March 5-6th, 2016, Miami

Fact sheet #2

When the gut microbiota gets out of balance

The gut microbiota is an incredibly complex network of interacting microbes that plays a key role in digestion and immune defense. It also influences endocrine functions and affects even the central nervous system. An ever increasing number of studies leaves no doubt that a diverse and well-balanced microbiota composition is essential for our well-being. Prof. Francisco Guarner from the University Hospital Vall d'Hebron (Barcelona / Spain), member of the Scientific committee of the "Gut Microbiota For Health World Summit" 2016 and one of the world's leading experts on gut microbiota gave an overview of how perturbations of the gut microbial equilibrium are linked to various disorders and diseases.

Francisco Guarner, Spain

In healthy individuals, the composition of the gut microbiota is very diverse, with protective bacterial strains outnumbering potentially harmful ones. This ensures an efficient and beneficial division of labour within the gut. However, a loss of diversity combined with emerging imbalances between the proportions of bacterial strains can have severe consequences. This disruption of equilibrium – called dysbiosis – is associated with a wide range of disorders. These include diarrhea, (IBS or inflammatory bowel diseases (IBD), colo-rectal cancer as well as certain liver diseases and allergies, and nutrition-related conditions such as obesity, type 2 diabetes and celiac disease. Altered compositions of the intestinal microbiota also affect the central nervous system as gut and brain are connected by a multitude of communication pathways used by bacterial metabolites and transmitters. So, it is not surprising that even mental and neuro-developmental disorders – for example depression, anxiety and autism – could be linked to dysbiosis of the gut microbiota. A reduction of microbial diversity in the gut is accompanied by instability of the ecosystem that is formed by these interacting micro-organisms: a dysbiotic microbiota-composition changes much more frequently than a healthy one and its resilience weakens, which means that the microbial community recovers only slowly and often insufficiently from challenges such as antibiotic treatment or acute diarrheal disease.

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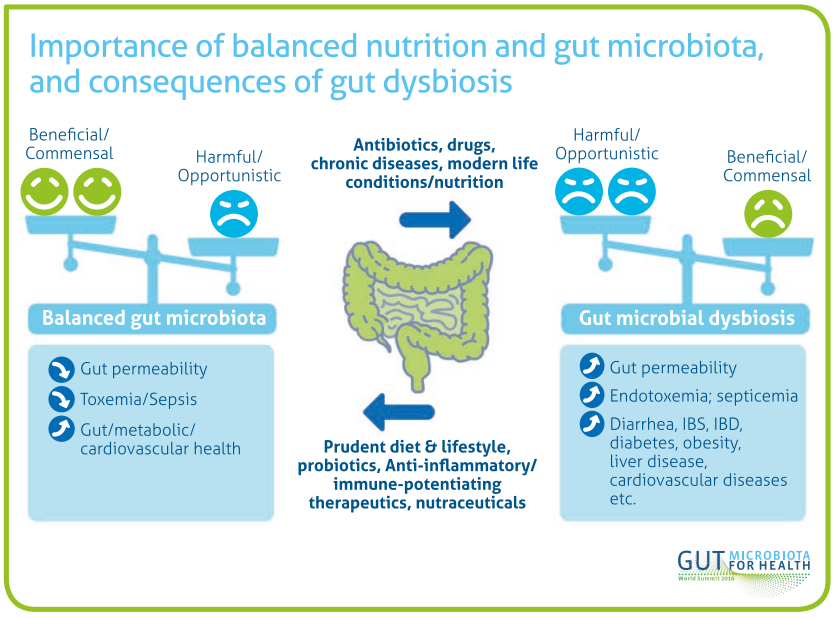
Fact sheet #2

Disrupted equilibrium and its causes

From a biochemical point of view, dysbiosis shares some common features: The number of bacteria that produce Short Chain Fatty Acids (SCFAs) – for example butyrate producers such as *Faecalibacterium*, *Roseburia* or *Eubacterium* – is decreased. This is unfavourable as SCFAs strengthen the gut barrier and the immune system and help to fight against pathogens. At the same time proportions of deleterious micro-organisms are raised: This includes bacteria that produce lipopolysaccharide (LPS), an endotoxin that can drive inflammation, as well as microbes that are resistant to oxygen which makes them able to approach and damage the epithelial cells that line the mucosa. Another threat to these cells that emerges in dysbiotic microbiota is the increased potential to form hydrogen sulphide, which is toxic for epithelial cells.



