MICROBIOTA

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SUMMARY

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> “THE PREVALENCE OF ALLERGIES IS SIGNIFICANTLY INCREASING. THEY CURRENTLY AFFECT 20-30% OF THE WORLD’S POPULATION”

Dear Readers, over the past two decades, the prevalence of allergies has significantly increased in developed and developing countries. Overall, 20-30% of the world’s population currently suffer from allergies. This increase is of concern since children appear to be particularly affected. According to the World Allergy Organization, one in four European children suffers from an allergy. Allergic diseases are of multifactorial origin and may result from both genetic and environmental factors, thus risk factors and aggravating factors such as pollution or smoking are increasingly characterized and taken into account in preventive treatments.

In this context and knowing that the microbiota is involved in the development of immune responses, what is the role of bacterial communities in the development of allergies? For example, recent epidemiological data from several studies have shown a potential effect of Cesarean sections (*i.e.* a disruption of early colonization in the newborn) on the development of allergic asthma. To provide some answers in this newsletter, Prof. Roberto Berni Canani (Naples, Italy) and his team have analysed the level of involvement of the gut microbiota in the pathophysiology of allergy. In addition to highlighting dysbiosis in cases of food allergy or atopic dermatitis, recent studies have shown that the decrease in short-chain fatty acids, produced by the microbiota according to the diet may be involved in the development of allergy *via* the immune system.

In addition to this detailed analysis, international studies showing the presence of *Fusobacterium nucleatum* in primitive and metastatic tissues of most patients with colorectal cancer, suggesting a role in tumour progression, are discussed. In a second commented article, the adaptation mechanisms of *Escherichia coli*, a bacterium found in large proportions in children with cystic fibrosis, to a fat-rich gut environment are stressed.

The feedback on the highlights of the GUT Summit (March 10-11, Rome, Italy) and of the 25th UEGW Congress (October 28-November 1, 2017, Barcelona, Spain) provides an opportunity to be kept informed of the latest advances in research. This is also the case for the press review, which focuses on the potential promising role of the gut microbiota on the efficacy of anti-cancer treatments with immunotherapy and on the relationship between delivery mode and infant microbiota regarding the intergenerational transmission of excess weight and obesity.

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OVERVIEW

TARGETING THE GUT MICROBIOTA TO COMBAT ALLERGIES

Dysbiotic gut microbiota plays an important role in the development of allergic diseases, in particular food allergies. The gut microbiota drives the maturation and function of the immune system, and genetic, environmental, and dietary factors may alter the commensal microbiota, leading to a dysregulation of immune function. Several factors responsible for dysbiosis have been associated with the occurrence of allergies, such as Caesarean delivery, the lack of breast milk, the use of drugs (mainly antibiotics and gastric acidity inhibitors), the use of antiseptic agents, and low-fibre/high-fat diets. No specific bacterial taxa have been consistently associated with allergies, but evidence suggests that gut dysbiosis occurs even before allergies present. Short-chain fatty acids (SCFAs) are crucial gut microbiota-derived metabolites involved in cross-talk with the immune system. Targeting the composition and function of the gut microbiota represents a promising strategy against allergic diseases, in particular, against childhood food allergies.

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The prevalence, persistence, and severity of allergic diseases and, in particular, food allergies (FA), has increased substantially in recent decades in the industrialised world under the pressure of gene-environment interactions leading to immune system dysfunction, mediated, at least in part, by epigenetic mechanisms [1, 2]. This changing scenario has led to an increase in hospital admissions, medical visits, treatments, and a greater burden of care on families. All these factors have a significant impact on social costs and quality of life, and place a great psychological burden on patients and families.

Food allergies are characterised by an abnormal immune response towards dietary antigenic peptides that are normally tolerated. The cause of FAs is still largely undefined. Based on current knowledge, genetic susceptibility alone cannot account for the changing pattern of FAs and there has been a renewed interest in the role of the environment in the sensitisation to food. Evidence suggests a key pathogenetic role of gut microbiota (GM) alterations (dysbiosis) in allergy development. A healthy GM has a crucial impact on the development of the gastro-intestinal tract and immune system. A dysbiotic GM is associated with various diseases, including allergies [3].

THE IMPORTANCE OF MICROBIAL EXPOSURE FOR IMMUNE TOLERANCE

The way in which dietary antigens are normally rendered non-immunogenic through immune tolerance has not yet been fully defined. Evidence suggests a pivotal role for regulatory T cells (Tregs) expressing the

transcription factor Foxp3 (Foxp3$^+$Tregs) and the complex interaction between the GM and immune and non-immune cells. The presence of both diet-and microbe-induced populations of Treg cells is required for full tolerance to food antigens [4]. During vaginal delivery, infants receive their first bacterial inoculum from the maternal vaginal tract, skin tissue, and often from faecal matter, exposing the immature immune system to a significant bacterial load [3]. The maturation of a healthy GM in early life allows for a change in the Th1/Th2 balance, favouring a Th1 cell response, while dysbiosis alters host-microbiota homeostasis, producing a shift in the Th1/Th2 cytokine balance towards a Th2 response [5]. Tregs are depleted in germ-free mice and in mice receiving an amino acid-based diet [4, 6]. Secretory IgA (sIgA) and innate immunity peptides exert a pivotal role in regulating GM composition. Deficiency in both innate and adaptive immunity (especially low levels of IgA) has been observed in children with multiple FAs [7]. A healthy GM promoting sIgA production facilitates the survival of protective bacterial strains within the gut lumen [8].

THE GUT MICROBIOTA AND ALLERGIES

The expression of an allergic phenotype is dependent on the interaction between two major factors: genetic predisposition and gene-environment interactions. An increasing number of studies suggests a correlation between factors that alter the GM in the first years of life and the development of allergies later in life. There is increasing evidence that early-life GM dysbiosis represents a critical factor underlying the development of allergies. The main factors responsible for dysbiosis are: birth by Caesarean section, lack of breast milk, drug use (mainly antibiotics and gastric acidity inhibitors), antiseptic agent use, timing of the introduction of solid foods, and junk food-based and/or low-fibre/high-fat diets [3, 9]. The maternal use of antibiotics before and during pregnancy, as well as antibiotic treatments during the first months of life, are also reported to be associated with an increased risk of cow's milk allergies (CMA) in children [10]. Data that may be used to characterise the microbiota of patients with FAs are still preliminary. We recently described GM dysbiosis in children affected by IgE-mediated CMA; CMA infants had significantly reduced levels of Bifidobacteriaceae, Streptococcaceae, Enterobacteriaceae, and Enterococcaceae, and presented significantly higher levels of selected strains from Ruminococcaceae and Lachnospiraceae families. The GM of subjects with CMA comprised 73% Bacteroidetes and Firmicutes taxa, which are also known to dominate the adult gut [11]. Although compelling evidence for an association between GM dysbiosis and FAs is emerging, heterogeneity in study design (involving sampling time points, the methods used to characterise microbiota, and allergic phenotypes studied) has made it difficult to establish a causal relationship between specific bacterial taxa and the development of allergies. No specific bacterial taxa have been consistently associated with FA and a broad range of microbes isolated from the human gut may be involved in tolerogenic mechanisms. The main evidence for allergy-associated GM is summarised in **Table 1**.

THE GUT MICROBIOTA PLAYS A CENTRAL ROLE IN THE PATHOGENESIS OF ALLERGIES

Evidence suggests that the gut microbiota-epigenetics axis, modulated by a number of environmental and dietary factors, plays an important role in the occurrence of allergies. This axis regulates a number of non-immune and immune tolerogenic mechanisms, and could be the ideal target for innovative, preventive, and therapeutic strategies against allergies.

▼ **TABLE 1**

The main features of gut microbiota associated with allergies.

