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YEAR AT A GLANCE

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EDITORIAL

Prof. Stéphane Schneider

Professor Stéphane Schneider heads the Nutritional Support Unit in the Gastroenterology and Nutrition Department Archet University Hospital in Nice (France). He is also head of the Nice University Hospital's food-nutrition liaison committee. Dr. Schneider is vice-president of the French-Speaking Society for Clinical Nutrition and Metabolism (SFNEP), and is the former chair of the Educational and Clinical Practice Committee of the European Society for Clinical Nutrition and Metabolism (ESPEN).

Microbes that reside in the human gut are involved in host digestive health, immunity, metabolism and even mental health, which makes them a potential source of novel therapeutics. Between 2013 and 2018, the number of publications focusing on the gut microbiota was 13,000, which represents four-fifths of the total number of publications on the topic over the last 40 years and increases year by year. Mainly, it is due to the advent of genetic tools over the last 15 years that allow scientists to characterise the composition and function of commensal microbes –especially the gut microbiome– without culturing them.

As every year, this "2018 Year at a glance" report summarizes the year's key findings in gut microbiota research in 2018. Although gut microbes have been explored for several decades, 2018 was an important year when it comes to research elucidating how specific nutrients and dietary patterns modulate the gut microbiota and major mechanisms involved in the crosstalk between microbes and the host. Examples of dietary components that affect human health through their impact on the gut microbiota include proteins (plant vs. animal protein), fat (unsaturated vs. saturated fat), carbohydrates (digestible and non-digestible, including artificial sweeteners), probiotics and polyphenols.

We also know that specific diets, including Western, gluten-free, omnivore, vegetarian, vegan, and Mediterranean, have differential effects on the gut microbiome. For instance, new data suggest that an extinction of *Lactobacillus* genus is behind the effects of high salt consumption on high blood pressure and on immune-mediated diseases.

Besides this, there has been an increased awareness of the importance of the beneficial effects of probiotics not only on gut health but also its indirect role in boosting emotional wellbeing and cognitive functions in neuropsychiatric conditions –such as Alzheimer's disease– but also in healthy adults.

Further, scientists are also studying in depth the mechanisms that take part in gut microbiota protective effects including shaping intestinal immune responses and enhancing colonization resistance against enteric pathogens. Some of them include close interactions between the microbiome and humoral immune responses mediated by immunoglobulin A and short-chain

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fatty acids production by gut commensal microbes for limiting *Salmonella* growth.

2018 has also been a very active year for our platform. The 7th edition of the annual event Gut Microbiota for Health World Summit, held in Rome in March, updated clinical researchers and healthcare professionals with a broad overview of the latest news around gut microbiota science. From food-microbes-host interactions in the human gut to personalized interventions to modulate the gut microbiota through diet and next-generation probiotics.

Our digital community grew up this year to reach exceed 63,000 members, including scientists, healthcare professionals and the general public. In 2018 the GMFH website had more than 688,000 visits.

As a platform dedicated to sharing information about gut microbiota, during 2019 we'll continue promoting the debate and updating the latest news about the amazing world of diet, nutrition and the gut microbiota. We'll start with the 8th Gut Summit event, the leading event on gut microbiota and health organized together with the American Gastroenterological Association (AGA) and the European Society of Neurogastroenterology and Motility (ESNM) that will take place March 23 & 24, 2019 in Miami, Florida (U.S.). In parallel, the resources section of our website will be updated with infographics and publications relevant to gut microbiota science.

Certain types of fiber may be more beneficial for the gut microbiome than others

Published on October, 15, 2018 by Andreu Prados.

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

The gut microbiome is currently considered to be a potential target for preventing conditions that have been associated with imbalances in gut microbial communities. In addition to medication, diet is a major modulator of gut microbiota composition, and this is explained by the way some fibers (containing microbiota-accessible carbohydrates) can be selectively utilized by commensal microbes, thus conferring a health benefit. However, studies have not yet explored which dietary fibers, apart from the subset of prebiotic fibers, may be more beneficial to gut health.

A new systematic review and meta-analysis, led by Dr. Katrina Campbell from Bond University in Australia, concludes that some types of fiber benefit the gut microbiota more than others.

The researchers analyzed 64 randomized clinical trials involving 2099 healthy participants (of which 58 studies were included for meta-analysis). During the study, healthy adults with increased fiber intake achieved through food or supplementation (different fibers and at different doses) were compared with placebo/low-fiber comparator groups.

Between-group differences in a-diversity of fecal microbiota at the end of the interventions was the primary outcome, whereas between-group differences in abundances of common bacterial groups, including *Bifidobacterium* and *Lactobacillus* species, and in fecal short-chain fatty acids were both secondary outcomes.

