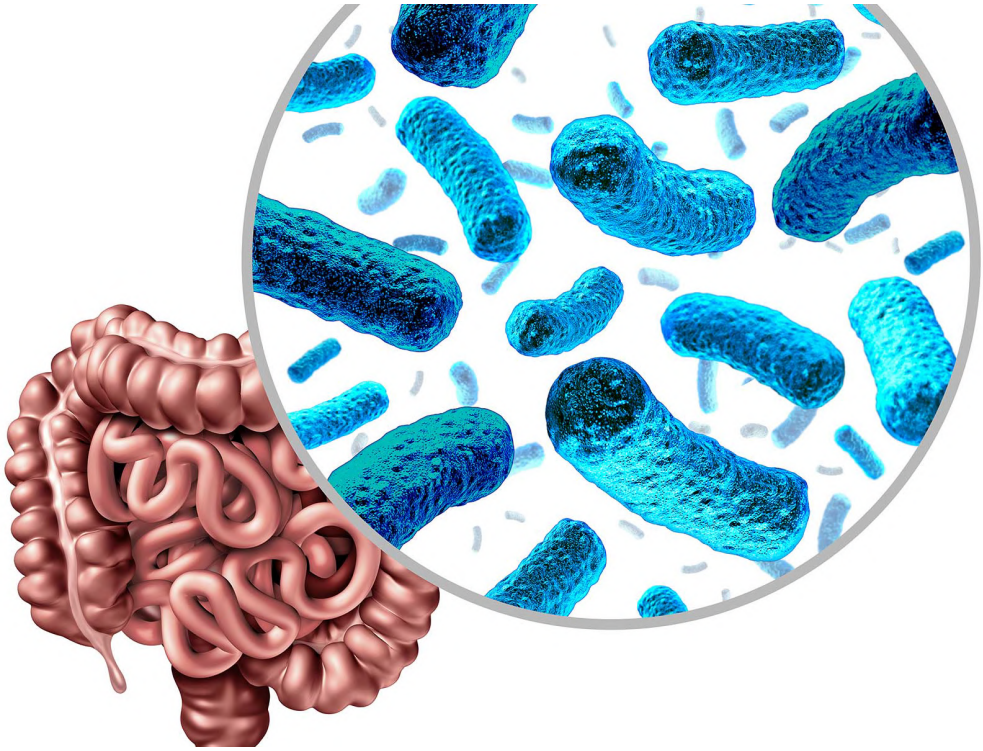
Current evidence-based strategies for modulating the gut microbiota: where do we stand?

Published on September 28th, 2020 by Andreu Prados

An altered balance of the community of microbes that reside in our body, especially within the gut, has been linked to a wide range of intestinal and extraintestinal diseases. What evidence-based strategies are currently available for modulating the gut microbiota?



Alteration in the balance of the community of microbes that reside in the body, especially within the gut, has been linked to a wide range of intestinal and extraintestinal diseases. While the causality for most of those conditions has yet to be established, the causal link between the microbiome and disease states has been shown for *Helicobacter pylori-associated* peptic ulceration and gastric cancer and *Clostridioides difficile* infection-associated diarrhea.

One of the most frequently studied therapeutic applications of microbiome science is the use of fecal microbiota transplantation (FMT) for recurrent *C. difficile* infection, first reported in 1958. FMT's therapeutic benefits can be explained by an increased diversity of bacteria, viruses, fungi and archaea that can engraft into the recipient host and help improve the gut microbiota's functional diversity. In addition, FMT is being tested in almost 300 clinical trials for a broad

Current evidence-based strategies for modulating the gut microbiota: where do we stand?

range of disease indications, including inflammatory bowel diseases, irritable bowel syndrome, acute pancreatitis, graft versus host disease, autoimmune diseases (e.g., multiple sclerosis), cancer, and even psychiatric conditions (e.g., epilepsy and Parkinson's disease).

Although FMT has been shown to be effective and safe for *C. difficile* infection, safety concerns related to disorders linked to changes in the gut microbiota have been reported. For instance, in the light of the current COVID-19 pandemic, screening of donors for severe acute respiratory syndrome coronavirus 2 is recommended.

Beyond undefined fecal microbiota transplants, targeted formulations used to shape host microbiota (defined microbial consortia) are an alternative for overcoming issues of reproducibility and scalability. The most frequently studied formulations are probiotics, and a recent update of their clinical benefits can be found elsewhere (e.g., usprobioticguide.com and probioticchart.ca).

