MICROBIOTA

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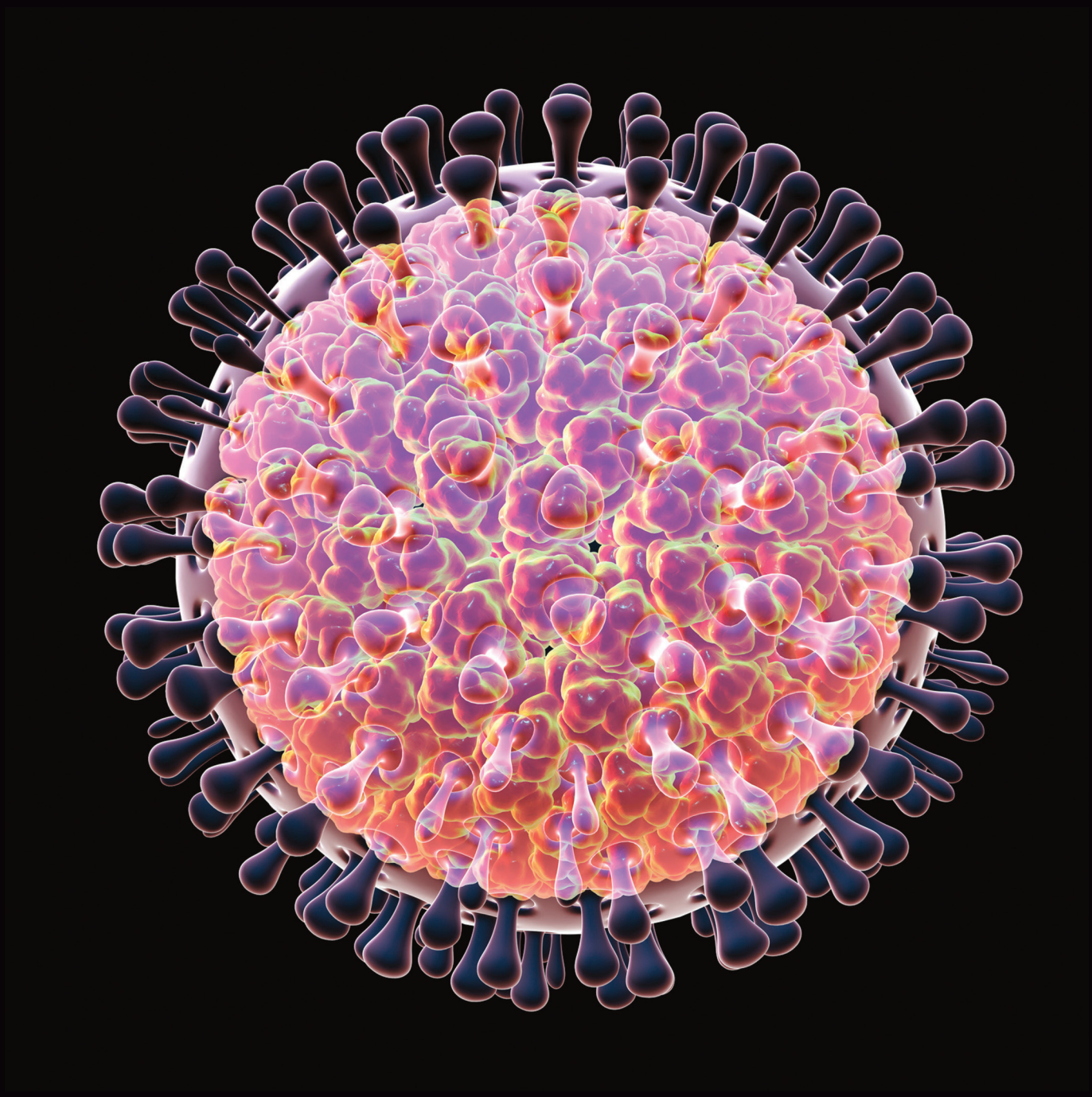

BIOCODEX
Microbiota Institute

SUMMARY

EDITORIAL

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Dear Readers, this newsletter highlights some of the articles in this edition, written by experts in the field, which should arouse your curiosity. Our decision to focus on the scientific area of Microbiotas (with a "M" and a "s") was motivated by the exponential rise in the number of discoveries and articles illustrating the importance of the relationships we have from birth with our microbiotas (gut, gastric, urologic, pulmonary…).

Individually, we do not all have the same risk of liver diseases. Only a small proportion of individuals, with equivalent alcohol consumption and comparable excess weight, develop hepatitis, cirrhosis or hepatocellular carcinoma.

In this edition, Dr. Anne-Marie Cassard and Prof. Gabriel Perlemuter (Clamart, France) describe how the gut microbiota has emerged as a key cofactor in the appearance of nutritional liver diseases; alcoholic liver disease (ALD) related to alcohol consumption and metabolic steatosis related to excess weight, also known as non-alcoholic fatty liver disease (NAFLD).

Data on the role of gut microbiota in aging processes are limited. In this edition, Prof. Harry Sokol (Paris, France) comments on recent work by Han *et al.* showing how some bacterial genes may be involved in life expectancy.

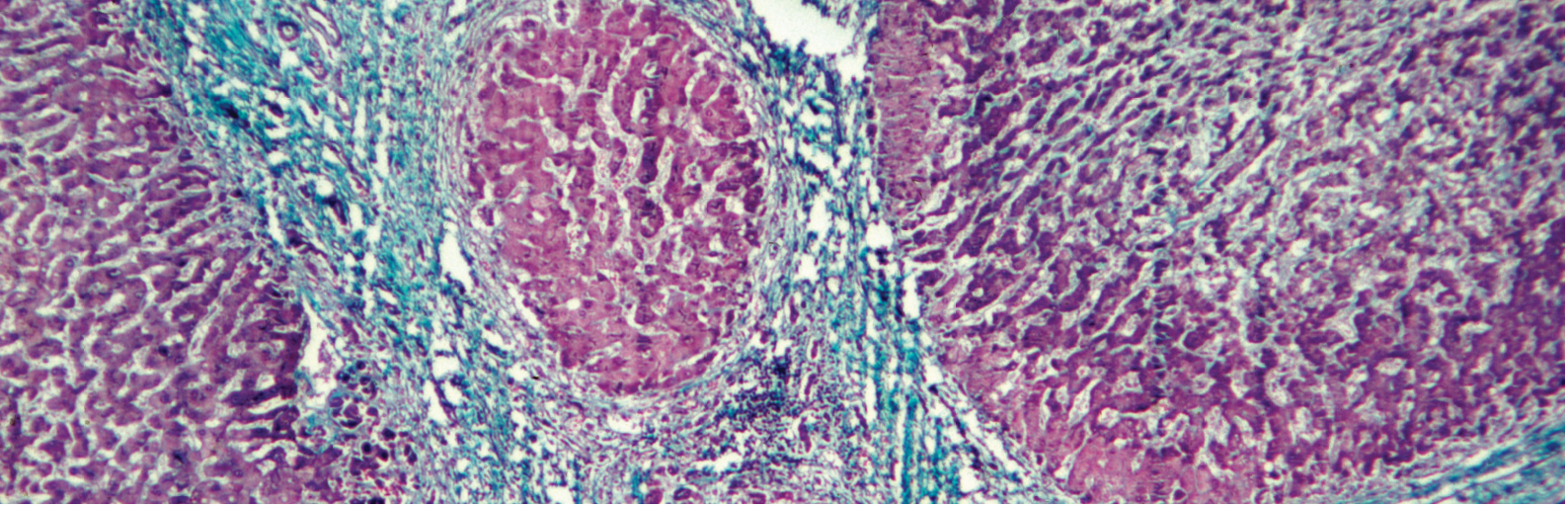
The gastrointestinal symptoms reported in children with autism have indicated an influence of microbiota on the pathophysiology of the disease. Prof. Emmanuel Mas (Toulouse, France) describes the promising results obtained by Kang *et al.* on digestive and behavioural disorders in children with autism following faecal microbiota transplantation.

In the literature review of Prof. Dinleyici (Eskisehir, Turkey), the resistance to chemotherapy induced by *Fusobacterium nucleatum* in colon cancer, the potential value of some probiotics in treating liver diseases, and the fact that the gut microbiota could be used as a diagnostic marker in certain digestive disorders are discussed.

Finally, Prof. Zakharenko (Moscow, Russia) presents his scientific selection from the NeuroGASTRO meeting organized by the European Society of Neurogastroenterology and Motility (24–26 August 2017; Cork, Ireland).

