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EDITORIAL



Dr. Mary Ellen Sanders

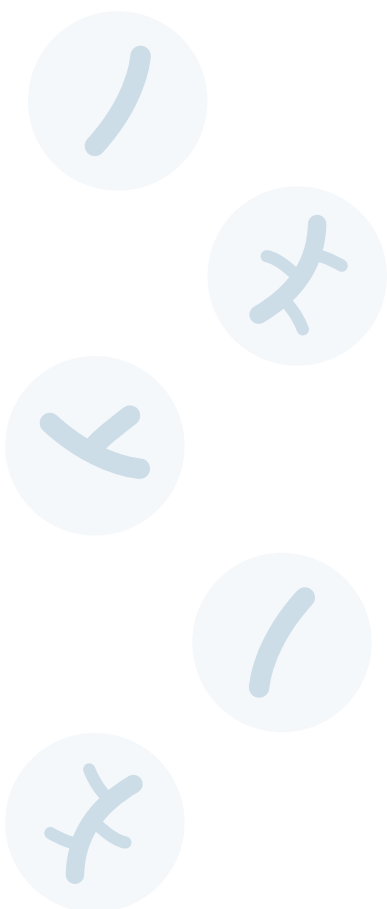
Mary Ellen Sanders is a consultant in the area of probiotic microbiology, with special expertise on paths to scientific substantiation of probiotic product label claims. Dr. Sanders served as the founding president of the International Scientific Association for Probiotics and Prebiotics (www.isappscience.org)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

In 1991, Dr. Joseph O'Donnell of the California Dairy Research Foundation commissioned me to write a comprehensive review on the health benefits of probiotics. The resulting paper was my entry into the probiotics field. In the introduction to this paper, I noted the controversial nature of the field, which was divided between scientists who considered the benefits of probiotics to self-evident and those who recognized the paucity of available data. In some respects, both sides were right. The historic use globally of lactic ferments to promote health was established. But clearly, controlled human studies were needed to confirm what benefits could be achieved, by whom, and by what probiotics. At that time, there were only a handful of controlled human trials that documented the impact of probiotics on human health.

The science on probiotics has advanced significantly over the past few decades, giving healthcare professionals better direction on appropriate clinical applications, and giving consumers more clarity on effective uses. This period of remarkable scientific advancement has been enabled in part by the

establishment of a globally accepted definition of probiotics — “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host”—developed in a FAO/WHO joint meeting and updated in a consensus statement by the International Scientific Association for Probiotics and Prebiotics (Hill *et al.*, 2014). In addition, today's scientists have access to sophisticated methods for studying probiotic interactions with the host and microbiota, enabling new insights.

A gap still exists, however, in our knowledge about exactly how probiotics work. In humans, we know probiotics interact in complex ways with the immune, endocrine, and neurological systems, and with gut physiology and gut microbiota, but the sequence of events between probiotic administration and a change in host phenotype are far from clear in most cases. For example, it is commonly assumed that a probiotic strain must first colonize in order to benefit host health, but a stably colonizing probiotic strain is the exception to the rule (Maldonado-Gómez *et al.*, 2016). Through both *in vitro* and *in*



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vivo experiments, researchers are exploring the myriad ways in which specific probiotics affect host health, including modulation of immune system activity, control of factors that influence gut barrier function, and ecological modifications within the gut microbiota. General or ‘core’ mechanisms of action such as production of short chain fatty acids are known for several well-studied species, but even these species have members with unique means of influencing health.

The field of gut microbiota and nutrition is evolving quickly, with evidence showing that the gut microbiota composition may respond in personalized ways to dietary interventions. Probiotics may turn out to be an important tool in personalized nutrition, and increased knowledge about mechanisms of

action may be a precursor to being able to effect precise changes in microbiota and host health status.