In addition to traditional probiotics, live microorganisms developed as therapeutic agents with defined clinical benefit claims (also called live biotherapeutics products or next-generation probiotics) are under investigation. Next-generation probiotics in particular include microorganisms that do not have a history of use as health-promoting agents to date, including genetically modified microorganisms, and will more likely follow a drug regulatory framework. Although the first next-generation probiotics focused on microorganism taxonomy, the most recent ones focus on the functional attributes of administered microorganisms.

The term probiotic implies that microorganisms should be alive at the time of ingestion. However, scientists have turned to compounds produced by microorganisms, released from food components or microbial constituents, including non-viable cells—also called postbiotics (and less frequently paraprobiotics, parapsychobiotics and ghost probiotics)—that have a potential to promote health and well-being when administered in adequate amounts. The case of heat-inactivated *Akkermansia muciniphila* to alleviate features of metabolic syndrome in overweight and obese subjects, for instance, is within the scope of a postbiotic.

Other strategies for modulating the gut microbiome include diet, prebiotics and the aforementioned postbiotics. Together with medication, diet is the factor that most affects gut microbiota composition and functional diversity, with microbial shifts apparent within just 24 hours, as well as in the long term. When it comes to prebiotics, they can be utilized by members of the host microbiota and/or by the co-administered live microbe. The flexibility of gut-dwelling bacteria in response to different types of fiber is also being studied as a way forward in developing personalized diets for tailoring the gut microbiota in the coming years.

It should also be acknowledged that not all diseases exhibit the same degree of gut microbiota alteration, and that may, in turn, affect the efficacy of selected strategies for modulating the gut microbiome. While *C. difficile* infection is an example of disease with profound gut microbiota changes, others only exhibit a subtle change in gut microbes. That makes it difficult to develop personalized predictions to dietary

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responses, diagnostics and therapeutics based on the gut microbiome. Moreover, multiple factors can affect the efficacy of procedures aimed at modulating the gut microbiota, including the means of gut microbiota modulation, preparative regimen and concurrent dietary intake, among others. Another caveat in the field is the current lack of a definition of what constitutes a healthy gut microbiota.

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References:

Wargo JA. Modulating gut microbes. Science. 2020; 369(6509):1302-3. doi: 10.1126/science.abc3965.

O'Toole PW, Marchesi JR, Hill C. Next-generation probiotics: the spectrum from probiotics to live biotherapeutics. *Nat Microbiol*. 2017; 2:17057. doi: 10.1038/nmicrobiol.2017.57.

David LA, Maurice CF, Carmody RN, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature*. 2014; 505(7484):559-563. doi: 10.1038/nature12820.

Delzenne NM, Bindels LB. Food for thought about manipulating gut bacteria. *Nature News and Views*. 2019; 577:32-34. doi: 10.1038/d41586-019-03704-z.

Collado MC, Vinderola G, Salminen S. Postbiotics: facts and open questions. A position paper on the need for a consensus definition. *Benef Microbes*. 2019; 10(7):711-719. doi: 10.3920/BM2019.0015.

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A panel of experts provide guidance regarding appropriate use and scope of the term 'synbiotic'

Published on September 7th, 2020 by Mary Ellen Sanders

The idea that prebiotics could be combined with probiotics to form synbiotics emerged in 1995. Now, a panel of experts under the auspices of the International Scientific Association for Probiotics and Prebiotics (ISAPP) updates the definition and scope of the word 'synbiotic'.

A history of synbiotics

The idea that a combination of both prebiotics and probiotics, then defined as synbiotics, can confer health benefits dates back to 1995. Later, in 2011, it was proposed that synbiotics could be designed in one of two ways, either as a complementary or synergistic synbiotic.

Since then, the field has advanced, including preclinical and clinical studies supporting the role of synbiotics in health and disease states.

In the light of the growing body of evidence for synbiotics, the existing definition of a synbiotic as a product composed of both prebiotics and probiotics imposed an undue limitation to the concept, and a new view of synbiotics was needed.

A new definition and scope for synbiotics

A panel of experts in the field of microbiology, gastrointestinal physiology, immunology, food and nutritional science and metabolism met under the

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auspices of the International Scientific Association for Probiotics and Prebiotics (ISAPP) in May 2019 to update the definition of synbiotics. The outcome of this panel has now been published as a consensus statement in *Nature Reviews Gastroenterology & Hepatology*.

