



GUT MICROBIOTA
RESEARCH & PRACTICE
edited by ESNM

GUT MICROBIOTA & GUT BARRIER

A selection of content from the
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EDITORIAL



Dr. Maria Rescigno

Maria Rescigno graduated in Biology in 1990 at the University of Milan, Italy. From 1991 to 1994 she worked at the University of Cambridge, UK, in the Department of Biochemistry, as a visiting scholar. From 2001 she directs her own group in Mucosal Immunology. She was the first to show that dendritic cells actively participate to bacterial uptake in the gut and the existence of a gut vascular barrier that resembles the blood brain barrier. She authored more than 140 publications in high impact journals. In 2016 Maria Rescigno has founded Postbiotica s.r.l. a start-up that exploits microbiota-derived metabolites as new pharmaceutical agents. From 2018 she is full professor at Humanitas University and group leader at Humanitas Research hospital, Milan.

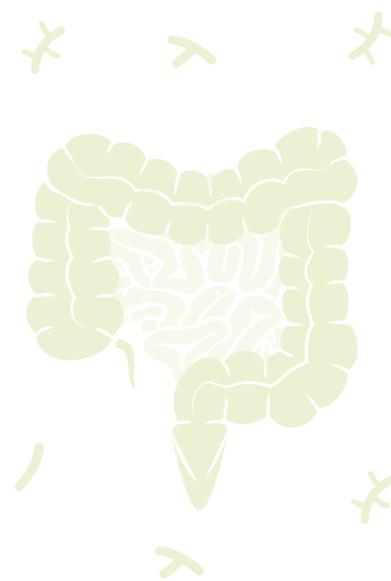
The human gut is the habitat to trillions of microbial cells with over 1,000 diverse microbial species that contribute to the primary functions of the gastrointestinal tract, including nutrition and defense. On the other hand, the gastrointestinal tract mucosa constitutes the major interface that separates the luminal environment from the internal milieu and it is also the body's primary site for interaction with the microbial world living within the gut lumen. The surface of the gastrointestinal mucosa is estimated at up to 4,000 square feet when laid out flat and, most importantly, contains adapted structures allowing bi-directional host-microbe communication (Lozupone *et al.*, 2012).

The gut barrier has to guarantee nutrient and metabolite exchange with the microbiota but at the same time also protection against the microbial world. The gut barrier consists of three major components including a mucus layer, an intact epithelial monolayer and a lamina propria with mucosal immune cells. All three layers contribute to well-functioning of the gut barrier (Spadoni *et al.*, 2017). The epithelial monolayer is not a static structure and the tight junctions that seal spaces between epithelial cells are regulated by the gut microbiota and dietary components (Shen, 2008; Zhou & Zhong, 2017; Ulluwishewa *et al.*, 2011).

Regarding intestinal barrier functions, it can be considered a functional unit involved in supporting water, nutrient and ion

transport, and limiting pathogens and harmful substances' penetration from the luminal content to the underlying immune system and the rest of the body (Zhou & Zhong, 2017). Translocation of nutrients to systemic tissues occurs via the portal vein, through the gut vascular barrier that impedes bacterial translocation to the liver (Spadoni *et al.*, 2015).

Western diets high in fats and sugars, modern lifestyles with stress and sedentarism and the indiscriminate use of antibiotics together with other frequently prescribed drugs –such as non-steroidal anti-inflammatory drugs and proton pump inhibitors– are major drivers of changes in microbiota composition and gut barrier disruption (Odenwald & Turner, 2017).



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Disruption of this barrier may result in an increased intestinal permeability, which in turn facilitates translocation of water, ions, macromolecules, microbial molecules (like lipopolisaccharide) and pathogens to the bloodstream and the underlying tissues. It leads to the popularization of the leaky gut syndrome, which is a term restricted to those situations where epithelial tight junctional function is impaired. That's why intestinal barrier function is nowadays emerging as a hallmark of intestinal homeostasis and host health (Odenwald & Turner, 2017).

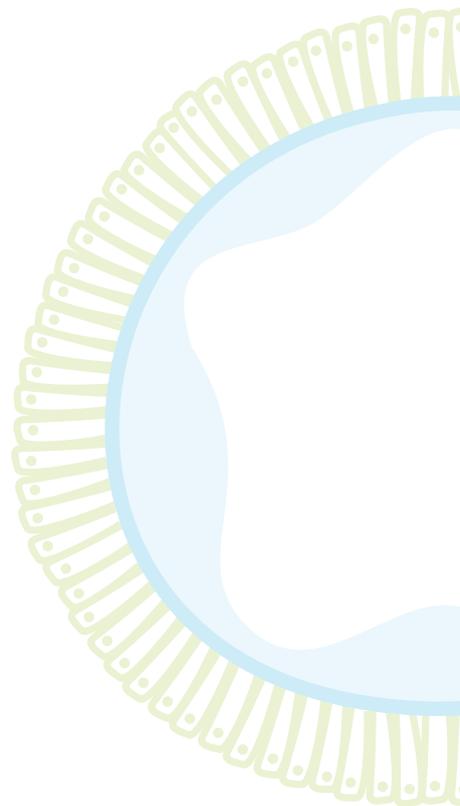
A dysfunctional intestinal barrier has been related with many gastrointestinal diseases, but also with systemic conditions, including autoimmune diseases (such as inflammatory bowel disease, celiac disease, autoimmune hepatitis, type 1 diabetes, multiple sclerosis, and systemic lupus erythematosus), allergic diseases or some neurological disorders (Mu *et al.*, 2017). Although the majority of associations between intestinal barrier function and disease are merely correlative, experimental research has demonstrated the role of barrier dysfunction in inflammatory bowel disease and coeliac disease pathogenesis (Quigley, 2016).