Mechanisms of action are also relevant to several other important issues in the field of probiotics. Increased knowledge about how probiotics work will help us determine the role of specific probiotics in reducing antibiotic use through global antibiotic stewardship programs. Furthermore, insights about mechanism may lead us to new treatments—comprising either traditional probiotics or next-generation probiotics—that apply to autoimmune diseases and other areas of unmet medical need.

Given the importance of keeping up with the literature on mechanisms and appropriate clinical uses of probiotics, educating the public and

health professionals about the evidence is of great importance. GMFH’s educational initiatives about the importance of the gut microbiota in health are valuable in this regard. This first “best of” document on probiotics focuses on their mechanisms of action, while a second “best of” document will cover evidence on clinical uses of probiotics.

What you will find in this document are several articles on probiotic mechanisms that were originally published on the Gut Microbiota for Health website. After you read through it, you can continue to follow Gut Microbiota for Health (www.gutmicrobiotaforhealth.com and @gmfx on Twitter) for ongoing coverage of this important scientific field.

Probiotics may turn out to be an important tool in personalized nutrition, and increased knowledge about mechanisms of action may be a precursor to being able to effect precise changes in microbiota and host health status.

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Hill, C. *et al.*, 2014. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nature Reviews Gastroenterology & Hepatology*, 11(8), pp.506-514.

Maldonado-Gómez, M.X. *et al.*, 2016. Stable Engraftment of *Bifidobacterium longum* AH1206 in the Human Gut Depends on Individualized Features of the Resident Microbiome. *Cell host & microbe*, 20(4), pp.515-526.

SELECTED CONTENT

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.



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

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).

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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 <i>et al.</i> , 2017; Sanders <i>et al.</i> , 2018) |
| Modulating composition and/or activity of host microbiota (e.g., through pili-mediated colonization) | (Hemarajata & Versalovic 2013; O'Connell Motherway <i>et al.</i> , 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 <i>et al.</i> , 2016) |
| Modulating gene expression in host tissues at distance from the gastrointestinal tract (e.g., liver, adipose tissues) | (Plaza-Diaz <i>et al.</i> , 2014) |
| Influencing hormone levels | (Clarke <i>et al.</i> , 2014) |
| Adhering to the mucosa and epithelium, inhibiting pathogen adhesion and/or growth | (Bermudez-Brito <i>et al.</i> , 2012) |
| Inhibiting pathogen virulence factor expression | (Corr <i>et al.</i> , 2009) |
| Producing enzymes (e.g., lactase to promote lactose digestion in the small intestine) | (De Vrese <i>et al.</i> , 2001) |
| Synthesizing vitamins | (Gu & Li 2016) |
| Producing bacteriocins | (Corr <i>et al.</i> 2009; Spinler <i>et al.</i> , 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).

