MICROBIOTA

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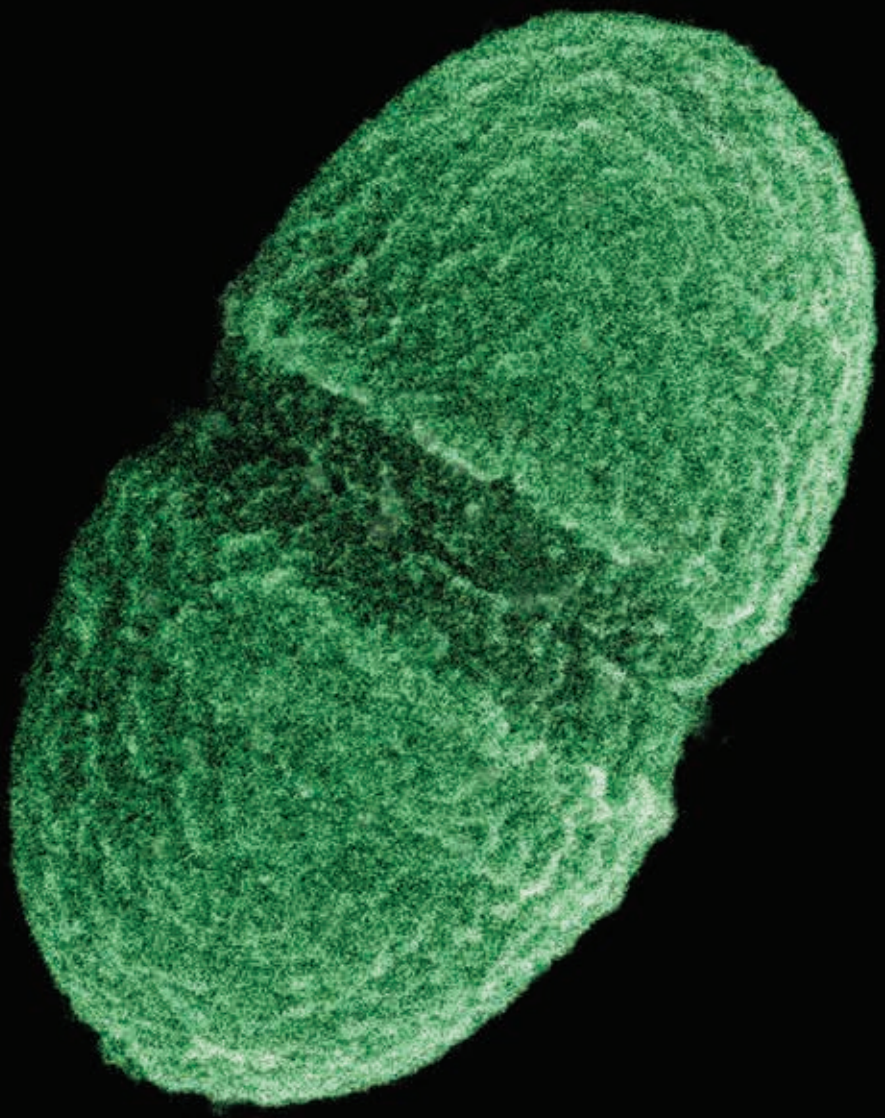

BIOCODEX Microbiota Institute

SUMMARY

EDITO

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Dear readers, according to the World Health Organization, certain digestive cancers (stomach, oesophagus, liver and colorectal) accounted for 23.8% of new cancers diagnosed worldwide in 2018. Colorectal cancer alone caused nearly 900,000 deaths globally last year. Although it has long been known that diet has an undeniable influence on the occurrence of digestive tumours, the related link between these diseases and the gut microbiota has been advanced more recently. This has led to a paradigm shift in which cancer is now considered to be a disease with a strong environmental component. Runaway fervour or fundamentally true? If one believes the scientific literature – which mirrors the evident international craze – the second option could well bring its share of discoveries.

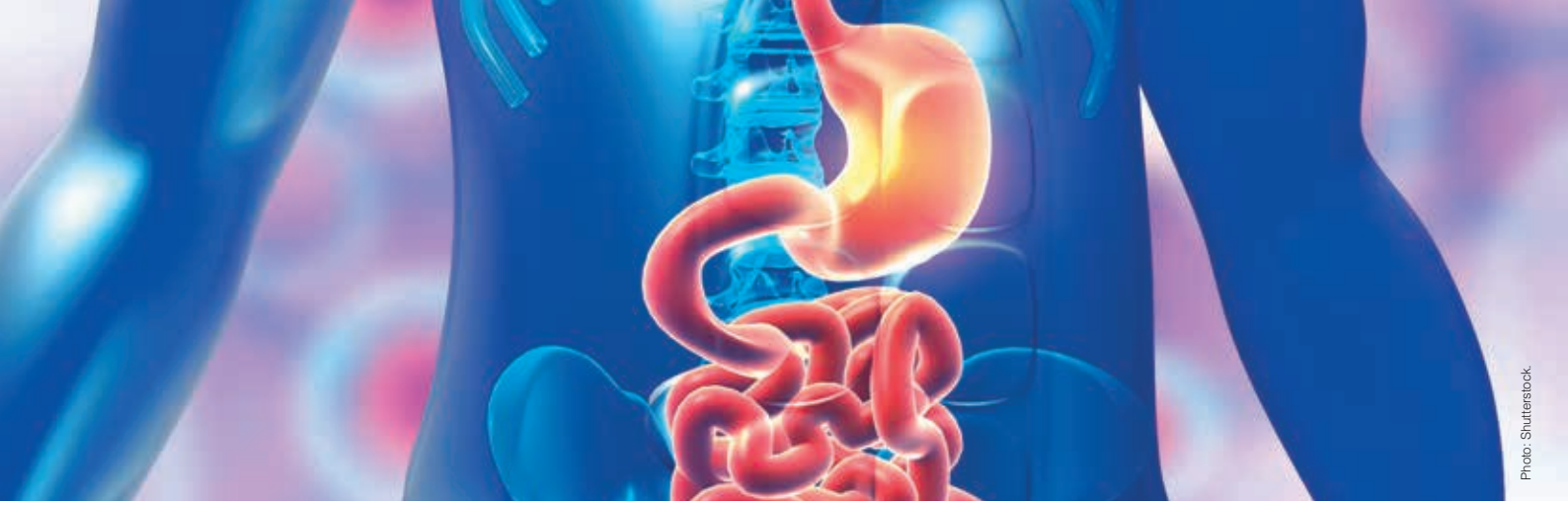
Recent preclinical and clinical research provides evidence for the links that the scientific community has suspected: how some *Fusobacterium* species could stimulate the development of a pro-inflammatory environment in the gut mucosa and promote the emergence and progression of colorectal tumours; how *Helicobacter pylori* – like other bacterial species and together with multiple factors – could promote gastric tumours; or how the intestinal microbiota could modulate the antitumor immune response. In other words, intestinal dysbiosis would be implicated in the entire tumour process, from pathogenesis to the response to chemotherapy and immune checkpoint inhibitor treatments.

Professor Iradj Sobhani (Université Paris-Est Créteil and Henri-Mondor University Hospital, Créteil, France) sheds some light on this latter point in particular. He describes current evidence showing that the intestinal microbial community, as a whole, metabolizes anticancer drugs like gemcitabine and lowers its efficacy, and also influences the effects of ionizing radiation treatments and postoperative healing. He also mentions the deleterious effects of antibiotic therapy underlying the variability of response to anti-PD-1 and anti-PD-L1 immunotherapies in patients with metastatic cancer. A review that highlights the importance of the intestinal microbiota as a factor of personalized medicine in the booming field of immuno-oncology.

> “DIGESTIVE CANCERS: INTESTINAL DYSBIOSIS IS IMPLICATED IN THE ENTIRE TUMOUR PROCESS”

Microbiology and oncology go hand in hand in this issue. An occasion for Professor Harry Sokol (Hôpital Saint-Antoine, Paris, France) to revisit an article published in *Science Translational Medicine* showing that autologous faecal microbiota transplantation could find a promising application in haematology. As far as patient benefits go, Professor Emmanuel Mas (Hôpital des Enfants, Toulouse, France) unveils an effective dietary treatment that is well tolerated in patients with Crohn’s disease.

Enjoy your reading.



