The Role of the Gut Microbiome in CardioMetabolic Disease

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More than 9,000,000 Unique Genes in Human Gut Bacterial Community: Estimating Gene Numbers Inside a Human Body

Buddy, Can You Spare a Gene?

Helping hands: The number of genes distributed among the friendly bacteria that live inside people’s bodies and on their skin far outnumbers the number of genes we inherit from our parents. Researchers are figuring out in greater detail which of these microbial genes benefit their human hosts and how.
According to one common estimate, the human gut contains at least a kilogram of bacteria alone. They contribute so much to human biology that it is difficult to say where the body ends and the microbes begin.
THE FIRST 15 MONTHS: HOW OUR MICROBIOME DEVELOPS AND DIVERSIFIES

We start out sterile in the womb. But every baby gets coated with microbes the moment it passes through the birth canal. (Babies born by cesarean section are colonized by microbes from their mother’s skin.) More germs take up residence inside our bodies in the months that follow, delivered by bacteria-laced milk and fingertips and contact with floors, high chairs, and affectionate pets. This chart shows how microbial diversity in the large intestine grew during the first 15 months of one child’s life.

**SOURCE:** http://www.wired.com/magazine/2011/09/mf_microbiome/

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**Antibiotics = Microbiome Killer**

Studies have revealed some alarming costs of taking antibiotics, which don’t discriminate between disease-causing bacteria and our natural microbiome. Graphed below is the diversity of gut bacteria from one important genus (*Bacteroides*) in a patient who took a weeklong course of clindamycin; different colors represent the different species. For nine months after exposure, the subject’s gut was left with nothing but one type, a clindamycin-resistant strain of *Bacteroides thetaiotaomicron*. Even two years out, the flora had not regained their former diversity.

**SOURCE:**
Individuals with low bacterial gene richness (23% of study population) were characterized by more marked overall adiposity, insulin resistance, and dyslipidaemia.

Low-bacterial-richness individuals showed a more pronounced inflammatory phenotype when compared with high-bacterial-richness individuals.


Emerging evidence suggests, however, that variation in our ‘other genome’ the collective genome of the microorganisms inhabiting our body, known as the microbiome may have an even greater role than human genome variation in the pathogenesis of obesity given its direct interaction with environmental factors.

Figure 3 | Functional and phylogenetic shifts in the LGC microbiome. Top, observed increase (red) or decrease (green) of functions and phylogenetic groups. Bottom, potential drivers (yellow) of inflammation related to decreased richness. Left, antibiotic-mediated perturbation of the richness; Right, proteobacterial lipopolysaccharide-mediated perturbation of the richness. AB, antibiotic; IR, insulin resistance.

We identified *Chryseomonas* in all atherosclerotic plaque samples, and *Veillonella* and *Streptococcus* in the majority. Taken together, our findings suggest that bacteria from the oral cavity, and perhaps even the gut, may correlate with disease markers of atherosclerosis.
Intestinal microbiota metabolism of t-carnitine, a nutrient in red meat, promotes atherosclerosis

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Intestinal microbiota metabolize choline and phosphatidylcholine to produce trimethylamines (TMA), which is further metabolized to a pathogenic species, indoleamine 2,3-dioxygenase (IDO). Two studies have reported that metabolism of certain microbiota metabolites may be associated with increased TMA levels. We demonstrate that intestinal microbiota metabolism of dietary t-carnitine, a myocardial nutrient abundant in red meat, also produces TMA and accelerates atherosclerosis in mice. Decreased serum levels of TMA were observed in the cholesterol-fed diet and in mice treated with antibiotics, indicating that the microbiota is required for TMA production. TMA levels were significantly higher in mice with atherosclerosis, but this did not occur in otherwise identical knockouts. To identify microorganisms, we performed ultralow-Leucine mixotrophic cultures of red meat and used metagenomic analysis to identify specific microbial species. Two species of the genus Lactobacillus were associated with increased TMA levels and their relative abundance correlated with severity of atherosclerosis in mice. These findings suggest that dietary t-carnitine may be a risk factor for atherosclerosis in humans. This is the first study to demonstrate a direct link between diet and atherosclerosis.
It was originally believed that the composition of the intestinal microbiota was relatively stable from early childhood; however, recent evidence suggests that diet can cause dysbiosis, an alteration in the composition of the microbiota, which could lead to aberrant immune responses.
Fig. 4 Effects of a healthy gut microbiota and dysbiosis on the gut and metabolic health of the host. A healthy microbiota comprises a balanced representation of symbions (bacteria with health-promoting functions) and pathobions (bacteria that potentially induce pathogony). A shift toward dysbiosis results from a decrease in symbions and/or an increase in pathobions and is likely to be triggered by environmental factors (such as diet, stress, antibiotics, and infection). Low bacterial gene counts have also been associated with altered gut microbial functions and dysbiosis and have been linked to increased fat accumulation, impaired host immune system, insulin resistance, obesity, and the metabolic syndrome. Individuals with these characteristics are more likely to develop metabolic diseases such as diabetes, cardiovascular diseases, and inflammatory bowel disease.

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The Human Gut Microbiome and Body Metabolism: Implications for Obesity and Diabetes
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Abstract
BACKGROUND—Obesity, metabolic syndrome, and type 2 diabetes are major public health challenges. Recently, interest has surged regarding the possible role of the intestinal microbiome as a potential novel contributor to the increased prevalence of these disorders.