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

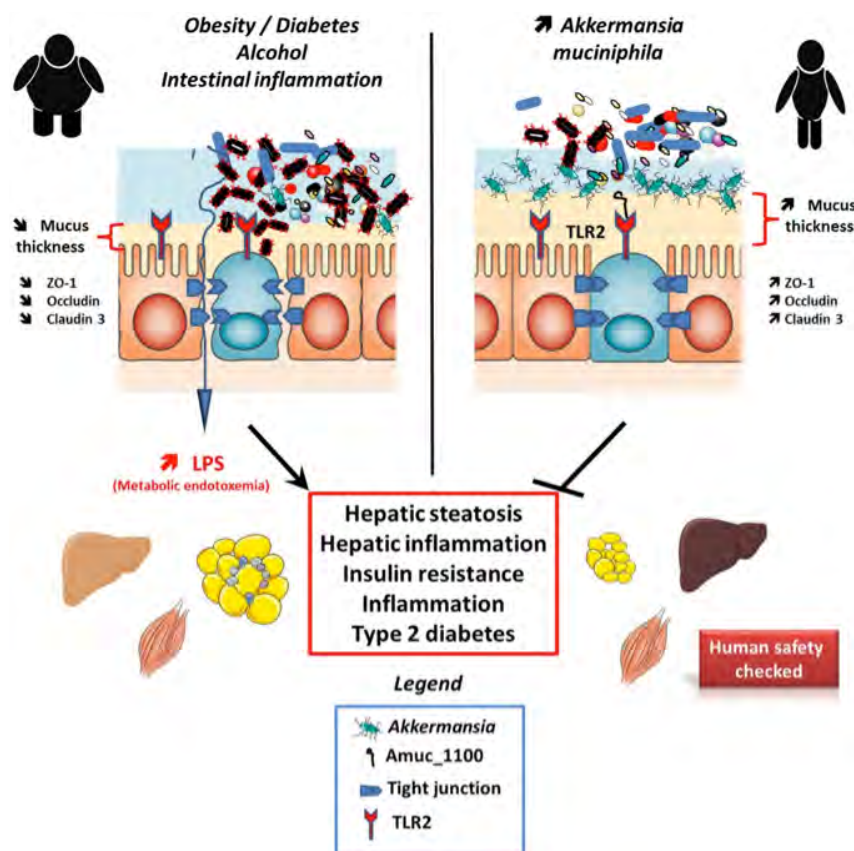
Next-generation probiotics

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



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

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

negatively correlated with obesity, 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.



Read the original post online at:

<http://www.gutmicrobiotaforhealth.com/en/brief-overview-mechanisms-action-traditional-next-generation-probiotics-affect-host-health/>

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Gut Microbiota Clinical Minute: Can probiotics prevent *Clostridium difficile* infection?

Published on July, 3, 2017 by Kristina Campbell.



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

In the new Gut Microbiota for Health “Clinical Minute” series, we get a scientific expert’s take on gut-microbiota-related questions of interest to healthcare professionals.

Dr. Nicole T. Shen is a first year gastroenterology and hepatology fellow in the Division of Gastroenterology and Hepatology at Weill Department of Medicine, Weill Cornell Medicine (USA). She is first author of a recent systematic review with meta-analysis on the efficacy of probiotics for prevention of *Clostridium difficile* infection (CDI). In the US and other countries, CDI is the most common cause of infection in health care settings; administration of broad-spectrum antimicrobials is an important risk factor.

Question:
What was the main clinical problem you were addressing with this meta-analysis?

NTS: Clinically, the question is: Are probiotics effective at preventing *C. diff* infection in hospitalized adults receiving antibiotics?

We were wondering why there was such a discrepancy in the recent large randomized multi-center trial, and then the systematic review with meta-analysis, and we wondered: what is the underlying answer to the two findings we’re observing? And why in practice are some hospitals using probiotics concurrently with antibiotics, and some hospitals not?

Question:
What was unique about your meta-analysis?

NTS: For the first time we looked at the effect that the timing of initiation of the probiotic had on efficacy.

No other systematic review with meta-analysis thought to look at trials that allowed inclusion of patients up to a certain point after the first antibiotic dose. Trials that had more narrowed inclusion criteria—only allowing up to two days after the first antibiotic dose—found significantly more benefit of probiotics than those that allowed

Probiotics should be considered in any patient starting antibiotics that is hospitalized and an adult.

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Gut Microbiota Clinical Minute: Can probiotics prevent *Clostridium difficile* infection?

later inclusion of subjects: those that were starting the probiotic three days or more after their first antibiotic dose.

We designed this before we went into the analysis, a priori, and we thought that was a good thing to investigate, because your gut flora changes so much right away with antibiotics.

Question:
Based on what you found, what can you tell clinicians about probiotics for the prevention of *C. difficile* infection?

NTS: From our findings in this paper, we think that probiotics should be considered in any patient starting antibiotics that is hospitalized and an adult.

That's to be done to reduce the risk of *C. diff* infection. Because we found a reduced risk of over 50%.

It's important to remember that these trials did not see any bacteremia or fungemia, but it is a real risk because we hear of it case reported. The trials excluded the patients you see in those case reports. We didn't study patients that were in the intensive care unit or pregnant, or have prosthetic heart valves—those are some of the main ones.