Many promising approaches to target and restore the epithelial barrier from both an anatomic and a functional point of view, especially in the preclinical setting, have been proposed. Among them, dietary fiber and probiotics have been shown to protect the gut barrier and counteract many of the deleterious effects triggered by Western dietary patterns and stress (Bron *et al.*, 2017; De Santis *et al.*, 2015).

The maintenance of a healthy intestinal barrier is therefore a prerequisite for homeostasis of gastrointestinal mucosal function, which is crucial for allowing the mucosal barrier absorptive capacity while maintaining effective defensive reactions against harmful substances and pathogens.

In this document Gut Microbiota for Health offers you an overview of key concepts regarding the importance of gut barrier in host homeostasis, along with the current preclinical and clinical evidence showing the role of diet in correcting intestinal barrier dysfunction.

Dietary fiber and probiotics have been shown to protect the gut barrier and counteract many of the deleterious effects triggered by Western dietary patterns and stress



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Targeting the epithelial barrier as a potential therapeutic goal

Research has shown the relevance of environmental triggers such as stress in driving intestinal barrier dysfunction. Besides this, dietetic strategies aimed at maintaining an adequate intestinal barrier function homeostasis has been involved as a potential avenue for preventing gut-related and systemic diseases.

- **Physiologic stress impacts intestinal permeability and both gut microbiota composition and function in adults.**

A multiple-stressor military training environment –considered as a model of physiologic stress– may lead to an increased intestinal permeability that has been correlated with increased plasma lipopolysaccharide and interleukin-6 inflammatory markers. Collection of fecal samples before and after the stress intervention also showed that less dominant bacteria taxa have increased and there was reported an alteration in 23% of bacterial metabolites.

- **A diet lack in fiber leads to gut microbiota disturbance and reduction in colonic mucus layer thickness.**

In mice, a diet lack in fiber may drive a degradation of the colonic mucus layer and results in more severe colitis by the enteric pathogen *Citrobacter rodentium*. Specific changes secondary to fiber deprivation include an increase in the proliferation of bacteria that

degrade mucus as alternative nutrient (including *Akkermansia muciniphila*) and a decrease in fiber-degrading bacteria such as *Eubacterium rectale*. Besides this, the lack of fiber also leads to physiological changes in mucus layer thickness and altered inflammatory markers. Although these preliminary findings allow us understanding why fiber is so important for health, researchers have used a simple model that does not necessarily reflects the complexity of the real gut ecosystem, which implies that more research is needed for a better characterization of host-microbiota interactions in the context of a diet lack in fiber.

- **The probiotic *Lactobacillus fermentum* CECT 5716 prevents stress-induced intestinal barrier dysfunction in rats.**

The probiotic *Lactobacillus fermentum* prevents intestinal epithelium dysfunction induced by both maternal separation and water avoidance stress in newborn rats. Mechanisms involved include a switch from the T helper 1 immune response phenotype to T helper 2-driven immune responses, together with an increase in exploratory behaviours.

- **Probiotics might have a role in restoring the weakened intestinal barrier in non-steroidal anti-inflammatory drugs-induced small intestinal damage.**

Among current treatments for preventing or reducing non-steroidal

anti-inflammatory drugs (NSAID)-induced intestinal damage, a narrative review suggests the potential of probiotics. Based on experimental and clinical data, probiotics have been reported as a potential effective therapeutic option for preventing NSAID-induced gastrointestinal side effects.

- **The probiotic *Lactobacillus rhamnosus* CNCM I-3690 counteracts high-fat diet induced metabolic impairments and gut barrier dysfunction in mice.**

The pathobiont *Bilophila wadsworthia* aggravates high fat diet-induced deleterious metabolic effects in mice, which can be partly reversed by a probiotic strain *L. rhamnosus* CNCM I-3690. This is a probiotic with documented anti-inflammatory properties, protective effects against intestinal barrier dysfunction and high-fat diet-induced metabolic alterations in mice.