Happy reading!

"THE « MICROBIOTA NEWSLETTER » IS FOCUSED ON THE IMPORTANCE OF THE VARIOUS MICROBIOTA. IT IS INTENDED TO BE « UNIVERSAL »…"



OVERVIEW

GUT MICROBIOTA AND LIVER DISEASES

For a given risk factor, there is an individual susceptibility to develop severe forms of liver diseases. We have shown that the gut microbiota is an essential susceptibility cofactor for alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD). The beneficial effects of some bacteria, such as *Akkermansia muciniphila* or prebiotics, have led to the development of new treatments. The gut microbiota also participates in fibrogenesis and liver carcinogenesis. By modulating immunity, the gut microbiota may also promote the chronic carriage of hepatitis B virus (HBV). In terms of clinical application, the first human studies suggest that the study of gut microbiota could lead to identification of patients at greatest risk of developing liver disease or, when cirrhosis is already present, patients at greatest risk of disease decompensation.

By Dr. Anne-Marie Cassard[1,2] and Pr. Gabriel Perlemuter[1,2,3]

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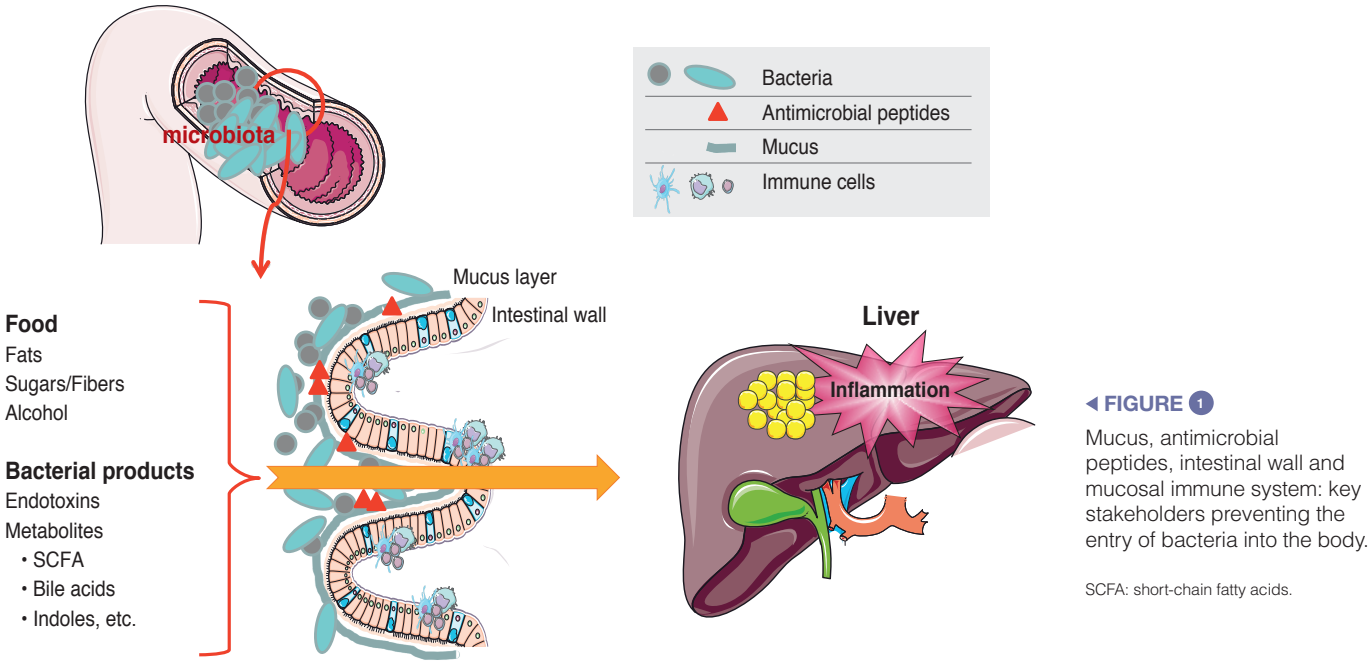
Human Liver with viral hepatitis and cirrhosis

NON-ALCOHOLIC FATTY LIVER DISEASE AND GUT MICROBIOTA

NAFLD is considered the leading cause of chronic liver disease in industrialized countries. It is estimated that about 30% of the population have NAFLD and this rate is close to 75% in overweight or obese individuals. While most patients remain asymptomatic, 20% of patients will develop hepatic inflammation (non-alcoholic steatohepatitis; NASH) that may lead to cirrhosis and then hepatocellular carcinoma (HCC).

A decrease in Bacteroidetes and an increase in *Clostridium coccoides* have been observed in patients with NASH, compared to healthy subjects or patients with only isolated steatosis. In addition, an increase in *Proteobacteria* and *Enterobacteriaceae*, including *Escherichia coli*, in obese adolescents with NASH has been reported. In other studies, NASH was associated with a decrease in Bacteroidetes [1] or an increase in *Bacteroides*, contrasting with a decrease in *Prevotella* [2]. These changes were associated with metabolic functional changes in gut microbiota in terms of carbohydrates, lipids, and amino acids.

The discovery of the causal role of the gut microbiota in the development of NASH is more recent [3]. Inducing obesity in mouse models generates, as in humans, a heterogeneous response; despite an identical diet and similar genetic background, under a fat-rich diet, only some mice develop metabolic complications



◂ **FIGURE 1**

Mucus, antimicrobial peptides, intestinal wall and mucosal immune system: key stakeholders preventing the entry of bacteria into the body.

SCFA: short-chain fatty acids.

AXENIC MICE

Axenic mice born under sterile conditions are free of any micro-organisms. This feature offers the possibility to colonize the gastrointestinal tract with any gut microbiota, or with a single bacterium or defined cocktail of bacteria (gnotobiotic mice). It should be noted that this may not be feasible for all human gut microbiota in axenic mice. In addition, the development of all immune mechanisms that depend on the gut microbiota is not fully compensated by the implantation of human gut microbiota. Moreover, recent data show that the integrity of the intestinal mucus layer is only achieved after eight weeks of colonization. Therefore, these limitations should be taken into account when using these models, which nevertheless remain an exceptional tool for studying the gut microbiota.

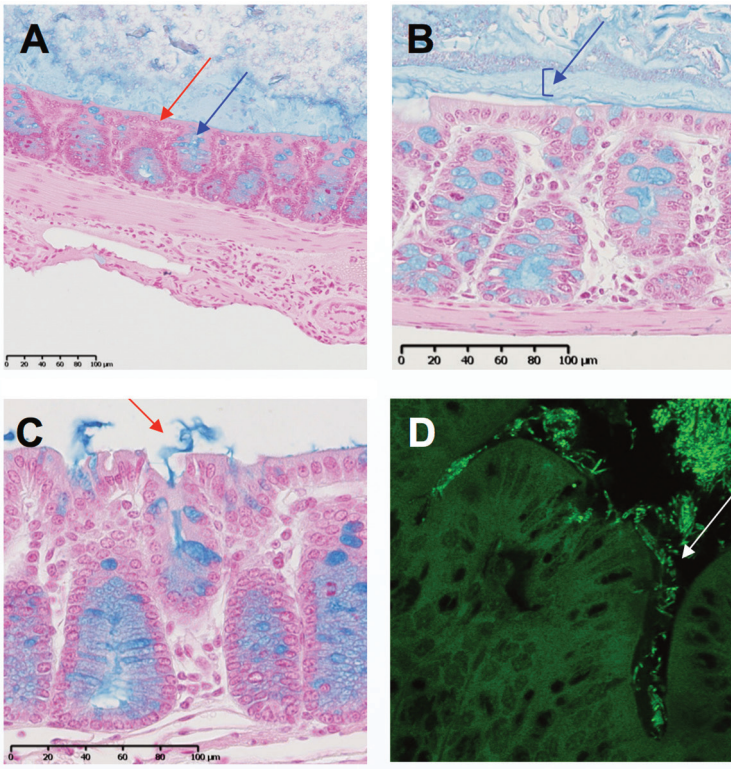
and NASH. To identify the causal role of the gut microbiota in NASH, we have transferred the gut microbiota from obese mice, with or without insulin resistance and liver involvement, to recipient axenic mice which have then received a high calorie diet. Only the mice that received the gut microbiota from donor mice with insulin resistance and liver damage developed the same anomalies, showing the causal role of the gut microbiota in the genesis of liver disease. The percentage of *Bacteroides* remained unchanged. However, a specific decrease in the *Bacteroides vulgatus* species was observed. Conversely, *Lachnospiraceae bacterium* 609 and *Barnesiella intestini hominis* species increased in mice that did not develop liver complications. The mechanisms through which the gut microbiota leads to metabolic syndrome and liver damage remain to be clarified.