So you have to take the findings and make sure you use them in the



DR. NICOLE T. SHEN

appropriate clinical context.

But even if you take those people that were excluded, there's still a large amount of people in the hospital that would benefit from starting a probiotic with the antibiotic.

Question:
Were any particular probiotic strains more effective than others?

NTS: No particular strain showed significantly higher efficacy than another, but the ones that were more studied were *Lactobacillus* in combination with another species: *Lactobacillus* with *Streptococcus*, *Lactobacillus* with Bifidobacteria; whereas *Saccharomyces* was really only studied by itself.

Lactobacillus acidophilus in combination with *Lactobacillus casei*

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Gut Microbiota Clinical Minute: Can probiotics prevent *Clostridium difficile* infection?

seemed to have the most support in the non-clinical settings. *Lactobacillus casei* in particular has a plausible pathophysiology for how it would attack *C. diff*.

Saccharomyces also has some good evidence, but the trials didn't study enough of the same probiotic that you can really draw that conclusion. The same issue comes up with dosing too.

Question:
How was your study different from the recent one by Vernaya & colleagues?

The study done by Vernaya and colleagues focused on papers investigating probiotic use with antibiotic use in hospitalized adults age greater than 60 on the outcome of CDAD (*C. diff*-associated diarrhea, also known as CDI or *C. diff* infection). Their search was much more limited as evidenced by finding only 5 papers to include. This limitation could be from the restriction to only papers published in English, age restriction

of subjects to over 60, and the search being last conducted November 2015. Additionally, one of their included trials by Lewis *et al.* did not focus on CDAD. This trial was excluded from our analysis, given that Lewis *et al.* tested patients for *C. diff* regardless of whether the patient had the symptom of diarrhea; patients can be colonized with *C. diff* without active infection.

With our search, we were able to identify more randomized controlled trials, that when included, suggested probiotic efficacy, in meta-analysis with reduced heterogeneity. Additionally, we investigated the effect of probiotic timing on efficacy with meta-regression, which was found to be significant.

SUMMARY:
Evidence supports the administration of probiotics close to the first antibiotic dose as a way to reduce the risk of CDI in hospitalized adults.

With our search, we were able to identify more randomized controlled trials, that when included, suggested probiotic efficacy, in meta-analysis with reduced heterogeneity.



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<http://www.gutmicrobiotaforhealth.com/en/gut-microbiota-clinical-minute-can-probiotics-prevent-clostridium-difficile-infection/>

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Mechanism of probiotic action in healthy individuals still unsettled

Published on June, 6, 2017 by Kristina Campbell.



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Kristina Campbell
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Cookbook, her freelance work
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A recent systematic review in *Genome Medicine*, authored by Nadja B. Kristensen and colleagues from the University of Copenhagen (Denmark), investigated the impact of probiotic supplementation on the fecal microbiota of healthy adults. The authors, who analyzed seven randomized controlled trials to reach their conclusion, found that probiotics do not change fecal microbiota composition.

The conclusion suggests a commonly assumed mechanism—alteration of gut microbiota composition—may not be how probiotics influence host health. Bacterial diversity in fecal microbiota samples is often used as a shorthand for a ‘healthy’ microbiota, since a diverse collection of species has been linked to measures of better health in many circumstances (although the opposite can also be true). Authors of the recent study found diversity was unchanged when healthy subjects consumed probiotic supplements, a result that was unsurprising to those knowledgeable about the field.

Dr. Mary Ellen Sanders, Executive Science Officer for the International Scientific Association for Probiotics and Prebiotics (ISAPP), wrote a commentary on the article, published in *BMC Medicine*.

“Do probiotics alter the fecal composition of healthy adults? The

answer seems to be no,” Sanders says in an email to GMFH editors. But she says, in the widespread media coverage of this study, many assumed that because one mechanism was ruled out, all mechanisms were ruled out.