- **Probiotics may modulate human disease through impacting intestinal barrier function.**

Data from in vitro cell lines, animal models and small clinical trials supports the protective role of probiotics in intestinal epithelial integrity, with the most solid evidence demonstrating their beneficial effects for the reduction of gastrointestinal disease symptoms rather than systemic disorders.

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Looking toward the future

The involvement of a compromised intestinal barrier function in gastrointestinal and systemic disorders underpins the need to take it into account as a new player for preventing or reverting the diseased state back to homeostasis and health.

The majority of research exploring the composition and function of the gut barrier comes mainly from preclinical models. Further research

in the clinical setting is therefore needed before making conclusions about the relevance of targeting it on human health and disease.

The fact that current nutrition studies not always include the systematic use of markers aimed to evaluate intestinal barrier function make it difficult inferring clear conclusions. Besides this, factors that influence barrier integrity should also be taken into account as confounders. The challenge moving forward will be to provide evidence

for dietary and microbiota influences on the gut barrier that have meaningful effects not only for an overall wellbeing, but also for preventing digestive and extra-intestinal conditions.

Intervention based on prebiotics, probiotics or postbiotics (microbial metabolites) may help restore the gut barrier function, but additional studies in the human setting with clear clinical outcome are required.



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SELECTED CONTENT

Gut microbiota changes are related to intestinal permeability in adults under physiologic stress

Published on May, 22, 2017 by Paul Enck.



Prof. Paul Enck has been Director of Research at the Department of Psychosomatic Medicine and Psychotherapy at University Hospital Tübingen in Germany since 2004. His main interests are psychophysiology and neurobiology, relating to the placebo response, eating and food intake and their disorders, nausea and vomiting and of gut functions in health and disease, including functional and inflammatory bowel disorders, and the role of the microbiota and pre- and probiotics along the gut-brain axis.

Previous research has shown that chemical and physical stress are major influencers of the physiology and ecology of the all microbes that have coevolved with a host. However, the physiologic effects of gut microbiome responses to physiologic stress have been poorly studied in humans.

A recent study, led by Dr. Stefan Pasiakos from the Military Nutrition Division at the United States Army Research Institute of Environmental Medicine in Natick (Massachusetts, USA), has found that changes in gut microbiota composition and metabolic activity are related to intestinal permeability in adults undergoing military training, an environment of physiologic stress.

The researchers studied the effects of a multiple-stressor military training environment as a model of physiologic stress-including prolonged physical and psychological stress, sleep deprivation, and environmental extremes-on gut microbiota composition and metabolic activity and intestinal permeability (IP) in 73 Norwegian Army Soldiers (2 females) > 18 years of age. Soldiers were provided with 3 Norwegian rations/day with or without protein- or carbohydrate-based supplements (control group received 3 rations/day, n=18; carbohydrate group received 3 rations/day and 4 carbohydrate-based snack bars/day, n=27; protein group received 3 rations/day and 4 protein-based

snack bars/day, n=28) during a 4-day cross-country ski march of a 51 km during which volunteers skied in 50:10 min per hour work-to-rest ratios while carrying a ~45 kg backpack (STRESS).

Dietary intake of each group can be found in the tables from the original paper. IP (assessed by quantifying the urinary excretion of orally ingested sucralose and mannitol), inflammatory biomarkers (assessed by plasma/serum lipopolysaccharide, serum high-sensitivity C-reactive protein and creatine kinase), stool microbiota composition, and stool and plasma metabolites were measured before and during the 4-day training exercise.

IP increased 62% during the 4-day training period, independent of diet group, and was correlated with increased plasma LPS and IL-6 inflammatory biomarkers. According to the authors, both altered intestinal barrier integrity and stress-induced muscle damage could potentially contribute to inflammation by inducing tight junction dysfunction.

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Gut microbiota changes are related to intestinal permeability in adults under physiologic stress

Stool samples were collected over the 2 d prior to STRESS, and the night of or day after completing STRESS in a self-selected subset of volunteers. Of all 73 participants, 38 volunteers provided stool samples, 26 of whom provided both pre- and post-STRESS samples. In all diet groups gut microbiota diversity increased and was mainly characterized by an increase in abundances of less dominant taxa at the expense of more dominant taxa such as *Bacteroides*; this included an increased relative abundance of potentially deleterious and infectious bacteria from several taxa.



When focusing on gut microbiota metabolic activity, 23% of bacterial metabolites were significantly altered in stool after the 4-day training period. Several associations between stool microbiota composition, stool and plasma metabolites, intestinal permeability, and inflammation were reported. Among stool metabolites associated with changes in IP during

military training were several amino acids and lipids and xenobiotics. Decreased concentrations of the metabolites arginine and cysteine were associated with increased IP.

In conclusion, these results demonstrate that a physical stressor such as in a military training environment may induce short-term increases in IP together

with alterations in markers of inflammation, and with gut microbiota composition and metabolic function. Provided that such changes are persistent and of disease-relevant quantity and quality, these data open the future possibility of targeting the gut microbiota for preventing IP during periods of physiologic stress in adults.