Study	N	OTUs	Diversity	Main features
Adlerberth *et al.* 2007	324: S, AD	N.R.	N.R.	No differences
Thompson-Chagoyan *et al.* 2010	46: FA	↑	N.R.	• *Lactobacilli* ↑ • *Bifidobacteria* ↓
Thompson-Chagoyan *et al.* 2011	46: FA	↑	N.R.	• *C. coccoides*, cluster *Atophium* ↑
Van Nimwegen *et al.* 2011	1,000: AD, asthma, S	N.R.	N.R.	• *C. difficile* ↑
Nakayama *et al.* 2011	11 : FA	=	=	• *Bacteroides, Propionibacterium, Klebsiella* ↑ • *Acinobacterium, Clostridium* ↓
Penders *et al.* 2013	571: AD	N.R.	N.R.	• *Clostridium* cluster I ↑
Abrahmsson *et al.* 2013	47 : asthma, rhinocongiuntivitis, AD	=	↓	No differences in *phyla* and genera
Ling *et al.* 2014	34: FA	↓	=	• *Bacteroidetes, Proteobacteria, Actinobacteria* ↑ • *Firmicutes* ↓
Azad *et al.* 2015	12: F S	↓	=	• *Enterobacteriaceae, Bacteroidaceae* ↓
Chen *et al.* 2015	23: S	N.R.	↓	• *Firmicutes, Proteobacteria, Actinobacteria* ↑ • *Bacteroidetes* ↓
Arrieta *et al.* 2015	223: S, asthma	=	=	• *Faecalibacterium, Lachnospira, Rothia, Velionella* ↓
Tang *et al.* 2016	15: AD	N.R.	N.R.	• *Campylobacter* ↑ • *Roseburia* ↓
Inoue *et al.* 2017	4: FA	N.R.	N.R.	• *Dorea, Akkermansia* ↓ • *Lachnospira, Vellionella, Suterella* ↑

OTUs: operational taxonomic units; AD = atopic dermatitis; FA = food allergy; FS = sensitisation to food antigens; S = sensitisation to aeroallergens or food allergens; N.R. = not reported

TABLE 2 **A summary of preclinical evidence for the use of probiotics against allergies.**

Biological effects		Bacterial strain	References
Maturation of the Intestinal Barrier		*Bifidobacterium* *Lactobacillus rhamnosus GG*	a; b; c; d
Immune response modulation; Th1/Th2 balance	**Th1 production**	*Bifidobacterium lactis/bifidum* *Lactobacillus acidophilus/reuteri* *Lactobacillus rhamnosus GG*	e; f; g
	Th2 suppression	*Bifidobacterium bifidum/infantis/longum* *Lactobacillus acidophilus/reuteri* *Lactobacillus rhamnosus GG* *B. clausii*	h; i; j; k
Regulation of the immune system	**Regulatory T (Treg) cell development**	*Bifidobacterium bifidum/infantis/lactis* *Lactobacillus acidophilus/reuteri/casei* *Lactobacillus rhamnosus GG*	h; g; j; l; m; n
	Tolerogenic dendritic cell development	*Bifidobacterium bifidum* *Lactobacillus reuteri/casei* *Lactobacillus rhamnosus GG*	h; o; p; n
Immunomodulation: suppression of immunoglobulin type E production		*Bifidobacterium bifidum/longum* *Bifidobacterium lactis Bb-12* *Lactobacillus acidophilus* *Lactobacillus rhamnosus GG*	j; q; r; s; f
Epigenetic modulation of Th1/Th2 gene expression		*Bifidobacterium breve* *Lactobacillus rhamnosus GG*	t

a: Sudo *et al.* 1997; b: Isolauri *et al.* 1996; c: Malin *et al.* 1997; d: Kaila *et al.* 1992; e: Kim *et al.* 2008; f: Torii *et al.* 2007; g: Maassen *et al.* 2000; h: Niers *et al.* 2005; i: Takahashi *et al.* 2006; j: Kim *et al.* 2008; k: Ciprandi *et al.* 2004; l: Sistek *et al.* 2006; m: Hart *et al.* 2004; n: Smits *et al.* 2005; o: Mohamadzadeh *et al.* 2005; p: Braat *et al.* 2004; q: Akahashi *et al.* 2006; r: Gill *et al.* 2008; s: Borchers *et al.* 2009; t: Ghadimi *et al.* 2012.

SCFAs are major GM metabolites involved in cross-talk with human cells. Among the SCFAs, butyrate exerts a pivotal role in the induction of immune tolerance, and butyrate deficiency has been observed in allergic patients [4]. The different types of dysbiosis may be hypothesised to lead to similar effects in terms of SCFAs, and/or the production of other microbiota-derived metabolites may facilitate the occurrence of allergies. Clostridia species, belonging to Cluster IV and XIVa, are the prominent source of SCFAs in the colon. Bacteria-produced SCFAs have been implicated in the regulation of both the proportion and functional capability of Tregs, which, in some studies, have been specifically attributed to butyrate production by spore-forming Clostridiales. An enrichment of taxa from the Clostridia class and Firmicutes phylum has been observed in human subjects with resolution of CMA [9]. Data from our laboratory showed that oral butyrate treatment leads to a dramatic inhibition of acute allergic skin response, anaphylactic symptom scores, reduced body temperature, increased intestinal permeability, and anti-βLG lactoglobulin (BLG) IgE, IL-4, and IL-10 production in a murine model of CMA, suggesting a protective role of butyrate against FAs [9]. Butyrate exhibits multiple mechanisms of action, however, many of these involve epigenetic regulation of gene expression through the inhibition of histone deacetylase (HDAC). The inhibition of HDAC9 and 6 increases *FoxP3* gene expression, as well as the production and suppressive function of Tregs [12]. We evaluated the direct effects of butyrate on peripheral blood mononuclear cells (PBMCs) from children affected by challenge-proven IgE-mediated CMA. PBMCs were stimulated with BLG in the presence or absence of butyrate. Preliminary results show that butyrate stimulates IL-10 and IFN-γ production and decreases the rate of DNA methylation of these two cytokines. The same effective butyrate dose induces demethylation of the FoxP3 promoter region and down-regulation of HDAC6/HDAC9 expression [2].

HOW TO MODULATE THE GUT MICROBIOTA?

Emerging evidence supports the use of selected dietary strategies and probiotic strains for the prevention and treatment of allergies (**Table 2**).

MODULATION OF THE GUT MICROBIOTA ASSOCIATED WITH ALLERGIES

Children exposed to farm environments have a lower risk of allergy development. Although it has not been conclusively proven, one of the plausible explanations for the protective effect associated with early-life farm exposure is the role of the GM, because individuals exposed to a farm environment possess a different microbial composition relative to those with other lifestyles [3]. Other epidemiological factors which protect against FAs include older siblings and exposure to pets in early life. Pet ownership is associated with high microbial diversity in the home environment. A recent study examining the influence of dietary patterns on the development of FAs at the age of two suggests that dietary habits may influence the development of FAs by changing the composition of the gut microbiota. In particular, an infant diet consisting of high levels of fruits, vegetables, and home-prepared foods was associated with less FAs [9] (**Figure 1**).