“Controlled intervention trials in healthy adults have shown benefits of probiotics,” she says. (See these meta-analyses on probiotics for the prevention of upper respiratory tract infections, urinary tract infections, allergy, and CVD risk.) “This article suggests that the primary mechanism of probiotic benefits may not be altering the composition of the fecal microbiota.”

But Sanders says alternative mechanisms exist: “Probiotics may act through changing the function of the resident microbes, not their composition. They may interact with host immune cells. They may inhibit opportunistic pathogens that are not dominant members of

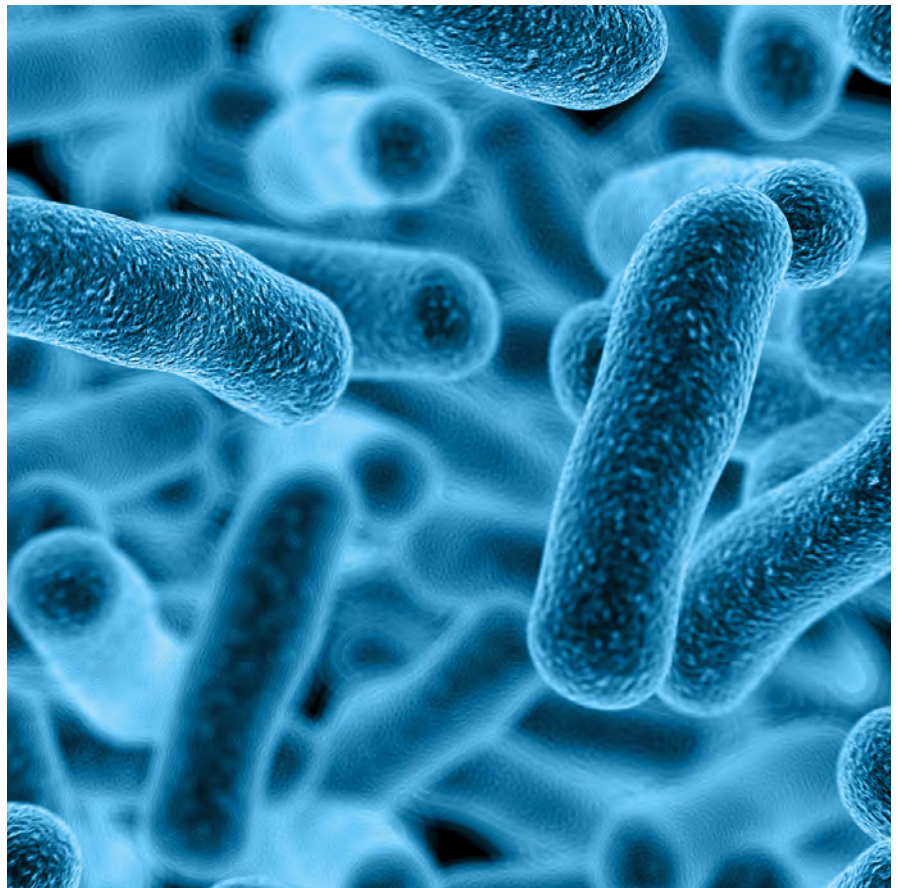
SELECTED CONTENT

Mechanism of probiotic action in healthy individuals still unsettled

the microbiota. They may promote microbiota stability. They may change the composition of microbiota in the small intestine or the proximal large intestine. So the fact that they don't change the composition of fecal microbiota does not mean that there is no means for them to impact host health."

Sanders' BMC Medicine article raises the question of whether a more fruitful line of study would be to examine how probiotic strains may promote stability of the existing gut microbiota. This kind of study would require comparisons of fecal microbiota at different points in time—before and after exposure to a stressor—in the same individual.

"This recent systematic analysis encourages us to think more broadly about how probiotics might benefit healthy individuals," says Sanders. "More research is needed to clarify the mechanism or mechanisms of probiotic action."