Healthy adults with an increased fiber intake had a higher abundance of *Bifidobacterium* spp. and *Lactobacillus* spp., together with higher fecal butyrate levels compared with placebo group/lower-fiber consumers. The selective increase in both *Bifidobacterium* spp. and *Lactobacillus* spp. supports the well known selective use of prebiotic fibers for the gut microbiota. In contrast, dietary fiber did not affect the relative abundance of other bacteria—including *Faecalibacterium prausnitzii, Roseburia* spp., *Eubacterium rectale* and *Ruminococcus bromii* —compared with placebo/low-fiber groups.

Studies were also subgrouped to disentangle the effect of fiber type (accepted prebiotic fibers, candidate prebiotic fibers or general fibers) on the gut microbiota. It was shown that fructans and galactooligosaccharides (accepted prebiotic fibers) led to a significantly greater abundance of *Bifidobacterium* spp. and *Lactobacillus* spp. By way

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of contrast, candidate prebiotic fibers only affected *Bifidobacterium* genus, while general fibers (fibers not classified as accepted or candidate prebiotics) did not affect the abundance of *Bifidobacterium* and *Lactobacillus* spp. This supports the idea that the degree of fermentability is a crucial feature of the dietary fiber to be used as a substrate for the gut microbiota (for instance, although resistant starch is an insoluble fiber, it is highly fermentable with the microbiota).

Food interventions, on the other hand, had no effect on *Bifidobacterium* and *Lactobacillus* spp. when compared with supplement interventions. The authors explain that this may be due to the small sample size and the use of mostly grains and cereals as a source of fiber, which did not allow for studying the impact of other fiber-rich foods on gut microbiota composition.

Meanwhile, no differences in *Bifidobacterium* spp. abundance were identified based on the doses of fiber administered. This may well imply that even low doses of fiber

(less than 5 g) are enough for gut microbiota fermentation to occur.

The assessed fiber interventions were not accompanied by changes in a-diversity and abundances of other bacteria apart from *Bifidobacterium* and *Lactobacillus*, and this supports the stability of gut microbiome structure and physiology. However, these data on a-diversity are in contrast with previous observational studies that have found positive correlations between ingested fiber and microbiota diversity, highlighting that the study's design may lead to bias when looking at the way dietary fiber has an impact on gut microbiota composition.

On the whole, data from this new meta-analysis shows that different fibers have a different impact on the gut microbiome. We look forward to more, well-designed studies that assess the impact of different dietary fiber types and at different doses to get a more complete view of the effects of dietary fiber on gut microbiota composition and metabolism.

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Omega-3 polyunsaturated fatty acids may lead to a reversible increase in some gut bacteria in healthy adults

Published on November, 29, 2018 by Stéphane Schneider.

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Considering that diet is—together with medication—one of the major influencing factors with regards to gut microbiota composition, research is now focusing on how dietary nutrients may affect gut microbial communities. Specifically, an association was previously found between essential omega-3 fatty acid DHA (docosahexaenoic acid) and gut microbiome diversity in healthy elderly people. However, evidence from randomized trials assessing the effect of omega-3 polyunsaturated fatty acids (PUFA) on human gut microbiota is scarce.

A new randomized clinical trial, led by Dr. Mark Hull from the Institute of Biomedical and Clinical Sciences at the University of Leeds (United Kingdom), has found that a daily intake of 4g of eicosapentaenoic and docosahexaenoic acids may lead to reversible changes in specific gut bacteria.

The researchers analyzed the effects of oral high-dose omega-3 PUFA on the fecal microbiota of 22 healthy middle-aged volunteers (median age 57 years; median body mass index 27 kg/m^2). A combination of 2 g/day eicosapentaenoic acid (EPA) and 2 g/day DHA were administered in capsules or drinks over an 8-week period in a randomized cross-over design. After each intervention, there was a washout period of 12 weeks. Fecal samples for microbiome analysis were collected at five time-points and omega-3 fatty acid levels were measured in red blood cell (RBC) membranes.

By and large, the effect of interindividual variability overcame the effect of the short-term omega-3 PUFA intervention on the gut microbiome composition. This was reflected by the fact that omega-3 PUFA supplementation, in either capsule or drink form, did not drive any gut microbiota taxonomic shift or changes in a and b diversity at the end of the study compared with baseline.

However, omega-3 PUFA interventions led to specific changes at family and genus levels, which returned to baseline once the intervention was complete. At the family level, *Clostridiaceae, Sutterellaceae* and *Akkermansiaceae* increased at the end of both interventions. At the genus level, *Bifidobacterium*, *Lactobacillus, Oscillospira* and *Lachnospira* increased. In contrast, there was a drop in the abundance of *Coprococcus* and *Faecalibacterium*.