The Toll-like receptors (TLR) are involved in the innate immune response. TLR5 is specific to flagellin-like bacterial compound and is involved in the inflammatory response. Mice deficient for TLR5 develop obesity associated with metabolic syndrome, as well as steatosis. The gut microbiota of these mice, when transferred to wild-type axenic mice, induces the pathological phenotype of the donor mice in recipient mice, showing again the causal role of the gut microbiota [4].

The gut microbiota also plays a role in liver fibrogenesis in NAFLD. Indeed, mice fed with a fat-rich diet show an increased proportion of lipopolysaccharide (LPS)-producing Gram-negative bacteria in the gut microbiota. Transferring this gut microbiota to mice in which the bile duct has been ligated (a model of liver fibrogenesis) increases the fibrotic process compared to mice receiving a gut microbiota from mice subjected to a control diet [5]. This result is related to the fact that the LPS receptor, TLR4, is expressed not only in Kupffer cells, but also in stellate cells in the liver. Its activation thus promotes the inflammatory process as well as the action of TGF-β, and subsequently fibrogenesis [6].

USE OF PREBIOTICS AND PROBIOTICS IN NAFLD

The use of pre- and probiotics to treat NASH in humans and mouse models has not yet led to the identification of clear therapeutic approaches. This is, at least partially, related to the lack of studies with clear endpoints and a sufficiently large number of patients. Some bacterial strains may improve some hepatic parameters (alanine transaminase [ALT] and liver triglycerides). Better results may be observed with *Lactobacillus* strains than with *Bifidobacterium* strains. Regarding prebiotics, such as inulin and



▲ FIGURE 2

Carnoy's-fixed colonic histological sections (3 µm). (**A, B, C**) Alcian blue and nuclear fast red staining. (**D**) Panbacterial probe Eub 338 Alexa 488 (green on confocal Zeiss Axio microscope) used for fluorescence *in situ* hybridization (FISH). HFP-Nanozoomer slide scanner (RS2.0, Hamamatsu®).

(**A**): nuclear fast red staining of colonic epithelial cells (red arrow) and Alcian blue staining of mucus (blue arrow). (**B**): the blue arrow shows the mucus layer. (**C**): the release of mucus is seen into the intestinal lumen (red arrow). (**D**): the bacteria are seen in the intestinal crypt under pathological conditions (white arrow).

fruco-oligosaccharide (FOS), improved transaminase levels and steatosis may be observed in mouse models.

ALCOHOLIC LIVER DISEASE (ALD) AND GUT MICROBIOTA

Dysbiosis is present in alcoholic rodent models. In humans, consuming alcohol induces a decrease in *Bifidobacteria*, *Lactobacilli*, and *Enterococci*. Based on equivalent alcohol consumption, we have shown that patients with severe acute alcoholic hepatitis (AAH) have a gut microbiota that is different from that of patients without AAH. To demonstrate whether this dysbiosis plays a causal role in ALD severity, we transferred the gut microbiota from alcoholic patients to recipient axenic mice. One group received the gut microbiota of an alcoholic patient without AAH and the second the gut microbiota of an alcoholic patient with severe AAH. After alcoholization, mice that received the gut microbiota from the patient with severe AAH developed more severe hepatic damage than mice of the other group, showing that the bacterial composition of the gut microbiota is directly involved in liver damage induction. In addition, after receiving the gut microbiota from patients with severe AAH, the condition of mice improved after a new faecal transplantation of the gut microbiota from alcoholic patients without AAH. This result suggests that correcting dysbiosis could play a therapeutic role.

In mouse models of ALD, we have shown that maintaining high levels of Bacteroidetes, among others, prevents the development of liver damage. Pectin, a fibre assimilated to a prebiotic that promotes Bacteroidetes growth has been used. Inhibiting the decrease in *Bacteroides* prevented the appearance of ALD damage [7]. The curative effects of pectin have also been tested in humanized mice that received the gut microbiota from patients with severe

MUCUS AND INTESTINAL DEFENSINS

The development of diseases, including liver diseases, in which the gut microbiota is involved, is very commonly associated with an impairment of the intestinal barrier. The underlying mechanisms involve changes in the amount, or even in the quality, of the mucus produced by goblet cells. In addition, the production of anti-microbial peptides, defensins (including Reg3β and Reg3γ), is frequently reduced. Successful treatments for NASH, at least in mouse models, are generally associated with a regression of these anomalies at the intestinal epithelium.

AAH. Under these conditions, we again observed a protective effect (unpublished data).

The changes in the gut microbiota in ALD are associated with an impaired intestinal barrier and correlate with an increase in endotoxemia. There is thus a decreased thickness of the mucus layer, as well as a reduced intestinal expression of antimicrobial peptides, such as lectins, Reg3β and Reg3γ [8, 9]. The various treatments that target the gut microbiota, which may be used to prevent or successfully treat ALD (gut microbiota transfer, pre- or probiotics), typically promote the integrity of the intestinal barrier [7, 10].

PROMISING PREBIOTICS AND PROBIOTICS FOR ALD

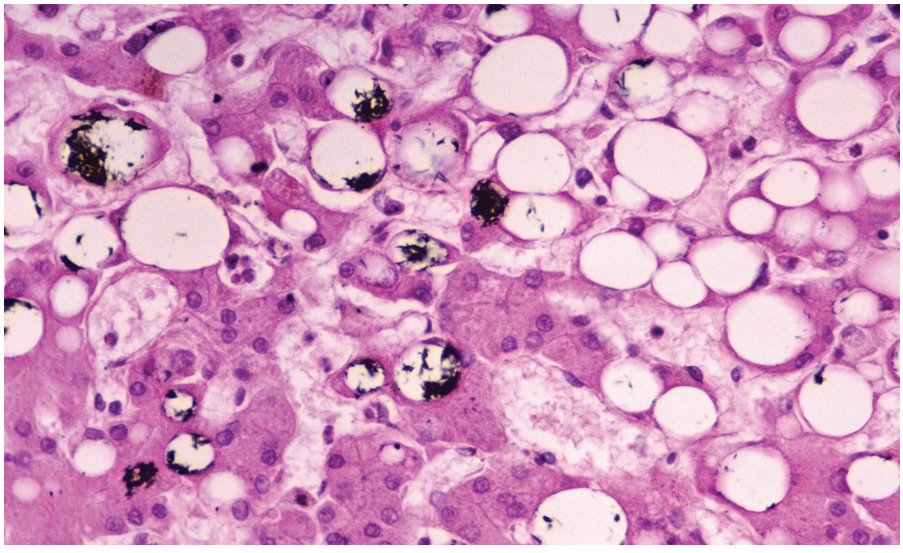
As for NASH, probiotics, mainly belonging to the lactobacillus and bifidobacteria family, improve ALT and liver triglyceride profiles in ALD in humans and mouse models. Among the tested lactobacilli and bifidobacteria, including *Bifidobacterium bifidum* and *Lactobacillus plantarum* 8PA3, the improved liver parameters are associated with a restoration of intestinal barrier integrity. The protective effects of *Lactobacillus GG* persist when the bacterium is inactivated by heat, suggesting that its metabolites are sufficient to mediate its effects. On the other hand, *Faecalibacterium prausnitzii*, known for its anti-inflammatory properties, is associated with the gut microbiota of alcoholic patients without AAH. Although the use of this bacterium, which has already shown its protective role in Crohn's disease, may be of interest in ALD, no study has been published to date [10]. Recently, we have shown that *A. muciniphila*, a bacterium that metabolizes the intestinal mucus, is decreased in individuals who consume alcohol. Restoring a high level of *A. muciniphila* improves liver damage in a mouse model of ALD [11].

The bacteria and fibres used in NASH or ALD, whether they are probiotics or prebiotics, have moderate effects on reducing liver damage. Understanding the mechanisms by which they act should help to better target their use. Thus, although *A. muciniphila* has recently been demonstrated to play a role as an energy "sensor", its protective effects against alcohol remain to be clarified. However, the beneficial effects are generally associated with a strengthening of the intestinal barrier which is probably a key mechanism by which pre- and probiotics exert their effects on the liver.