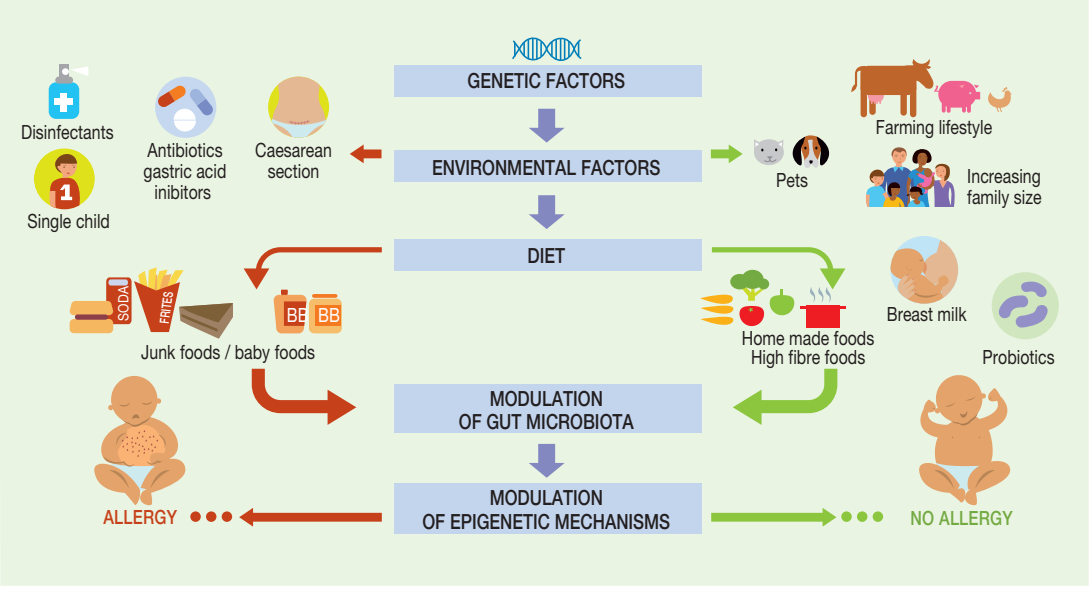

FIGURE 1

The gut microbiota as a target for intervention against allergy.
Several environmental and dietary factors may modulate the diet-microbiota-epigenetics axis, influencing the occurrence of allergies.

Probiotics, defined as ingested microbes that provide health benefits to the host, may be beneficial by modulating the GM [13]. Evidence of probiotic use against respiratory allergies remains preliminary (**Table 2**). However, meta-analyses have revealed that the use of selected probiotics, from gestation through to the first six months of life, could reduce the incidence of atopic eczema in children with a family history of allergic disease [14].

We have previously demonstrated that addition of the probiotic, L. rhamnosus GG (LGG), to a hypoallergenic formula accelerates the acquisition of immune tolerance and protects against the occurrence of other atopic manifestations in children with CMA [15-17]. When we compared the faecal microbiota among infants receiving this tolerance-inducing probiotic therapy, we found significant positive correlations between the abundance of genera with a potential to produce butyrate and the concentration of faecal butyrate [11]. Strain-level demarcations for butyrate-producing genera (including Roseburia, Coprococcus, and Blautia), identified in infants who acquired tolerance to cows' milk, suggest that LGG treatment contributes to the acquisition of tolerance by altering the strain-level community structure of taxa with a potential to produce butyrate [11]. Accordingly, oral immunotherapy supplemented with another L. rhamnosus strain (CGMCC 1.3724) has been shown to be effective in inducing peanut non-responsiveness in 82% of allergic children [18].

CONCLUSION

The trillions of bacteria that populate our gut critically regulate key physiological functions against allergies. Environmentally induced changes in GM composition and function (decreased butyrate production, for example) create dysbiosis that is linked to an increased risk of allergy. Understanding how gut bacterial communities interact with the immune system is opening the way to novel preventive treatment strategies for allergies.

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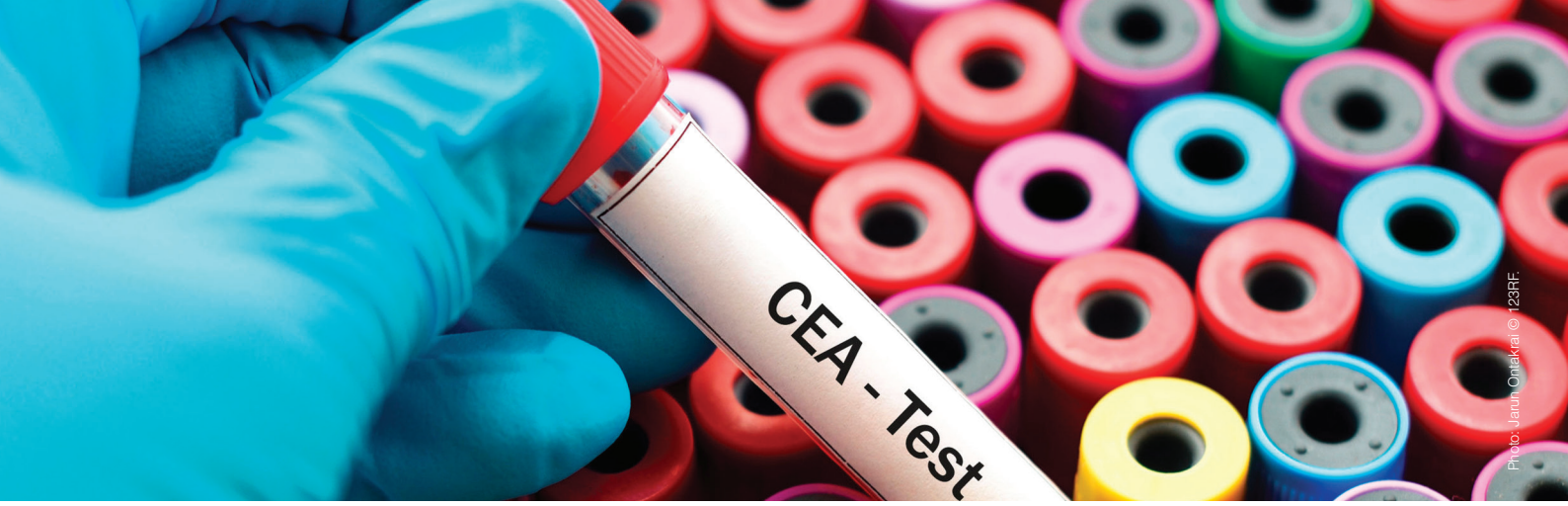

COMMENTED ARTICLE
ADULTS' SECTION

By Prof. Harry Sokol
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THE ROLE OF *FUSOBACTERIUM* IN COLORECTAL CANCER

Comments on an original article by Bullman et al. (Science 2017) [1]

Colorectal cancers (CRCs) comprise a complex mixture of malignant cells, non-transformed cells, and microorganisms. *Fusobacterium nucleatum* is one of the most prevalent bacterial species in CRC tissues.

Here, the authors show that colonisation of human CRC with *Fusobacterium* and its associated microbiome (including the *Bacteroides, Selenomonas* and *Prevotella* species) is maintained in distal metastases, demonstrating microbiome stability between paired primary and metastatic tumours. *In situ* hybridisation analysis revealed that *Fusobacterium* is mainly associated with cancer cells in metastatic lesions. In mouse xenografts of human primary colorectal adenocarcinomas, *Fusobacterium* and its associated microbiome remains viable despite successive passages. Treatment of CRC xenografted mice with metronidazole, an antibiotic, reduces *Fusobacterium* load, cancer cell proliferation, and overall tumour growth.