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Kristensen NB, Bryrup T, Allin KH, Nielsen T, Hansen TH, Pedersen O. Alterations in fecal microbiota composition by probiotic supplementation in healthy adults: a systematic review of randomized controlled trials. *Genome Medicine* 2016; 8:52. doi: 10.1186/s13073-016-0300-5



Read the original post online at:

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Examining the role of gut microbiome in travellers' health

Published on August, 16, 2017 by Andreu Prados.



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

Previous research has shown that a primary function of the gut microbiome is providing colonization resistance against many orally acquired pathogens; several exogenous factors, such as antibiotic treatments, could reduce host resistance to infections. The potential for manipulating the gut microbiome in the context of travellers' health has not been previously explored in depth in a scientific review.

A 2016 review, led by Dr. Mark S. Riddle from the Enteric Diseases Department at the Naval Research Center in Silver Spring (USA) and Dr. Bradley A. Connor from the Department of Medicine at Weill Cornell Medical College and The New York Center for Travel and Tropical Medicine in New York (USA) explores the role of the human gut microbiome in travellers' health.

First of all, the review explores the role of gut microbiome in host resistance to enteric infections, also termed colonization resistance. Both density and complexity gradient of commensal microbiota found in a matrix of intestinal mucous, which are highest at the lumen and gradually decrease closer to the surface of the enterocytes, prevent and limit pathogen colonization and growth through several mechanisms. Both direct mechanisms (production of bacteriocins, competition for nutrients, cross-feeding, and conversion of host derived metabolites) and indirect mechanisms (production of immuno- modulatory

molecules and stimulation of hematopoiesis) work in parallel to provide resistance to acute enteric infections.

The applicability of the mechanisms of colonization resistance is explored in the context of common causes of travellers' diarrhoea including *Shigella spp.*, *Salmonella typhimurium* and *Campylobacter jejuni*. Interestingly, the authors hypothesized that the traveller's unique gut microbiome may predispose him or her to enteric infection, to a greater or lesser extent. For instance, travellers from Sweden to high-risk destinations for enteric infection are more susceptible to infection with *Campylobacter* if their pre-travel microbiome has a lower number of bacterial species. These data show that specific structure and composition features of the gut microbiome could induce protection against common travellers' infections.

The researchers presented a study comparing the gut microbiome of individuals who developed travellers'

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Examining the role of gut microbiome in travellers' health

diarrhoea (TD) associated with Enterotoxigenic *Escherichia coli* (ETEC), norovirus or mixed pathogens, and TD with no pathogen identified, to healthy travellers. The study found a dysbiotic profile of a high Firmicutes:Bacteroidetes ratio in the travellers who developed diarrhoea, regardless of etiologic agent or presence of a pathogen. Besides this, the bacterial composition of the gut microbiome of the healthy travellers showed also a gut dysbiosis that was similar to those in the diarrhoeal groups. Further comparison of the healthy traveller microbiome to those from healthy subjects who were part of the Human Microbiome Project also revealed a significantly higher Firmicutes:Bacteroidetes ratio in the healthy travellers. These results show that travel itself may alter the composition of the gut microbiome in travellers regardless of the development of travellers' diarrhoea.

On the other hand, observational studies (here; here) across multiple traveller populations have shown that travelling, in particular to regions of Asia but also to destinations such as the Netherlands, among those who developed TD and/or took antibiotics

while travelling, is a risk factor for acquiring extended spectrum beta-lactamase resistant bacteria. Although it seems that the acquisition of multi-drug-resistant (MDR) organisms is transient, studies evaluating different drug classes on MDR acquisition and long-term health consequences are needed.

Finally, the authors discussed possible ways to manipulate the gut microbiome for prevention or treatment of TD:

> Diet changes: by using a gnotobiotic mouse model to evaluate short-term dietary changes on the gut microbiota and intestinal transit times, it was found that even short-term changes in eating patterns familiar to travellers can have long-term effects; their impact on transit time may persist upon returning to the pre-travel diet.