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OVERVIEW

DIGESTIVE CANCERS AND INTESTINAL MICROBIOTA: FROM ONCOGENESIS TO RESPONSE TO TREATMENT

With an increasing prevalence that has made it the leading cause of death in many western countries, cancer is now regarded more as an emergent disease arising from environmental factors than a disease caused by constitutional genetic aberrations, which are now known to be much less common than previously thought. A paradigm shift favoured by the development of molecular biology techniques, a better understanding of the underlying mechanisms and the identification of associated biomarkers. For several decades, epidemiologists have observed a connection between cancer and diet, which has made the intestinal microbiota – and thus dysbioses – a focal point in the study of cancer. This connection has now found a mechanistic explanation involving energy metabolism, inflammation and immunity: influenced by diet, some bacteria can affect tumour progression, the response to cancer treatments and the side effects of these treatments.

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The associations between certain cancers and dysbiosis, the mechanisms by which the intestinal microbiota can promote human cancers, and an inventory of diagnostic and/or therapeutic biomarkers, particularly in anticancer immunotherapy, are summarized in **Table 1**.

As in the case of obesity and diabetes, it is important to identify bacterial markers for diagnostic purposes but also to study bacterial functions in order to better understand the impact of the environment on these cancers.

In obese individuals, for example, an imbalanced diet in terms of quantity and quality can rapidly alter the intestinal microbiota and the functions of its constituent bacteria [1]. By characterizing the intestinal microbiota in these individuals, it can be possible to identify a specific dysbiosis and thus assess the probability of success or failure of a corrective diet. Many emergent diseases such as cancer have undergone similar developments and are benefiting from new avenues of pathophysiological research.

OESOPHAGUS-STOMACH

In physiological conditions, the oesophageal microbiota is similar to that of the oral cavity, with an abundance of Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria and Fusobacteria and predominance of the genus *Streptococcus* in the oesophagus. In gastroesophageal reflux disease (GERD) and Barrett's oesophagus (BE), conditions which promote preneoplastic changes, the microbiota composition is closer to that of the stomach, with an abun-

▼ TABLE 1

The place of the gut microbiota in digestive cancers

	SITE	EFFECT	MECHANISM
Neisseria elongate	Oral	↓↓ Pancreatic tumours	Homeostasis
Streptococcus mitis	Oral	↓↓↓ Pancreatic tumours	Idem
Porphyromonas gingivalis	Oral	↑↑↑ Pancreatic tumours	Dysbiosis and inflammation
Parvimonas micra	Oral	↑↑↑ Colorectal tumours	Epigenotoxicity, Immune tolerance
Helicobacter pylori	Stomach	↑↑↑ Gastric tumours ↓↓↓ Adenocarcinoma	Th17 immune pathway ?
Helicobacter hepaticus	Liver, intestine bile ducts	Pancreatic tumours ↑↑↑ Liver tumours	Alteration of DNA, NF-kB Wnt pathway, suppression antitumor immune response
Streptococcus gallolyticus	Intestine	↑↑↑ Colorectal tumours	Symbiotic relationship and Immune tolerance; synthesis of bile salts
Bacteroides fragilis	Intestine	↑↑↑ Colorectal tumours	Immune tolerance Th17 Promotion Wnt, NF-kB, pathway STAT3, direct effect? Genotoxicity (fragilysin)
Enterococcus faecalis	Intestine	↑↑↑ Colorectal tumours	Pro-inflammatory ROS production Genotoxicity
Clostridium septicum	Intestine	↑↑↑ Colorectal tumours	Pro-inflammatory Risk of septic complications
Fusobacterium spp.	Intestine	↑↑↑ Colorectal tumours ↑↑↑ Oesophageal tumours	Immune tolerance Dysbiosis marker OeS Immune tolerance
Escherichia coli	Intestine, pancreas	↑↑↑ Colorectal tumours ↓↓ Pancreatic tumours	Invasion, DNA breaks Production nitrate compounds metabolism; dysbiosis Genotoxicity (colibactin)
Lactobacillus spp.	All sites	↓↓↓ Tumours flammatoire	Promotes homeostasis, anti-inflammatory
Bifidobacterium spp.	All sites	↓↓↓ Tumours ↓↓ Side effects of immunotherapy	Competition with anti-inflammatory pathogens Homeostasis
Clostridium cluster IV	All sites	↓↓↓ Tumours	Homeostasis; anti-inflammatory effects

dance of Bacteroidetes, Proteobacteria and *Fusobacterium*. *Paradoxically, Helicobacter pylori*, a gastric bacterium known to be a cofactor in the development of gastric neoplasias (cancer and MALT lymphoma), appears to exert a protective role against oesophageal adenocarcinomas which are on the rise in western countries. In reality, different bacterial species in addition to *H. pylori*, such as *Pasteurella stomatis, Dialister pneumosintes, Slakia exigua, Parvimonas micra* and *Streptococcus anginosus*, are implicated in the development of gastric tumours. Recent work suggests that *Enterobacteriaceae*, especially *Rumi-nococcus*, might play an important role in the immune escape of gastric and oesophageal adenocarcinomas [2].

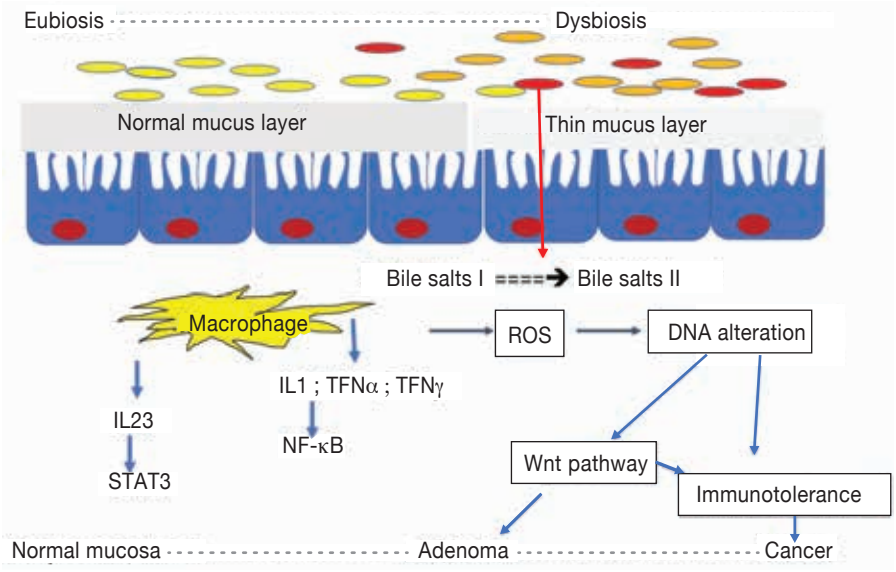
COLORECTAL CANCER (CRC) AND MODEL OF TUMOUR IMMUNE ESCAPE

Since the first descriptions of an association between colonic dysbiosis and CRC [3, 4], the hypothesis that the oral flora participated in the dysbiosis implicated in CRC has been updated in light of original work on the link between oral-gut transmission and colon dysbiosis [5]. Disruption of the bacterial equilibrium often occurs at the expense of beneficial species like Bifidobacteria and Lactobacilli, which help maintain the immune response [2]. Since these bacteria can no longer provide a counterweight to pro-inflammatory bacteria, an asymptomatic chronic inflammation, long been known to promote oncogenic processes, develops in the colonic mucosa. Now, the current western diet (high in animal protein and sugars) is known to favour pro-inflammatory bacteria at the expense of anti-inflammatory bacteria. In contrast, a Mediterranean diet (rich in plant fibre) limits these damaging effects [6]. When fibre intake is insufficient, the bacteria recruited as a result of excessive consumption of animal protein and fat erode the mucosa, taken as a source of fibre, and expose the intestinal epithelium to potentially virulent bacteria (**Figure 1**). At the cellular level, the main biological signalling pathways such as the Wnt and the canonical NF-kB (*nuclear factor-kappa B*) pathway, respectively responsible for cell renewal and higher production of pro-inflammatory cytokines, are stimulated by this diet [6]. This phenomenon can be likened to a shift of the immune response toward tolerance, due to an overabundance of other bacterial populations such as *Parvimonas micra* and *Streptococcus fragilis* [7]. In animals, *Bacteroides fragilis* and *Escherichia coli*, which are present in overabundance in advanced CRC (TNM stage III or IV), maintain an inflammatory state in the colonic mucosa and promote tumour development [8].