Reference:

Karl JP, Margolis LM, Madslie EH, *et al.* Changes in intestinal microbiota composition and metabolism coincide with increased intestinal permeability in young adults under prolonged physiologic stress. *Am J Physiol Gastrointest Liver Physiol.* 2017; doi: 10.1152/ajpgi.00066.2017.



Read the original post online at:

<http://www.gutmicrobiotaforhealth.com/en/gut-microbiota-changes-related-intestinal-permeability-adults-physiologic-stress/>

SELECTED CONTENT

A fiber-deprived diet may degrade the colonic mucus barrier and promote enteric pathogen infection in mice

Published on December, 28, 2016 by Andreu Prados.



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

Dietary fiber from plant-based foods is the most common fuel for some bacterial species in the gut microbiota and in some contexts has been shown to play a key role in protecting the host against immune-mediated diseases such as food allergies and even neurological disorders. A diet rich in microbiota-accessible carbohydrates (MACs), which are complex carbohydrates found in fruits, vegetables, whole grains, and legumes, has a crucial role in shaping the gut microbial ecosystem. In this context, conserving and restoring the human gut microbiome by increasing consumption of dietary fiber is a current nutritional challenge. However, little is known about the underlying mechanisms by which fiber deprivation impacts the gut microbiota and influences disease risk.

A recent study, led by Dr. Eric Martens from the University of Michigan Medical School in Ann Arbor (USA), has found that a fiber-deprived diet may lead to a degradation of the colonic mucus layer and enhance enteric pathogen infection in mice.

The researchers studied interactions between dietary fiber, gut microbiota and the colonic mucus barrier in a gnotobiotic mouse model, in which germ-free mice were colonized with synthetic human gut microbiota with a known full genetic signature that allowed tracking of their activity over time. The 14 selected species were chosen to represent the five dominant phyla and collectively hold a versatile capacity for degrading indigestible polysaccharides.

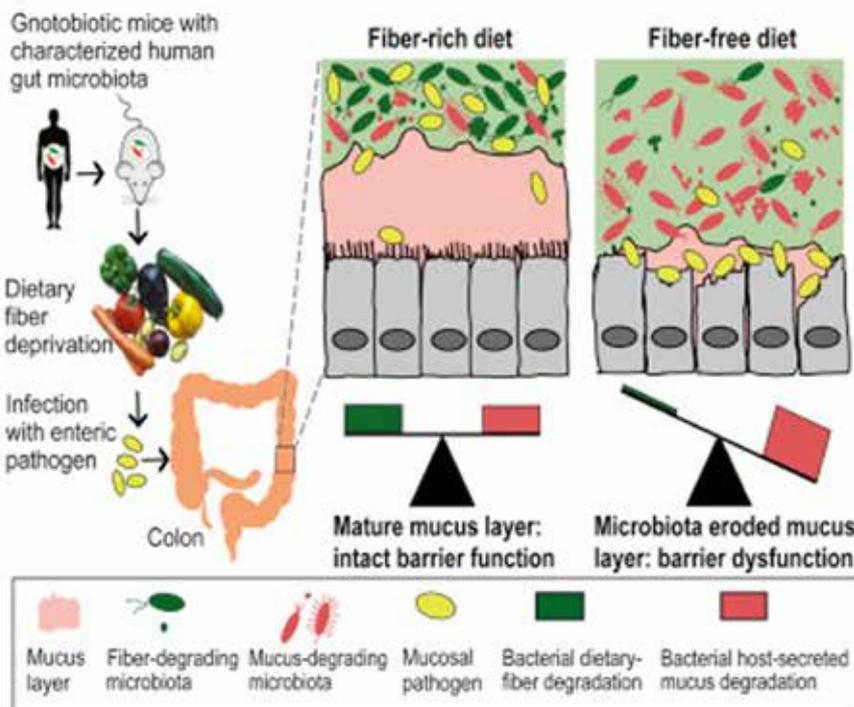
Three groups of mice were maintained by constant feeding of one of three different diets: fiber-rich

(contained intact fiber particles present naturally in food), fiber-free, or prebiotic (contained a mixture of purified polysaccharides, matching those used in prebiotic formulations). To imitate fluctuating exposures to dietary fiber in humans, four other groups were alternated between the fiber-rich and fiber-free or prebiotic and fiber-free diets on a daily or 4-day basis. During either chronic or intermittent dietary fiber deficiency, there was an increase in the proliferation of mucus-degrading species such as *Akkermansia muciniphila* and *Bacteroides caccae* and a decrease in fiber-degrading bacteria such as *Eubacterium rectale* and *Bacteroides ovatus* both in faecal samples and in the colonic lumen and mucus layer.

The increased abundance of mucin-degrading bacteria was explained by their ability to degrade mucus as an alternative nutrient, as the lack of naturally complex plant

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fiber (free-fiber and prebiotic diets) led to a higher expression of carbohydrate active enzymes, sulfatases, and proteases that enable gut bacteria to utilize dietary fiber and mucosal polysaccharides.