CONTENT—Recent advances in metagenomic DNA sequencing technologies have resulted in the widespread application of whole-genome sequencing technologies for metagenomic DNA analysis of complex ecosystems such as the human gut. Current evidence suggests that the gut microbiomes affect nutrient acquisition, energy harvest, and a myriad of host metabolic pathways.

CONCLUSION—Advances in the Human Microbiome Project and human metagenomics research will lead the way toward a greater understanding of the importance and role of the gut microbiome in metabolic disorders such as obesity, metabolic syndrome, and diabetes.

Obesity, metabolic syndrome, and type 2 diabetes are major public health challenges, affecting approximately 30 million children and adults in the US. More than 9% of the US population has diabetes, of which 17.0 million people have the metabolic syndrome (1). During the past 30 years, obesity has dramatically increased in prevalence in the US. More than 31.1 million adults (36%) are obese, and approximately 13.4 million (17%) of children and adolescents (age 2–19) years are obese (2). In the US in 2010 (2), all of the states had a prevalence of obesity of over 25%. The heterogeneity of these disorders has been determined through both anthropometric and genetic studies. These metabolic disorders are believed to be caused by a combination of genetic susceptibilities and lifestyle changes. Recently, interest has surged in the possible role of the intestinal microbiome as a potential contributor to the rapidly increased prevalence of obesity (5–7). This review focuses on recent advances in the understanding of the gut microbiome and techniques to assess the
Figure 1 | Benefits of genetic richness. By comparing the complement of microbial genes in the guts of obese and non-obese individuals, Le Chatelier et al. show that people with relatively less-complex microbiomes have higher overall body adiposity and more inflammation-associated characteristics, indicating that they are at higher risk of metabolic diseases than people with a greater gut-bacterial richness. Cotillard et al. demonstrate that microbial richness increases, and inflammation decreases, in obese and overweight people with low microbial richness who commence an energy-restricted diet, but that such dietary interventions have little effect in individuals with already high microbial richness.
"Fat Bugs"

- Recently, two phyla of mainly anaerobic beneficial bacteria have been linked to obesity:
  - Firmicutes
  - Bacteroidetes

- Their impact is through an imbalance of these phyla

- Lean subjects have a ratio of:
  <80% Firmicutes to >20% Bacteroidetes

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**Fig. 5.** Schematic view of how the gut microbiota effects host fat storage. The microbiota acts through Fiaf to coordinate increased hepatic lipogenesis with increased LPL activity in adipocytes, thereby promoting storage of calories harvested from the diet into fat. See text for further details.
The gut microbiota contributes to host metabolism by several mechanisms including increased energy harvest from the diet, modulation of lipid metabolism, altered endocrine function, and increased inflammatory tone. The gut microbiota could thus be considered to be an environmental factor that modulates obesity and other metabolic diseases.

“Host remodeling of the gut microbiome and metabolic changes in pregnancy,”

*Cell*, 150: 470-480, 2012
Gut microbes sometimes move between mice that are housed together. Microbes from obese people don’t readily move between animals, while microbes from lean people can take hold in another mouse’s gut, keeping the animal slim. A high-fat diet, however, blocks the transfer of lean-promoting microbes and their protective effects. Credit: Nebojsa  

SOURCE: ScienceNews October 5, 2013; Vol.184 #7
Gut bacterial microbiota and obesity
European Society of Clinical Microbiology and Infectious Diseases, CMI, 19, 305–313

“We identify NAS-altered microbial metabolic pathways that are linked to host susceptibility to metabolic disease, and demonstrate similar NAS-induced dysbiosis and glucose intolerance in healthy human subjects. Collectively, our results link NAS consumption, dysbiosis and metabolic abnormalities, thereby calling for a reassessment of massive NAS usage.”
Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome

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Abstract

The intestinal tract is inhabited by a diverse community of microorganisms collectively referred to as the gut microbiome. While gut microbes provide important benefits to host health, the relationship between gut microbes and host health is complex and influenced by environmental and lifestyle factors. In this study, we investigated the role of dietary emulsifiers, commonly used in food products, in modulating gut microbiota composition and host health. We observed that relatively low concentrations of two commonly used emulsifiers, namely carboxymethylcellulose and polysorbate-80, induced low-grade inflammation and obesity/metabolic syndrome in wild-type (WT) mice. These emulsifiers promoted robust colitis in mice predisposed to this disorder. Emulsifier-induced metabolic syndrome was associated with microbiota encroachment, altered species composition, and increased pro-inflammatory potential. These results suggest that dietary emulsifiers may have significant impacts on gut health and should be considered in the context of global health and disease prevention.

Microbes May Slim Us Down After Gastric Bypass

By Andrew C. Nussey on 31 March 2015, 8:00 PM | \textit{Comment}

Usually, science starts in the lab and then moves to patients. Gastric bypass surgery has taken the opposite path. Originally offered as a treatment for severe obesity, the surgery's effects on the digestive system and microbiome have turned out to be far more mysterious and fascinating than anyone expected. Now, a new study probes another of the surgery's effects: its impact on microbes in the gut and how changing these microscopic communities might drive weight loss.

The most popular type of gastric bypass surgery is called Roux-en-Y. Surgeons make a small pouch from the top of the stomach and separate it from the rest of the organ, then connect that directly to the middle of the small intestine. Originally, doctors believed that patients who underwent gastric bypass lost weight for a simple reason: Their stomach couldn't hold as much food, and they couldn't absorb as many nutrients.