HEPATOCELLULAR CARCINOMA (HCC)

Primary liver tumours develop through a chronic process including cirrhosis, itself the result of hepatitis B or C virus infection. Epigenetic mechanisms resulting from the action of microorganisms lead to extinction of certain key genes such as p16 (INK4A), glutathione S-transferase P 1 (GSTP1), CDH1 (E-cadherin), *Ras association domain containing protein 1* (RASSF1A), p21 (WAF1/CIP1), all of which are hypermethylated by HBV, as well as the Suppressor of Cytokine Signalling 1 (SOCS-1) and the STAT1 gene, hypermethylated by HCV. These genes delay the occurrence of cancer but hypermethylation inhibits their expression. Bacteria can intervene to promote these processes: *Helicobacter hepaticus* increases cancer risk, either

▼FIGURE 1 Bacterial disequilibrium and transformation of normal mucosa in colon cancer model



directly by activating the Wnt and NK-kB pathways, or by facilitating the HVC-induced process. Just like environmental factors (viruses, chemical pollutants, etc.), certain enterobacteria such as *E. coli*, have been identified as cofactors for activation of the carcinogenic process. In metabolism, a disruption of Firmicutes/Bacteroidetes populations, a known risk factor for obesity, enhances the risk for HCC by crowding out protective species such as *Lactobacillus, Bifidobacterium, Parabacteroides* and *Oscillibacter* [9, 10].

PANCREATIC CANCER

Patients with pancreatic cancer have a high density of *Enterobacteriaceae, Pseudomonadaceae, Moraxellaceae* and *Enterococcaceae* in tumour tissue, while *Acinetobacter, Aquabacterium, Oceanobacillus, Rahnella, Massilia, Delftia, Deinococcus,* and *Sphingobium* are abundant in the duodenal lumen. As in CRC, the dysbiosis linked to this cancer also includes changes in the oral flora, characterized by an overabundance of *Porphyromonas gingivalis* and an underabundance of *Neisseria elongate* or *Streptococcus mitis*. One more example of the link between intestinal dysbiosis and gastrointestinal cancers. As far as treatment is concerned, it is important to note that *Gammaproteobacteria* can increase resistance to gemcitabine, the standard of care for pancreatic cancer.

ANTITUMOR IMMUNE RESPONSE AND DYSBIOSIS

Axenic (germ-free) animals develop fewer tumours, probably due to immune tolerance and less reactive inflammatory activity, which could be explained by the absence of a physiological microbiota. The microbiota can contribute to cancer development through different mechanisms: first of all, activation of inflammation by dysbiosis and reorientation of the immune system; production of genotoxins (colibactin, fragilysin) and virulence factors by bacteria able to directly alter host DNA; induction of oxidative stress by production of reactive oxygen species (ROS); and finally, by bacterial production of secondary metabolites (secondary bile acids, etc.). In the colon model, for example, there are four distinct subtypes corresponding to different metabolic, immune or inflammatory pathways [11]. In the CRC subtype with T lymphocyte infiltration, the T cells have a reduced ability to express cytokines or attack target cells due to persistent stimulation by tumour antigens. This phenomenon is known as T cell exhaustion. It is the most common mechanism of immune escape. Regardless of the initial recruitment of lymphocytes – cytotoxic or facilitator – the tumour continues to grow [9]. Regulatory T cells (Tregs) will facilitate the immunosuppressive effect by producing factors such as TGF-β. Tregs are preferentially recruited in the exhaustion phase. Furthermore, the intratumoral density of Tregs is a negative prognostic marker. By producing immunosuppressive cytokines (IL-10 and TGF-β), Tregs interfere with the specific action of cytotoxic T cells which normally target the tumour. In particular, Tregs increase the immune down-regulating protein CTLA-4 or CD152 (cytotoxic T-lymphocyte-associated protein 4) of these T cells. This protein has become a target of modern immunotherapies. Tregs act with the help of Th17 cells and STAT3 (*Signal Transducer and Activator of Transcription 3*), involved in the process of carcinogenesis in various organs. Th17 cells produce pro-inflammatory cytokines (IL-17 and IL-23) which promote tumour growth by increasing the production of Th1 cytokines and that of a chemokine (C-X-C motif) ligand 9 and 10 (CXCL9 and CXCL10). Th17 cells have similar characteristics to stem cells and can self-renew. The cytokine environment at the site of the tumour affects the different models of Th17 cell expression: in colorectal, hepatocellular and pancreatic cancer, tumour infiltration by Th17 cells is an unfavorable prognostic marker because it promotes immune tolerance to the tumour. The dysbiosis in the mucosal lining modulates the expression of IL17, IL-23, STAT3.

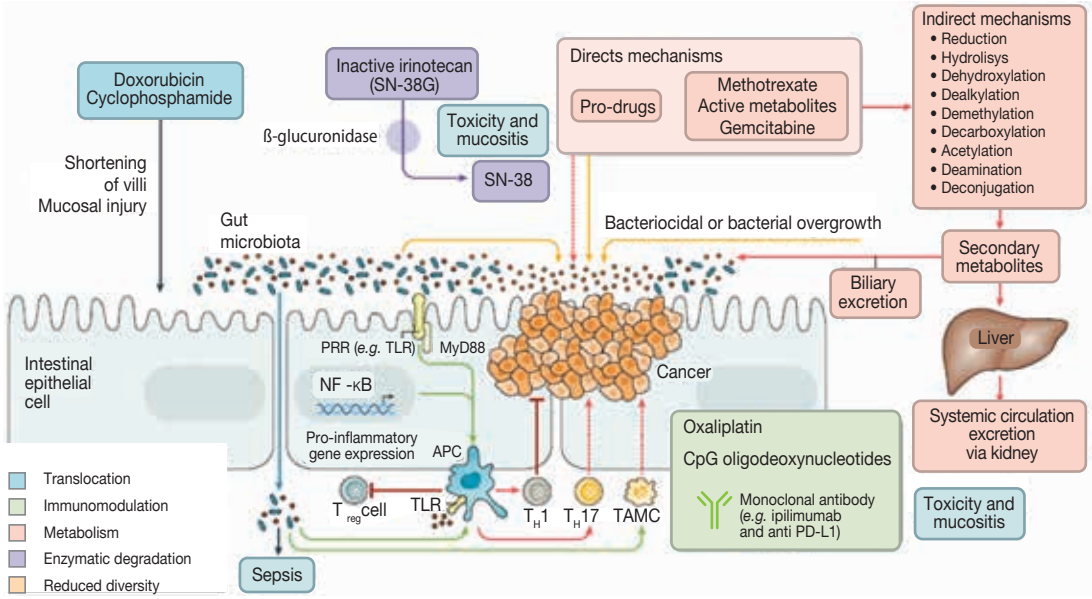
MICROBIOTA AND CANCER TREATMENTS

The intestinal microbiota has been shown to modulate the response to anticancer chemotherapy and immunotherapy in mouse models and in humans. Lung and kidney cancers and melanoma have been studied in clinical trials. This effect is never attributable to a single species: it is always a reflection of the impact of the intestinal microbial community as a whole on immunity or a function shared by different bacterial species. These bacterial communities influence the response to therapy in

▶ FIGURE 2

Mechanisms of chemotherapy toxicity seen from the microbiota standpoint

Based on the TIMER theory (Translocation, Immunomodulation, Metabolism, Enzymatic degradation and Reduced diversity and ecological variation) [12].



T_{reg} cell: T cell regulator
TLR: toll-like receptor
APC: antigen presenting cell

terms of side effects/toxicity and resistance to treatment (**Figure 2**). For example, proteobacteria, particularly *Mycoplasma hyorhinis*, possess cytidine-deaminase activity which metabolizes gemcitabine and thereby reduces its efficacy. Likewise, cyclophosphamide has variable antitumor effects according to dose; its efficacy is modulated by gram-positive (including *Enterococcus hirae*) and gram-negative species (including *Barnesiella intestinihominis*) [12].

Anticancer immunotherapies have been successfully used in malignant melanoma. These are the most promising therapies involving immune checkpoint inhibitors targeting PD-1 and CTLA-4. It was first noted that in metastatic renal or lung cancer patients, the use of antibiotics could modulate the activity of anti-PD-1 or anti-PD-L1 immunotherapies [13]. Subsequently, a large American study in metastatic melanoma treated with immunotherapy found that a good response to treatment (longer progression-free survival and overall survival) depended on the colonic microbial composition: faecal microbiota transplantation from the patients to recipient mice showed that intestinal dysbiosis was indeed the root cause of the variability in response to anti-PD-1 immunotherapy [14, 15].