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The functional consequences of the increase in short-chain fatty acid producers —*Bifidobacterium, Lactobacillus*, *Lachnospira* and *Roseburia* —after the 8 weeks of omega-3 PUFA supplementation deserves further research. Researchers hypothesize that these findings might explain the role of SCFA signaling in omega-3 PUFA chemopreventive activity, whereas mechanistic studies are needed to resolve the matter.

The type of omega-3 PUFA administration (capsules vs. drinks) also had a different effect on the abundance of genera at the end of the study. For example, the increase in both *Roseburia* and *Lachnospira* was only observed during the drink intervention.

On the other hand, microbiome changes did not correlate with omega-3 PUFA exposure quantified with RBC omega-3 fatty acid incorporation or development of omega-3 PUFA-induced diarrhea.

Furthermore, incorporation of omega-3 PUFA within RBC did not vary depending on the type of formulation (capsules vs. drinks). However, EPA and DHA administered in drinks led to a larger decrease in omega-6 PUFA arachidonic acid (AA) compared with capsules. This larger drop in AA content explained the increase in the omega-3:omega-6 ratio—a commonly used biomarker for assessing omega-3 PUFA bioactivity—after consumption of drinks compared with capsules.

As for adverse reactions from the intervention, some patients experienced minor and moderate dyspeptic symptoms and diarrhea.

In conclusion, these findings show that even short-term interventions driven by omega-3 PUFA may lead to reversible changes in the gut microbiota, which can only be appreciated at the family and genus level. On the other hand, the fact that the food matrix drives differential changes in the gut microbiota opens the avenue for taking them into account as a confounder in human nutrition microbiome studies.

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Metabolic benefits of a low-carbohydrate diet on non-alcoholic fatty liver disease may be partly mediated by the gut microbiota

Published on April, 12, 2018 by Andreu Prados.

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

A carbohydrate-restricted diet has been emerging as an effective dietary intervention for non-alcoholic fatty liver disease (NAFLD) in humans. NAFLD is the most prevalent form of liver disease in western countries, affecting an estimated up to 30% of the population and has been reported to be an independent risk factor for increased mortality related to cardiovascular and liver diseases. However, the mechanisms involved in how this diet may benefit patients with NAFLD are not fully understood.

A recent study, led by Dr. Jan Borén from the Department of Molecular and Clinical Medicine at the University of Gothenburg and Sahlgrenska University Hospital (Gothenburg, Sweden), has found that metabolic benefits of a carbohydrate-restricted diet in obese NAFLD patients may involve shifts in gut microbiota composition.

The researchers performed an intervention with an isocaloric low-carbohydrate diet with increased protein content (<30 g of carbohydrates and an average of 3,115 kcal per day) for 14 days in 10 obese subjects with NAFLD and used multi-omics to investigate its effects on host metabolism and the gut microbiota. Whole-genome shotgun sequencing of faecal samples obtained from participants at baseline and at 1, 3, 7, and 14 days allowed investigation of the impact of the dietary intervention on the gut microbiome.

Reduced carbohydrate consumption improved liver lipid metabolism and reduced inflammation in obese subjects with NAFLD. Although the researchers reported only minor weight loss at the end of the study, magnetic resonance spectroscopy showed a significant reduction in liver fat in all the individuals that was apparent since the first day after the start of the diet intervention. Beyond reductions of liver fat, marked reductions of other cardiometabolic risk factors -including very-low density lipoprotein (VLDL)-triglycerides, fasting plasma triglyceride concentrations and plasma apolipoprotein C-III, which is an inhibitor of VLDL clearance- were also detected. Besides this, reduced carbohydrate consumption decreased plasma concentrations of the inflammatory markers interleukin-6 and tumour necrosis factor alpha and plasma concentrations of the peptide hormone fibroblast growth factor 21 (FGF21) -a novel metabolic regulator that has been reported to be increased in subjects with NAFLD and that correlates with hepatic fat content, which suggests it could be used as a diagnostic marker for NAFLD.

Metabolic benefits of a low-carbohydrate diet on non-alcoholic fatty liver disease may be partly mediated by the gut microbiota

The effects of reduced carbohydrate consumption on liver fat were paralleled by marked decreases in hepatic *de novo* lipogenesis and large increases in serum b-hydroxybutyrate concentrations (a marker for mitochondrial b-oxidation). These results suggest that the reduced hepatic lipid accumulation could be related to blunted *de novo* lipogenesis and increased b-oxidation.

It is also worth mentioning that benefits of the low-carbohydrate diet on liver fat metabolism involved shifts in the gut microbiota composition in NAFLD patients. Major shifts in the gut microbiota occurred after only 1 day of the dietary intervention and stabilized after 1 week on the low-carbohydrate diet. 25 genera and 94 bacterial strains were significantly altered, of which *Streptococcus, Lactococcus* and *Eggerthella* were increased; the carbohydrate- degrading bacteria *Ruminococcus, Eubacterium*, *Clostridium* and *Bifidobacterium* were decreased over the study period. Reductions in faecal concentrations of short-chain fatty acids were also observed as a result of decreased carbohydrate fermentation. Previous research has shown that carbohydrate-restricted diets may promote marked shifts in the composition of the gut microbiota and those microbial changes may therefore be involved in the development and progression of NAFLD.