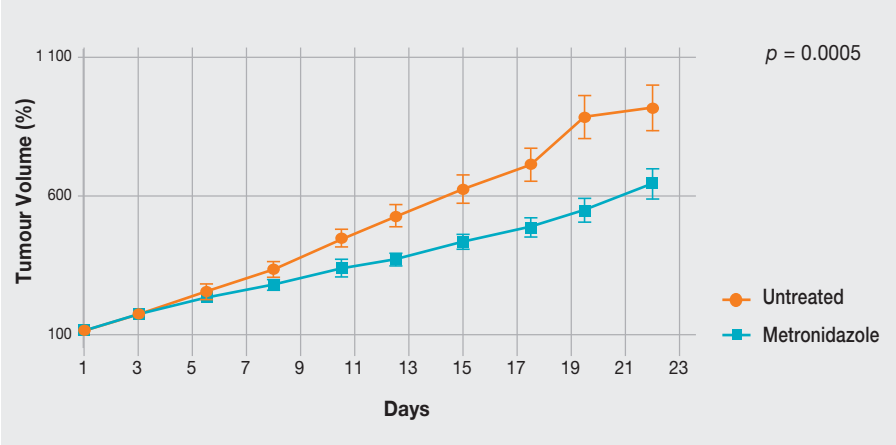
These observations should prompt further investigation of antimicrobial interventions as a potential treatment for patients with *Fusobacterium*-associated CRC.

WHAT IS ALREADY KNOWN ABOUT THIS TOPIC?

Cancer-associated microbiota is known to influence cancer development and progression, including CRC. The microbiota of CRC patients is dysbiotic, and several studies conducted without any preconceptions have revealed an enrichment in *F. nucleatum* in tumour tissues and adenomas compared to non-cancerous colonic tissues [2]. These findings have been confirmed in studies conducted worldwide based on several cohorts of CRC patients. High levels of *F. nucleatum* have been associated with less T-cell tumour infiltration (T-cell infiltration is, however, a factor of good prognosis) [3], advanced disease, and a lower rate of patient survival. In addition, patients with *F. nucleatum*-associated CRC often presented with a right colonic location of cancer, *BRAF* mutation, and microsatellite instability. Studies based on various experimental models have suggested a protumourigenic role of *Fusobacterium*, which potentiates tumour growth in mouse models of CRC, xenografts derived from CRC cell lines, and *in vitro* CRC cell lines. The suggested mechanisms range from increased adhesion and invasion of tumour cells to modulation of the host immune response or ac-

▼ FIGURE 1

Tumour volume (in %) in mice with Fusobacterium-positive tumours, treated or not treated with metronidazole (adapted from [1]).
Metronidazole treatment of mouse xenografts of human colorectal cancer cells reduces growth of tumours colonised by *Fusobacterium*.



KEY POINTS

- *Fusobacterium* is present in a viable form in primary and metastatic tissues in most CRC patients.
- When present, *Fusobacterium* promotes tumour growth.
- In murine models, antibiotic treatment targeting *Fusobacterium* significantly reduces the growth of *Fusobacterium*-positive tumours.

tivation of the Toll-like receptor 4 pathway. However, some animal or cellular studies have shown no carcinogenic effects of Fusobacterium [4].

WHAT ARE THE MAIN RESULTS OF THIS STUDY?

To explore the role of *Fusobacterium* and its associated microbiota in CRC, the authors analysed the microbiota of five independent cohorts of CRC patients. For frozen samples (11 cases), the culture-based detection of *Fusobacterium* was positive in more than 70% of cases, showing that the bacterium was alive within the tumour tissue. Furthermore, when metastatic tissue was available and of good quality, *Fusobacterium* was also detected using culture methods. The molecular method (qPCR) demonstrated greater sensitivity, with more than 80% and more than 60% positivity for primary and metastatic tissues, respectively. The *Fusobacterium* identified in metastatic tissues was the same as that identified in the primary lesion. In addition to *Fusobacterium*, other bacteria with the same profile were identified, such as *Bacteroides fragilis* or *Bacteroides thetaiotaomicron*, however, unlike *Fusobacterium*, the strains identified in metastases were different from those identified in the primary lesion. In a cohort of 77 patients, the authors observed that there was no link between positive *Fusobacterium* culture and tumour recurrence. To determine whether the presence of *Fusobacterium* plays a role in carcinogenesis or is only passively involved in the oncogenic process, the authors used several systems, including human tumour cell xenografts in immunodeficient mice. They observed that *Fusobacterium*-positive tumours were easily implanted in mice while this was not the case for *Fusobacterium*-negative tumours. Finally, treatment with metronidazole, a highly active antibiotic targeting *Fusobacterium*, significantly reduced tumour growth (**Figure 1**).

WHAT ARE THE PRACTICAL CONSEQUENCES?

The treatment of metastatic CRC remains a major clinical issue. This study shows that some bacteria of the microbiota, especially those belonging to the *Fusobacterium* genus, continue to be viable in both the primary tumour and metastatic tissues in most patients, and play a role in CRC progression. The use of antimicrobial treatments targeting these bacteria is therefore a strategy to be considered, while trying to be as specific as possible, because other bacteria may play a protective role or be involved in the response to conventional anticancer therapies and immunotherapies [5].

CONCLUSION

Based on several independant cohorts, this study shows that *Fusobacterium* is present in a viable form in primary and metastatic tissues in the majority of CRC patients, and is suggested to play a role in promoting tumour progression. These observations should prompt further investigation of antimicrobial interventions as a potential treatment for patients with *Fusobacterium*-associated CRC.

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COMMENTED ARTICLE
CHILDREN'S SECTION

By Prof. Emmanuel Mas
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ADAPTATION OF COMMENSAL *ESCHERICHIA COLI* IN THE INTESTINAL TRACT OF YOUNG CHILDREN WITH CYSTIC FIBROSIS

Comments of the original article by Matamouros et al. (Proc Natl Acad Sci USA 2018) [1]

The mature human gut microbiota is established during the first years of life, and altered intestinal microbiomes have been associated with several human health disorders. *Escherichia coli* usually represents less than 1% of the human intestinal microbiome, whereas in cystic fibrosis (CF), greater than 50% relative abundance is common and correlates with intestinal inflammation and faecal fat malabsorption. Despite the proliferation of *E. coli* and other Proteobacteria in conditions involving chronic gastrointestinal tract inflammation, little is known about adaptation of specific characteristics associated with microbiota clonal expansion.

This study shows that *E. coli* isolated from faecal samples of young children with CF has adapted to growth on glycerol, a major component of faecal fat. *E. coli* isolates from different CF patients demonstrate an increased growth rate in the presence of glycerol compared with *E. coli* from healthy controls, and unrelated CF *E. coli* strains have independently acquired this growth trait. Furthermore, CF and control *E. coli* isolates have differential gene expression when grown in minimal media with glycerol as the sole carbon source. While CF isolates display a growth-promoting transcriptional profile, control isolates engage stress and stationary-phase programmes, which likely results in slower growth rates. These results indicate that there is selection of unique characteristics within the microbiome of individuals with CF, which could contribute to individual disease outcomes.

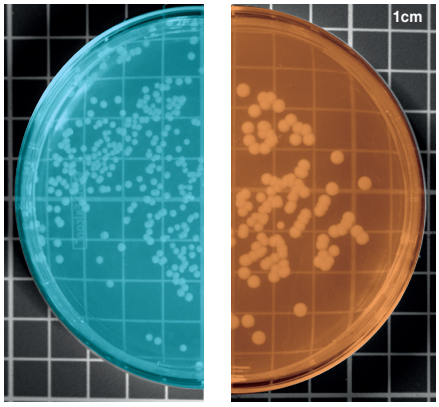
WHAT IS ALREADY KNOWN ABOUT THIS TOPIC?

The main digestive issue in cystic fibrosis (CF) is exocrine pancreatic insufficiency. This is present in 85% of cases and requires supplementation with pancreatic extracts. Despite this supplementation, fat malabsorption may persist. The proportion of *Escherichia coli* (*E. coli*) in the human gut microbiome is usually less than 1% but may reach up to 70-80% in patients with CF. There is clonal expansion within a given patient, but the strains are different between patients, which suggests an adaptation of *E. coli* to its environment. Some strains of *E. coli* are involved in gut inflammation and colorectal cancer (CRC). According to recent data, digestive inflammation, dysbiosis, or an increased risk of CRC may be associated with CF.