These data are to be compared with data on TLR4 polymorphisms that are related to the variable response to immunotherapy. TLR (toll-like receptors) are transmembrane or cytosolic receptors which belong to the large family of receptors of the innate immune system (PRR, pattern recognition receptors), expressed by epithelial cells and immune cells in the intestine. Binding of a TLR with a microbial ligand triggers an intracellular signalling cascade which usually leads to an inflammatory response through activation of NF-kB. Host immune status has proved to be the main factor in the response to all antineoplastic treatments, directly and by alterations of the intestinal microbiota. It should also be noted that other therapeutic techniques such as radiotherapy and surgery are also affected by the microbiota: ionizing radiation is less toxic to axenic mice compared to conventional mice; postoperative healing of patients after colon cancer surgery depends on the type of dysbiosis.

CONCLUSION

The colonic microbial composition is influenced by environmental factors and can affect the development and progression of malignant tumours through metabolic, inflammatory and immune pathways. Studies are under way to better understand resistance to and toxicity of anticancer treatments. It is likely that modulation of the intestinal microbiota will become a way to optimize anticancer therapy in the future.

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COMMENTED ARTICLE
ADULTS' SECTION

RECONSTITUTION OF THE GUT MICROBIOTA OF ANTIBIOTIC-TREATED PATIENTS BY AUTOLOGOUS FAECAL MICROBIOTA TRANSPLANT

Commentary on the original publication by Taur et al. (Science Translational Medicine 2018 [1])

Antibiotic treatment can deplete the commensal bacteria of a patient's gut microbiota and, paradoxically, increase their risk of subsequent infections. In allogeneic hematopoietic stem cell transplantation (allo-HSCT), antibiotic administration is essential for optimal clinical outcomes but significantly disrupts intestinal microbiota diversity, leading to loss of many beneficial microbes. Although gut microbiota diversity loss during allo-HSCT is associated with increased mortality, approaches to re-establish depleted commensal bacteria have yet to be developed. A randomized, controlled clinical trial has been initiated to compare autologous faecal microbiota transplantation (auto-FMT) *versus* no intervention; the intestinal microbiota profiles of 25 allo-HSCT patients (14 who received auto-FMT treatment and 11 control patients who did not) were analysed. Changes in gut microbiota diversity and composition revealed that the auto-FMT intervention boosted microbial diversity and re-established the intestinal microbiota composition that the patient had before antibiotic treatment and allo-HSCT. These results demonstrate the potential utility of faecal sample banking for auto-FMT for posttreatment remediation of a patient's gut microbiota after microbiota-depleting antibiotic treatment during allo-HSCT.

By Prof. Harry Sokol
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WHAT DO WE ALREADY KNOW ABOUT THIS SUBJECT?

Antibiotic treatment damages the intestinal microbiota and increases the risk of gastrointestinal infection. Although this effect has been recognized for more than 60 years, remediation of the antibiotic-depleted gut microbiota has yet to become standard clinical practice. In patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT), antibiotics are routinely given to treat or reduce the risk of serious infection. Prospective studies of allo-HSCT patients demonstrated that the intestinal microbiota is markedly altered during treatment, with profound loss of obligate anaerobic bacteria including immunomodulatory species such as those belonging to the *Clostridia* class and Bacteroidetes phylum [2]. The clinical consequences of these alterations are also apparent in allo-HSCT: disruption of beneficial obligate anaerobes correlates with complications that include systemic infection with vancomycin-resistant *Enterococcus* (VRE), *Clostridium difficile* infection, and graft-*versus*-host disease (GVHD) [2, 3]. Overall, patients who lose gut microbiota diversity at the time of hematopoietic stem cell engraftment have higher rates of transplant-related death [4].

WHAT ARE THE MAIN INSIGHTS FROM THIS STUDY?

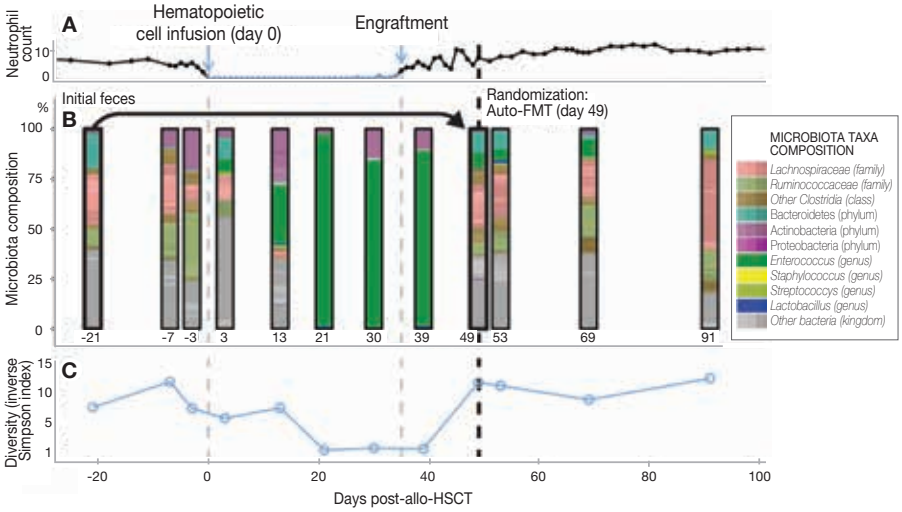
Allo-HSCT patients remain immunocompromised for many months after engraftment, and although immunocompromised patients, including allo-HSCT recipients, have undergone heterologous FMT without

KEY POINTS

- The intestinal microbiota is markedly disrupted during allo-HSCT and this disruption can play a role in the associated complications
- Auto-FMT is a feasible and effective strategy for reconstitution of the microbiota after the disruption caused by allo-HSCT
- The consequences of microbiota reconstitution in terms of haematological outcomes remain to be evaluated

▼ FIGURE 1

Timeline for a study patient undergoing allo-HSCT and who received auto-FMT.
A. Neutrophil count over time. **B**. Microbiota composition over time. Post-engraftment, the patient received many antibiotic treatments and the microbiota was markedly disrupted with domination by *Enterococcus* from day 21. **C**. After auto-TMF, gut microbiota composition and diversity were restore.



side effects [5], the authors reasoned that autologous FMT would be safer by minimizing the risk of exposure to potentially pathogenic microorganisms not previously encountered by the patient. The authors initiated a randomized, controlled clinical trial to determine the feasibility of auto-FMT for restoring the gut microbiota and for decreasing complications related to allo-HSCT. Here, they present an analysis of the gut microbiota compositional changes in 25 patients enrolled and randomized from whom faecal samples were longitudinally collected.

The authors first confirmed in their cohort of 753 patients (3,237 longitudinally collected faecal samples) that allo-HSCT and the different associated antibiotic treatments induced a marked decrease in gut microbiota diversity, reaching a nadir 5 days after allo-HSCT, which persisted for at least 6 weeks and which in most patients had not recovered at day 100 post-allo-HSCT.

As part of the randomized study, faecal samples from patients collected before allo-HSCT were frozen at -80°C and stored. One to 5 weeks (mean, 13 days) after allo-HSCT, upon engraftment (defined by recovery of the neutrophil count to > 500/mm^3), patients were re-evaluated and another faecal sample was taken. If there was a paucity of bacteria from the Bacteroidetes phylum, patients were randomized. The results of microbiota analyses from the first 25 evaluable patients (14 from the auto-FMT group and 11 from the control group) are presented. Auto-FMT was administered as a single retention enema after colonic preparation with polyethylene glycol, similar to the preparation for a colonoscopy. The authors show that auto-FMT not only restores the diversity of the intestinal microbiota but also its composition pre-allo-HSCT.

WHAT ARE THE CONSEQUENCES IN PRACTICE?

Several studies show that the intestinal microbiota and disruptions thereof play a role in the common infectious and non-infectious complications encountered during allo-HSCT. This first study shows that the collection and storage of a patient's faecal samples prior to allo-HSCT to be re-administered after engraftment is a feasible and effective strategy to reconstitute the microbiota. It remains to be seen whether patients who underwent auto-FMT have better outcomes with regard to these complications and if they have a better overall survival. If the efficacy of this strategy is confirmed, it could also be considered in other situations where significant microbiota disruption is expected, such as broad spectrum or prolonged antibiotic treatment or anticancer chemotherapy.

CONCLUSION

Although the benefits in terms of haematological outcomes and overall survival still need to be evaluated, auto-FMT is a promising strategy to re-establish the intestinal microbiota after the disorders induced by the antibiotic treatment associated to the allo-HSCT.