Regarding functional changes in the gut microbiome in response to the dietary intervention, the low-carbohydrate diet promoted microbial shifts toward folate production that is potentially used by humans. Besides this, the low-carbohydrate diet upregulated expression of genes involved in folate-dependent one-carbon metabolism in the liver. However, a causal relationship cannot yet be inferred and other sources of increased circulating folate should be explored: for instance, enhanced dietary folate absorption in the small intestine secondary to the carbohydrate-restricted diet.

Finally, liver transcriptomic analysis on biopsy samples from a second cohort of 7 subjects that followed the low-carbohydrate diet for 7 days showed downregulation of the fatty acid synthesis pathway and upregulation of folate-mediated one-carbon metabolism and fatty acid oxidation pathways. The significant correlations in 5 individuals between serum folate and liver fat show that folate could play a role in improved liver fat metabolism. However, other metabolites involved in lipid and amino acid metabolism, several of them with antioxidant properties, were also increased during the dietary intervention and therefore could be also involved in the metabolic benefits of the low-carbohydrate diet.

In conclusion, gut microbial shifts after only 1 day of a low- carbohydrate diet may be partially behind the improved lipid metabolism and reduced inflammation in obese NAFLD patients. These results emphasize the need for further research exploring diet-microbiota interactions in the long term for preventing and/or treating NAFLD through targeting the gut microbiome.

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Probiotics' effectiveness and safety in preventing *Clostridium difficile* infection in patients receiving antibiotics and a close look of their novel mechanisms of action:

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A recent Cochrane review shows that probiotics appear to be effective and safe in preventing *Clostridium difficile* infection

Published on August, 27, 2018 by Paul Enck.

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

The administration of broad-spectrum antibiotics is an important risk factor for *Clostridium difficile* infection (CDI) in the Western world. Recent research has suggested that probiotics may help reduce the incidence of *C. difficile*-associated diarrhea (CDAD) among children and adults in both hospital and outpatient settings.

A new systematic review and meta-analysis, led by Dr. Bradley Johnston from Dealhousie University (Canada), concludes that probiotics are associated with a lower risk of symptomatic *C. difficile* infection without an increase in adverse events in children and adults who have been prescribed antibiotics.

Among the initial 39 randomized trials, which included a total of 9955 participants, 31 trials that compared co-administration of antibiotics and probiotics vs. placebo or no treatment for preventing CDI in 8672 children and adults patients receiving antibiotics (both in inpatient and outpatient care) were selected. Of these, 26 were placebo-controlled, four trials had a no treatment control group and in one study the control arm intervention was not reported. The results of this recent Cochrane review have been summarized in a clinical evidence synopsis published by the Journal of the American Medical Association (JAMA).

The primary outcome was the incidence of *C. difficile*-associated diarrhea (CDAD). Secondary outcomes included detection of *C. difficile* or toxin in stool, adverse events, antibiotic-associated diarrhea, and length of hospital stay. The overall quality of evidence for each of the outcomes was rated according the Grading of Recommendations Assessment, Development and Evaluation (GRADE), which takes into account the following categories of limitations: 1) risk of bias, 2) inconsistency, 3) indirectness, 4) imprecision, and 5) reporting bias.

The short-term administration of probiotics during the course of antibiotic therapy was associated with a lower risk of developing CDAD vs. placebo or no treatment by 60% on average, based on moderate-quality evidence using GRADE. For every 40 patients who had been prescribed antibiotics and were treated with probiotics, one case of CDAD could be avoided (number needed to treat = 40).

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Statistical analysis showed that probiotics were most effective (with a 70% risk reduction on average) among participants at a higher than 5% risk of developing CDAD (number needed to treat for an additional benefit outcome = 12; moderate certainty evidence). However, the same did not occur in trials including participants with a baseline risk equal or less than 5% (low to moderate certainty evidence).

The most common side effects reported in the studies under assessment included abdominal cramping, nausea, fever, soft stools, flatulence, and taste disturbance. Co-administration of probiotics and antibiotics was associated with a lower risk of adverse events, including abdominal cramping and nausea (NNT, 37) and antibiotic-associated diarrhea (NNT, 17) vs. placebo or no treatment based on very low-quality evidence and low-quality evidence using GRADE, respectively. Adverse events were more frequent among patients in the control groups and serious adverse events relating to probiotics have not been documented. It should be noted that the risk in the intervention group was based on the assumed risk in the comparison group and the relative effect of the intervention.