The panel updated the new definition of a synbiotic (sometimes incorrectly referred to as 'symbiotic') as **"a mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host"**.

Microorganisms that must be targeted by the prebiotic can include either members of the individual gut microbiota or microorganisms co-administered in the synbiotic.

The panel also defined two subsets of synbiotics: complementary and synergistic.

- A **'complementary synbiotic'** (this is indeed the original definition of a synbiotic) consists of a probiotic combined with a prebiotic that target the host microbiota (each component works independently to achieve one or more health benefits and must meet the minimum criteria for a probiotic or a prebiotic).
- A **'synergistic synbiotic'** is designed so that the substrate is selectively utilized by the co-administered live microorganism(s) (each component does not necessarily meet criteria for a probiotic or a prebiotic, as long as the synbiotic itself has health benefits).

Target areas of the host and considerations for study design

Another new aspect of the definition of synbiotics is that **it is focused not only on humans, but also on companion or agricultural animals**. The health properties of a synbiotic can also be reported within a specific population in the target host (e.g., healthy humans at different developmental stages). **Beyond the intestinal microbial ecosystem, a synbiotic can also be applied to any part of the human body colonized by microorganisms (e.g. skin) in the form of foods, non-foods, nutritional supplements or drugs**.

The beneficial effect(s) of a synbiotic on health must be confirmed in the target host, which has implications when studying the efficacy of synergistic synbiotics versus complementary synbiotics. For synergistic synbiotics, evidence of selective utilization of the substrate and a health benefit should be demonstrated in the same study. In contrast, in complementary synbiotics, the selective utilization of the prebiotic has already been established so the synbiotic only needs to show a health benefit of the combined ingredients.

In both cases, the probiotic and the prebiotic in the synbiotic should be appropriately characterized, safety must be established for the intended use, and the active ingredients must be sufficiently stable.

A challenge in the field includes the demonstration of both the selective utilization of the substrate by microbes and health benefits; not all clinical trials allow for disentangling synbiotics' mechanisms of action. In addition, the biomarkers or symptoms used to assess the one or more health benefits of a particular synbiotic need to be validated.

Evidence in humans supporting the use of synbiotics

Dose, duration and composition of a synbiotic shape their final potential for efficacy, together

A panel of experts provide guidance regarding appropriate use and scope of the term 'synbiotic'

with external and internal factors including host diet, medication use and genetic background. Many different combinations of live microorganisms and selectively utilized substrates could qualify as synbiotics as long as there is evidence in human studies supporting their health benefits.

Blinded, randomized, controlled trials have shown orally administered complementary synbiotics can aid in the following:

Prevention of surgical infections.
Treatment of non-alcoholic fatty liver disease.
Prevention of sepsis in infants.
Treatment of metabolic syndrome.
Treatment of type 2 diabetes mellitus.
Treatment of dyslipidemia.
Treatment of inflammation.
Treatment of irritable bowel syndrome.
Eradication of Helicobacter pylori.
Treatment of polycystic ovarian syndrome.
Treatment of chronic kidney disease.
Prevention and treatment of atopic dermatitis.

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 and is currently the organization's executive science officer.

References:

Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. *J Nutr*. 1995; 125(6):1401-12. doi: 10.1093/jn/125.6.1401.

Kolida S, Gibson GR. Synbiotics in health and disease. *Annu Rev Food Sci Technol*. 2011; 2:373-93. doi: 10.1146/annurev-food-022510-133739.

Swanson KS, Gibson GR, Hutkins R, et al. The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of synbiotics. *Nat Rev Gastroenterol Hepatol*. 2020. doi: 10.1038/s41575-020-0344-2.

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Scientists re-classify the *Lactobacillus* genus into 25 genera including groups of closely related species

Published on September 7th, 2020 by Mary Ellen Sanders

More than 250 species have been assigned to the genus *Lactobacillus* in recent decades. Now, a group of 15 scientists from all over the world have reclassified the genus *Lactobacillus* into 25 genera, which include 23 novel genera.