But quickly, the picture got more complicated. In many people with type 2 diabetes, the change wasn't just initial, but also immediate. And it's hard to explain by the gradual weight loss that happens later. Patients also describe not feeling as hungry, or craving foods like ice cream that they hadn't enjoyed before. "Food doesn't call out to them anymore," says Lee Kaplan, a molecular biologist and gastroenterologist at Harvard Medical School and Massachusetts General Hospital, both in Boston.

There are likely many mechanisms at work. Some may stem directly from how the altered digestive system works—secreting different levels of hormones, for example—or changes in nerve cells that communicate with the gut. Kaplan and Harvard University microbiologist Peter Turnbaugh, who had been studying gut microbes in obese and lean animals, were intrigued by other work suggesting that in both humans and rats, the microbial balance in fecal samples changed after gastric bypass. Along with a postdoc in Kaplan's lab, Alice Leu, they decided to test whether the surgery itself caused the changes in the population of gut microbes—known as the microbiome.
In many people with type 2 diabetes, the disease vanishes almost immediately after surgery, too quickly to be explained by the gradual weight loss that happens later.

Patients also describe not being as hungry, or craving foods like salad that they hadn't liked much before.
Microbes in the gastrointestinal tract are under selective pressure to influence the health of their host. They manipulate host eating behavior to increase their fitness, sometimes at the expense of the host's fitness. Microbes may do this through two potential mechanisms: (i) generating cravings for foods that they specialize on or foods that suppress their competitors, or (ii) inducing dysphoria until we eat foods that enhance their fitness.
**Review Article**

**Influence of a high-fat diet on gut microbiota, intestinal permeability and metabolic endotoxaemia**

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**Abstract**

Dysbiosis and increased intestinal permeability are important factors in the development of obesity, insulin resistance and related metabolic disorders. The role of dietary fat in the development of these conditions is well established. It has been suggested that high-fat diet (HFD) alters the gut microbiota composition and induces translocation of endotoxin (LPS). However, the mechanisms by which HFD may alter the intestinal microbiota and increase intestinal permeability remain to be elucidated. This review aims to summarise the current knowledge and the role of the intestinal microbiota and LPS in the development of obesity and related disorders such as insulin resistance and metabolic endotoxaemia.

**Key words**: High-fat diet; Lipopolysaccharide; Gut microbiota; Intestinal permeability

The role of gut microbiota in the development of diseases such as obesity, diabetes and atherosclerosis has received much attention during recent years. Alterations in the gut microbiota may play a role in the pathogenesis of several diseases. The gut microbiota is composed of a diverse community of microorganisms that interact with the host in a complex and dynamic manner. The gut microbiota plays an important role in the development of obesity, insulin resistance and related metabolic disorders. The role of dietary fat in the development of these conditions is well established. It has been suggested that high-fat diet (HFD) alters the gut microbiota composition and induces translocation of endotoxin (LPS). However, the mechanisms by which HFD may alter the intestinal microbiota and increase intestinal permeability remain to be elucidated. This review aims to summarise the current knowledge and the role of the intestinal microbiota and LPS in the development of obesity and related disorders such as insulin resistance and metabolic endotoxaemia.

**Fig. 1.** The possible pathways linking high fat consumption to metabolic endotoxaemia and chronic diseases. CM, chylomicrons; IAP, intestinal alkaline phosphatase; LPS, lipopolysaccharide.
The pathways of antigen invasion through Paracellular and Transcellular routes.

"Via alterations in the intestinal permeability, intestinal barrier function becomes compromised whereby access of infectious agents and dietary antigens to mucosal immune elements is facilitated, which may eventually lead to immune reactions with damage to pancreatic beta cells and can lead to increased cytokine production with consequent insulin resistance."
Our findings support a hypothesis of translocated gut bacteria as a potential trigger of obesity and diabetes, and suggest that the anti-diabetic effects of bariatric surgery might be mechanistically linked to, and even the result of, a reduction in plasma levels of LPS.
CONCLUSIONS

“This is the first report of gut dysbiosis in Japanese patients with type 2 diabetes as assessed by RT-qPCR. The high rate of gut bacteria in the circulation suggests translocation of bacteria from the gut to the bloodstream.”

“A metagenome-wide association study of gut microbiota in type 2 diabetes

“MGWAS analysis showed that patients with type 2 diabetes were characterized by a moderate degree of gut microbial dysbiosis, a decrease in the abundance of some universal butyrate-producing bacteria and an increase in various opportunistic pathogens, as well as an enrichment of other microbial functions conferring sulphate reduction and oxidative stress resistance.”
In conclusion, our data suggest that, in a compromised metabolic state such as type 2 diabetes, a continual snacking routine will cumulatively promote their condition more rapidly than in other individuals because of the greater exposure to endotoxin.
Type 2 diabetes (T2DM) is believed to be caused by a series of multiple risk factors such as genetic liability, age, overweight or obesity, and an unhealthy lifestyle. Recently, accumulated evidence has suggested that the intestinal microbiota plays an important role in the pathogenesis of T2DM as a potential novel contributor.
Do symbiotic bacteria subvert host immunity?
Lora V. Hooper
Nature Reviews Microbiology 7, 367-374 (May 2009)
Cross-talk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity


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We recently isolated *Akkermansia muciniphila*, which is a mucin-degrading bacterium that resides in the mucus layer. The presence of this bacterium inversely correlates with body weight in rodents and humans.