The authors have assumed that a selection of *E. coli* strains exist in patients with CF, as these strains are capable of surviving in a gut environment containing excess fat and abnormal mucus.

▼ FIGURE 1

Accelerated growth of *Escherichia coli*, isolated from stools of cystic fibrosis (CF) children, in minimal medium supplemented with glycerol (GlyMM) (adapted from [1]).



WHAT ARE THE MAIN RESULTS OF THIS STUDY?

E. coli was isolated from the stools of six young children with CF and two controls. The authors assessed the growth of these bacteria in a minimal medium for which the only source of carbon was glucose (GluMM) or glycerol (GlyMM) supplementation. *E. coli* growth was faster in GlyMM plates for strains isolated from CF children compared to those isolated from controls (**Figure 1**). These differences were not observed under anaerobic conditions. Since the gut environment is essentially anaerobic, oxygen may play an important role, and in the vicinity of the epithelium, the oxygen gradient is minimal.

Genetic analysis has shown that the *E. coli* strains were distinct. In addition, the eight isolates had more than 11,000 SNPs (*single nucleotide polymorphisms*) present in one or more children with CF, which were absent in controls. Transcriptomic analysis (RNA-sequence analysis) in the GluMM or GlyMM medium was performed on isolates from two CF children and two controls. These isolates were selected due to their growth in GlyMM medium and their position within the phylogenetic tree. Among the genes expressed differentially, 213 were overexpressed (glycerol absorption and metabolism) and six were under-expressed (glucose cell transport) in GlyMM medium, in a similar way in both CF children and controls. In GluMM medium, only 20 genes were expressed differentially between CF children and controls, compared to 405 genes in GlyMM medium (377 genes were not induced in CF children) (**Figure 2**). The genes that were under-expressed in CF in GlyMM medium encode proteins involved in stress, acid resistance, and biofilm formation; the genes overexpressed in CF or under-expressed in controls encode proteins involved in growth mechanisms. In CF, the increased growth in GlyMM medium is not related to metabolic reprogramming, but to a loss of growth inhibition and a stress response.

WHAT ARE THE PRACTICAL CONSEQUENCES?

This study leads to an understanding of the mechanisms involved in CF-associated dysbiosis with regards to *E. coli*. In order to correct this dysbiosis and limit, at least in part, gut inflammation, it is important to optimise the absorption of intestinal fat to ensure reduced glycerol levels.

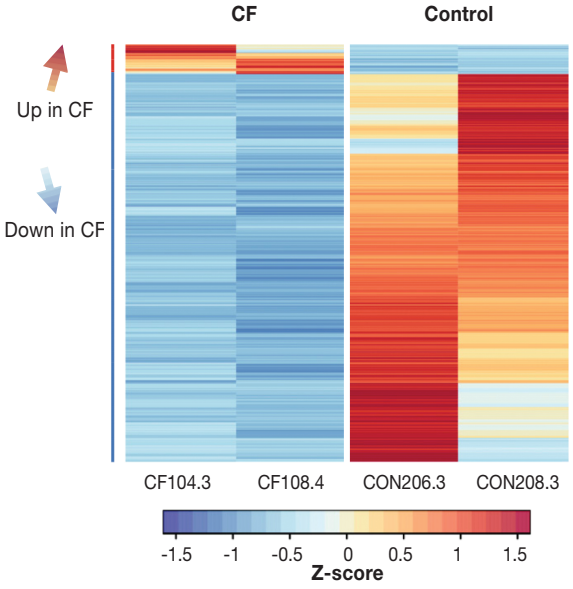
An improvement in the intestinal barrier, especially with regards to mucus for this disease, may also reduce the availability of oxygen necessary for the growth of these *E. coli* strains.

KEY POINTS

- Gut dysbiosis may be observed in CF. In particular, there is a significant increase in *E. coli* levels.
- Due to fat malabsorption, intestinal glycerol levels are increased. In CF, selected strains of *E. coli* are adapted to these conditions with differentially expressed genes and a loss of growth inhibition.

CONCLUSION

In CF, the high intestinal level of glycerol due to fat malabsorption results in *E. coli* adaptation with clonal proliferation. Understanding these mechanisms may allow us to develop new therapeutic approaches and improve patient management.



◀ FIGURE 2

Genes differentially expressed between *Escherichia coli* isolated from stools of cystic fibrosis children and controls, in minimal medium supplemented with glycerol (GlyMM) [1].

CF: cystic fibrosis

Reference

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CONGRESS REVIEW

UNITED EUROPEAN GASTROENTEROLOGY ueg week

By Dr. Aldo Maruy Saito
Paediatric gastroenterologist, Cayetano Heredia Hospital / Cayetano Heredia University in Peru, Lima, Peru

2017 UEG WEEK

UNITED EUROPEAN GASTRO-ENTEROLOGY BARCELONA

OCTOBER-NOVEMBER 2017

BARCELONA

The 25th edition of the UEG WEEK was held in Barcelona between October 28 and November 1, 2017. The scientific programme of the event reflected the growing interest in gut microbiota (GM) and its importance relative to gastrointestinal disorders, a topic that was the subject of many sessions and multiple posters. The event was a success given the large number of participants in the scheduled sessions.

GM COMPOSITION AND FUNCTIONS

Dr. Ralijic-Stojanovic stressed that sequence analysis of 16S rRNA has made it possible to confirm that the taxonomy of many cultured intestinal microorganisms was incorrect. For example, *Clostridium difficile*, which does not belong to the *Clostridium butyricum* genus, is in fact a distant relative of *Clostridium perfringens*, in contrast to what was previously assumed [1]. Dr Ralijic-Stojanovic recalled that between the ages of 7 and 12 years, the GM is still different to that in adults. He concluded by stressing that GM composition is individual, specific, and stable, and may vary depending on age, diet, and lifestyle.

In his presentation, Dr. Bäckhed reported that, while the role of the GM in metabolism is well known (optimisation of caloric availability, intake of enzymes absent in humans, and the role in vitamin K synthesis and short-chain fatty acid production), some more recent publications have revealed that the level of butyrate-producing bacteria is reduced in patients with type 2 diabetes, increased levels of *Prevotella* improve glucose metabolism, and *Christensenellaceae* bacteria may be considered as an anti-obesogenic probiotic [2]. Dr. Bäckhed concluded that the GM should be considered as an environmental factor that contributes to host physiology and metabolism.

The GM is very complex, and despite the advances in recent years, all its secrets are yet to be revealed.

GM AND LIVER DISEASES

The role of the GM in liver diseases is being increasingly understood, and some authors have even suggested the existence of a "gut-liver axis". Dr. Gasbarrini discussed the role of GM in liver inflammation and fibrosis, showing that severe alterations in GM have been observed in cirrhotic patients, with increased levels of *Enterobacteriaceae*, *Veillonellaceae*, and *Streptococcaceae*, and decreased levels of *Clostridiacea*, *Lachnospiraceae*, and *Eubacteriaceae*. Dr. Gasbarrini believes that an insufficient resilience, resulting in adaptation through the acquisition of a dysbiotic microbiota, may contribute to the onset of GM-associated chronic diseases. Intestinal barrier breakdown is the cornerstone to progression of fibrosis and severity of liver cirrhosis.

Another interesting aspect was also discussed: depending on the mechanism underlying liver injury, the GM may induce or prevent hepatic fibrosis. Possible ways to restore a healthy GM include GM modulation (diet, rifaximin, probiotics or prebiotics) or "reinitialisation" through faecal microbiota transplantation.