> Probiotics and prebiotics in TD prevention: probiotics including *Saccharomyces boulardii* (study here) and *Lactobacillus GG* (study here) have been shown to have a role in the prevention of TD, with greater effectiveness in travellers to the developing world compared to other regions. Prebiotics including

a galacto-oligosaccharide mixture in travellers with low and high risk of TD were also shown to yield a significant reduction in diarrhoea in the prebiotic group as compared to those who consumed placebo.

> Probiotics and prebiotics in TD treatment: there are insufficient data to recommend either probiotics or prebiotics products for treatment of acute travellers' diarrhoea.

In conclusion, travelling is associated with changes to the gut microbiome and recent research suggest that the host microbiome may be an important factor involved in protecting travellers from acute enteric infections. Although diet and probiotics and prebiotics have all been reported to be effective in preventing TD, further studies in humans are needed in order to elucidate how the host gut microbiome may protect travellers from enteric infections.



References:

Riddle MS, Connor BA. The traveling microbiome. *Curr Infect Dis Rep.* 2016; 18(9):29. doi: 10.1007/s11908-016-0536-7.



Read the original post online at:

<http://www.gutmicrobiotaforhealth.com/en/examining-role-gut-microbiome-travellers-health/>

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Probiotics may help reduce stress-induced intestinal barrier dysfunction in newborn rats

Published on August, 21, 2017 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 intestinal epithelium is considered a novel target for addressing several acute and chronic gastrointestinal conditions. It also could have a potential role in targeting systemic diseases. It is an active component of the mucosal immune system. When considering the complex ecosystem combining the gastrointestinal epithelium, immune cells and resident microbiota, several probiotics like *Lactobacillus fermentum* exhibit immunoregulatory effects in healthy adults (here; here). However, little is known about their effects in newborns.

A new study, led by Dr. Michel Neunlist from the French Institute of Health and Medical Research (INSERM) and Université de Nantes (Nantes, France), has found that the probiotic *L. fermentum* could prevent and/or treat gastrointestinal disorders related to intestinal epithelium dysfunction in newborn rats.

The researchers administered either *L. fermentum* (109 colony forming units /100 g body weight/day) or water to newborn rats. Intestinal permeability was measured following maternal separation and water avoidance stress. Zonula occludens-1 (ZO-1) distribution and expression analysis was also performed, together with assessment of anxiety-like behaviour, ethological parameters, and locomotor activity using the elevated plus maze test. Cytokine secretion of activated splenocytes was evaluated in addition.

L. fermentum prevented intestinal epithelium dysfunction induced by both maternal separation and water

avoidance stress, in vivo. Besides this, it reduced intestinal permeability to both fluorescein sulfonic acid and horseradish peroxidase in the small intestine (in particular in the ileum), but not in the colon, of newborn rats.

Regarding mechanisms involved in mediating reduction of epithelial permeability, it was found that *L. fermentum* reduced water avoidance stress-induced changes in intestinal permeability and corticosteronemia. Specifically, when assessing the impact of *L. fermentum* and water avoidance stress upon the organization and distribution of the key tight junction-associated protein ZO-1 in intestinal epithelial cells, the researchers found that *L. fermentum* increased in vivo ZO-1 expression and prevented stress-induced ZO-1 disorganization in intestinal epithelial cells.

For studying whether *L. fermentum* could modulate the immune system, production of interferon-gamma (IFN γ), a key cytokine of T helper 1 (Th1)