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COMMENTED ARTICLE
CHILDREN'S SECTION

TREATMENT OF ACTIVE CROHN'S DISEASE WITH AN ORDINARY FOOD-BASED DIET THAT REPLICATES EXCLUSIVE ENTERAL NUTRITION

Commentary on the original publication by Svolos et al. (Gastroenterology 2019 [1])

By Prof. Emmanuel Mas
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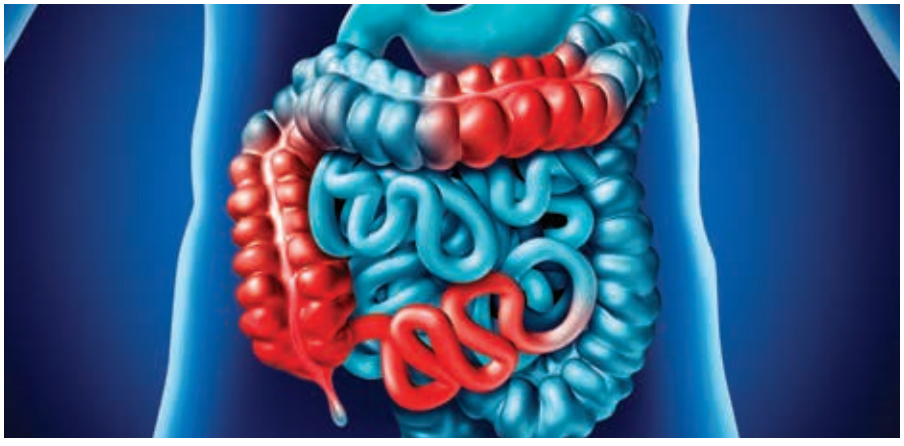
Exclusive enteral nutrition (EEN) is the only established dietary treatment in Crohn's disease (CD), but its acceptability is limited. There is a need for new dietary treatments for CD.

The effects of a personalized diet (CD-TREAT), based on the composition of EEN, were evaluated by analysing the intestinal microbiota, inflammation and clinical response in rats, in healthy adults, and in children with relapsing CD.

Ultimately, it was shown that CD-TREAT replicates EEN changes in the gut microbiota, decreases gut inflammation, is well tolerated and is potentially effective in patients with active CD.



WHAT DO WE ALREADY KNOW ABOUT THIS SUBJECT?

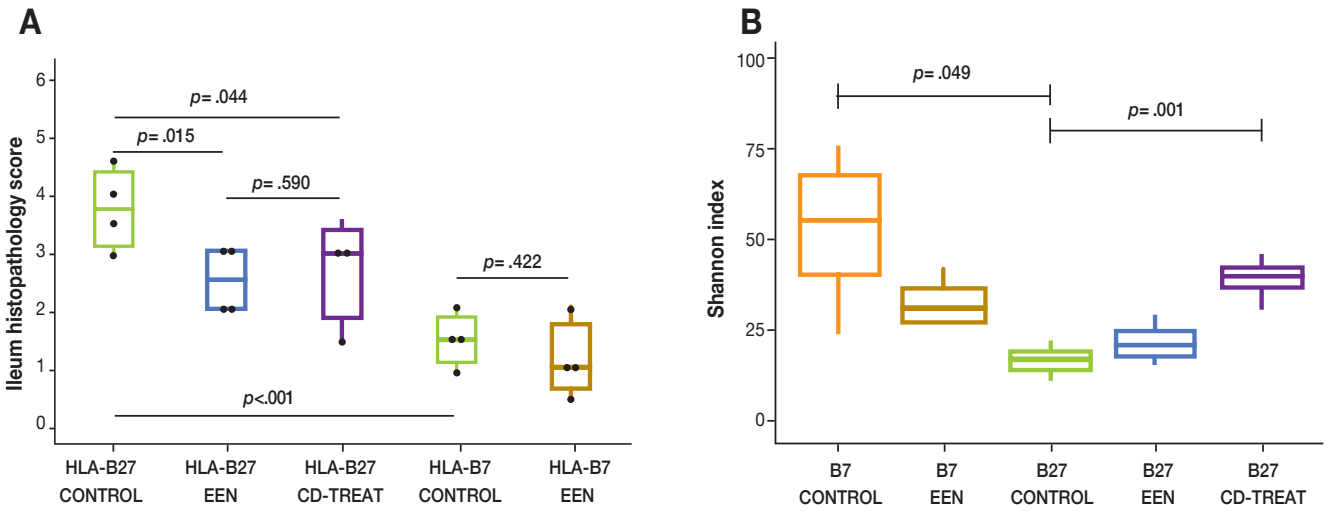
Exclusive enteral nutrition (EEN) is an effective treatment of Crohn's disease with ileus involvement, achieving good results (mucosal healing in 80% of cases) that are superior to those obtained with corticotherapy. However, the main obstacle is the acceptability of receiving, for at least 8 weeks, exclusive enteral nutrition. EEN is delivered by nasogastric tube or, as for Modulen IBD®, by the oral route. The mechanism of action of EEN is not fully understood but several studies suggest that it acts by modulating the intestinal microbiota.

WHAT ARE THE MAIN INSIGHTS FROM THIS STUDY?

This study aimed to determine whether an ordinary diet (CD-TREAT), *i.e.* oral intake of ordinary foods but based on a nutrient composition similar to that of Modulen IBD®, could be effective in Crohn's disease. The proportion of carbohydrate was decreased and that of protein increased. A multivitamin tablet provided the micronutrients from EEN.

▼ FIGURE 1

Influence of diet in rats with (HLA-B27) and without (HLA-B7) gut inflammation on ileal inflammation (A) and caecal microbiome diversity (B).



KEY POINTS

- A suitable oral diet could be as effective as exclusive enteral nutrition in Crohn's disease
- Its effect on the intestinal microbiota mimics that of exclusive enteral nutrition
- It offers an alternative to exclusive enteral nutrition which is poorly accepted by patients

A crossover study was conducted in 25 healthy adult volunteers who received CD-TREAT or EEN for one week each, with a washout period in between. CD-TREAT was easier to follow and more satiating than EEN. Microbiota richness and alpha diversity were not altered by these diets. However, the relative abundance of 58 (49.3%) and 38 (32.3%) bacterial genera changed significantly after EEN and CD-TREAT, respectively, of which 28 changed in the same direction. There were changes in the concentrations of different metabolites (some short chain fatty acids – acetate, propionate and butyrate significantly decreased after EEN and CD-TREAT) and faecal pH increased by about 1 unit.

Animal experiments were performed in 5 groups of rats, HLA B27 (inflammatory) and B7 (non-inflammatory): B27-EEN, B27-CD-TREAT, B27-CONTROL, B7-EEN and B7-CONTROL. EEN and CD-TREAT decreased ileal inflammation (**Figure 1A**), with lower expression of IL-6 in the B27-CD-TREAT group compared to the B27-CONTROL group (p = 0.036). After the 4-week intervention, bacterial diversity was higher in cecum (**Figure 1B**) and in feces in the B27-CD-TREAT and B27-EEN groups versus B27-CONTROL. Both diets caused changes in faecal concentrations of some short chain fatty acids.

Lastly, 5 children to mild to moderate Crohn's disease, (wPCDAI score 22.5 to 42.5) were treated with CD-TREAT for 8 weeks. One child discontinued after 9 days because of symptom exacerbation. After 4 weeks, 3 children (60%) had a clinical response (wPCDAI score change > 17.5) and 2 children (40%) were in clinical remission (wPCDAI score < 12.5). After 8 weeks, 80% of children (4 of 5) had a clinical response and 60% (3 of 5) were in clinical remission. The mean baseline level of faecal calprotectin of 1,960 mg/kg decreased by 53% and 55%, respectively, after 4 and 8 weeks (**Figure 2**). Calprotectin decreased to normal in only one child.

WHAT ARE THE CONSEQUENCES IN PRACTICE?

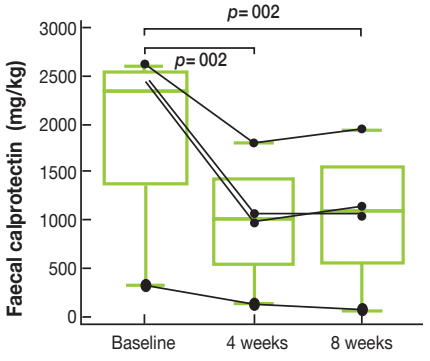
This study shows that this diet is more feasible when given orally and that it mimics the effects of EEN with Modulen IBD® on the gut microbiota. CD-TREAT also improves clinical signs and reduces gut inflammation.