In conclusion, these results suggest the role probiotics administered concomitantly with antibiotics play in preventing CDI and reducing adverse events and antibiotic-associated diarrhea in children and adults. As patients who are not immunocompromised or severely debilitated have not been included in the study, there remains an urgent need for trials on these populations.

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A brief overview of the mechanisms of action by which traditional and next-generation probiotics affect host health

Published on January, 19, 2018 by Patrice D. Cani.

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Probiotics have a range of documented effects on human health, with hundreds of studies from the past several decades showing their ability to alter physical or behavioural phenotypes in humans. These human efficacy trials provide the necessary evidence to guide probiotic use. In designing a trial, however, the researchers often wonder how to select the best strain for the task in order to increase the likelihood of success. In this context, preclinical testing — using *in vitro*, *ex vivo*, and animal models — becomes highly important. Controlled studies of this kind provide a window into the mechanisms involved in a probiotic-mediated health effect.

In this manner, many probiotic mechanisms of action have been uncovered. According to the 2014 International Scientific Association for Probiotics and Prebiotics (ISAPP) expert consensus document on the definition of probiotic, some mechanisms seem to be rare among different strains, but others are widespread among strains of the same species (Hill *et al.,* 2014). For instance, some *Lactobacillus* species can act through immune modulation: specifically, by depleting pro-inflammatory Th17 immune cells systemically through the production of tryptophan metabolites, which activate the aryl hydrocarbon receptor (Zelante *et al.,* 2013). But individual strains may have multiple mechanisms of action and a comprehensive understanding of these mechanisms does not yet exist for traditional probiotic strains (Lebeer *et al.,* 2018).

Probiotics have a range of documented effects on human health, with hundreds of studies from the past several decades showing their ability to alter physical or behavioural phenotypes in humans.

A brief overview of the mechanisms of action by which traditional and next-generation probiotics affect host health

Traditional probiotics

From the perspective of the host, the mechanisms of action of traditional probiotics may include (but not exclusively) the following:

MECHANISM OF ACTION	FURTHER READING
Producing metabolites such as short-chain fatty acids and histamine	(Gao *et al.,* 2017; Sanders *et al.,* 2018)
Modulating composition and/or activity of host microbiota (e.g., through pili-mediated colonization)	(Hemarajata & Versalovic 2013; O'Connell Motherway *et al.,* 2011)
Enhancing epithelial barrier integrity	(Rao & Samak 2013)
Modulating the host immune system	(Yan & Polk 2011)
Central nervous system (CNS) signaling (e.g., neurotransmitters)	(Wang *et al.,* 2016)
Modulating gene expression in host tissues at distance from the gastrointestinal tract (e.g., liver, adipose tissues)	(Plaza-Diaz *et al.,* 2014)
Influencing hormone levels	(Clarke *et al.,* 2014)
Adhering to the mucosa and epithelium, inhibiting pathogen adhesion and/or growth	(Bermudez-Brito *et al.,* 2012)
Inhibiting pathogen virulence factor expression	(Corr *et al.,* 2009)
Producing enzymes (e.g., lactase to promote lactose digestion in the small intestine)	(De Vrese *et al.,* 2001)
Synthesizing vitamins	(Gu & Li 2016)
Producing bacteriocins	(Corr et al. 2009; Spinler *et al.*, 2017)

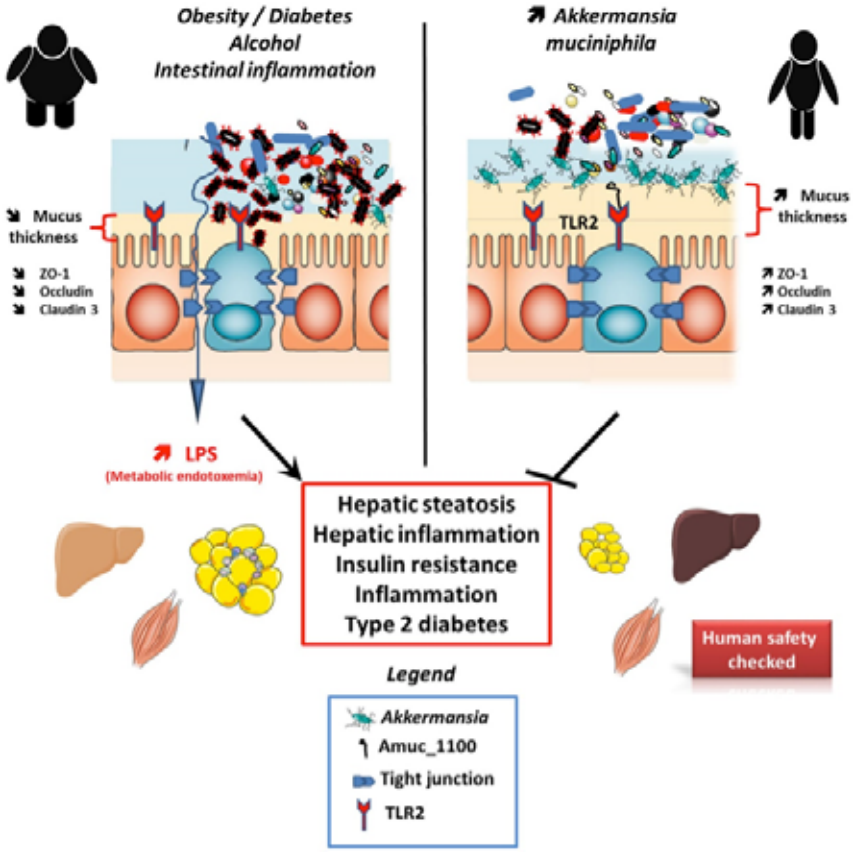
Research that has looked deeper at each of these mechanisms has found that many are actively mediated by various probiotic effector molecules — likely numbering in the thousands. Examples of probiotic effector molecules in *Lactobacillus* and *Bifidobacterium* strains include surface-located molecules, metabolites related to tryptophan and histamine, as well as CpG-rich DNA and various enzymes (e.g. bile salt hydrolases) (Lebeer *et al.,* 2018).