Dr. Kobyliak presented a poster [3] on a study conducted in patients with non-alcoholic fatty liver disease (NAFLD), who received a probiotic combined with flaxseed oil and wheat germs or a placebo for eight weeks. The results show that the concomitant administration of probiotics and omega 3 reduces liver fat and serum lipid levels, improves the metabolic profile, and reduces the chronic inflammatory state. Dr. Kobyliak concluded that modulating the GM through the use of probiotics is a new option in the management of NAFLD.

⁘ This confirms the influence of the GM on liver diseases and the possibility of alternative solutions through the use of probiotics.

GM AND CHRONIC INFLAMMATORY BOWEL DISEASES (CIBD)

CIBDs are a heterogeneous group of immune-mediated chronic inflammatory diseases that affect the gastrointestinal tract. There are two main phenotypes of CIBD: ulcerative colitis (UC) and Crohn's disease (CD). The relationship between the GM and CIBD is the subject of a growing number of publications.

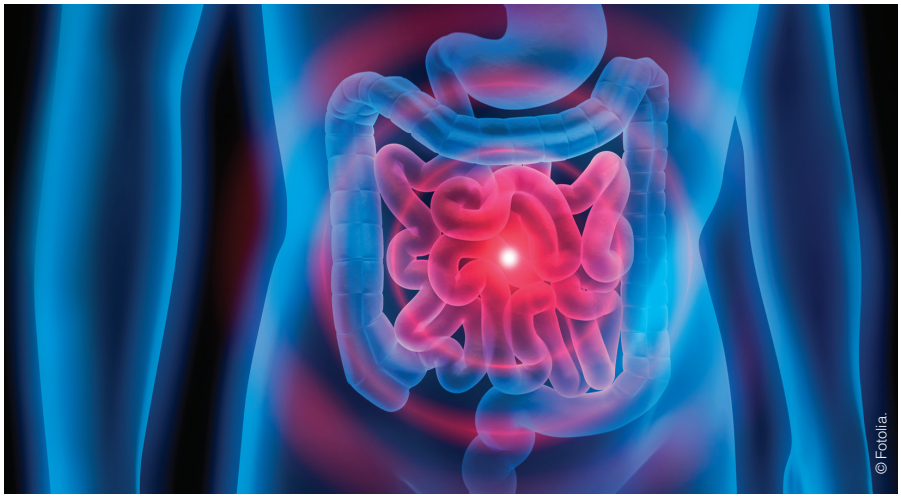
Dr. Sokol discussed the pathogenesis of CIBDs and the fact that they are mediated by activation of the immune system through the GM in sensitive hosts under the influence of the environment. CIBD patients are known to have an abnormal microbiota with reduced diversity, which becomes increasingly reduced when the disease is active. Dr. Sokol stressed that there is an increase in proteobacteria and a decrease in Firmicutes, which may or may not be correlated with the onset of disease. Thus, the level of adherent/invasive *E. coli* (proteobacteria) is significantly increased in CD patients, but not in UC patients or healthy subjects. On the other hand, the level of *Faecalibacterium prausnitzii* (Firmicutes), which has anti-inflammatory effects, is decreased in CIBD patients.

The environmental impact on GM is well known (mode of delivery, diet, antibiotics) and could also affect CIBD. Based on a report of a Danish cohort, Hviid *et al.* [4] observed a correlation between the number of antibiotic cycles received by a child and the risk of developing CIBD, which is greater for CD than UC.

Regarding pathogenesis, current controversy focuses on whether changes in the GM cause inflammation or vice versa; which came first: the chicken or the egg? Dr. Sokol believes that they are both at the same level, since the clinical manifestations of CIBD occur due to the implementation of a vicious circle between the GM and inflammation, and both may be the cause.

The data provided thus confirm the important role of GM bacteria in the pathogenesis of CIBD; however, our knowledge of the role of fungal GM in the pathogenesis of these diseases is limited. In this regard, Qiu *et al.* presented a poster [5] setting out the 15 main genera of fungi found in UC patients and healthy subjects (controls). For the *Wickerhamomyces*, *Sterigmatomyces*, and *Penicillium* genera, a positive correlation was observed with the expression of pro-inflammatory cytokines in the colonic mucosa, while the correlation was negative for *Nigrospora*. The authors concluded that the colonic fungal microbiota of UC patients is different to that of control subjects and that its alterations may be associated with mucosal inflammation and pathogenesis of UC.

⁘ Differences between the pathogenesis of CD and that of UC may be explained, in some cases, by the presence of a bacterial or fungal alteration of the GM.



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GUT MICROBIOTA FOR HEALTH
World Summit 2018

SATURDAY 10 AND SUNDAY 11 MARCH, 2018

ROME (ITALY)

BARCELÓ ARAN MANTEGNA HOTEL

CONGRESS REVIEW

GUT MICROBIOTA FOR HEALTH
World Summit 2018

By Dr. Julien Scanzi
Hepato-gastroenterology, Estaing University Hospital of Clermont-Ferrand and Thiers Hospital Centre, UMR INSERM/UdA U1107 Neuro-Dol, Clermond-Ferrand Faculties of Medicine, France

FOCUS ON THE 2018 GMFH

GUT MICROBIOTA FOR HEALTH SUMMIT

MARCH 2018

ROME, ITALIA

The 7th GMFH summit was held in Rome on March 9-11, 2018. Once again, this year, internationally renowned physicians and researchers met to share the latest scientific advances in the field of microbiota; “a leading field of research”, as stated by Francisco Guarner, Chair of the Scientific Committee and leader of an ambitious programme.

ANTIBIOTICS AND GUT MICROBIOTA

The congress began with a Biocodex symposium on the impact of antibiotics on the gut microbiota. Dr L. Armand-Lefevre recalled that antibiotics cause major alterations in the microbiota, in particular due to both the broad spectrum of antibiotics as well as high intestinal concentrations. In addition, microbiota resilience following antibiotic therapy may be slow and incomplete. In addition to the well-known short-term side effects, such as diarrhoea, taking antibiotics in early childhood is associated with an increased risk of obesity, allergies, and autoimmune diseases, as specified by Dr A. Mosca. How can these risks be reduced? Firstly, by trying to prescribe fewer antibiotics in a better way, moreover, if antibiotic prescription is necessary, by combining them with a probiotic. This is particularly the case for the probiotic, *Saccharomyces boulardii* CNCM I-745, which limits dysbiosis and facilitates microbiota resilience following the discontinuation of antibiotics. Prof. C. Kelly has also shown that *S. boulardii* CNCM I-745 decreases the level of primary bile acids and increases that of secondary bile acids, thus reducing the risk of *Clostridium difficile* infection.

OUR MUCUS NEEDS FIBRE TO DEFEND US

Our fibre consumption has decreased over recent decades, at least in the West, from more than 150 g per day a few generations ago to a dozen grams per day nowadays. This directly impacts the composition of our intestinal mucus. Prof. M. Desai’s Luxembourg team has shown, using a mouse model, that a low-fibre diet results in the intestinal mucus being more strongly degraded by the microbiota via glycoproteins contained in the mucus

as an energy substrate. The resulting degraded mucus no longer plays its role against pathogenic bacteria such as *Citrobacter rodentium*, resulting in lethal colitis in these mice [1].

NEW BIOMARKERS IN COLORECTAL CANCER

The potential role of the microbiota in colorectal carcinogenesis is well known. In a metagenomic study conducted in collaboration with Prof. J. Wang's team in China, Dr M. Arumugam demonstrated the existence of a"microbial signature" of colorectal cancer (CRC), based on the identification of four biomarkers which were significantly expressed in CRC patients compared to healthy subjects, in geographically different populations (China, Denmark, France, Austria). Of these biomarkers, two bacterial genes of *Fusobacterium nucleatum* (*Fn*) and *Parvimonas Micra* (*Pm*) were significantly over-expressed in cases of CRC [2]. Another recent study has confirmed the role of *Fn* as a biomarker of CRC, which significantly increased the sensitivity of immunological screening and made it possible to retrieve 75% of CRC cases which were negative on immunological testing [3].