CONCLUSION

This study provides proof-of-concept that a novel and better tolerated dietary treatment could be effective in Crohn's disease. These findings need to be confirmed in large, controlled, randomized clinical trials.

▼ FIGURE 2

Changes in faecal calprotectin in children on CD-TREAT.



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JFHOD

Journées Francophones d'Hépato-gastroentérologie & d'Oncologie Digestive

2019

obésité

CONGRESS REVIEW

By Dr. Dragos Ciocan
Hepato-gastroenterology and Nutrition, Hôpital Antoine-Béclère, Clamart, France

REVIEW OF THE MAIN CONTRIBUTIONS RELATED TO THE INTESTINAL MICROBIOTA

MARCH 2019

PARIS, FRANCE

The *Journées francophones d'hépato-gastroentérologie et d'oncologie digestive* (French language Hepatogastroenterology and Digestive Oncology Congress) was held in Paris from 21 to 24 March 2019, with an attendance of more than 5,000 French-speaking doctors and researchers. A number of original studies on the intestinal microbiota (IM) were presented.

FAECAL TRANSPLANTATION

Faecal microbiota transplantation (FMT) is a therapeutic strategy which is used in current clinical practice only for recurrent *Clostridium difficile* infections [1]. Dr. Eymeric Chartrain presented the experience acquired by the Clermont-Ferrand University Hospital reference centre between 2014 and 2018 on the use of FMT in this indication. FMT was effective in 95% of cases with minor side effects occurring in only 16% of patients. Furthermore, patients reported a significant improvement in quality of life at 6 months post-FMT. The total cost of a FMT intervention is approximately 3,100 euros. Despite this high cost, FMT helps lower health care costs by reducing morbidity and mortality in these patients and is a rational and effective option.

The role of FMT is being studied in many diseases involving the IM, including chronic inflammatory bowel diseases (IBDs). Professor Harry Sokol presented the results of a small, randomized, single blind, placebo-controlled pilot trial in 17 patients evaluating the role of FMT in adults with colonic or ileocolonic Crohn's disease during a flare-up, who were treated with oral corticosteroids. The primary endpoint – donor IM colonization in the recipient at week 6, defined by recipient IM at week 6 more similar to that of the donor (Sorensen similarity index ≥ 0.6) than to that of the patient pre-FMT – was not reached. Nevertheless, among the secondary endpoints, the FMT group had a reduction in endoscopic disease severity whereas the control group had an increase in inflammation. Colonization by donor IM was associated with sustained remission and patients without donor IM colonization had a recurrence earlier. In addition, the IM com-

position was predictive of steroid-free clinical remission. Despite the small sample size, this study suggests that FMT could be effective after corticosteroid-induced clinical remission in patients with active Crohn's disease. Several larger studies including one conducted by Professor Sokol's group are in progress.

ENTEROBACTERIACEAE MODULATE THE EFFECTS OF FUNGI IN COLITIS

While the role of the bacterial and fungal IM is known in IBDs, the impact of bacteria-fungal interactions on intestinal inflammation is less clear. Dr. Bruno Sovran presented a study which looked precisely at these interactions in a mouse colitis model. The authors found that administration of *Saccharomyces boulardii* CNCM I-745 improved colitis whereas administration of *Candida albicans* caused it to worsen. However, pre-treatment with colistin, which kills gram-negative bacteria (including proteobacteria) led to a loss of effect of fungi. Administration of colistin-resistant *E. coli* which restored the enterobacterial population in colistin-treated mice also re-established both the beneficial effects of *S. boulardii* CNCM I-745 and the deleterious effects of *C. albicans* on colitis severity. These observations suggest that Enterobacteriaceae are necessary for improved gut colonization by fungi and may explain the effects of some probiotics in colitis [2].

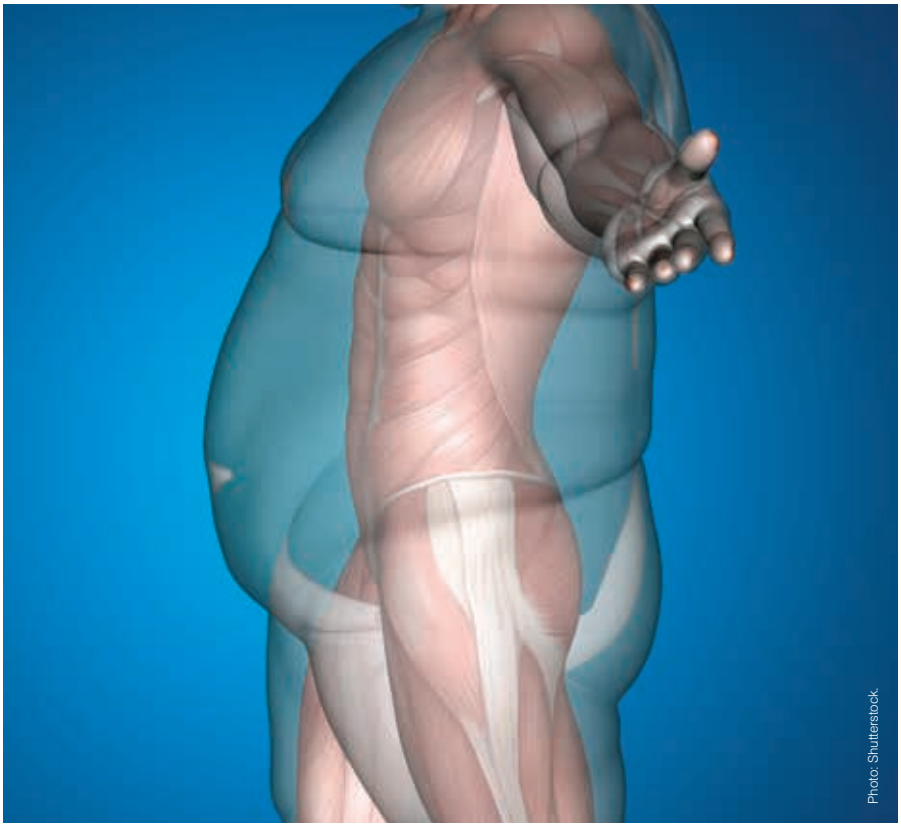
THE GUT-BRAIN AXIS IN OBESITY

It is now well known that the IM plays a role in the pathophysiology of obesity. The IM can also modulate cognitive and psychological functions via the gut-brain axis [3]. Obesity is a risk factor for cognitive impairment, independently of other comorbidities, but the mechanisms are obscure. The MEMOB study, presented by Dr. Sophie Cambos, investigated memory dysfunctions in obese subjects and their correlation with the IM. In this prospective, longitudinal, monocentric study in obese and normal weight subjects, the obese subjects prior to bariatric surgery had memory dysfunctions in comparison with a control population. Analysis of the microbial profile revealed a link between the abundance of *Eggerthellales* and memory functions: the greater the *Eggerthellales* abundance, the worse the memory results. These data suggest that obesity – and therefore the associated microbiota alterations – might accelerate cognitive decline via the gut-brain axis.

MICROBIOTA AND THE LIVER

A Biocodex workshop entitled "Microbiota and the liver, from mechanisms to treatment" took place during the meeting. Professor Gabriel Perlemuter reviewed the latest advances concerning the role of the IM in liver diseases. Among the most prominent recent studies, the IM has been found to play a role in susceptibility to developing alcoholic liver disease and non-alcoholic fatty liver disease when using proton pump inhibitors. These drugs promote overgrowth of *Enterococcus* in the IM, leading to more translocation to liver where it induces liver inflammation [4]. Several pilot studies also investigated the role of FMT in liver diseases (hepatitis B, hepatic encephalopathy and severe corticoresistant acute alcoholic hepatitis) and reported some efficacy in these indications.

Dr. Anne-Marie Cassard discussed the manipulation of the IM in the case of liver disease. She presented data from her group showing that low levels of *Bacteroides* are associated with the development of alcohol-induced liver injury. Correcting this IM imbalance by administration of pectin, a soluble fibre, prevented and improved the alcoholic-induced liver lesions [5]. However, not all fibres induce the same changes in the IM, even though they have the same beneficial effect on the host. Furthermore, among the different strategies studied which target the IM and have shown some effectiveness on liver injury (antibiotics, FMT, probiotics, prebiotics), only antibiotics and FMT can induce long-lasting changes in the IM.