A brief overview of the mechanisms of action by which traditional and next-generation probiotics affect host health

Next-generation probiotics

Great potential lies in harnessing novel human-derived microbes to perform specific health functions; for each candidate, however, regulators must evaluate many factors: the microbe's beneficial properties, its antibiotic resistance profile, history of safe use (where it exists), publication of its genomic sequence, toxicological studies in agreement with novel food regulations, and qualified presumptions of safety (Brodmann *et al.*, 2017). As these next-generation probiotics may open up new therapeutic possibilities, understanding their mechanisms of action is no less important than for traditional probiotics. In the two leading next-generation probiotic candidates, studies to date show they may share mechanisms of action with traditional probiotics, but they may also have novel mechanisms — the details of which will emerge with further investigation.

Akkermansia muciniphila appears to be an important bacterium in metabolic health; levels of these bacteria in the human gut are negatively correlated with obesity,



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The gut microbiota—and key bacterial species in particular—may influence the outcomes of immunotherapy for cancer, such as anti-PD-1 treatment.

A brief overview of the mechanisms of action by which traditional and next-generation probiotics affect host health

diabetes, cardiometabolic diseases, and low-grade inflammation (Cani & de Vos, 2017). Our preclinical work found pasteurized *A. muciniphila* reduced fat mass development, insulin resistance, and dyslipidemia in mice; the bacteria also modulated both the host urinary metabolome and energy absorption in the intestines. The mechanism appeared related to immune modulation through a protein (called Amuc_1100*) on the outer membrane of *A. muciniphila*, which interacted with Toll-like receptor 2. And speaking of immunity, this impact of *A. muciniphila* seems to be of great importance not only in the context of the metabolic syndrome but also for reducing the onset of type 1 diabetes (Hänninen *et al.,* 2017). Even more strikingly, a series of recent papers (Jobin 2018; Kaiser 2017; Routy *et al.,* 2018; Matson *et al.,* 2018) have shown that the gut microbiota — and key bacterial species in particular — may influence the outcomes of immunotherapy for cancer, such as anti–PD-1 treatment. For example in humans, responders (as compared to non responders) revealed an increased relative abundance of *A. muciniphila* and favorable drug response; interestingly, poorly responding mice could be turned into responders by treating them with *A. muciniphila.*

Strains of another next-generation probiotic candidate, *Faecalibacterium prausnitzii*, may initiate a complex anti-inflammatory pathway in the host, with recent reports showing short-chain fatty acid (butyrate) production probably plays a role in the strains' ability to induce the anti-inflammatory cytokine IL-10 in peripheral blood mononuclear cells.

Toward therapeutic precision

The past several decades have seen many data emerge on the applications of probiotics in human health, and a continually increasing understanding of probiotic mechanisms will lead us into a new era of therapeutic possibility. Ongoing rigorous investigative work will help us achieve a comprehensive understanding of the 'personality' of each probiotic bacterium, including the ways in which each one succeeds in affecting host health — and this will ultimately help us move toward personalized medicine.

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Probiotics may drive emotional changes in healthy volunteers

Published on July, 5, 2018 by Paul Enck.

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

Previous data in animals and humans have shown the potential of manipulating the gut microbiome to modify emotional and cognitive behavior and brain function. For instance, *Bifidobacterium longum* 1714 has been tested for central effects in mice and humans, but studies assessing how probiotics may affect behavior and brain function in healthy volunteers are scarce.