With this advance in the recognition of a "microbial signature" of CRC, it may be possible to screen asymptomatic individuals for CRC in the near future based on an immunological test for blood in the stools coupled with microbiota analysis.

IMPACT OF THE MICROBIOTA ON THE RESPONSE TO IMMUNOTHERAPY

It has been known for a few years that the gut microbiota has an impact on the efficacy of chemotherapies. Recently, studies have also shown that the microbiota plays a major role in the response to immunotherapy. Based on a study of 26 metastatic melanoma patients, Prof. F. Carbonnel's team showed that the type of microbiota is correlated with the response to ipilimumab (anti-CTLA-4). Patients with a microbiota rich in *Faecalibacterium* and other Firmicutes demonstrated a high response rate to ipilimumab and a significantly increased survival rate. The occurrence of ipilimumab-induced colitis was also more common in this group [4]. Similarly, another recent study based on 112 metastatic melanoma patients has shown that their responses to anti-PD-1 varied, and their microbiota, alpha-diversity, and relative abundance in *Ruminococcaceae* (a family whose main member is *Faecalibacterium*) were the main predictive factors for response [5].

FOCUSING ON FAECAL MICROBIOTA TRANSPLANTATION

As was the case last year, faecal microbiota transplantation (FMT) was the subject of a workshop and was often referred to in the various presentations. Drs. G. Ianiro and Z. Kassam recalled the very promising results of FMT for ulcerative colitis (two positive randomised controlled trials and one trial which showed a positive trend with FMT although significance was not reached), metabolic syndrome, hepatic encephalopathy, irritable bowel syndrome, and digestive GVH (graft-versus-host) allograft. Apart from recurrent *Clostridium difficile* infection, repeated FMT appears to be essential for "engraftment" and treatment efficacy. Administration in capsules seems to be the future for this technique but questions remain, in particular around intake dose and frequency, since these parameters are also likely to vary according to indication. Access to FMT is increasingly facilitated by the emergence of "stool banks", in particular, in countries in which microbiota transplants have been assigned the status of organ/tissue rather than medicine. For example, in the United States, 98% of the population is within a two-hour drive of a centre practicing FMT. Thus, this practice has been widely used in recent years, but remains to be standardised and possibly adapted to patients according to their disease and microbiota.

AKKERMANSIA MUCINIPHILA: A NEW-GENERATION PROBIOTIC?

Discovered in 2004, *A. muciniphila* is a bacterium that prevails in the mucus. It degrades mucin, stimulates butyrate production, and produces a pili-like protein, Amuc1100, that appears to play an important role in the immune response and barrier function of the intestinal mucus. It appears to have beneficial properties since its presence is inversely correlated to obesity, metabolic syndrome, and some cardiovascular diseases [6, 7]. In mice, its administration has beneficial effects on metabolic syndrome, and the first clinical data in humans should soon be available.


Photo: Svetlana Kolpakova © 123RF.

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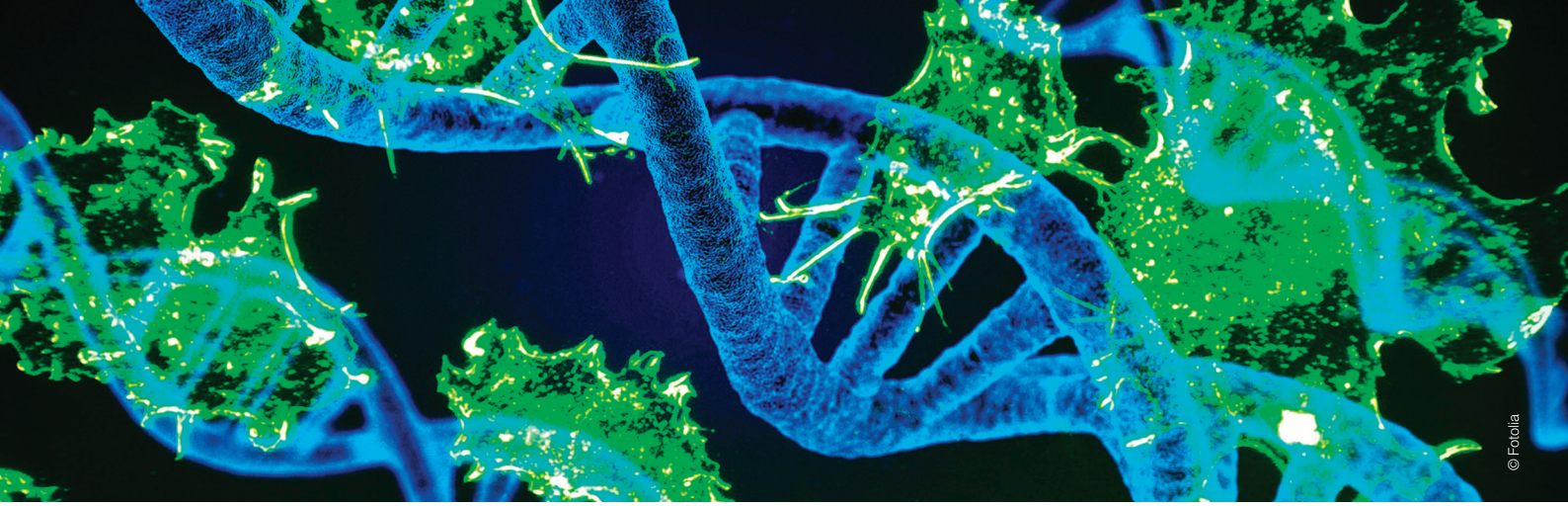

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LITERATURE SELECTION

By Prof. Ener Cagri Dinleyici
Professor in Pediatrics, Eskisehir Osmangazi University Faculty of Medicine; Department of Pediatrics, Eskisehir, Turkey

INTESTINAL MICROBIOTA MODULATES TUMOUR RESPONSE IN CANCER PATIENTS

On February 4, 2018, World Cancer Day, the World Health Organization (WHO) stated on their website "Nearly every family in the world is touched by cancer, which is now responsible for almost one in six deaths globally. On World Cancer Day (February 4), the WHO highlights that cancer no longer needs to be a death sentence, as the capacity exists to reduce its burden and improve the survival and quality of life of people living with the disease" [1].

Over the last 10 years, tremendous advances have been made for cancer patients using new treatment strategies, including immune checkpoint inhibitors that target cytotoxic T-lymphocyte-associated antigen (CTLA-4) and programmed death 1 (PD-1) protein. However, therapeutic responses to these new treatment modalities are often heterogeneous, and some non-responder patients have been reported. The intestinal microbiome has been suggested to be an important host factor for non-responder patients, along with tumour genomics. Previous studies on microbiota and cancer have mainly focused on alterations in the intestinal microbiota of cancer patients (oncobiome) or microbiota precursors in order to define early-stage cancers, mainly colorectal cancers. However, promising new results regarding the influence of intestinal microbiota on anti-tumour immune responses have emerged. Two new studies were published in the first issue of *Science* this year.

• Gopalakrishnan *et al.* [2] evaluated the intestinal and oral microbiome in 112 patients with malignant melanoma, receiving anti-PD-1 immunotherapy, and compared baseline microbiota composition between cancer responders and non-responders. They revealed significant differences in the diversity and composition of intestinal microbiota between responders and non-responders. Significantly higher alpha diversity and relative abundance of *Ruminococcaceae/Faecalibacterium* was observed in responders, and this favourable intestinal microbiota composition has been suggested to enhance systemic and anti-tumour immunity among patients with melanoma. Patients with a low diversity and relatively high abundance of *Bacteroidales* (unfavourable intestinal microbiome) have impaired anti-tumour immune responses.