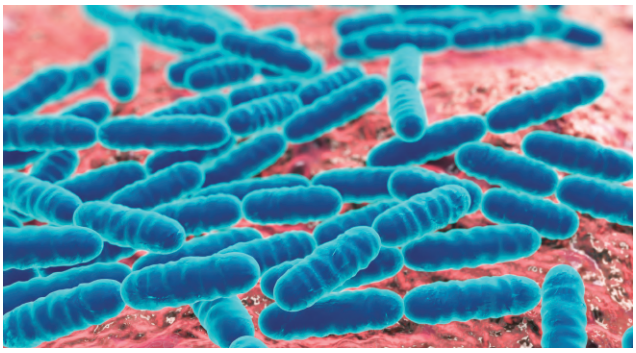
The *Lactobacillus genus*, described for the first in 1901, contains species of rod-shaped bacteria that have long been companions for humans in fermented foods and as members of digestive and vaginal cavities. Many currently used probiotics come from the *Lactobacillus genus*. Nicknamed 'lactobacilli', this group of microbes is multifunctional, with benefits ranging from extending the shelf life of foods (e.g., to make yogurt or cheese from milk) to improving health when administered in the form of probiotic foods and supplements.

Using current DNA analysis tools, an international collaboration of researchers realized that the genetic makeup of bacteria grouped into the *Lactobacillus genus* was so diverse that it deserved a new nomenclature classification.

Looking at bacterial whole-genome sequences of each *Lactobacillus* species has enabled 15 scientists to reclassify the genus *Lactobacillus* into 25 genera. These *Lactobacillus* taxonomy changes are summarized in this ISAPP infographic for scientists and in this ISAPP infographic for consumers.

Scientists have reclassified the genus *Lactobacillus* into 25 genera, including the emended genus *Lactobacillus* (*L. delbrueckii* group and *Paralactobacillus*) and 23 novel genera:

Acetilactobacillus,
Agrilactobacillus,
Amylolactobacillus,
Apilactobacillus,
Bombilactobacillus,
Companilactobacillus,
Dellaglioa,
Fructilactobacillus,
Furfurilactobacillus,
Holzapfeliat,
Lacticaseibacillus,
Lactiplantibacillus,
Lapidilactobacillus,
Latilactobacillus,
Lentilactobacillus,
Levilactobacillus,
Ligilactobacillus,
Limosilactobacillus,
Liquorilactobacillus,
Loigolactobacilus,
Paucilactobacillus,
Schleiferilactobacillus,
Secundilactobacillus.



This new *Lactobacillus* taxonomic classification means that species that are more closely related on the basis of shared physiological and metabolic properties belong to the same genus. In turn, this may facilitate our understanding of common mechanisms that could mediate probiotic health benefits, as acknowledged in a previous ISAPP consensus document.

While the genera names of some commercially relevant lactobacilli have changed (e.g. from *Lactobacillus casei* to *Lacticaseibacillus casei*), in other cases it remains the same (e.g. *Lactobacillus delbrueckii subsp. bulgaricus*). **Further, while genus names may have changed, names that refer to species have not**.

Scientists re-classify the Lactobacillus genus into 25 genera including groups of closely related species

For species commonly associated with probiotics, the new genera names begin with the letter "L". This means that the abbreviated form of genus/species—such as *L. rhamnosus*—may still be used.

A handy web tool was developed by researchers in the project to assist in learning the new names.

On the whole, over 250 species previously assigned to the genus *Lactobacillus* are now referred to with a new genus name. Changes in the nomenclature of bacteria within the genus *Bifidobacterium* are also expected in the foreseeable future.

For scientists and healthcare practitioners, the changes in *Lactobacillus* taxonomy and nomenclature have two implications:
- A brief explanation of the changes in genus names may need to be provided to academic journal editors or reviewers.
- When searching the scientific literature for the health benefits of a specific probiotic strain, searches need to be carried out under both the old and new genus name.

> This new *Lactobacillus* taxonomic classification may facilitate our understanding of common mechanisms that could mediate probiotic health benefits

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 and is currently the organization's executive science officer.

References:
International Scientific Association for Probiotics and Prebiotics. New names for important probiotic Lactobacillus species. 2020 Apr 12 [cited 20 April 2020]. In: ISAPP Science Blog [Internet]. Sacramento: ISAPP 2020. [about 2 screens]. Available from: https://isappscience.org/new-names-for-important-probiotic-lactobacillus-species/.

Zheng J, Wittouck S, Salvetti E, et al. A taxonomic note on the genus *Lactobacillus*: Description of 23 novel genera, emended description of the genus *Lactobacillus* Beijerinck 1901, and union of *Lactobacillaceae* and *Leuconostocaceae*. Int J Syst Evol Microbiol. 2020. doi: 10.1099/ijsem.0.004107.