We demonstrated that *A. muciniphila* treatment reversed high-fat diet-induced metabolic disorders, including fat-mass gain, metabolic endotoxemia, adipose tissue inflammation, and insulin resistance. *A. muciniphila* administration increased the intestinal levels of endocannabinoids that control inflammation, the gut barrier, and gut peptide secretion.
"We recently discovered that the administration of prebiotics (oligofructose) to genetically obese mice increased the abundance of A. muciniphila by ~100-fold."
“the authors further nailed down the concept by treating diabetic mice with the bacteria as a probiotic and demonstrated that the enrichment of the intestinal mucosal layer with the bacteria improved the glycaemic control and metabolic endotoxaemia, as previously described.”

This last set of data is comforted by the increased number of regulatory T cells (Tregs) within the adipose depot, which was increased by metformin or *A. muciniphila* treatment, suggesting that this single bacterium could attenuate metabolic inflammation by inducing the generation of Tregs and suppressing the production of pro-inflammatory cytokines.
In conclusion, we report that the pleotropic effects of metformin include alteration of the enterohepatic recirculation of bile acids, modulation of gut microbiota and changes in gut hormones, especially GLP-1. These findings suggest that the gastrointestinal tract is an important target organ of metformin and are consistent with the evidence that oral formulations of metformin are more effective than intravenous administration.
Bile acids appear to function as nutrient signaling molecules primarily during the feed/fast cycle as there is a flux of these molecules returning from the intestines to the liver following a meal.

Bile acids as regulatory molecules
Oral administration of probiotics has been shown to significantly reduce cholesterol levels by as much as 22 to 33% or prevent elevated cholesterol levels in mice fed a fat-enriched diet. These cholesterol-lowering effects can be partially ascribed to BSH activity (other possible mechanisms not discussed here include assimilation of cholesterol by the bacteria, binding of cholesterol to the bacterial cell walls, or physiological actions of the end products of short-chain fatty acid fermentation).
FIG. 1. (A) Chemical structure of bile acids. Primary bile acids are synthesized in the liver from cholesterol and are conjugated with either glycine or taurine prior to secretion. The carboxyl group of the bile acid and the amino group of the amino acid are linked by an amide bond. (B) Reaction catalyzed by BSH enzymes. BSHs cleave the peptide linkage of bile acids, which results in removal of the amino acid group from the steroid core. The resulting unconjugated bile acids precipitate at low pH. (C) Detection of BSH activity (as described in reference 18). L. plantarum, which was grown overnight in MRS broth, was streaked onto MRS (Difco) agar (A) or MRS agar supplemented with 0.2% (w/v) glycylglycine (Sigma) (B) and incubated anaerobically for 48 h. The white precipitates around colonies and the clearing of the medium are indicative of BSH activity (see reference 18).

<table>
<thead>
<tr>
<th>TABLE 1. BSH homologs in the genomes of sequenced probiotic strains†</th>
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<tbody>
<tr>
<td><strong>Strain</strong></td>
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<tr>
<td>Lactobacillus plantarum WCF51*</td>
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<tr>
<td>Lactobacillus johnsonii NCC3533*</td>
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<tr>
<td>Bifidobacterium longum NCC2705*</td>
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<tr>
<td>Lactobacillus acidophilus NCIMB ATCC200396*</td>
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<tr>
<td>Lactobacillus brevis ATCC 3507</td>
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<tr>
<td>Lactobacillus paracasei ATCC 33323*</td>
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<tr>
<td></td>
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<tr>
<td>Bifidobacterium longum DJ010A†</td>
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</table>

* The information was collected in July 2005.
* † data were obtained from the National Center for Biotechnology Information genome site (http://www.ncbi.nlm.nih.gov/); ‡ data were obtained from the Joint Genome Institute microbial genome site (http://genomes.jgi-psf.org/).
* † data were obtained from the National Center for Biotechnology Information genome site (http://www.ncbi.nlm.nih.gov/).
Bile acids are hormones that regulate their own synthesis, transport, in addition to glucose and lipid homeostasis, and energy balance. The gut microbial community through their capacity to produce bile acid metabolites distinct from the liver can be thought of as an “endocrine organ” with potential to alter host physiology, perhaps to their own favor.
We have observed that the pretreatment levels of bile acids derived from gut bacteria and nutrient inputs are correlated with response to simvastatin. It is becoming increasingly clear that gut microbial symbiots are critical for normal digestion and defense, and also play an important role in development of disease and in metabolizing orally ingested therapeutics. There is increasing recognition that intestinal bacteria can metabolize drugs and alter an individual's response to drug treatment depending on specific bacterial strains present.

We identified three secondary, bacterial-derived bile acids that contribute to predicting the magnitude of statin-induced LDL-C lowering in good responders. Bile acids and statins share transporters in the liver and intestine; we observed that increased plasma concentration of simvastatin positively correlates with higher levels of several secondary bile acids.
“The findings, along with recently published results that the gut microbiome plays an important role in cardiovascular disease, indicate that interactions between genome, gut microbiome and environmental influences should be considered in the study and management of cardiovascular disease.”

July 2015

A novel risk model including the gut microbiome explained up to 25.9% of HDL variance, significantly outperforming the risk model without microbiome. Strikingly, the microbiome had little effect on low-density lipoproteins or total cholesterol.