A new double-blind, placebo-controlled randomized study, led by Dr. Veronika Schöpf of the Institute of Psychology at University of Graz (Austria), has found that healthy volunteers who took a probiotic for 4 weeks showed changes in emotion-related brain activation patterns.

The researchers sought to study the effects of administering 4 weeks' worth of multi-strain oral probiotics[1] on behavior, brain function and gut microbial composition in healthy volunteers (20-40 years). Participants were divided equally into three groups: one active intervention group (probiotic) and two control groups (placebo and no intervention), with 15 participants in each group. Functional magnetic resonance imaging (fMRI) was used to measure changes in emotion-related brain activation patterns. Stool samples were collected to investigate the gut microbial composition before and after the probiotic intervention.

Probiotic administration for 4 weeks improved self-reported behavioral measures of positive affect (in terms of hopelessness and risk aversion) and cognitive reactivity, as measured with four self-reported depression and anxiety questionnaires, namely, Positive and negative affect schedule (PANAS), Symptoms checklist-90 (SCL-90), Allgemeine Depressionsskala (ADS), and Leiden index of depression severity (LEIDS).

Probiotic administration was also associated with changes in brain activation patterns in response to emotional memory and emotional decision-making tasks. Besides this, blood oxygenation level signal changes in fMRI emotion recognition tasks correlated with self-reported behavioral measures in the probiotic group. Probiotic participants changed their decision about the selection of the most unpleasant stimuli less frequently than the control subjects during the emotional decision task.

[1] 7.5 x 10^6 colony forming units/g containing nine bacterial strains: *Lactobacillus casei* W56, *Lactobacillus acidophilus* W22, *Lactobacillus paracasei* W20, *Bifidobacterium lactis* W51, *Lactobacillus salivarius* W24, *Lactococcus lactis* W19, *Bifidobacterium lactis* W52, *Lactobacillus plantarum* W62 and *Bifidobacterium bifidum* W23.

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Furthermore, the influence of the probiotic on decision-making processes was reported by changes in neural activity in the cingulum and precuneus in the emotional decision task. These results show that probiotic-induced changes in self-reported measures of emotional behavior can be confirmed by measuring neural correlates of emotional decision-making and emotional memory processes.

On the other hand, changes in emotion-related brain activation patterns were also accompanied by subtle but significant shifts in the gut microbiota composition. In this regard, two operational taxonomic units belonging to *Bacteroides* sp. (a well-known producer of short-chain fatty acids) and *Alistipes* sp. increased in the probiotic group.

Finally, a relationship was found between gut microbial composition, blood oxygenation level signal changes in the cingulum and cerebellum and behavioral measures. Due to the involvement of cingulum and cerebellum in decision-making and emotional processing, these results suggest that probiotic effects on behavior are reflected in imaging measures. Furthermore, microbial composition was associated with self-reported behavioral measures. Specifically, the scores from the depression questionnaire ADS were associated with a higher abundance of metabolic pathways involved in starch and sucrose metabolism.

In conclusion, these data show the distinct probiotic influence at behavioral, neural and microbiome levels in healthy volunteers. These results are in line with a well-known study led by Professor Emeran Mayer, which showed how administration of a fermented milk product with a probiotic for 4 weeks affected the activity of brain regions involved in controlling the central processing of emotion and sensation; they are also in line with a study from McMaster University.

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Gut microbiota may be involved in pediatric autoimmune neuropsychiatric disorders related to streptococcal infections

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Celiac disease (CeD) is a complex immune mediated disorder that is triggered by abnormal immune responses to the dietary protein gluten, which is found in grains like wheat, barley, and rye. Normally, immune tolerance to dietary proteins prevents inflammatory immune responses from developing. However, in those with CeD, the presence of HLA susceptibility genes plus unknown environmental or immune triggers lead to a pro-inflammatory Th1 response towards gluten proteins. While gluten exposure and genetic risk are both required for CeD, only a proportion of genetically susceptible individuals will go on to develop the disease, highlighting a critical role of environmental modifiers. Epidemiological studies have suggested a link between infections or a dysbiotic microbiota and CeD, but mechanistic studies and experimental data to support these associations are lacking. Moreover, the events that lead to the loss of tolerance to these innocuous dietary proteins in the gut, like gluten, are not well understood.

A new study, led by Dr. Lorenza Putignani from the Bambino Gesù Children's Hospital in Rome (Italy), has found that gut microbiota may promote gut inflammation and activation of an immune response in PANS/PANDAS patients.

The researchers collected three fecal samples over consecutive days and, using 16S ribosomal ribonucleic acid (rRNA)-based metagenomics, they analyzed the gut microbiota composition of a cohort of 30 PANS/PANDAS patients aged 4-16 years (20 males and 10 females), comparing them with 70 healthy controls.