The colonic mucus layer thickness from proximal colon to rectum was highest in the colonized group fed the fiber-rich diet. Besides this, mucus production was altered in colonized mice fed the fiber-free diet and led to altered host intestinal

responses. Faecal lipocalin – a neutrophil protein involved in low-grade inflammation – was increased in the group of colonized mice fed the fiber-free diet compared to those fed the fiber-rich diet. Secondly, colon length was shorter in colonized fiber-free diet mice when compared to colonized fiber-rich fed mice. Altogether, these data show that fiber deprivation led the gut microbiota to degrade the colonic mucus barrier and altered some host responses.

Finally, in order to test whether the reduction in colonic mucus layer thickness was associated with increased pathogen susceptibility, the researchers examined changes in gut microbial communities in response to *Citrobacter rodentium*, a murine pathogen that resembles the human enteric species *Escherichia coli*. When mice were infected with *C. rodentium*, this invading pathogen flourished more in the guts of mice fed a fiber-free diet. Besides this, many of those mice began to show signs of illness and lost weight over time. Measurements of inflamed tissue area in different intestinal segments showed that the colonized fiber-free diet group experienced inflammation that covered significantly more surface area, resulting in more severe colitis by *C. rodentium*. These results show that a fiber-deprived gut microbiota promotes heightened pathogen susceptibility.

To sum up, a fiber-deprived diet may promote expansion and activity of colonic mucus-degrading bacteria, with a consequently negative impact on the colonic mucus layer and increased susceptibility to a gastrointestinal pathogen through reduction of this barrier.



Reference:

Desai MS, Seekatz AM, Koropatkin NM, et al. A dietary fiber-deprived gut microbiota degrades the colonic mucus barrier and enhances pathogen susceptibility. *Cell*. 2016; 167(5):1339-53. doi: 10.1016/j.cell.2016.10.043.



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SELECTED CONTENT

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

Published on August, 21, 2017 by Paul Enck.



Prof. Paul Enck has been Director of Research at the Department of Psychosomatic

Medicine and Psychotherapy at University Hospital Tübingen in Germany since 2004. His main interests are psychophysiology and neurobiology, relating to the placebo response, eating and food intake and their disorders, nausea and vomiting and of gut functions in health and disease, including functional and inflammatory bowel disorders, and the role of the microbiota and pre- and probiotics along the gut-brain axis.

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. 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* (10^9 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

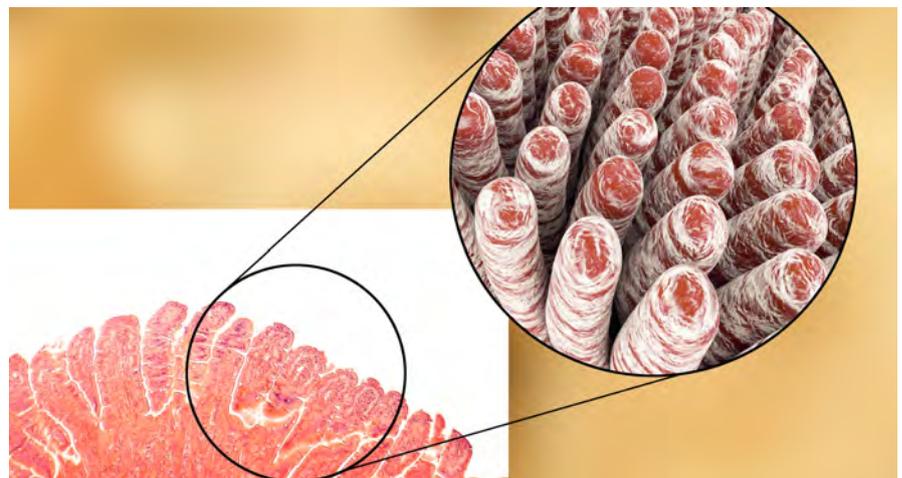
L. fermentum prevented intestinal epithelium dysfunction induced by both maternal separation and water avoidance stress, *in vivo*

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

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) 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.

L. fermentum reduced water avoidance stress-induced changes in intestinal permeability and corticosteronemia



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.



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Gut microbiota modulation offers a new therapeutic approach for treating non-steroidal anti-inflammatory drug-induced small intestinal damage

Published on May, 15, 2017 by Andreu Prados.



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Non-steroidal anti-inflammatory drugs (NSAIDs) -including aspirin, ibuprofen, naproxen, indomethacin, and piroxicam, among others- constitute one of the most frequently prescribed types of drugs that often cause mucosal lesions, not only in the stomach/duodenum, but also in the small intestine. Although several novel treatments have been explored to prevent or reduce NSAID-induced intestinal lesions (i.e., gastrointestinal-sparing NSAIDs, anti-ulcer drugs, anti-secretory agents, antibiotics, probiotics, and food constituents), little is known whether the gut microbiota is involved in ulcer formation as well as in its treatment.