OTHER LIVER DISEASES

Studies showing the involvement of the gut microbiota in other liver diseases are scarce.

Mice invalidated for mdr2 (mdr2$^{-/-}$) are a model for primary biliary cholangitis (PBC). When these mice are bred under sterile conditions (germ-free mice), their phenotype is biologically and histologically exacerbated. An increase in cholangiocyte senescence, related to the decreased production of secondary bile acids due to the absence of gut microbiota, is likely to be the cause of this worsening. A treatment with ursodeoxycholic acid alleviates liver damage [12].



Liver steatosis © Science Source / BSIP.

MUCUS-ASSOCIATED BACTERIA

A number of intestinal bacteria may be associated with mucus. These are referred to as adherent bacteria. These bacteria belong to bacterial species capable of degrading the mucus and using it as a substrate for their growth. A limited number of bacteria will cross the sterile mucus layer to interact with the intestinal epithelium, even in the intestinal crypts. Thus, during dysbiosis, when the bacterial composition is being established, it may also be very informative to analyse the spatial distribution of bacterial species in the mucus, the surface intestinal epithelium, and the crypts. Spatial reorganization alone may impair the intestinal barrier. It should be noted that investigative techniques are not yet robust enough and are therefore infrequently used.

During infection with HBV, the gut microbiota is believed to play a role through changes in the immune system. Mice in which HBV is artificially replicated have been used as a model. While viral replication normally decreases in adult mice, this is not the case in younger mice, except in mice lacking the expression of TLR4. In addition, adult mice treated with antibiotics do not show any rapid decrease in HBV replication. The authors of this study relate these observations to the risk of chronic carriage when the individual is infected with HBV in childhood, and conclude that the gut microbiota regulates liver immunity against HBV [13].

The effect of a gut microbiota transfer has been tested in humans after failure of a treatment with entecavir or tenofovir. Patients were treated for at least three years but remained positive for HBeAG. A stool transfer was performed by gastroscopy every four weeks, from HBAg-negative donors, until HBeAg negativity was achieved. The gut microbiota transfer induced a decrease in HBeAg in the five treated patients, but in none of the 13 control patients [14]. These results suggest that in hepatitis B, the gut microbiota could also be a therapeutic target.

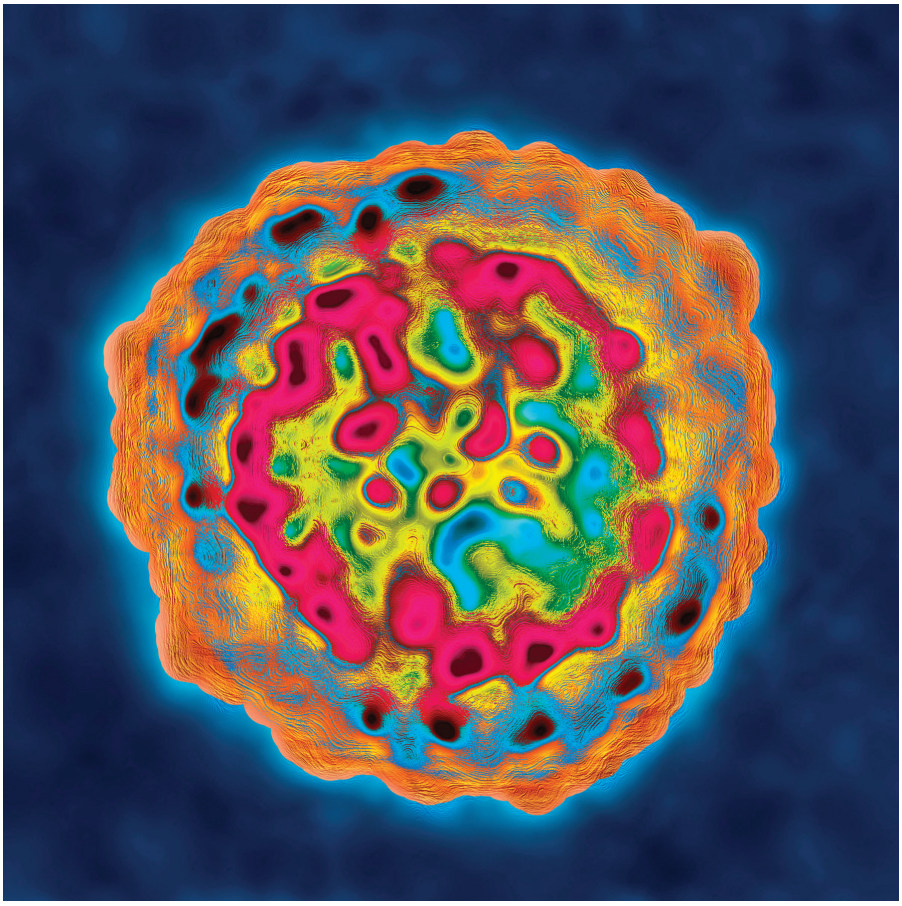
MICROBIOTA AND HEPATOCELLULAR CARCINOMA

The activation of the TLR4 pathway could play a triggering role in the late stages of carcinogenesis, in particular, through the inhibition of apoptosis [15]. Nevertheless, in another model of carcinogenesis, contradictory data have been observed since the inhibition of the TLR4 pathway promotes tumour growth [16]. In humans, the overexpression of TLR 2, 4 and 9 may be associated with a poor prognosis. An indirect relationship has been reported between obesity, dysbiosis, and liver carcinogenesis; dysbiosis observed in obese mice is associated with changes in bacterial metabolite production. In particular, an increased production of deoxycholic acid is observed. This bile acid enhances the senescence of stellate cells in the liver and subsequently promotes liver carcinogenesis [17]. In mouse models, some combinations of bacterial strains used as probiotics prevent HCC growth. The mechanism is believed to involve the growth of some anti-inflammatory bacteria of the gut microbiota, as well as a decreased tumour infiltration by Th17 cells [18].

CLINICAL APPLICATION

In humans, some publications suggest that studies on gut microbiota could already have a clinical relevance. Nevertheless, the number of publications remains limited and these should be confirmed by independent teams or cohorts.

Using metagenomic techniques, a specific gut microbiota was shown to be associated with the presence of cirrhosis. It was noted that bacteria, theoretically from the mouth, were found in the stools, indicating a bacterial translocation. Using 15 gene biomarkers, the authors proposed a diagnosis of cirrhosis based on stool analysis. The area under the curve (AUC) for this test was 91.8% (95% CI: 88.1 95.5) in the study cohort and 83.6% (95% CI: 73.0 94.3) in the control cohort [19]. Based on the gut microbiota in NAFLD patients, it was possible to distinguish between those with advanced fibrosis (stages 3-4) and those with less severe fibrosis (stages 0-2) [20]. Studying the circulating microbiome could also be an interesting approach [21].



Hepatitis B virus © Cavallini James / BSIP.

For patients with cirrhosis, it may be possible to predict the risk of decompensation based on gut microbiota analysis, and a cirrhosis dysbiosis ratio (CDR) has been proposed [22, 23]. Very recently, it has been suggested that studying the fungal microbiome could also be useful in this context [24].

Regarding treatment, a recent randomized therapeutic trial involving 20 patients (10 gut microbiota transplantation patients and 10 controls) with hepatic encephalopathy has shown that microbiota transfer was well tolerated, decreased the number of hospitalizations, and improved cognitive disorders, without improving liver function (MELD, Model for End-stage Liver Disease, and albumin levels were unchanged) [25].

CONCLUSION

The gut microbiota plays a major role in liver diseases. The dysbiosis observed in liver diseases is both a cause and a consequence of the diseases. The gut microbiota interacts with the liver through multiple mechanisms which involve changes in bacterial metabolites, such as bile acids, and changes in intestinal barrier and immune function. The study of gut microbiota for liver diseases will develop further since improvements in diagnostic and prognostic performance are expected through such study and a more personalized medicine might be implemented. In addition, an improvement in patient prognosis is expected by modifying the gut microbiota or altering the metabolic pathways that interact with the gut microbiota.

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COMMENTED ARTICLE
ADULTS' SECTION

GUT MICROBIOTA INFLUENCES LONGEVITY

Comments of the original article by Han et al. (Cell 2017) [1]

By Prof. Harry Sokol
Gastroenterology and Nutrition Department, Saint-Antoine Hospital, Paris, France

Gut microbiota homeostasis has a major influence on the health and aging of the host. The development of genetically-modified probiotics represents a new promising therapeutic approach to promote healthy aging.