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CONGRESS REVIEW

GUT MICROBIOTA FOR HEALTH

By Pr. Francisco Guarner
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GUT MICROBIOTA FOR HEALTH WORLD SUMMIT 2019

MARCH 2019

MIAMI, USA

During its 8th edition last March, the GMFH devoted considerable place to diet and the way it interacts with the gut microbiome, preventing or promoting diseases.

DIET AND THE GUT MICROBIOME

Diet is a key element for the symbiotic interactions between gut microbes and the host, and it is considered as one of the main drivers in shaping the gut microbiota across lifetime, as reviewed by Jack A. Gilbert (UC, San Diego), Susan Devkota (Cedars-Sinai, Los Angeles), and Lipping Zhao (Rutgers, New Jersey). Foods deliver numerous substrates for microbial metabolism and the microbiome is a chemical factory that synthesizes metabolites important for human health. Macro- and micronutrients in food influence the structure and functions of the gut microbial ecosystem in such way that diet appears to be the most important determinant of similarity in gut microbial composition across humans [1].

Self-reported dietary data from the American Gut project [2] suggest that the number of unique plant species that a subject consumes is associated with microbial diversity, rather than self-reported categories such as "vegan" or "omnivore". Higher microbial diversity and higher abundance of short chain fatty acid (SCFA) producer species was found in individuals eating more than 30 types of plants per week as compared to those eating less than 10 types of plants per week. The faecal metabolome also differed between both groups. In addition, individuals who consume more than 30 types of plants compared to those who consume 10 or fewer plants had significantly lower abundance of antibiotic resistance genes.

Dysbiosis of the gut microbiome is a definable state with mechanistic implications. It is not just a change in microbial diversity but a rupture of the mutualistic balance between microbiota and host, where inadequate diet plays a detrimental role. During homeostasis, colonocyte metabolism is directed towards oxidative phosphorylation, resulting in high epithelial oxygen consumption. The consequent epithelial hypoxia helps maintain a microbial community dominated by *obligate* anaerobes, which provide benefit by converting fibre into fermentation products (SCFA) absorbed by the host. Conditions that alter metabolism of the epithelium,

such as a fibre poor diet, increase epithelial oxygenation, thereby driving an expansion of *facultative* anaerobes, a hallmark of dysbiosis in the colon [3]. The shift in the colonic microbiota composition from obligate to facultative anaerobes, associated with many chronic human illnesses, might have a common underpinning in colonocyte dysfunction. As highlighted by Susan Devkota, if choosing a strict or extreme dietary regime, consuming mixed fibre types can support the microbiome and prevent nutrient deficiencies.

THE "FOUNDATION GUILD"

Lipping Zhao pointed out that our ancestors had much higher intake of dietary fibres than current consumption rates. Reduced intake of fibres and diminished prevalence of SCFA-producing bacteria may underlie many chronic diseases such as type 2 diabetes. In a randomised controlled intervention trial with Chinese type 2 diabetes patients [4], high intake of diverse dietary fibres (WTP diet) selectively promoted abundance of a group of acetic and butyric acid producer strains in the gut. The WTP diet is based on wholegrains, traditional Chinese medicinal foods and prebiotics. The WTP diet improved glucose homeostasis by reducing glycated haemoglobin, fasting blood glucose and meal tolerance test.

Abundance of the SCFA producers in faeces correlated with the metabolic outcomes and the blood levels of glucagon-like peptide-1 and peptide YY, which induce insulin secretion. Moreover, reduction of faecal pH by SCFA production correlated with inhibition of detrimental bacteria that promote inflammation and suppress glucagon-like peptide-1 production. In addition to providing SCFAs to directly benefit the host, this group of SCFA producers played important ecological functions in the gut microbiota. Lipping Zhao suggested that they work as the "foundation guild" for structuring the healthy gut microbiota. To help patients regain a healthy gut microbiota, "this foundation guild must be re-seeded and re-established", he said.

FODMAPS AND IBS

As reviewed by Magnus Simren (University of Gothenburg), the low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) diet is now being recommended by up to 85% of doctors to treat functional abdominal symptoms. Clinical trials suggest that some patients have a short-term favourable response to a low FODMAP diet, but whether this dietary advice is clearly better than the first line dietary therapy for IBS is uncertain. Of concern, short-term use of the low FODMAP diet has been associated with potentially unfavourable changes in gut microbiota composition, including reduction of fermentative species (*Bifidobacterium, Faecalibacterium* and *Clostridium cluster* XIVa) and increased dysbiotic index scores [5].

A randomized controlled trial compared effects of the low FODMAP diet or the prebiotic GOS on gut microbiota composition [6]. Changes in faecal microbiota differed between both groups after a 4-week treatment period, particularly in relation to bifidobacteria (increase in the prebiotic group and decrease in the low FODMAP group) and *Bilophila wadsworthia* (the opposite pattern). Despite distinct effects on microbiota, reductions of symptoms were very similar in both groups. Of interest, the decrease in symptoms persisted during the 2-week follow-up after cessation of prebiotic intake, but reappeared immediately after discontinuation the low FODMAP diet. Modulation of gut microbiota as a treatment strategy for IBS seems promising, but long-term safety aspects need to be taken into account. Diets that reduce symptoms but deteriorate gut health (and general health in the long term) should not be the first choice.

SYMBIOTIC TRIAL TO PREVENT NEWBORN SEPSIS

Sepsis in early infancy results in one million annual deaths worldwide, most of them in developing countries. Pinaki Panigrahi presented an intervention study to prevent sepsis among infants in rural India [7]. An oral symbiotic preparation (*Lactobacillus plantarum* plus fructooligosaccharide) significantly reduced sepsis and death in newborns (risk ratio 0.60, 95% confidence interval 0.48–0.74). This finding suggests that a large proportion of neonatal sepsis in developing countries could be effectively prevented using probiotic-prebiotic treatment.

Photo: Adobe Stock.

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Photo: Getty Images.

LITERATURE SELECTION

THE IMPACT OF THE PARENTS' MICROBIOME ON THE DESCENDANTS' HEALTH

By Prof. Markku Voutilainen
Turku University Faculty of Medicine; Turku University Hospital, Department of Gastroenterology, Turku, Finland

Infant gut is colonized by maternal vaginal and fecal bacteria during vaginal birth. Microbial colonization of the gut starts during fetal life, although its role remains debatable. The hypothesis of developmental origins of health and disease (DOHaD) suggests that the conditions during fetal life have an impact on the early life of the newborn and also result increased risk for chronic diseases of the offspring.

Professor Friedman has reviewed developmental programming [1]. Maternal obesity, diabetes, and western-style diet have an impact on infant stem cells, immune system and gut microbiota. The gut of the newborn is first colonized by aerobes and facultative anaerobes, which are replaced by strict anaerobes. This modifies innate immune signalling, T helper cell immune responses, and endotoxin tolerance. Maternal obesity may disrupt normal microbial colonization and increase the risk of immunologic and metabolic diseases later in the life. Antibiotic treatment during pregnancy increases the risk of childhood obesity. Children born for obese mothers have lesser abundance of two families of fecal Proteobacteria. Furthermore, maternal high-fat diet causes the loss of key bacteria and decrease in bacterial diversity of the infant fecal microbiota.

Also paternal diet may have impact on the health status of the following generations. Zhang and co-workers examined the impact of unhealthy diet in animal model [2]. They fed male rats in two successive generations (F0 and F1) with with high fat, sucrose and salt diet. The control group was fed with normal diet. The high fat-sucrose-salt diet was associated with increased aspartate aminotransferase levels in the next generation (F2). Unhealthy diet was also associated with higher body weight. In female F2 rats, the Shannon index of gut microbiota indicated significantly higher diversity. Variation in the abundance of bacterial genus was associated with liver function abnormalities. Unhealthy diet in F0 and F1 generations was associated with increased serum cholesterol and lipoprotein levels in male F2 rats.

This data suggest that parent's unhealthy diet causes dysbiosis of the gut microbiota of the offspring and may increase the risks of overweight and several chronic diseases (T2 diabetes, liver and cardiovascular diseases).

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ESOPHAGEAL MICROBIOME – THE CAUSE OR CONSEQUENCE IN ESOPHAGEAL DISEASES?

Gastroesophageal reflux disease is common in western world. Barrett's esophagus (BE) is the complication of reflux disease and the major risk factor of esophageal adenocarcinoma, which has a five-year survival rate less than 20%.