• Matson *et al.* [3] also evaluated the composition of baseline intestinal microbiota in patients with metastatic melanoma before receiving anti-PD-L1 therapy. Among the responders to treatment, *Bifidobacterium longum, Collinsella aerofaciens*, and *Enterococcus faecium* have been shown to be predominant members of the microbiota. These authors suggest that the commensal microbiome may exhibit a mechanistic impact on anti-tumour immunity in patients with metastatic melanoma.

In the light of the results from these two previous clinical studies, it is thought that **baseline intestinal microbiota may play a critical role in mediating the immune-stimulant response in melanoma patients receiving immunotherapy**, such as anti-PD-L1 therapy. Further prospective

studies are needed to reveal the precise interactions between the microbiome and cancer, not only in melanoma patients, but in terms of potential relevance for all types of cancer and the different treatment strategies.

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MATERNAL OBESITY DURING PREGNANCY AND DELIVERY MODE

THEY SHAPE INFANT MICROBIOTA COMPOSITION AND WEIGHT STATUS AT ONE AND THREE YEARS OF AGE

Obesity is a global health problem in children as well as adults, and microbiota composition and alterations in patients with obesity have been evaluated. There is an increasing trend for Caesarean delivery worldwide. Excessive maternal weight or obesity during pregnancy is associated with higher rates of Caesarean delivery, and children delivered by Caesarean section are more likely to develop obesity compared to those delivered vaginally.

- **Study of m and weight status in 935 mother-infant pairs**

Microbiota composition and alterations in patients with obesity and new-borns delivered by Caesarean section have been previously evaluated [1]. The *Canadian Healthy Infant Longitudinal Development* (CHILD) study is a prospective longitudinal birth cohort study which is designed to collect information at time points that are considered to be particularly critical to the health and development of children in terms of defining the influence of genetics, epigenetics, and the microbiome during early life [2]. Hein Tun et al. [1] enrolled 935 mother-infant pairs in the study, and evaluated maternal weight status during pregnancy, infant gut microbiota composition (including 16S ribosomal RNA sequencing) after a median of one month, and body mass index z scores adjusted for age and sex at one and three years of age.

Their results revealed that 7.5% of infants were overweight at the age of one, and 10.4% were overweight at the age of three. Infants born vaginally to overweight or obese mothers were three times more likely to be overweight at the age of one, while Caesarean-delivered infants of overweight mothers had a five-fold risk of being overweight at the age of one. A similar risk was apparent at the age of three. An abundance in Firmicutes species in the infant gut microbiota, particularly *Lachnospiraceae*, is associated with excessive maternal pre-pregnancy weight and excessive childhood weight at the ages of one and three. The genera of *Lachnospiraceae* involved differed between infants delivered vaginally and those delivered via Caesarean birth.

- **Intergenerational transmission of overweight and obesity in case of cesarean delivery**

This study of 935 mother and infant pairs revealed evidence of a novel sequential mediator pathway involving birth mode and greater abundance of *Lachnospiraceae*, regarding the inter-generational transmission of excessive weight and obesity, especially for Caesarean delivery. The prevention of obesity in women of reproductive age is widely recognised to be important both for their health and for that of their offspring.

Hanson *et al.* [3] highlighted that interventions to reduce or prevent obesity before conception and during pregnancy could substantially contribute to achieving the global Sustainable Development Goals, in terms of health, wellbeing, productivity, and equity in current and future generations. Regarding the current progress towards understanding the microbiome, microbiome composition will play an important role in wellbeing in the future.

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CALLS FOR RESEARCH PROPOSALS

BIOCODEX MICROBIOTA FOUNDATION

The international Scientific Committee of the Foundation met on March 11 in Rome during the 7th *Gut Microbiota for Health World Summit*. The project of Prof. Bernd Schnabl, Associate Professor at the Department of Medicine at the University of California in San Diego (La Jolla, USA), entitled *"A precision medicine approach to treat alcoholic hepatitis"*, was selected and Prof. Bernd Schnabl was formally awarded a grant of €200,000 during a ceremony on April 14 by Dr. Marie-Emmanuelle Le Guern, President of the Foundation, and Prof. Harry Sokol, President of the International Scientific Committee.

A national call for proposals launched in certain countries has also led to results (Table). Calls for proposals in Belgium, Turkey, Mexico and Morocco are still active.

- **Please visit the website www.biocodexmicrobiotainstitute.com**

Country	Theme of the call for proposals	Amount	Winner	Selected project
Canada	Dietary interactions with the GI microbiome in GI disorders	€25,000	Dr Alberto Camminero Fernandez, McMaster University, Hamilton	The role of commensal microbiota on dietary tryptophan metabolism: implications for inflammatory bowel disease
France	Gut microbiota and human health	€25,000	Dr Paul McLellan, Saint-Antoine Hospital, Paris	Use of the bacterial protein MAM as a biomarker of intestinal inflammation in Crohn's disease
Finland	Gut microbiota and its interactions with various pathologies	€12,500	Dr Anne Salonen, University of Helsinki	Gut microbiota in relation to early growth and development of childhood obesity
		€12,500	Dr Verra Kainulainen, University of Helsinki	Commensal bacteria in the attenuation of intestinal inflammation – molecular mechanisms of functionality of isolated novel strains
Ukraine	Intestinal microbiota and pathology of the biliary tract	€10,000	Dr Yuriy Stepanov, Institute of Gastroenterology of the National Academy of Medical Sciences of Ukraine, Dnipro	Investigation of the association between disorders of intestinal microbiocenosis and functional disorders of the biliary tract in overweight and obese children
USA	Dietary interactions with the GI microbiome in GI disorders	$50,000	Dr Rashim Singh, Houston University	Flavonoids and microbiome interactions via triple recycling and their roles in food-borne carcinogen-induced colorectal cancer
Russia	Gut microbiota	€25,000	Prof. Irina Grigoreva, Research Institute of therapy and preventive medicine, Novosibirsk	Metagenomic analysis of changes in intestinal microbiota in patients with cholelithiasis before and after cholecystectomy

Given the success of this initiative, the entire operation will be repeated in 2019.

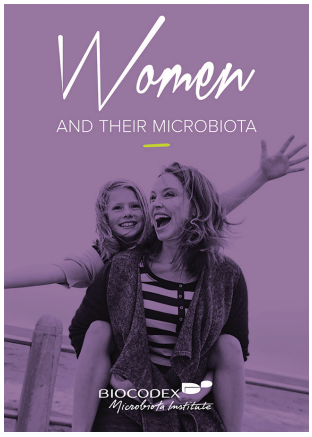
Internationally, a new theme has been selected: *"Gut microbiota and drug metabolism"*.

Projects related to the following topics will be considered:

- microbiota metabolism / chemical processing of drugs with impact on their efficacy or profile of adverse effects;
- influence of the gut microbiota on drug pharmacokinetics (regardless of their direct processing) with impact on efficacy or profile of adverse effects.

BIOCODEX MICROBIOTA INSTITUTE

One year after its launch, **the website of the Institute has evolved** to better meet your needs. It is now possible to download thematic files from the home pages dedicated to the general public and health professionals.



FOR THE GENERAL PUBLIC

- Already available:
  Women and their microbiota
- Forthcoming:
  Allergies: the role of microbiota

FOR HEALTH PROFESSIONALS

- Already available:
  Microbiota and child health
- Forthcoming:
  Functional gastrointestinal disorders in children and in adults

- **Please visit www.biocodexmicrobiotainstitute.com**

MEET BIOCODEX AT THE FOLLOWING CONGRESSES:

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AUGUST 29-SEPTEMBER 1, 2018

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