In this study, 3,983 *Escherichia coli* mutants were screened and 29 bacterial genes involved in host aging were identified. When these genes were deleted, the longevity of the host (the worm, *Caenorhabditis elegans*) was increased. A dozen of these mutant bacteria also had a protective effect against tumour progression and beta-amyloid accumulation. Mechanistically, five of these mutant bacteria extended longevity by inducing the secretion of a polysaccharide, colanic acid (CA), which regulates mitochondrial dynamics and the unfolded protein response (UPR) in the host. The administration of purified CA polymers was sufficient to increase longevity *via* ATFS-1, a transcription factor activated by the UPR. In addition, the mitochondrial changes and the effects on longevity induced by CA were conserved between species. Overall, these findings identify molecular targets based on micro-organisms and microbial metabolites that increase longevity by acting on the host mitochondria.

WHAT IS ALREADY KNOWN ABOUT THIS TOPIC?

Largely due to advances in the treatment of infectious diseases, modern society is progressively aging and is composed of an ever-increasing proportion of elderly individuals. Improving healthy aging and preventing aging-related diseases and disabilities has become a priority of current medical research. Although our understanding of aging has improved lately, few products promoting longevity have been discovered to date. An increasing number of studies suggest that the gut microbiota is closely related to the aging process of the host [1]. This community of microbial species not only generates metabolites that are essential for various host functions, but is also involved in the effects of exogenous chemical molecules.

Changes in bacterial composition of the gut microbiota have been observed in the elderly, and modulating the microbiota by nutritional interventions could have health benefits in this context. However, most of our knowledge on the gut microbiota is limited to composition data, whereas the functions of each microbial gene and the mechanisms involved in the modulation of

KEY POINTS

- The systematic analysis of *E. coli* genes has led to the identification of several bacterial genes involved in host longevity.
- Some of the genes involved act by inducing the secretion of a polysaccharide, CA, which regulates mitochondrialdynamics and the UPR in the host.
- The interactions between microbiota and mitochondria could play a role in other physiological functions.

host aging remain unknown. This is partly due to the great complexity of the gut microbiota in mammals and the technical challenges specific to the identification of micro-organisms that modulate longevity.

The nematode *C. elegans*, with its short and easily assessable life cycle, as well as its defined microbiota, is a powerful model for dissecting the interactions between microbes and host aging [1]. Under usual laboratory conditions, *C. elegans* is cultured in the presence of a single bacterial strain of *E. coli*. From early nematode adulthood, the bacterial cells colonize the intestinal lumen and represent the totality of the gut microbiota. Using this simple model, studies have demonstrated the crucial role of the microbiota in the regulation of host longevity. Some bacterial variants have been identified as determinants of the duration of the host life cycle [2], and small molecules secreted by bacteria, such as some non-coding RNAs and nitric oxide, have been involved in host longevity in this context [3]. However, no systematic analysis, aimed at identifying bacterial genetic factors that modulate host longevity, has been performed.

WHAT ARE THE MAIN RESULTS OF THIS STUDY?

In this study, a high-throughput screening platform has been set up to identify microbial factors for host longevity from a complete collection of 3,983 *E. coli* mutants. Using this systematic approach, a series of microbial genetic factors, regulating host health and longevity through the modulation of several already known regulation pathways of aging, have been identified. A new mechanism has also been identified, involving induction of the production of a secreted polysaccharide, CA, by *E. coli*. Indeed, bacteria mutated in the *hns* and *lon* genes, two repressors of CA production, have an increased life-cycle duration, and this effect is lost when the gene encoding CA production (*RcsA*) is deleted (**Figure 1**). The authors then determined that CA acts *via* regulation of mitochondrial dynamics and the UPR in the host.

Furthermore, these results suggest, beyond the role of the microbiota in modulating longevity, that the interactions between gut bacteria and mitochondria, their former intracellular ancestral cousin, could play an important role in physiology.

WHAT ARE THE PRACTICAL CONSEQUENCES?

This study demonstrates that the microbiota is involved in aging phenomena. There is still much to do before a potential application is established in humans, however, this work, in addition to the specific CA approach, encourages investigation of the modulation pathway of the gut microbiota to promote healthy aging. Moreover, this work also suggests that the interactions between microbiota and mitochondria could be important in other ways and this therefore deserves further investigation.

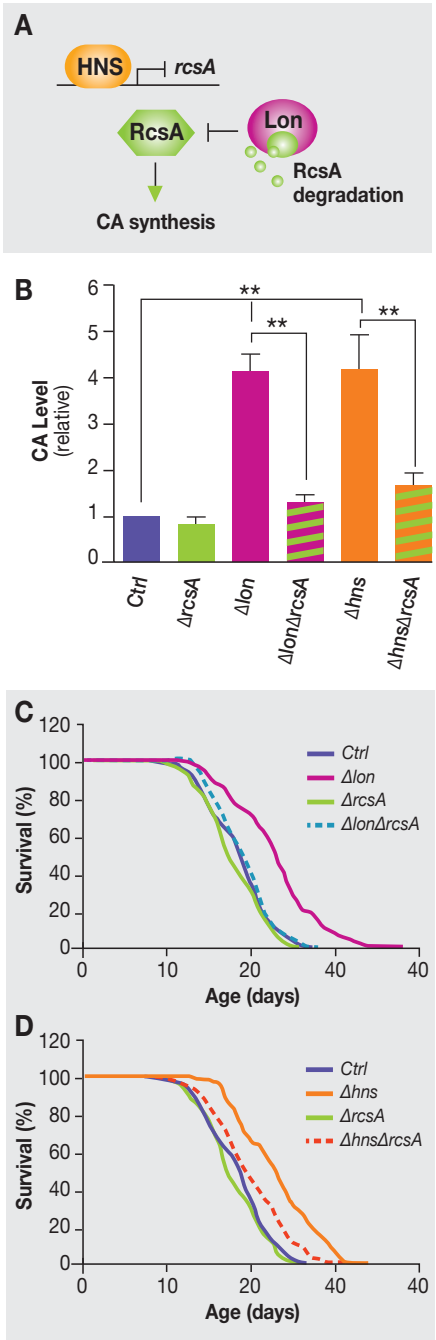
CONCLUSION

The gut microbiota, through the production of metabolites, such as CA, has an impact on longevity. CA acts through the regulation of mitochondrial dynamics and the UPR in the host.

FIGURE 1

Genetic mechanisms involved in the regulation of aging through the secretion of colanic acid (CA).

A. Diagram of CA biosynthesis..
B. CA production is increased in *hsn* (Δ*hsn*) and *lon* (Δ*lon*) mutants and this is suppressed when *rcsA* (Δ*rcsA*) is deleted.
C and **D**. The Δ*rcsA* deletion suppresses the gain of survival provided by the Δ*hsn* and Δ*lon mutants*.



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COMMENTED ARTICLE
CHILDREN' SECTION

MICROBIOTA TRANSFER THERAPY ALTERS GUT ECOSYSTEM AND IMPROVES GASTRO-INTESTINAL AND AUTISM SYMPTOMS: AN OPEN-LABEL STUDY

Comments of the original article by Kang et al. (Microbiome 2017) [1]

By Prof. Emmanuel Mas
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Autism spectrum disorders (ASD) are complex neurobiological disorders that impair social interactions and communication, and lead to restricted, repetitive, and stereotyped patterns of behaviour, interests, and activities. The causes of these disorders remain poorly understood, however, gut microbiota, comprising 10^{13} bacteria in the human intestines, have been implicated because children with ASD often suffer gastrointestinal (GI) problems that correlate with ASD severity. Several previous studies have reported abnormal gut bacteria in children with ASD. The gut microbiome-ASD association has been tested in a mouse model of ASD, in which the microbiome was mechanistically linked to abnormal metabolites and behaviour. Similarly, a study of children with ASD found that oral non-absorbable antibiotic treatment alleviated GI and ASD symptoms, albeit temporarily. Here, a small open-label clinical trial evaluated the impact of Microbiota Transfer Therapy (MTT) on gut microbiota composition and GI and ASD symptoms of 18 ASD-diagnosed children.