The causes of dysbiosis are manifold but modern hygiene and the widespread use of antibiotics belong to the most important ones. To which extent these medical and lifestyle practices have perturbed the ancestral microbial environment in members of western societies becomes clear when compared to humans who live under pre-industrial conditions. They have a higher microbial diversity than North-Americans or Europeans, and share commonalities in their gut microbiotas that are clearly distinct from “western” microbiotas. However, the crucial question of how dysbiosis and associated diseases are causally linked is still open. While certain microbial changes might be the results of underlying conditions others are likely to be disease inducing. The existence of such causal relationships is suggested by trials showing that metabolic and inflammatory conditions as well as certain cognitive and behavioral patterns can be transferred from one animal to another through transplanting fecal microbiota samples.

March 5-6th, 2016, Miami

Fact sheet #2

How to treat dysbiosis

Currently, several treatment options to revert dysbiosis and thus reduce the risk of disease are being investigated. Fecal microbiota transplantation (FMT) has proven to be highly effective to treat *C. difficile* colitis, and is one of the best therapeutic option to prevent relapses. FMT seemed to be successful in improving insulin sensitivity in type 2 diabetes patients, but the beneficial effect was not permanent. With IBD the results achieved so far are inconsistent. According to Prof. Guarner no dramatic improvement is to be expected. Studies testing FMT in autism spectrum disorders are under way. "All in all, FMT is not a therapeutic strategy with large scale applicability, because of several critical limitations, including lack of standardization, lack of identification of the microbes that deliver the beneficial effect versus those which may transfer health hazards and loss of viability of oxygen sensitive species during the procedure," said Prof. Guarner.

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> *Francisco Guarner, Spain*

Dietary strategies, which are now being systematically tested open up promising pathways. Foods aiming at increasing the amount of beneficial bacterial species may prevent or improve dysbiosis-related diseases. Prebiotics – nutritional ingredients that provide "food" for beneficial bacteria – improve metabolic activity of the gut microbiota by increasing the production of short chain fatty acids and the abundance of beneficial species such as *Faecalibacterium* and *Akkermansia*. It could be shown for example, that a diet enriched with prebiotics supported caloric restriction in obese individuals with type 2 diabetes.

The potential of probiotics

Beneficial bacteria in the form of probiotics have attracted the attention of experts and the general public for quite a while as they too seem to offer important options. Swamping the ecosystem of the small bowel, probiotics induce anti-inflammatory mechanisms and strengthen the mucosal barrier. Trials demonstrate that probiotics are efficacious for instance in prevention and treatment of diarrhea but also some forms of IBS, certain allergies and potentially in hepatic encephalopathy. Ongoing studies explore the potential role of long term probiotic consumption for preventing and treating metabolic disorders such as obesity and type 2 diabetes. "Although the

March 5-6th, 2016, Miami

Fact sheet #2

magnitude of benefit of such dietary strategies may be moderate, they are safe and can easily and quickly be applied," said Prof. Guarner.

The health-sustaining potential of probiotics, though, is still far from being fully exploited. As Prof Guarner pointed out, certain members of the human microbiota may represent novel candidates for new probiotics. These microbes include *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* together with other butyrate-producing bacteria such as *Roseburia species* and *Eubacterium hallii*. "Whether these microbes can be used in foods, dietary supplements or drugs will depend on demonstration of safety and efficacy for these uses and on regulatory frameworks," said Prof. Guarner, stressing the importance of thorough investigations: "For these new probiotics, which may comprise little-studied species, it would seem advisable to proceed on a strain-by-strain basis until we have gathered sufficient information and mechanistic understanding for extrapolation to the species level. It could turn out that not so much single strains but bacterial communities comprising defined strains that have been obtained from human samples, with adequate evidence of safety and efficacy, prove to be an optimal tool to correct dysbiosis and reduce risk of diseases derived from dysbiotic states."

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