An altered bacterial community structure was detected in PANS/PANDAS patients when compared to controls. As ecological analysis revealed the presence of two main clusters of subjects based on age range, the researchers split data from patients into two groups—4 to 8 years old and >9 years old—to remove possible age-related bias. A lower level of a-diversity was observed for PANS/PANDAS patients compared with control subjects, which seems to suggest a relationship between the disease and gut microbiota composition, regardless of the patients' age.

The loss of biodiversity in the younger PANS/PANDAS group was limited and not so evident in all a-diversity indices, suggesting that this group of patients is characterized by a low degree of dysbiosis. At the phylum level, the younger PANS/PANDAS group had a reduction of *Firmicutes* and TM7 phyla and a major enrichment in *Bacteroidetes* compared with controls. The authors argue that this disequilibrium between *Firmicutes* and *Bacteroidetes* may be responsible for altered metabolic function in these patients as *Bacteroidetes* plays a relevant role in host physiology and changes in its relative abundance have been associated with metabolic disorders such as obesity. Specifically, this younger group was characterized by a strong increase in *Bacteroides*, *Odoribacter* and *Oscillospira* belonging to *Bacteroidetes phyla* and an absence of *Erysipelotrichaceae* species that have been found to attract more IgA molecules than other gut microbial families, thus possibly helping to explain the IgA deficiency usually detected in PANS/PANDAS patients. Furthermore, the 4 to 8 years old group exhibited an increase of several pathways involved in modulating the antibody response to inflammation within the gut, as well as a decrease in short-chain fatty acids, D-alanine, tyrosine and dopamine pathways involved in certain neuronal functions. Meanwhile, the metabolic profile was also characterized by a lack of important anti-inflammatory elements such as dioxin degradation and unsaturated fatty acids.

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The older group of patients exhibited a less uniform bacterial profile and the researchers were unable to identify distinct biomarkers. They therefore argue that the high level of heterogeneity within this group could be explained by the repeated antibiotic treatments they have undergone during their lives.

Control subjects exhibited increased D-alanine metabolism and higher levels of *Roseburia* genus members, the latter being involved in gut homeostasis through preserving gut barrier function and promoting butyrate production with an anti-inflammatory effect.

Finally, in a subset of PANS/PANDAS patients with anti-streptolysin O titer (ASLOT) values higher than 500 units and time until detection <5 months from gut microbiota analysis, significant correlations were found between ASLOT—a measure of the blood plasma levels of antistreptolysin O antibodies used in tests for the diagnosis of a streptococcal infection—and bacterial genera.

A negative correlation was found between genera belonging to *Firmicutes phylum* (*Dehalobacterium, Corynebacteriu, Gemella* and *Lactobacillus*) and ASLOT, which seems to be in agreement with the low percentage of this phylum among the younger group of PANS/PANDAS patients. Meanwhile, a positive correlation was observed with *Odoribacter*. Given the role of *Streptococcus pyogenes* infections in PANS/PANDAS etiology, these data suggest that streptococcal influence may influence gut microbiota composition and host inflammation, contributing to the development of disease.

In conclusion, these findings suggest that streptococcal infections alter gut microbiota composition, leading to a pro-inflammatory status by influencing specific gut bacterial communities. Further research is needed to explore the role of gut microbiota as a novel biomarker of the disease and its involvement in patients' treatment.

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Gut microbiota-IgA interactions may play a critical role in maintaining colonic homeostasis

Published on September, 6, 2018 by Andreu Prados.

The gut microbiota's composition and activity can be modulated by both environmental and host-derived factors. Among them, the homeostatic functions of immunoglobulin A (IgA) on gastrointestinal commensal bacteria has recently been confirmed in humans with IgA deficiency. [...]

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https://www.gutmicrobiotaforhealth.com/en/gut-microbiota-iga-interactions-may-play-a-critical-role-in-maintaining-colonic-homeostasis/

Gut microbiota-derived propionate protects mice against *Salmonella* infection

Published on September, 14, 2018 by Andreu Prados.

Other than gut microbiota's well-known functions, which include nutrient metabolism and absorption, xenobiotic and drug metabolism, and immune development, its role in protecting against pathogens has been poorly characterized. Previous research has identified some microbiota-mediated colonization resistance mechanisms, while little is known about whether microbial metabolites may also limit pathogen colonization. [...]

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Current insights and challenges when studying the human gut microbiome

Published on July, 19, 2018 by Patrice D. Cani.

New developments in genetics and metagenomics over the past 15 years have led scientists to produce an in-depth characterization of the composition and function of the gut microbiome as a novel organ in the close intersection between health and disease. As a result, the number of publications discussing the gut microbiota over the past five years represents more than 80% of all publications over the past 40 years on the topic, thus reflecting how microbiome research is changing basic science and medicine. [...]

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