A recent narrative review, led by Dr. Tetsuo Arakawa from the Department of Gastroenterology at the Osaka City University Graduate School of Medicine in Japan, has suggested that probiotics and rebamipide could be useful for addressing NSAID-induced small intestinal damage.

The researchers questioned whether NSAID-induced damage in the small intestine involves the gut microbiota, covering from animal research to human pathologies. An initial experimental study showed that germ-free rats were resistant to indomethacin-induced intestinal lesions. Besides this, NSAID-induced ileal ulcers in gnotobiotic rats were present in those mono-associated with *Eubacterium limosum* and *Escherichia coli* but not in those mono-associated with *Bifidobacterium* and *Lactobacillus*. These results show that composition of the intestinal microbiota is involved in NSAID-induced small intestinal damage. Specifically, first NSAIDs

induce barrier dysfunction through inhibition of cyclooxygenase and subsequent deficiency of prostaglandin and mitochondrial malfunction. Then, toll-like receptor 4 (TLR4) on macrophages recognizes lipopolysaccharide (LPS) found in Gram-negative bacteria that can pass across a weakened barrier. The myeloid differentiation primary-response 88/nuclear factor- κ B signalling pathway leads to the release of proinflammatory cytokines such as tumor necrosis factor- α (TNF- α) and interleukin 1 β (IL-1 β). This proinflammatory response finally ends with neutrophil infiltration into the mucosa and submucosa of the small intestine, causing damage. However, when interpreting these results it should be kept in mind that the human small intestine harvests not too many bacteria when compared to the large intestine.

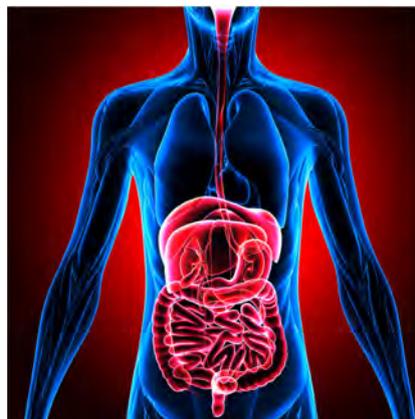
When it comes to studying the significance of dysbiosis in NSAID-induced small intestinal damage,

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Gut microbiota modulation offers a new therapeutic approach for treating non-steroidal anti-inflammatory drug-induced small intestinal damage

the researchers discuss their own study, which demonstrated a possible association between small intestinal bacterial overgrowth (SIBO) and NSAID-induced small intestinal damage in chronic NSAID users. Besides this, a meta-analysis is reported that showed proton pump inhibitors -drugs that are often used for the prevention of NSAID-induced injuries to the upper GI tract- are associated with SIBO and may exacerbate NSAID-induced small intestinal damage.

Potential therapeutic candidates for NSAID-induced small intestinal damage were identified, and included probiotics and rebamipide -a mucoprotective drug that has been clinically used for treating gastritis



and peptic ulcers. Although antibiotics may be effective in preventing the NSAID-induced small intestinal damage, the authors emphasized that when used long-term they may increase the risk of development of multi-drug resistant

bacteria. Probiotics were reported as an effective therapeutic option for preventing NSAID-induced small intestinal damage based on experimental data and on studies of patients taking probiotics compared to those receiving control treatment. Rebamipide may inhibit NSAID-induced small intestinal damage through modulating the composition of the gut microbiota in mice.

On the whole, gut microbiota plays a relevant role in NSAID-induced small intestinal damage pathogenesis. According to data presented, targeting it through probiotics or rebamipide could be a way to prevent NSAID-induced small intestinal damage.

Rebamipide may inhibit NSAID-induced small intestinal damage through modulating the composition of the gut microbiota in mice



Reference:

Otani K, Tanigawa T, Watanabe T, *et al.* Microbiota plays a key role in non-steroidal anti-inflammatory drug-induced small intestinal damage. *Digestion*. 2017; 95(1):22-8. doi: 10.1159/000452356.



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SELECTED CONTENT

The probiotic *L. rhamnosus* CNCM I-3690 counteracts pathobiont-driven metabolic effects and gut barrier dysfunction in mice

Published on August, 30, 2018 by Andreu Prados.



Andreu Prados holds a Bachelor of Science Degree in Pharmacy & Human Nutrition

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The prevalence of obesity and related metabolic conditions is increasing worldwide and has become a major public health issue. Recent research has highlighted the gut microbiome's contribution to the development of non-communicable diseases, although little is known about underlying mechanisms and causal relationships.

A new study led by Prof. Harry Sokol, a gastroenterologist and researcher from the French National Institute for Agricultural Research (INRA) and the French Medical Research Institute (INSERM), has found that the pathobiont *Bilophila wadsworthia* aggravates high fat diet-induced deleterious metabolic effects in mice, which were partly reversed by a probiotic strain *Lactobacillus rhamnosus* CNCM I-3690.