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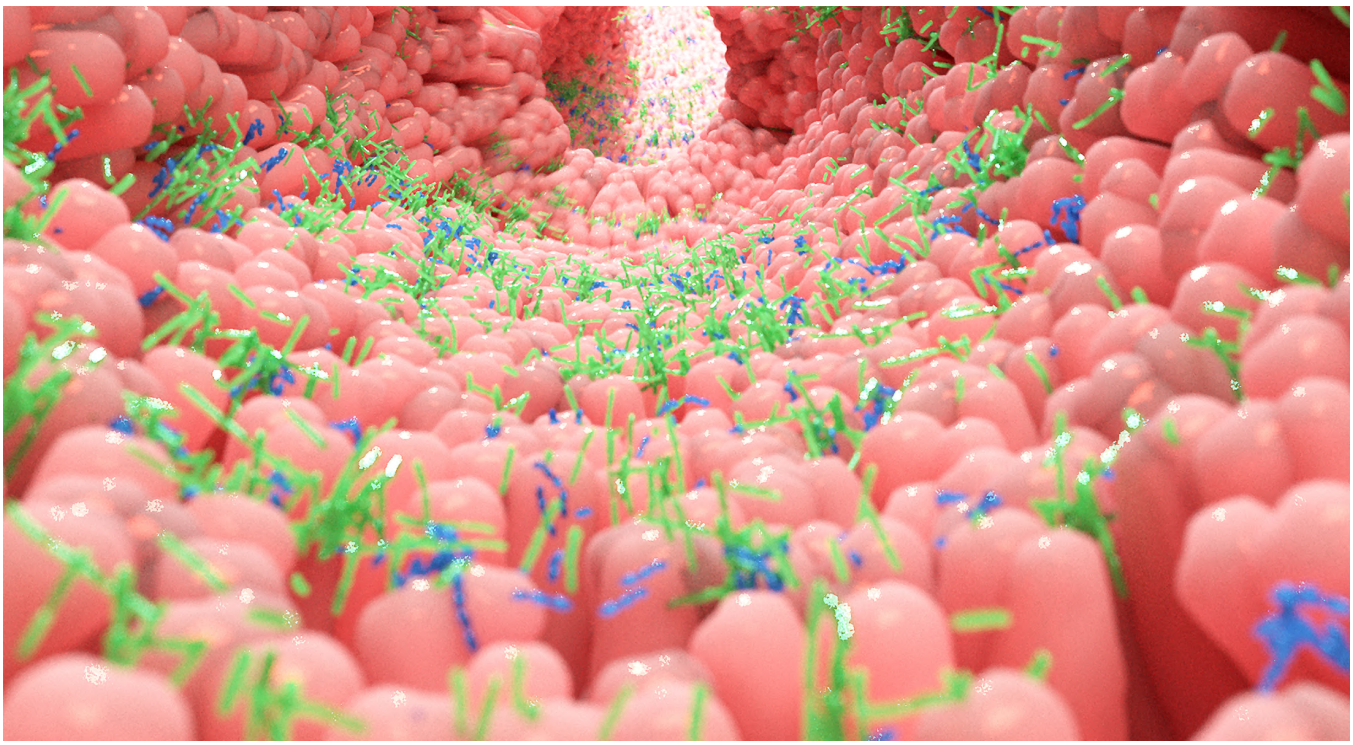
Challenges and next steps in using human fecal microbiota transfer to germ-free mice models as a means of translating microbiome science to therapeutic medicine

Published on July 2nd, 2020 by Rene van den Wijngaard

Human microbiota-associated mice studies are considered a cornerstone model in microbiome research and may contribute to microbiome-based therapies moving quickly towards clinical use. A new perspective from Jens Walter and colleagues explores the model's limitations and makes suggestions for improving experimental rigor when testing for causality in microbiome research.



An altered gut microbiota (inaccurately stated as "dysbiosis") has been linked to almost every human disease or condition. However, one of microbiome research's challenges is that of disentangling whether changes in gut microbiota composition and/or function are causal or consequential to a specific disease or condition, or, alternatively, whether microbiota changes and disease are both driven by a third factor.

In a systematic review in Cell, Jens Walter and colleagues address the challenges and limitations of establishing causality in microbiome research based on human microbiota-associated or humanized gnotobiotic rodents.