Conclusions: Our studies suggest that the gut microbiome may play an important role in the variation in BMI and blood lipid levels, independent of age, gender and host genetics. Our findings support the potential of therapies altering the gut microbiome to control body mass, triglycerides and HDL.
“In summary, we present evidence that it is possible to identify obese individuals who will benefit most from a simple dietary intervention based on the gut microbiota composition before the intervention. Clostridial species, in particular, were indicative of the amenability of the gut microbiota to dietary modification, which in turn was associated with the host’s lipid metabolism.”

Front Biosci (Schol Ed). 2013 Jan 1;8:754-65.
Causes and consequences of low grade endotoxia and inflammatory diseases.
Gilaro TG, Chang S, Gilliam EA, Maitra U, Deng H, Li L.
Department of Biological Science, Virginia Polytechnic Institute and State University, Blacksburg, VA 24060, USA.

Abstract
Increasing clinical observations reveal that persistent low-grade inflammation is associated with the pathogenesis of severe chronic diseases such as atherosclerosis, diabetes, and aging-related neurological diseases. Intriguingly, low levels of circulating Gram-negative bacterial endotoxin lipopolysaccharide (LPS) appear to be one of the key culprits in provoking a non-resolving low-grade inflammation. Adverse life styles, chronic infection, and aging can all contribute to the rise of circulating endotoxin levels and lead to low-grade endotoxia. As a consequence, low-grade endotoxia may skew host immune environment into a mild non-resolving pro-inflammatory state, which eventually leads to the pathogenesis and progression of inflammatory diseases. This review aims to highlight the recent progress in the causes and consequences of low-grade endotoxia, as well as the emerging molecular mechanisms responsible.
“After 100 years of symbiotic association with the human host, the microbiota is characterized by a rearrangement in the Firmicutes population and an enrichment in facultative anaerobes, notably pathobionts. The presence of such a compromised microbiota in the centenarians is associated with an increased inflammatory status, also known as inflammageing, as determined by a range of peripheral blood inflammatory markers.”
“This may be explained by a remodeling of the centenarians’ microbiota, with a marked decrease in *Faecalibacterium prauznitzii* and relatives, symbiotic species with reported anti-inflammatory properties. As signature bacteria of the long life we identified specifically *Eubacterium limosum* and relatives that were more than ten-fold increased in the centenarians.”
Gut microbiota controls adipose tissue expansion, gut barrier and glucose metabolism: novel insights into molecular targets and interventions using prebiotics

Beneficial Microbes, March 2014; 5(1): 3-17

“Thus the “forgotten organ” of the gastrointestinal microbiota is a prime candidate to be in influenced by evolutionarily unprecedented postprandial luminal carbohydrate concentrations. The present hypothesis suggests that in parallel with the bacterial effects of sugars on dental and periodontal health, acellular ours, sugars, and processed foods produce an inflammatory microbiota via the upper gastrointestinal tract, with fat able to effect a “double hit” by increasing systemic absorption of lipopolysaccharide.”
Figure 2: Schematic of the hypothesis

Notes: The acellular dense carbohydrates of modern foods are proposed to produce an inflammatory microbiota from the mouth onwards, initially producing periodontal disease. The small bowel is exposed to lipopolysaccharide (LPS) and other pathogen-associated molecular patterns (PAMPs) from the oral microbiota, and proinflammatory modulation of its own small populations of bacteria by concentrated acellular carbohydrates. With systemic absorption enhanced by dietary fats, the inflammatory bacterial compounds induce leptin resistance and hyperphagia. The contents of the grey box represents the existing understanding of the effects of diet-induced obesity on energy homeostasis.

Abbreviations: CCK, cholecystokinin; PYY, peptide YY; CART, cocaine and amphetamine regulated transcript; CR1, cannabinoid receptor type 1; MCH, melanin concentrating hormone.
Although these data are controversial, they suggest that specific phyla, classes or species of bacteria, or bacterial metabolic activities could be beneficial or detrimental to patients with obesity.

The gut microbiota is, therefore, a potential nutritional and pharmacological target in the management of obesity and obesity-related disorders.
Table 1: Effects of probiotics or synbiotics with antibiotic properties in patients with overeating

<table>
<thead>
<tr>
<th>Microbiota</th>
<th>Study design</th>
<th>n</th>
<th>Duration</th>
<th>Treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faecalibacterium prausnitzii</td>
<td>Randomized, double-blind, placebo-controlled intervention</td>
<td>61 individuals with gut dysbiosis</td>
<td>4 weeks</td>
<td>Metronidazole 400 mg bid for 2 weeks</td>
<td>Reduced body weight, BMI, waist and hip circumference, and LDL cholesterol in the probiotic versus the placebo group</td>
</tr>
<tr>
<td>Lactobacillus rhamnosus</td>
<td>Randomized, double-blind, placebo-controlled intervention</td>
<td>41 participants with gut dysbiosis</td>
<td>12 weeks</td>
<td>Metronidazole 400 mg bid for 2 weeks</td>
<td>Reduced body weight, BMI, waist and hip circumference, and LDL cholesterol in the probiotic versus the placebo group</td>
</tr>
<tr>
<td>Akkermansia muciniphila</td>
<td>Randomized, double-blind, placebo-controlled intervention</td>
<td>15 individuals with type 2 diabetes mellitus</td>
<td>5 weeks</td>
<td>Metronidazole 400 mg bid for 2 weeks</td>
<td>Reduced body weight, BMI, waist and hip circumference, and LDL cholesterol in the probiotic versus the placebo group</td>
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<tr>
<td>Bifidobacterium lactis</td>
<td>Randomized, double-blind, placebo-controlled intervention</td>
<td>31 individuals with gut dysbiosis</td>
<td>6 weeks</td>
<td>Metronidazole 400 mg bid for 2 weeks</td>
<td>Reduced body weight, BMI, waist and hip circumference, and LDL cholesterol in the probiotic versus the placebo group</td>
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</table>