MTT involved a two-week antibiotic treatment, a bowel cleanse, and then an extended faecal microbiota transplant using a high initial dose followed by daily and lower maintenance doses for 7-8 weeks. The Gastrointestinal Symptom Rating Scale revealed an approximate 80% reduction in GI symptoms at the end of treatment, including significant improvements with regards to symptoms of constipation, diarrhoea, indigestion, and abdominal pain. Improvements persisted for eight weeks after treatment. Similarly, clinical assessments showed that behavioural ASD symptoms decreased significantly and remained at this level for eight weeks after treatment ended. Bacterial and phage-deep sequencing analyses revealed successful partial engraftment of donor microbiota and beneficial changes in the gut environment. Specifically, overall bacterial diversity and the abundance of *Bifidobacterium*, *Prevotella*, and *Desulfovibrio*, among other taxa, increased following MTT, and these changes persisted after treatment was stopped (patients were followed for eight weeks).

WHAT IS ALREADY KNOWN ABOUT THIS TOPIC?

Autism spectrum disorders (ASD) are common, affecting 1-2% of children worldwide. The underlying mechanisms are believed to involve both genetic and environmental factors. ASD children experience various GI symptoms (constipation, diarrhoea, and bloating). Gut microbiota dysbiosis has thus been suspected and may alter the gut-brain axis, the hypophyso-pituitary adrenal axis, and the production of various compounds (serotonin, dopamine, short-chain fatty acids, etc.). A pilot study has shown an improvement under treatment with oral vancomycin, with no sustained effect. A recent study has shown an increase in Firmicutes/Bacteroidetes ratio due to a decrease in Bacteroidetes, and at the mycotic level, a non-significant increase in the *Candida* genus [2].

WHAT ARE THE MAIN RESULTS OF THIS STUDY?

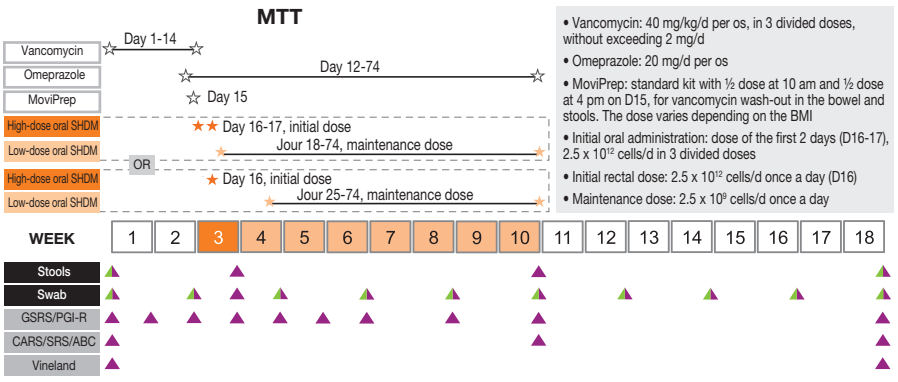
This open-label study included 18 children with ASD, aged 7-17 years, and 20 controls. The two groups were comparable in terms of age, sex, and body mass

▼ FIGURE 1

Study flowchart (from [1]).

The study consisted of Microbiota Transfer Therapy (MTT) for 10 weeks and then a follow-up period of eight weeks. The dates corresponding to samples taken (stool and rectal swab) and questionnaires completed are presented in the lower part for ASD children (purple) and controls (green).

SHDM: standardized human digestive microbiota; BMI: body mass index.



index (BMI), however, in the ASD group, there was a higher number of births by Caesarean section, an increased use of non-standard infant milk, and more allergies. The diet of ASD children and their mothers contained less fibre.

After a preparation with vancomycin for 14 days and a bowel cleanse at Day 15, ASD children received a high dose of standardized human gut microbiota (SHGM), orally or rectally, followed by a low maintenance dose of SHGM for 7-8 weeks. An anti-acid treatment with omeprazole was given from Day 12 to promote the implantation of the SHGM (**Figure 1**).

KEY POINTS

- Microbiota Transfer Therapy includes an initial digestive preparation, followed by faecal transplantation with a high initial dose and low maintenance dose, combined with a treatment involving a proton pump inhibitor (PPI).
- This treatment improved GI and behavioural symptoms in ASD children, associated with a change in gut microbiota.

This Microbiota Transfer Therapy (MTT) was well tolerated and showed an improvement in GI symptoms (constipation, diarrhoea, indigestion, and abdominal pain) which were assessed using a questionnaire (Gastrointestinal Symptom Rating Scale; reduction by 80%) in 16 out of the 18 ASD children; this effect persisted after eight weeks of follow-up. An improved bowel movement was also observed. Similarly, an improvement in ASD-related behavioural symptoms was also shown.

Initially, there was a decrease in diversity of bacteria in ASD children, compared to controls; this diversity increased after MTT and remained higher at the end of follow-up, compared to the beginning of the study. MTT also altered the relative abundance of *Bifidobacterium*, *Prevotella*, and *Desulfovibrio* (**Figure 2**).

WHAT ARE THE PRACTICAL CONSEQUENCES?

This study shows that a change in gut microbiota leads to an improvement in GI and behavioural symptoms in ASD children. However, a prolonged treatment is needed for the implantation of beneficial germs and a sustained effect. It is still early to provide therapeutic counselling. Indeed, the results of this pilot study need to be confirmed in a larger study with groups better defined in terms of GI symptoms (type and severity); the role of vancomycin, bowel cleansing, omeprazole, and SHGM in clinical improvement should also be assessed in further studies.

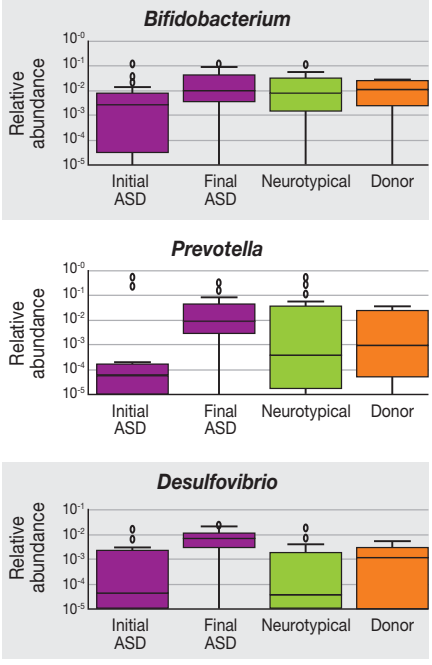
CONCLUSION

Microbiota Transfer Therapy is a promising approach in the management of ASD children and their GI disorders. Indeed, the improvement in GI and behavioural symptoms persisted for eight weeks after the end of treatment.

▼ FIGURE 2

Change in faecal microbiota after Microbiota Transfer Therapy: change in the relative abundance of bacterial genera (from [1]).

ASD: autism spectrum disorders.



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CONGRESS REVIEW

ESNM
European Society
of Neurogastroenterology
& Motility

NeuroGASTRO 2017

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FOCUS ON THE ESNM MEETINGS

EUROPEAN NEUROGASTRO-ENTEROLOGY MEETINGS

AUGUST 2017

CORK, IRELAND

HUMAN + MICROBIOTA = SUPERORGANISM

NeuroGASTRO 2017, the congress organised by the European Neurogastroenterology and Motility Society, recently took place in Cork (Ireland), a city steeped in history. The period of co-evolution between humans and their microbiota has led to a deep interpenetration of functions in a single superorganism, notably consisting of the central nervous system and microbiota [1]. Over the last five years (2011–2016), 5,651 studies on human microbiota have been published (Paul Cotter, Ireland) and there is no longer any doubt that gut microbiota plays a role in the human body (Paul O'Toole, Ireland). According to Magnus Simrén (Sweden), choosing the appropriate method to analyse the microbiome may facilitate the identification of key inter-relationships between changes in the composition of the gut microbiota and some gastroenterological symptoms. At the same time, according to Orla O'Sullivan (Ireland), we continue to overemphasise the role of drugs and do not pay enough attention to the role of the gut microbiota, lifestyle, and nutrition in disease prevention and treatment.

MICROBES IN THE PREVENTION AND TREATMENT OF DISEASE

Timothy Dinan (Ireland) mentioned the significant role played by gut microbiota on the production and metabolism of short-chain fatty acids, tryptophan, serotonin, and cytokines. The gut microbiota is now considered as an

effective factor which must be taken into account as it may be involved in the success of certain treatments, as well as in preventing various diseases. Practical examples of such approaches were presented by Marjana Rajilic-Stojanovic (Serbia) in relation to irritable bowel syndrome, Jessica Biesiekierski (Belgium) in relation to food allergies, and Hans Törnblom (Sweden) and Inge Depoortere (Belgium) in the field of nutrition, among others. The basis for treating gastroenterological patients is diet. According to Marcus Claesson (Ireland), when choosing a diet, it is important to consider its effect not only on the nature of the stool or individual symptoms, but also on the ability to positively change the composition of the intestinal microbiota. In recent years, the use of diets without FODMAPs (Fermentescible Oligo or Di or Monosaccharides and Polyols) has become widespread. However, in patients with Irritable Bowel Syndrome (IBS) with intestinal dysbiosis, the effectiveness of these diets is lower (Hans Törnblom, Sweden), with a significant decrease in the number of Bifidobacteria (Anton Emmanuel, United Kingdom) and resumption of clinical symptoms when treatment is stopped (Aspiroz Fernando, Spain).

