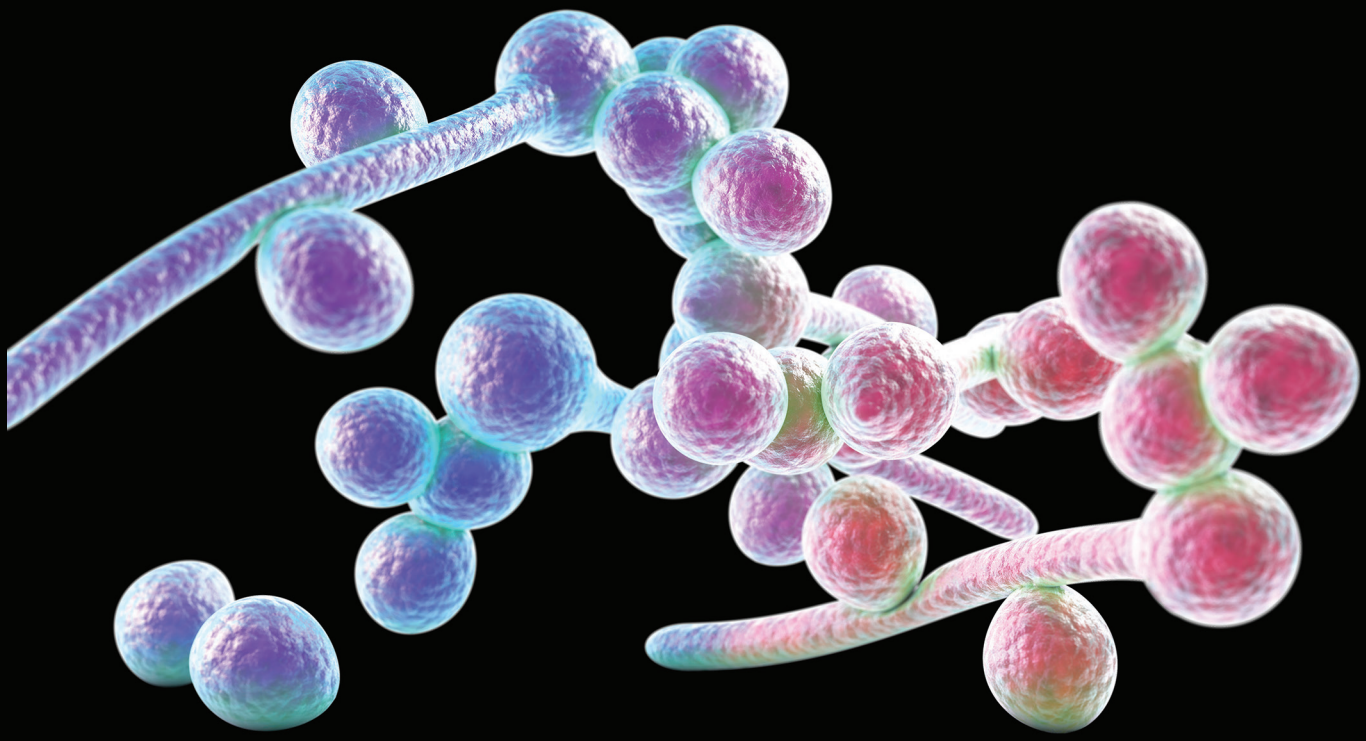
MICROBIOTA

16 BIOCODEX NEWSLETTER | SEPTEMBER 2022



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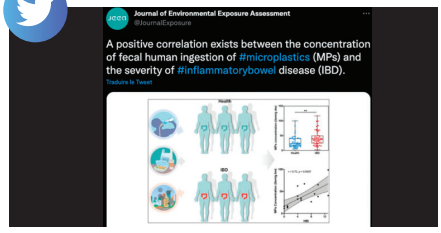
SUMMARY

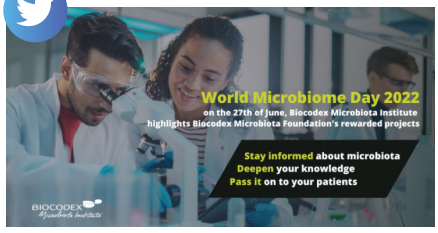
WHAT DID YOU MISS ON SOCIAL MEDIA?



IBD AND MICROPLASTICS

A recent study reveals that people who had **a high concentration of microplastics in their faeces were more likely to have IBD.** Is this enough to build a causal association?