**Note:** All probiotics or synbiotics with antibiotic properties were used in conjunction with a probiotic intervention to assess their effect on gut dysbiosis. The results indicate a decrease in body weight, BMI, waist and hip circumference, and LDL cholesterol in the probiotic versus the placebo group.
They were balanced for their baseline characteristics and randomly assigned to three groups receiving FM containing 10(7), 10(6) or 0 (control) cfu LG2055/g of FM, and were asked to consume 200 g FM/d for 12 weeks. Abdominal visceral fat areas, which were determined by computed tomography, at week 12, changed from baseline by an average of -8.5% (95% CI: -11.9, -5.1; P < 0.01) in the 10(7) dose group, and by -8.2% (95% CI: -10.8, -5.7; P < 0.01) in the 10(6) dose group. Other measures including BMI, waist and hip circumferences, and body fat mass were also significantly decreased from baseline at week 12 in both groups; interestingly, the cessation of taking FM for 4 weeks attenuated these effects. In the control group, none of these parameters significantly decreased from baseline. These findings demonstrate that consumption of LG2055 at doses as low as the order of 10(8) cfu exhibited a significant lowering effect on abdominal adiposity, and suggest that constant consumption might be needed to maintain the effect.
Intestinal permeability – a new target for disease prevention and therapy

Stephan C Bischoff1*, Giovanni Barbara2, Wim Buurman3, Theo Ockhuizen4, Jörg-Dieter Schulzke5, Matteo Serino6, Herbert Tilg7, Alastair Watson8 and Jerry M Wells9

Abstract

Intestinal permeability is a feature of intestinal barrier function, which is increasingly recognized as being of relevance for health and disease. However, these terms are poorly defined, their assessment is a matter of debate, and their clinical significance is not clearly established. In this review, we aim to present the intestinal barrier and its components, but also the processes of interactions of intestinal symbionts without eliciting chronic inflammation. All these diseases are characterized by increased intestinal permeability, with intestinal barrier function increasingly recognized as being of relevance for health and disease. Accordingly, this review focuses on how intestinal barrier function is maintained and how it can be disrupted.

Introduction

The intestinal barrier is a highly dynamic, complex, and multifunctional biological structure that forms the first line of defense against potential luminal pathogens and antigens. The intestinal barrier consists of the physical barrier (epithelial and muscular layers) and the immunological barrier (mucosal immune system). The two barriers are connected and interact with each other, and their functions are closely linked. The physical barrier prevents the entry of luminal antigens and pathogens, while the immunological barrier provides an immune response against the enteric pathogens and antigens. The intestinal barrier functions as a physical barrier to prevent the entry of luminal antigens and pathogens, and as an immunological barrier to provide an immune response against the enteric pathogens and antigens. Every part of this barrier is characterized by increased intestinal permeability, which is increasingly recognized as being of relevance for health and disease. Accordingly, this review focuses on how intestinal barrier function is maintained and how it can be disrupted.

In the final part, we discuss selected diseases associated with increased intestinal permeability such as critically ill patients, inflammatory bowel diseases, celiac disease, food allergy, irritable bowel syndrome, and more recently recognized – obesity and metabolic diseases. All these diseases are characterized by inflammation that might be triggered by the translocation of luminal components into the host.

Circulating zonulin increased with body mass index (BMI), waist to hip ratio (WHR), fasting insulin, fasting triglycerides, uric acid and IL-6, and negatively correlated with HDL-cholesterol and insulin sensitivity.” In multiple regression analysis, insulin sensitivity (p = 0.002) contributed independently to circulating zonulin variance, after controlling for the effects of BMI, fasting triglycerides and age.
Intestinal permeability—a new target for disease prevention and therapy

Introduction

The intestinal barrier is a barrier to the passage of substances from the intestinal lumen to the bloodstream. The term "intestinal barrier" is often used interchangeably with "gut barrier" or "intestinal permeability." The barrier is composed of the intestinal epithelium, which is composed of enterocytes, and the underlying lamina propria, which contains immune cells. The barrier serves to prevent the translocation of pathogens, toxins, and allergens from the intestinal lumen to the systemic circulation. Any disruption of the barrier can lead to systemic inflammation and can contribute to the development of various diseases, including inflammatory bowel disease (IBD), celiac disease, and colon carcinoma.

However, the exact mechanisms underlying the development of intestinal barrier dysfunction are not fully understood. Several factors have been proposed to support the gut barrier, including diet, probiotics, prebiotics, and pharmacological interventions. In this review, we will discuss the current evidence supporting the role of the gut barrier in health and disease and the potential interventions that can support the gut barrier.