IRRITABLE BOWEL SYNDROME AND PROBIOTICS

One of the ways in which the human microbiota can be manipulated, in an attempt to influence certain diseases, is the rational use of pre- and probiotics. Considering the strain-specific effects and the significant volume of publications now available, *Bifidobacterium infantis* 35624 garnered the greatest interest among the participants. According to the data presented by Timothy Dinan (Ireland), a meta-analysis of clinical trials indicated that *B. infantis* 35624, when compared to 12 other probiotic strains, exhibited the most favourable effects on the health of patients with IBS (reduced abdominal pain/discomfort, bloating, and/or intestinal disorders when compared to a placebo; $p < 0.05$). According to Gerald Sullivan (Ireland), maximum efficacy of *B. infantis* 35624 is achieved when used at a dose of 10^8 CFU/mg for at least four weeks. Analysis of the key properties of individual probiotic strains and identification of their mechanisms of action will allow us to better understand their potential use in disease prevention.

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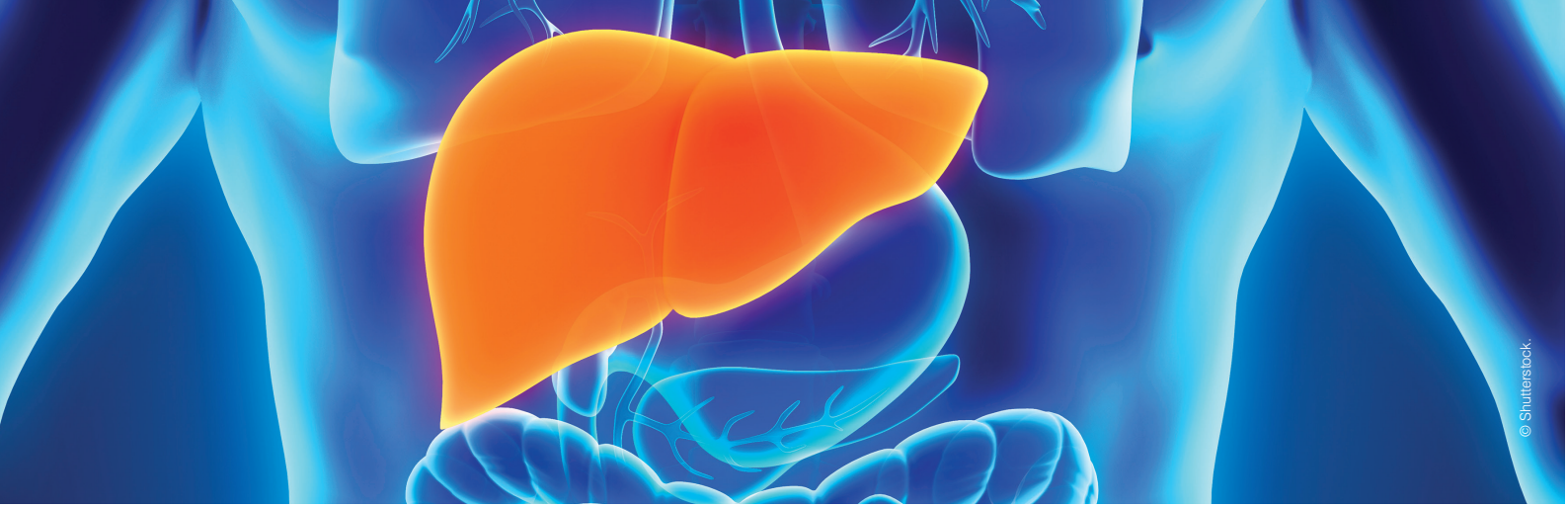

LITERATURE SELECTION

CURRENT UNDERSTANDING OF THE RELATIONSHIP BETWEEN INTESTINAL MICROBIOTA AND THE LIVER

By Prof. Ener Cagri DINLEYICI
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The intimate relationship between the liver and the gastrointestinal tract is well-known. Based on our, albeit incomplete, knowledge of the composition of intestinal microbiota and its role, numerous studies have recently been published on the potential link between gut microbiota composition and liver disease in both animals and humans. In this regard, growing evidence has shown that the gut microbiome plays a key role in liver health. Considering these findings, new strategies for the prevention and/or treatment of liver disease have begun to be evaluated.

• Non-alcoholic fatty liver disease (NAFLD)

Experimental and clinical studies have shown that gut microbiota dysbiosis is linked to NAFLD. Our increased understanding of the gut microbiota in recent years has enhanced knowledge of its metabolic and immunological potential and microbial/host interactions, primarily in the gut, but also in the liver and other organs. For this reason, the intestinal microbiota has become a target for therapeutic interventions in the management of NAFLD, and probiotics have been suggested as a treatment for NAFLD. Understanding the mechanism of action of probiotics in the treatment of NAFLD remains underdeveloped, although experimental studies have shown a direct modulation of intestinal microbiota with the administration of probiotics. The first experimental study to use probiotics showed an improved histological aspect of the liver, reduced hepatic lipids, and reduced liver enzymes [1]. Experimental studies have also shown that probiotics are effective in reducing hepatic lipid content, inflammation and endotoxemia, as well as serum lipid parameters. Some limited but promising studies have shown that probiotics may play a role in the treatment of NAFLD, however, there are currently no official recommendations for the routine use of probiotics or consensus on probiotic strain(s), dosage, or duration of treatment.

• Acute drug-induced liver failure

Another recent study showed that probiotics may play a role in the prevention of acute liver failure. The main causes of acute liver failure are drug use, viral infections, and auto-immune diseases. Regardless of aetiology, acute liver failure can be associated with high morbidity and mortality. Lei Yu and colleagues, from Guizhou Medical University in China, pu-

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blished their recent experimental studies in *Scientific Reports* in May 2017 [2]. The authors evaluated the potential protective effects of *Saccharomyces boulardii* CNCM I-745 on D-galactosamine-induced liver injury in mice, and showed that *S. boulardii* CNCM I-745 induces changes in gut microbial composition and alleviates acute liver failure.

• Faecal microbiota transplantation for hepatic encephalopathy

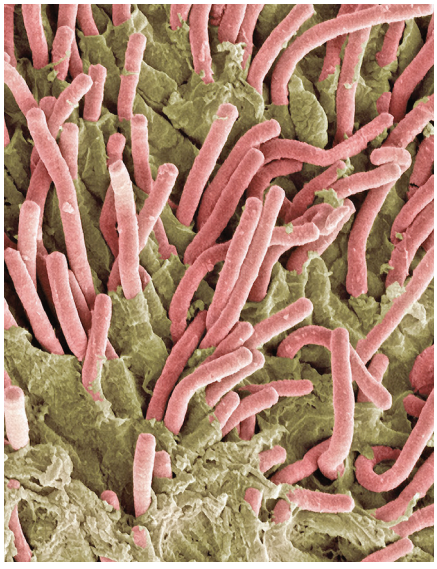
Jasmohan S. Bajaj and colleagues recently published their research on faecal microbiota transplantation (FMT) in patients with hepatic encephalopathy, in *Hepatology* journal (June 2017). Liver cirrhosis is the end-stage condition of liver disease and hepatic encephalopathy can be observed during the disease and recur despite standard treatment options. Previous studies have shown impaired/changed microbiota composition in patients with hepatic encephalopathy. This is the first randomized prospective study among cirrhotic patients on the use of FMT with a single, rationally identified donor for patients with hepatic encephalopathy. Bajaj *et al.* investigated the clinical outcomes of 20 cirrhotic patients with hepatic encephalopathy based on a comparison between a group receiving FMT, preceded by antibiotic treatment, and a standard-of-care treatment group between October 2015 and July 2016. Despite some limitations, this study demonstrated that faecal transplantation from a rationally selected donor was "safe" and was associated with a lower hospitalization rate and improved cognitive tests among cirrhotic patients with recurrent hepatic encephalopathy [3].