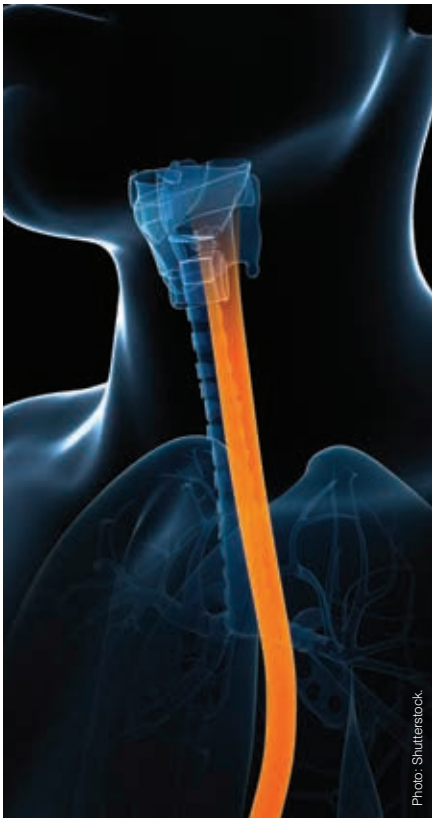
Recent review examined the role of esophageal microbiome in BE and esophageal cancer (3). Esophagus is exposed to swallowed oral microorganisms and also microbes of the refluxed gastric contents. Esophageal microbiota is not similar to oral nor gastric microbiota. The first bacteria detected in the esophagus were *Strectococcus viridans* and group D *Streptococcus*. Later six phyla were observed by broad-range 16S ribosomal DNA gene clone sequencing including Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, and *Streptococcus*. BE and high-grade dysplasia were associated with the highest number of bacteria. In patients with esophagitis and BE the number of *Streptococcus* was diminished while gram-negative anaerobes and microaerophiles were increased.

BE and esophageal adenocarcinoma are associated with increased number of *Escherichia coli*. Another gram-negative species detected in esophageal cancer patients is *Fusobacterium nucleatum*. Also oral dysbiosis may be related to the increased risk of esophageal cancer, while gastric *Helicobacter pylori* seems to protect against esophageal cancer. Gastric dysbiosis such as increase of *Clostridiales* and *Erysipelotrichaceae* is associated with esophageal squamous carcinoma. Also fungi, for example *Candica albicans* and *C. glabrata* are often detected in esophageal samples from patients with esophaghageal adenocarcinoma. An epidemiologic study showed dose-dependent association between penicillin use and increased risk of esophageal cancer. Also proton pump inhibitors modify gastric and esophageal microbiome.

The present data of esophageal microbiota were obtained from small, selected, and symptomatic patient populations in cross-sectional studies. Thus no conclusions of causality between esophageal microbiota and esophageal diseases can be made. Only a small portion of patients with BE develop adenocarcinoma and further studies are needed to define the role of esophageal dysbiosis in the pathogenesis of cancer. One topic for further research is the impact of proton pump inhibitors on esophageal microbiota and on the risk for esophageal diseases [3].

Eosinophilic esophagitis (EoE) is an allergic chronic inflammatory disease that is the most common cause of dysphagia in children and young adults in developed countries. EoE has common inflammatory features with other allergic diseases and allergen exposure probably has a central role in EoE pathogenesis. Capucilli and Hill have reviewed EoE epidemiology, pathogenesis and treatment [4]. The esophageal microbiota may be involved in the pathogenesis of EoE. The esophagus is colonized by hundreds of bacterial species and members of Firmicutes and Bacteroidetes phyla are the commonest [4]. In patients with active EoE, the genera *Streptococcus* and *Atopobium* are decreased while *Neisseria* and *Corynebacterium* are increased. Another study showed that the total amount of esophageal bacteria and *Haemophilus* genus specifically were increased in EoE. Proton pump inhibitors that are used in the treatment of EoE, cause an enrichment of Proteobacteria phylum. Esophageal bacterial load is increased in EoE patients irrespective of treatment or the severity of esophageal mucosal eosinophilia. Like in other allergic and autoimmune diseases, antibiotic treatment and caesarean delivery are associated with increased risk of EoE [4].

Studies were cross-sectional and there is no data on the stability of esophageal microbiota over time. More studies are needed to define the role of esophageal microbiota in the pathogenesis and activation of EoE.



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By Agnès Louvrier
Products manager, Biocodex France

FRANCE INAUGURATES THE MICROBIOTA UNIVERSITY

Committed to the sharing of knowledge on the human microbiota and an expert in the field, the Biocodex Microbiota Institute has launched the first edition of the Microbiota University.

Between December 2018 and February 2019, eight cities hosted high quality scientific meetings, led by renowned experts. The goal was to provide an opportunity for rich exchanges on a variety of topics and to emphasize the importance of a balanced gut microbiota in human health. This "Tour de France" of expertise met with great success, bringing together more than 500 health professionals – physicians as well as pharmacists – to explore the latest news in microbiota research.

Each evening started off with a review presented by Professor Philippe Marteau, from Hôpital Saint-Antoine in Paris, covering some of the fundamental knowledge in the field: dysbiosis and associated gastrointestinal disorders (antibiotic-associated diarrhoea, *Clostridium difficile* infections, inflammatory bowel diseases [IBDs], irritable bowel syndrome [IBS]), but also the efficacy of probiotics in treating these conditions.

Alongside Philippe Marteau was a roster of speakers in the different cities:

- Prof. Harry Sokol (Hôpital Saint-Antoine, Paris), who discussed the indication for faecal microbiota transplantation and described the ongoing research;
- Prof. Gabriel Perlemuter (Hôpital Antoine-Béclère, Paris), who explained the role of the gut microbiota in the initiation and progression of some liver diseases;
- Prof. Pascal Derkinderen (Nantes University Hospital), who elaborated on data from studies suggesting a role of dysbiosis in the pathophysiology of neurodegenerative and central nervous system disorders;
- Prof. Karine Clément (Hôpital de la Pitié-Salpêtrière, Paris), who presented scientific evidence for the role of the gut microbiota in triggering metabolic diseases;
- Prof. Iradj Sobhani (Hôpital Henri-Mondor, Créteil), who described the role of certain bacterial species in the development of colorectal cancer.

You can find a video of each presentation on the Biocodex Microbiota Institute website:
https://www.biocodexmicrobiotainstitute.com/en/pro/services-for-professionals/video-library

CALL FOR RESEARCH PROPOSALS

BIOCODEX MICROBIOTA FOUNDATION

The 2019 international call for proposals, dedicated to the theme *"Gut microbiota and drug metabolism"*, came to an end last March with a €200 000, grant awarded by the International Scientific Committee to Professor Emily Balskus (Chemistry and Chemical Biology - Harvard University, Cambridge, MA, USA) for her project **"Targeting gut microbial drug metabolism to enhance the treatment of Parkinson's disease"**.

At the same session, the Committee also awarded the 2019 *"Super Award"* to Dr. Paul McLellan (Gastroenterology and Nutrition - Hôpital Saint-Antoine, Paris, France) for his project entitled **"Use of the bacterial protein MAM as a biomarker of intestinal inflammation in Crohn's disease"**, which competed among the winners of the eight national calls for proposals in 2018. Dr. McLellan was awarded a €20,000 grant in addition to the French grant of €25,000.

In 2020, the international call for proposals will be on the theme **"Role of microbiota in post-antibiotic or post-infectious functional bowel disorders"**. The submission deadline is 30 November 2019.

• **Visit www.biocodexmicrobiotafoundation.com to find out more.**

THE PRO OF THE NET

BIOCODEX MICROBIOTA INSTITUTE

The Institute's website is getting a new look. To make it easier to access available content and propose new topic sections, the "health professionals" and "general public" home pages have been completely redesigned.

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MEETINGS

FIND BIOCODEX AT THE FOLLOWING MEETINGS:

ESNM 2019
5 TO 7 SEPTEMBER
LISBON, PORTUGAL

UEG WEEK 2019
19 TO 23 OCTOBER
BARCELONA, SPAIN

APDW 2019
12 TO 15 DECEMBER
CALCUTTA, INDIA

WE VALUE YOUR OPINION

Launched two years ago, the Microbiota newsletter deciphers the latest scientific advances on the gut microbiota and allows you to discover the incredible wealth of this field of research. The time has now come to take stock: in order to find out if it meets your expectations and to collect your feedback, we invite you to submit your comments online.

Please take a few minutes to help us make the Microbiota newsletter even better.

And don't hesitate to subscribe!

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Congress Reviews

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