Prof. Harry Sokol corresponded with GMFH editors to clarify the study's results and their clinical relevance for metabolic syndrome pathogenesis.

According to Professor Sokol: "Over-representation of *B. wadsworthia* has been associated with animal protein-based diets and diets rich in fats. The negative effect of the increased abundance of this pathobiont on intestinal inflammation had been demonstrated, but despite its documented association with dietary fats, it remained unknown whether *B. wadsworthia* imposed negative consequences on metabolic host function."

As expected, a high fat diet (HFD) led to increased fecal *B. wadsworthia* expansion together with dysregulated glucose-related metabolic parameters compared with mice maintained on the control diet. HFD also modulated gut microbiota composition.

1. *wadsworthia* aggravated HFD-induced metabolic impairments, which depended to a certain extent on the levels of *B. wadsworthia* harbored in the intestine. The altered metabolic parameters included fasting glucose, serum liver enzymes (aspartate transaminase and alanine transaminase), hepatic steatosis and total cholesterol and high-density lipoprotein plasmatic levels. The hepatic lipid content was significantly higher in mice harboring high-density levels of *B. wadsworthia* compared with those harboring low levels of *B. wadsworthia*, which shows the synergistic effects of *B. wadsworthia* and HFD in inducing host metabolic syndrome.

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The probiotic *L. rhamnosus* CNCM I-3690 counteracts pathobiont-driven metabolic effects and gut barrier dysfunction in mice

Besides this, *B. wadsworthia* further potentiated HFD-induced intestinal barrier dysfunction and inflammation and dysregulated bile acid composition in the cecum by increasing levels of conjugated bile acids.

To counteract the negative effects of *B. wadsworthia* on glucose homeostasis and liver function, the researchers looked at targeting the microbiota through a probiotic. Prof. Sokol explained that the probiotic *Lactobacillus rhamnosus* strain CNCM I-3690 was selected based on its previously demonstrated anti-inflammatory properties, protective effects against intestinal barrier dysfunction and HFD-induced metabolic alterations in mice, as well as for its ability to induce a reduction in the *Desulfohalobium* family, to which *B. wadsworthia* belongs. Specifically, *L. rhamnosus* CNCM I-3690 prevented *B. wadsworthia* expansion in the cecum and small intestine,

suppressed *B. wadsworthia*-related dysregulation of glucose homeostasis in HFD mice with a higher *B. wadsworthia* level and corrected the effect of HFD on insulin levels.

Although *B. wadsworthia* and *L. rhamnosus* CNCM I-3690 had a slight impact on gut microbiota composition, both affected several pathways involved in inflammation and fat and glucose metabolism. Notably *L. rhamnosus* CNCM I-3690 corrected the gut microbiota dysfunction induced by *B. wadsworthia*—such as lower fecal butyrate and propionate concentrations and high taurine conjugated bile acid concentration—as well as intestinal barrier dysfunction.

In conclusion, these findings have shown the contribution of the known pathobiont *B. wadsworthia* to metabolic pathogenesis. As the administration of *L. rhamnosus* CNCM I-3690 counteracted some of the

deleterious metabolic effect led by *B. wadsworthia* and dietary lipids, these findings highlight the potential of targeting the gut microbiota and intestinal barrier as a potential therapeutic strategy in managing metabolic diseases.

The fact *Bilophila* exacerbates the effect of a high fat diet underscores the need to target the gut microbiome and that probiotics are promising candidates to do so.

According to Prof. Sokol: “A preventive approach using probiotics is particularly relevant in metabolic syndrome. These results open up a new avenue for exploration and they now need to be confirmed in humans. Our next steps are to confirm these results in humans and particularly the effects of *L. rhamnosus* CNCM I-3690 first on *B. wadsworthia* levels and secondly on metabolic syndrome markers.”

L. rhamnosus CNCM I-3690 corrected the gut microbiota dysfunction induced by *B. wadsworthia*, as well as intestinal barrier dysfunction



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SELECTED CONTENT

A review explores the influence of probiotics on intestinal barrier integrity in various disease states

Published on September, 20, 2018 by Megan Mouw.



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.

The enormous surface area of the human intestinal barrier is key to maintaining a delicate physiological homeostasis. On one hand, it must be optimized for absorption of water and nutrients; on the other hand, it must act as a tight barrier against chemical and microbial challenges – all while protecting us from unnecessary reactions to compounds that are harmful to our health. Dysfunction of the intestinal barrier is associated with many disorders through an increase in intestinal permeability, more colloquially known as leaky gut. Recent findings have highlighted the importance of the gut microbiota in maintaining proper health, and have led to the notion that specific probiotic bacterial strains may be beneficial to the intestinal barrier.