Recent studies on the link between intestinal microbiota composition and liver diseases have shown that modulation of the intestinal microbiota could be a treatment option for liver diseases. Further randomized clinical trials assessing specific probiotic strains or FMT are needed before these strategies can be recommended for treatment.

NEW HOPE FOR CANCER PATIENTS: TARGETING MICROBIOTA

MEASURING AND/OR MODIFYING INTESTINAL MICROBIOTA COMPOSITION (MAINLY *FUSOBACTERIUM NUCLEATUM*) AS A MEANS OF IMPROVING COLORECTAL CANCER TREATMENT

Colorectal cancer is one of the most common malignancies in the world. Progress in disease control could be accelerated by increasing the use of screening at the age of 50 or even earlier. Surgical intervention with chemotherapy is often effective, however, relapses and resistance to treatment are regularly observed [1]. Understanding the mechanisms of chemo resistance in colorectal cancer is key to optimizing current therapeutic strategies. *F. nucleatum* is involved in the development of colorectal cancer via the fusobacterial adhesin, FadA [2, 3]. In a recent study published in *Cell* (July 2017), Wu *et al.* [4] investigated the contribution of intestinal microbiota to chemo resistance in adult patients with colorectal cancer. The tumoural microenvironment has recently been shown to play a decisive role in the chemotherapeutic response [5]. Yu *et al.* showed that *F. nucleatum* was abundant in the colorectal cancer tissues of patients who relapsed following chemotherapy and *F. nucleatum* promoted cancer resistance to chemotherapy by orchestrating a molecular network of Toll-like receptors, micro-RNAs, and autophagy. Previous experimental studies showed that the composition of the intestinal microbiota might affect local immune responses which, in turn, may have an impact on the success of chemotherapy and immunotherapy. Further strategies, including research into *F. nucleatum*, will yield valuable insights into clinical management and may improve survival for colorectal cancer patients. . *F. nucleatum* is associated with a risk of colorectal cancer recurrence, and measuring *F. nucleatum* post-surgery may be an effective approach to evaluate patient outcomes. Wu and colleagues also suggested that colorectal cancer patients with high levels of *F. nucleatum* may be treated with conventional chemotherapy in combination with anti-*F. nucleatum* treatment and/or an autophagy inhibitor [4]. Recent and ongoing clinical trials have focused on the interaction between microbiota composition and different types of cancer. Zitvogel and colleagues have suggested that future anti-neoplastic treatments could combine modulation of the microbiome with immunotherapy using more conventional approaches that directly target malignant cells [6].



Fusobacterium © SPL / BSIP.

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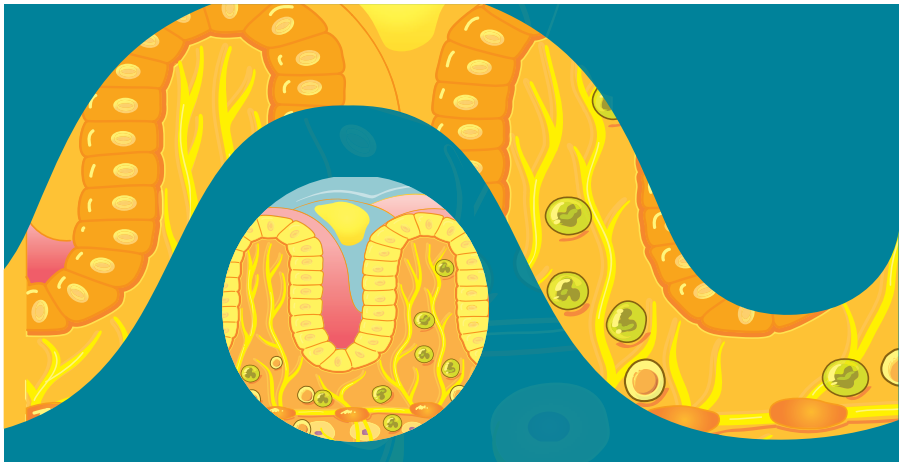
MICROBIOTA EVALUATION FOR THE DIAGNOSIS OF GASTROINTESTINAL DISORDERS: A MARKER FOR DIFFERENTIAL DIAGNOSIS?

Recent studies have shown that gut dysbiosis is associated with chronic inflammatory bowel diseases (CIBD) and Irritable Bowel Syndrome (IBS), as well as other factors such as genetic susceptibility. Evaluation of intestinal microbiota composition, thanks to next-generation sequencing, has facilitated analysis and produced reliable taxo-nomic information. New studies have aimed to define new microbiota markers for some diseases, especially gastro-intestinal disorders. Lopetuso and colleagues evaluated the differences in gut microbiota composition among symptomatic uncomplicated diverticular disease, IBS, and CIBDs in healthy adults in Italy. In accordance with previous studies, gut microbiota diversity was significantly reduced in all three disease groups, compared to healthy controls. The study showed that:



- The concentration of Bacteroidetes appeared to decrease in patients with diverticular disease, IBS and CIBD compared to healthy control subjects, in contrast to concentrations of Firmicutes and Proteobacteria which appeared to gradually increase;

- The gut microbiota composition in patients with diverticular disease was relatively similar to that of healthy adults, except for a reduction in *Bacteroides fragilis*. A similar ratio of Firmicutes:*Bacteroides* has been observed between diverticular disease and Crohn disease. *Faecalibacterium prausnitzii* was more abundant in patients with diverticular disease;

- In patients with IBS, *Clostridium difficile*, *Streptococcus spp.*, *Parabacteroides distasonis*, and *B. fragilis* disappeared, while *Dialister spp.*, followed by *F. prausnitzii*, were the most abundant species;

- In ulcerative colitis patients, Bacteroidetes and *C. difficile* were reduced, the former showing the greatest reduction in concentration, while *B. fragilis*, *Dialister spp.* and *Roseburia spp.* were increased when compared to healthy controls. It should be noted that the disappearance of *F. prausnitzii* was the main difference between the ulcerative colitis group and other groups. The second most important modification was the absence of *B. fragilis* in ulcerative colitis patients, compared to healthy controls;

- Patients with Crohn's disease demonstrated the highest level of *Proteobacteria*; *P. distasonis* was the most abundant species, followed by *Dialister spp.*, *Ruminococcus gnavus*, *C. difficile*, and *Streptococcus spp.* An increase in *R. gnavus* and decrease in *F. prausnitzii* was also demonstrated in patients with Crohn's disease.

This study revealed some differences in gut microbiota composition between patients with IBS, diverticular disease, and CIBD, and differences with healthy controls. To date, it is unclear whether these changes in intestinal microbiota composition are the cause or result of these conditions. However, the study of Lopesuto *et al.* highlights that analysis of gut microbiota, with appropriate genomic and statistical methods, should be the first step towards optimizing treatment, including the potential use of probiotics.

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CALL FOR PROPOSALS

BIOCODEX MICROBIOTA FOUNDATION

The foundation, launched last June by BIOCODEX laboratory to support research on microbiotas, has launched an international call for proposals with a budget of €200,000, the theme of which is **"Liver diseases and gut microbiota"**. The specific rules are available for download at: www.biocodexmicrobiotafoundation.com/international-call-projects-2018, and the application form must be completed and submitted by November 30, 2017.

Furthermore, national calls for proposals are being deployed in some countries. The first call for proposals is conducted in France. The theme is: **"Gut microbiota and human health"**. The specific rules are available for download at: www.biocodexmicrobiotafoundation.com/national-call-projects, and the application form must be completed and submitted by December 31, 2017.

"PRO" OF THE INTERNET

BIOCODEX MICROBIOTA INSTITUTE

The new website of the *Biocodex Microbiota* Institute **provides health professionals with scientific information** on human microbiotas, in conjunction with the "Microbiota" newsletter. **The website is enriched daily** with new news and synthesis of the most recent publications, interviews…

- **Do not hesitate to consult it regularly: www.bmi-pro.com**

MEETINGS

MEET BIOCODEX AT THE FOLLOWING CONGRESSES:

- UEGW 2017
- **OCTOBER 28-NOVEMBER 1, 2017**
- FIRA GRAN VIA, BARCELONA

- VIDEO-DIGEST
- **NOVEMBER 16-18, 2017**
- CONGRESS CENTER, PARIS

- PRACTICAL PEDIATRICS MEETINGS
- **JANUARY 26 AND 27, 2018**
- CONGRESS CENTER, PARIS

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