Table 8 Factors proposed to support the gut barrier

<table>
<thead>
<tr>
<th>Dietetic approach</th>
<th>Avoidance of high amounts of sugar and fat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Avoidance of energy-dense Western-style diet</td>
</tr>
<tr>
<td></td>
<td>FODMAP diet (Fermentable, Oligo-, Di-, Mono-saccharides and Polyols)</td>
</tr>
<tr>
<td></td>
<td>Prebiotics/fibers</td>
</tr>
<tr>
<td></td>
<td>Glutamine</td>
</tr>
<tr>
<td></td>
<td>Other immune-modulating formula</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Probiotic approach</th>
<th>Selected probiotics (e.g. Lactobacillus plantarum MB452)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probiotic cocktails (multispecies concept)</td>
</tr>
<tr>
<td></td>
<td>Symbiotics (combination of probiotics and prebiotics)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs/others</th>
<th>Short-chain fatty acids (SCFA) (e.g. Butyrate)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Metformin</td>
</tr>
<tr>
<td></td>
<td>Quercetin and other flavonoids</td>
</tr>
</tbody>
</table>

"Importantly, one study has shown that L. plantarum can regulate human epithelial TJ proteins in vivo and to confer protective effects against chemically induced disruption of the epithelial barrier in an in vitro model"
These data suggest that GP (1% Concord grape polyphenols) act in the intestine to modify gut microbial community structure, resulting in lower intestinal and systemic inflammation and improved metabolic outcomes. The gut microbiota may thus provide the missing link in the mechanism of action of poorly absorbed dietary polyphenols.
In general, studies evidence that dietary polyphenols may contribute to the maintenance of intestinal health by preserving the gut microbial balance through the stimulation of the growth of beneficial bacteria (i.e., lactobacilli and bifidobacteria) and the inhibition of pathogenic bacteria, exerting prebiotic-like effects.
### Table 3: Animal model studies.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Animal</th>
<th>Phenolic compound/diet</th>
<th>Dose</th>
<th>Treatment duration</th>
<th>Microbial technique</th>
<th>Population increase</th>
<th>Population decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hara et al. (1999) [69]</td>
<td>Pigs</td>
<td>Tea polyphenols</td>
<td>0.2% (free access)</td>
<td>2 weeks</td>
<td>Plate count</td>
<td>Lactobacilli</td>
<td>Total bacteria</td>
</tr>
<tr>
<td>Ishihara et al. (2003) [61]</td>
<td>Calves</td>
<td>Green tea extracts</td>
<td>1.5 g/day</td>
<td>4 weeks</td>
<td>Plate count</td>
<td>Bifidobacterium spp.</td>
<td>Lactobacillus spp.</td>
</tr>
<tr>
<td>Smith and Watcher (2004) [68]</td>
<td>Rats</td>
<td>Prunus cerasus extracted from Ailanthus altissima</td>
<td>0.7% (low-tannin diet) and 2.4% (high-tannin diet)</td>
<td>5.5 weeks treatment + 2.5 weeks washout</td>
<td>PCR-DGGE + DAPI stain hybridization</td>
<td>Bacteroides fragilis group</td>
<td>Bacteroides-Prevotella-Parvulus group</td>
</tr>
<tr>
<td>Dokura et al. (2000) [62]</td>
<td>Rats</td>
<td>Red wine polyphenol powder</td>
<td>50 mg/kg</td>
<td>36 weeks</td>
<td>Plate count</td>
<td>Lactobacilli</td>
<td>Bifidobacteria</td>
</tr>
<tr>
<td>Sombra et al. (2006) [63]</td>
<td>Rats</td>
<td>Apple juice</td>
<td>free access</td>
<td>4 weeks</td>
<td>Plate count</td>
<td>Lactobacilli</td>
<td>Propionibacteria</td>
</tr>
<tr>
<td>Sombra et al. (2002) [64]</td>
<td>Rats</td>
<td>Apple pomace</td>
<td>3% suppl, diet</td>
<td>6 weeks</td>
<td>Plate count</td>
<td>Verrucomicrobiaceae</td>
<td>Bacteroides</td>
</tr>
<tr>
<td>Larros et al. (2009) [65]</td>
<td>Rats</td>
<td>Beeswax</td>
<td>1 g/kg/day</td>
<td>23 days</td>
<td>Plate count</td>
<td>Lactobacilli</td>
<td>Bifidobacteria</td>
</tr>
<tr>
<td>Merin et al. (2012) [66]</td>
<td>Rats</td>
<td>Hackberry extract (leaf)</td>
<td>10 mg/kg (leaf)</td>
<td>4 weeks</td>
<td>FISH</td>
<td>Lactobacilli (berry extract)</td>
<td>Bifidobacteria (leaf and berry extract)</td>
</tr>
<tr>
<td>Villeneuve et al. (2014) [67]</td>
<td>Broiler chicks</td>
<td>Grape pomace concentrate (GPC)</td>
<td>69% GPC (free access)</td>
<td>21 days</td>
<td>Plate count</td>
<td>E. coli</td>
<td>Enterococcus spp.</td>
</tr>
<tr>
<td>Lacan et al. (2013) [68]</td>
<td>Rats</td>
<td>Laxative wild blueberries</td>
<td>20 g/day (approx. 3.3 mg anthocyanin/day)</td>
<td>6 weeks</td>
<td>Metagenomic sequencing</td>
<td>Enterococcus spp.</td>
<td>Lactobacillus spp.</td>
</tr>
</tbody>
</table>

### Figure 6.23 — Origins of Urinary Dysbiosis Markers

Undigested dietary polyphenols are the predominant substrate for growth of most intestinal microbes. Each species has adapted a metabolic preference that sustains its growth while producing compounds that suppress the growth of competing species. Certain species of bacteria and most yeast prefer carbohydrate substrates that are limited in most individuals by rapid uptake in the upper small intestine. Restricted uptake found in small bowel syndrome or genetic carbohydrate absorptive defects enhance the potential for overgrowth of the carbohydrate-prefering species.