In a review published by the British Journal of Nutrition, author Dr. Peter Bron and co-authors systematically catalog the current available preclinical and clinical evidence for the use of probiotics in improving various disease states. Specifically, authors review the potential of probiotics to modulate the gut barrier in cases of bacterial and viral infection, obesity and diabetes, necrotizing enterocolitis, inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS).

Bacterial and viral pathogens:

Bacterial or viral pathogens pose a common challenge to the mucosal barrier of the gastrointestinal (GI) tract. To date, attenuated pathogenic bacteria have been used to study the diarrhoea-ameliorating capability of probiotics in animals, with a generally poor success rate. Rodent *in vivo* infection models have demonstrated that probiotics

can attenuate the severity of infection caused by several gastrointestinal pathogens, including *Helicobacter pylori*, *Citrobacter rodentium*, *Listeria monocytogenes* and *Salmonella typhimurium*, among others. It should be noted that both endogenous microbiota and probiotics may act in parallel via direct and indirect mechanisms to antagonize pathogens, making it difficult to disentangle the primary contribution of the microbiota from the role of the exogenous probiotic. However, the obvious ethical challenges posed by designing well-controlled human studies means that there have been few human infection studies to date.

Obesity and diabetes:

Metabolic endotoxemia, or high levels of gut microbiota-derived lipopolysaccharide (LPS) in the plasma, is implicated in the development

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of metabolic diseases associated with obesity and type 2 diabetes. LPS, which is derived from the outer cell wall components of gram-negative bacteria, is typically prevented from translocating to the plasma by the intestinal barrier. In mice, *Bifidobacteria* have been associated with reduced intestinal LPS levels and improved mucosal barrier function. Human studies, of which there have been few, are nonetheless in agreement with mouse studies which indicate that probiotic supplementation of *Bifidobacterium*, or prebiotic supplementation promoting *Bifidobacterium* growth, may reduce the incidence of endotoxemia. Outside of *Bifidobacterium*, various *Lactobacilli* species and *Akkermansia muciniphila* have also been shown to positively affect metabolic disorder parameters. Authors note that these health improvements may not be entirely attributed to the bacterial species in question, as in most cases, the exact underlying mechanism driving health improvements is still unknown. Furthermore, very few studies have evaluated whether similar effects can be achieved in human studies, marking a major caveat in our scientific understanding.

Necrotising enterocolitis:

Immaturity of the intestinal barrier is a defining characteristic of necrotising enterocolitis (NEC), an



acute inflammatory disease with high mortality affecting low-birth weight infants. Overall, evidence from neonatal animal models suggests that probiotics can strengthen the immature gut barrier – a hallmark of NEC – thereby reducing disease severity. In the few human studies that have been conducted, probiotic administration reduced pathogen loads in the developing preterm intestine. Authors warn however, that at this time, medical experts still hesitate to recommend the routine use of specific probiotic treatment and await large and well-designed safety and efficacy trials.

Irritable bowel syndrome:

Irritable bowel syndrome (IBS) is a gastrointestinal disorder characterised

by recurrent abdominal pain and a change in stool consistency or frequency. Although the scientific debate is ongoing, studies suggest that the gut microbiota likely contributes to IBS symptoms. Reduction of IBS-like symptoms has been achieved in animal models following intentional disruption of the epithelial barrier. Studies have shown that the addition of a variety of probiotic strains, particularly the lactic acid bacteria, have the potential to restore intestinal barrier function, highlighting the promise of probiotics as a treatment option for this syndrome. However the results of existing trials are difficult to interpret due to the use of different strains and combinations, as well as general limitations in study design. Prebiotic compounds that favor the production of lactic

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acid and butyrate also deserve attention, as they may be administered together with specific probiotic strains (synbiotics) to stimulate synergistic effects between probiotics, the endogenous microbiota, and their metabolites.

Inflammatory bowel disease:

Inflammatory bowel diseases, which include Crohn's disease (CD) and ulcerative colitis (UC) are very serious inflammatory conditions of the gut that often require powerful immunosuppression to induce remission. In light of their seriousness, the authors write that it

is somewhat fanciful to suggest probiotics may treat active IBD, though they may be useful in maintaining remission. Results from recent studies on CD however, have been disappointing. More promising results have been reported for the use of probiotics in inducing and maintaining remission of UC. For instance, one study found that over a period of 12 weeks, probiotic treatment was equivalent to mesalazine for the maintenance of UC remission.

In the concluding remarks, authors highlight that to date, key work on probiotics and intestinal barrier integrity has already been done in

animal models and *in vitro*, while relatively little is known about equivalent processes in humans. Still, a variety of studies imply that mucosal barrier function can be improved by probiotic treatment, which underpins the need for studies in well diagnosed diseased populations. Only once these human studies have been completed will the scientific community have enough evidence to confidently recommend health-promoting probiotic treatments to medical practitioners and patients alike.

Studies have shown that the addition of a variety of probiotic strains, particularly the lactic acid bacteria, have the potential to restore intestinal barrier function



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