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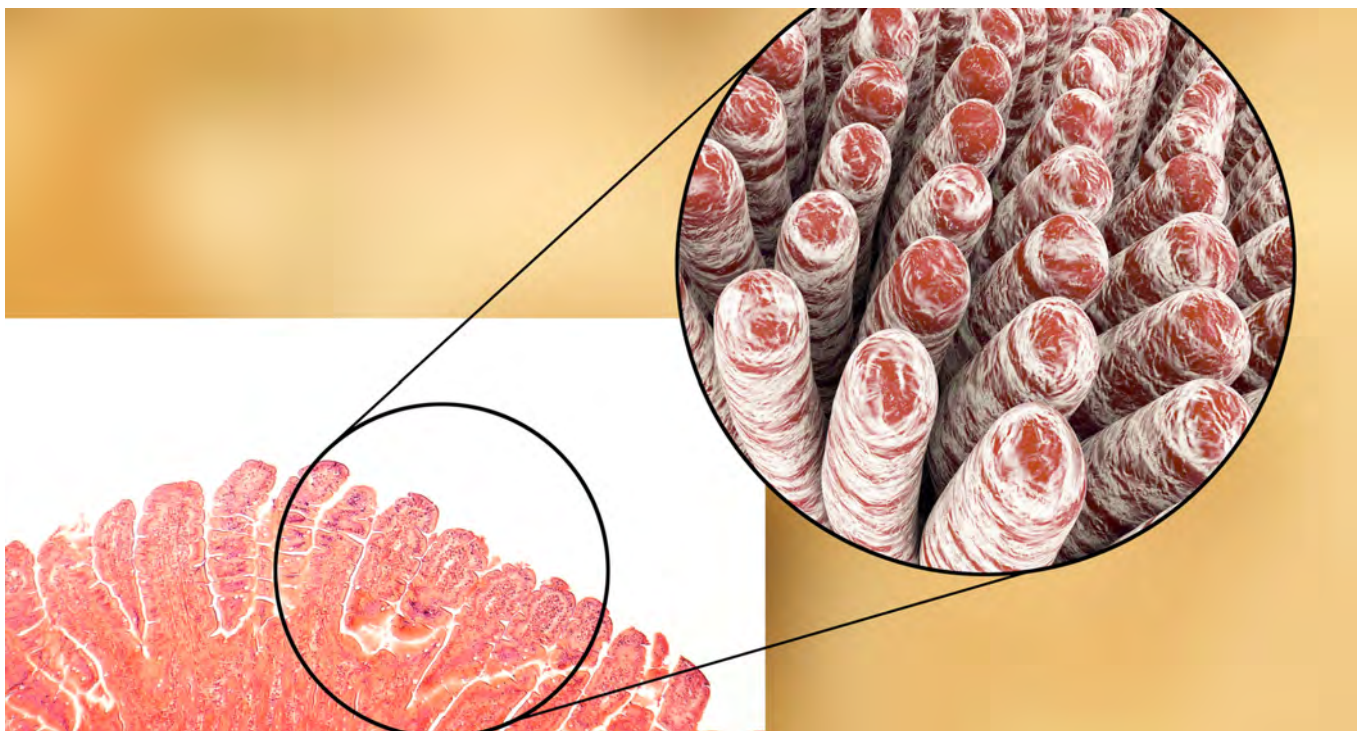
responses, and interleukin-4 (IL-4), a marker of Th2 responses, were assessed in splenocytes following T cell activation. In activated splenocytes, *L. fermentum* increased IFN γ secretion and decreased IL-4 secretion. This Th1-skewing phenotype could contribute to the preventive effect of *L. fermentum* against Th2-driven pathologies

including allergies and asthma; however, further follow-up studies are needed to determine this effect.

Besides modulating systemic immune response, *L. fermentum* increased exploratory behaviour in newborn rats as measured using the elevated plus maze test, while it did not exert any effect on anxiety-like

behaviour, as measured by differences between open and closed arm exploration.

In conclusion, *L. fermentum* CECT 5716 could help manage gastrointestinal disorders related to an altered intestinal epithelium in newborn rats.



Reference:

Vanhaecke T, Aubert P, Grohard PA, *et al.* *L. fermentum* CECT 5716 prevents stress-induced intestinal barrier dysfunction in newborn rats. *Neurogastroenterol Motil.* 2017; 29(8). doi: 10.1111/nmo.13069.



Read the original post online at:

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