**Source:** Laboratory Evaluations in Integrative and Functional Medicine, by Richard Lord, PhD & J. Alexander Bralley, PhD, pg. 370
Effect of acute and chronic red wine consumption on lipopolysaccharide concentrations.


BACKGROUND: Chronic red wine (RW) consumption has been associated with decreased cardiovascular disease risk, mainly attributed to an improvement in lipid profile. RW intake is also able to change the composition of gut microbiota. High fat intake has recently been reported to increase metabolic endotoxemia. The gut microbiota has been proposed as the main resource of plasma lipopolysaccharides (LPSs) in metabolic endotoxemia.

OBJECTIVE: We analyzed the effect on LPS concentrations of chronic RW consumption and acute RW intake in relation to high fat intake in middle-aged men.

DESIGN: For the chronic study, 10 middle-aged male volunteers were randomly assigned in a crossover trial, and after a washout period, all subjects received RW, dealkylized red wine (DRW), or gin for 20 d. Serum endotoxin and LPS-binding protein (LBP) concentrations were determined after the washout period and after each of the treatments, and changes in fecal microbiota were quantified. For the acute study, 5 adult men underwent a fat overload or a fat overload together with the consumption of RW, DRW, or gin. Baseline and postprandial serum LPS and LBP concentrations and postprandial chylomicron LPS concentrations were measured.

RESULT: There were no significant differences in the change in LPS or LBP concentrations between chronic RW, DRW, and gin consumption. Bifidobacterium and Prevotella amounts were significantly increased by RW and consumed negatively with LPS concentrations. There were no differences in postprandial serum LPS, LBP, or chylomicron LPS concentrations between acute RW, DRW, or gin intake together with a fatty meal.

CONCLUSION: Chronic RW consumption increases Bifidobacterium and Prevotella amounts, which may have beneficial effects by lowering LPS concentrations. This trial was registered at controlled-trials.com as ISRCTN88720134.

Larch arabinogalactan: clinical relevance of a novel immune-enhancing polysaccharide.

Kelly G.S.

Abstract

Larch arabinogalactan is composed of greater than 88-percent arabinogalactan, a highly branched polysaccharide consisting of a galactan backbone with side-chains of galactose and arabinose sugars. Larch arabinogalactan is an excellent source of dietary fiber, and has been approved as such by the FDA. It has been shown to increase the production of short-chain fatty acids, principally butyrate and propionate, and has been shown to decrease the generation and absorption of ammonia. Evidence also indicates human consumption of larch arabinogalactan has a significant effect on enhancing beneficial gut microflora, specifically increasing anaerobes such as Bifidobacteria and Lactobacillus. Larch arabinogalactan has several interesting properties which appear to make it an ideal adjuvant supplement to consider in cancer protocols. Experimental studies have indicated larch arabinogalactan can stimulate natural killer (NK) cell cytotoxicity, enhance other functional aspects of the immune system, and inhibit the metastasis of tumor cells to the liver. The immune-enhancing properties also suggest an array of clinical uses, both in preventive medicine, due to its ability to build a more responsive immune system, and in clinical medicine, as a therapeutic agent in conditions associated with lowered immune function, decreased NK activity, or chronic viral infection.

“It has been shown to increase the production of short-chain fatty acids, principally butyrate and propionate, and has been shown to decrease the generation and absorption of ammonia. Evidence also indicates human consumption of larch arabinogalactan has a significant effect on enhancing beneficial gut microflora, specifically increasing anaerobes such as Bifidobacteria and Lactobacillus.”
“Therefore, we here review the recent arguments that support the view that an alteration in the microbiota to host immune system balance leads to an increased translocation of bacterial antigens towards metabolically active tissues, and could result in a chronic inflammatory state and consequently impaired metabolic functions such as insulin resistance, hepatic fat deposition, insulin unresponsiveness, and excessive adipose tissue development.”
We show that cold exposure leads to marked shift of the microbiota composition, referred to as cold microbiota. Transplantation of the cold microbiota to germ-free mice is sufficient to increase insulin sensitivity of the host and enable tolerance to cold partly by promoting the white fat browning, leading to increased energy expenditure and fat loss. During prolonged cold, however, the body weight loss is attenuated, caused by adaptive mechanisms maximizing caloric uptake and increasing intestinal villi and microvilli lengths.
After the intake of apples (2 apples a day for 2 weeks) by eight healthy adult humans, the number of bifidobacteria in feces increased, and the numbers of Lactobacillus and Streptococcus including Enterococcus tended to increase. However, lecithinase-positive clostridia, including C. perfringens, decreased and Enterobacteriaceae and Pseudomonas tended to decrease.
“The conservative physician will recognize that much of what happens is transient, but sometimes as he matures, he forgets unfortunately that his own methods of therapy are trembling on the same shifting sands that cover the treatment and alas also the bones of those who have gone before.”