A different gut microbiota as compared to a control has been published for almost every disease or condition, ranging from gut-related

Challenges and next steps in using human fecal microbiota transfer to germ-free mice models as a means of translating microbiome science to therapeutic medicine

conditions to obesity, cancer and neuropsychiatric diseases. However, until now the microbiome's causal involvement only has robust evidence for *Helicobacter pylori-associated* peptic ulcer and gastric cancer and *Clostridioides difficile* infection-associated diarrhea.

The model used most frequently in microbiome research for making causal inferences is the transplantation of human fecal microbiota into germ-free mice (also known as human microbiota-associated or humanized gnotobiotic mice). Then, scientists examine disease phenotypes and identify mechanisms in germ-free mice colonized with the fecal microbiota of patients compared with mice colonized with the microbiota of healthy controls.

Those models have limitations, however, which affect data interpretation. One important limitation is that **gut microbiota changes occurring in the donor host (e.g., in the context of a specific disease vs. healthy controls) will in most cases experience an ecological shift after engraftment to mice, and that does not necessarily represent the gut microbial community associated with the donor's pathology**. As a result, due to the genetic, behavioral, physiological and anatomical differences between host species, the altered microbiome patterns observed in donor human subjects may be difficult to replicate in human microbiota-associated mice.

By systematically reviewing 38 studies that utilized human microbiota-associated mice for assessing the role of the gut microbiome in the etiology of a wealth of disease states, a successful phenotype transfer was reported in 36 out of 38 studies. Nevertheless, taking into account the complex etiology of the diseases under study and the lack of specificity of human gut microbiome changes and disease states, the authors concluded that causal claims for the microbiome in the disease states under study are improbable.

The major pitfalls detected in studies using human microbiota-associated mice models include:

- Not testing for an altered gut microbiome either in the donor (diseased vs. healthy humans) or in the recipient mice.
- Not replicating the donor's gut microbiome changes in recipient rodents.
- Not identifying underlying mechanisms (i.e., the causal component of the microbiome) linking the altered microbiome with disease.
- A lack of standardization of experimental designs coupled with inappropriate statistical analyses (e.g., the small number of donors used, which fails to capture the large inter-individual variability of the human gut microbiome). In this regard, the authors pointed out that interpretations of results should be limited to pathophysiological and behavioral mechanisms rather than clinical symptoms in humans, especially in studies reporting human phenotypes such as autism-like behavior, which do not naturally occur in mice.

Beyond causality versus association, other challenges in translating microbiome science addressed by Colin Hill during the last Gut Microbiota for Health World Summit 2020 in Madrid include the lack of precise language, numeracy and interpretation of complicated microbiome figures and analyses.

Challenges and next steps in using human fecal microbiota transfer to germ-free mice models as a means of translating microbiome science to therapeutic medicine

Finally, the authors make some **suggestions for establishing causal relationships between an altered gut microbiome and human disease, state or condition with scientific rigor and without hype. They suggest:**

1. Determining the microbiome alterations associated with the pathology by comparing donor samples from individuals with a disease with those who are healthy.
2. Using an appropriate number of donors to take into account the high inter-individual variation in the gut microbiome.
3. Performing statistical analyses by using donor numbers instead of the number of recipient mice.
4. Not pooling donor samples before inoculating rodents (the common practice of pooling donor samples increases the chance of false positive findings).
5. Testing if microbiome engraftment occurred and whether an altered gut microbiome in terms of composition and/or functions was transferred to recipient animals.
6. Discussing honestly the limitations of animal models and avoiding overstatements on causal claims. Microbiome science requires precision of language and numerical accuracy coupled with a healthy dose of skepticism to keep from getting carried away by hype.
7. Exploring mechanisms and causal components of the microbiome for the progression of the microbiome field.

Editorial Head – Netherland Dr van den Wijngaard's research 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). He undertook his PhD training at Amsterdam UMC where he next became a scientific staff member in the Department of Gastroenterology and Hepatology. He carries out his research activities in the Gut Research group at the Tytgat Institute for Liver and Intestinal Research.

References:
Walter J, Armet AM, Finlay BB, Shanahan F. Establishing or exaggerating causality for the gut microbiome: lessons learned from human microbiota-associated rodents. *Cell*. 2020; 180(2):221-32. doi: 10.1016/j.cell.2019.12.025.

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