Find the answer on p.18 by Dr. Alberto Caminero



WORLD MICROBIOME DAY 2022

In June, the WMD 2022 tweet from Biocodex Microbiota Institute generated the most shares and comments with **4 k engagements**

ALTERED GUT MICROBIOTA IN AUTISM SPECTRUM DISORDER-RELATED BEHAVIORS

By GMFH

17.1 k engagements

EDITO

Dr Maxime Prost, MD
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> “EVIDENCE TO SUGGEST THAT THE GUT MICROBIOME IS ALTERED IN STRESS-RELATED DISORDERS CONTINUES TO GROW, DELINEATING A SPECIFIC GUT MICROBIAL PROFILE ASSOCIATED WITH THE DEVELOPMENT OF STRESS-RELATED DISORDERS.”

Dear readers,

Gut brain axis. If you are a regular reader of *Microbiota* Magazine, you know that research is gradually revealing the bidirectional system of communication between the gut microbiome and the brain. You also have read that this gut-brain communication is key to better understand how gut microbiota is associated with some diseases development. Let’s use the example of irritable bowel syndrome (IBS). Even if the pathophysiology of IBS is not fully understood, it is considered as a bidirectional altered communication between the digestive tract and the central nervous system (Overview, *Microbiota* 13). There is another example with complex neurodevelopmental disorders: autism spectrum disorders (ASD). Once again, the pathophysiological mechanisms behind are still poorly understood but some consistent findings suggest robust interactions between gut microbiota and the brain (Overview, *Microbiota* 15).

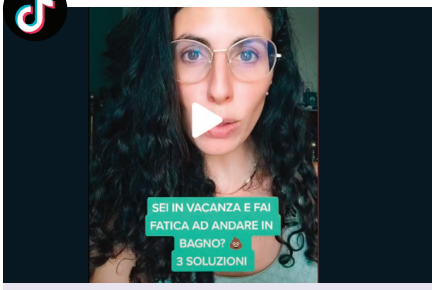
In this issue, Pr. Sian Joanna Hemmings describes another example of this crucial bidirectional communication. She reviews current literature on the microbiome-gut-brain axis, and how this bidirectional system of communication may play a role in the etiology of stress-related disorders as post-traumatic stress disorder (PTSD), anxiety disorders and major depressive disorder (MDD). According to the author, “*evidence to suggest that the gut microbiome is altered in stress-related disorders continues to grow, delineating a specific gut microbial profile associated with the development of stress-related disorders. This specific gut microbial profile may facilitate identification of reliable biomarkers of disease-associated risk and predict predisposition to develop these disorders.*”

Gut-brain axis communication, but also interaction and association, this triptych is Microbiota Magazine 16’s guiding thread. Whether it is the association between IBD and microplastics in stool (by Dr. Alberto Caminero) or the interaction between the oral microbiota and Covid-19 (by Dr. Jay Patel), this is obvious: everything is linked!

Enjoy your reading.

GUT MICROBIOTA
By **lavanguardia.com**
4.4k shares

MICROBIOTA AND SEROTONIN
By **Gisela Cobo**
9.7k engagements and 1k shares



HOW TO PREVENT CONSTIPATION IN VACATIONS
By **Dr. Roberta Costanzo**
6.2k engagements

Photo: Shutterstock.

OVERVIEW

GUT MICROBIOTA AND STRESS-RELATED DISORDERS

Stress-related disorders, including posttraumatic stress disorder (PTSD), major depressive disorder (MDD) and anxiety disorders, are common psychiatric disorders with a dysfunctional response to stress a key pathogenic mechanism. These disorders are highly complex and debilitating, and are associated with increased mortality and morbidity. There is considerable evidence implicating the role of the gut microbiota in psychiatric disorders, including stress-related disorders. Delineating a specific gut microbial profile associated with the development of these psychiatric disorders may facilitate identification of reliable biomarkers of disease-associated risk and predict predisposition to develop such disorders. Moreover, the gut microbiota can easily be manipulated and could, therefore, offer a simple and sustainable treatment option to alleviate symptoms of stress-related disorders. This article reviews current literature on the microbiome-gut-brain axis, and how this bidirectional system of communication may play a role in the aetiology of PTSD, MDD and anxiety disorders.

By Pr. Sian M. J. Hemmings

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STRESS-RELATED DISORDERS

Psychiatric disorders are chronic, debilitating disorders that significantly impair daily functioning, and are among the top ten leading causes of burden of disease worldwide [1]. Exposure to environmental stressors and trauma is associated with increased incidence of post-traumatic stress disorder (PTSD), major depressive disorder (MDD) and anxiety disorders [2, 3]. These stress-related disorders are associated with increased mortality, reduced life expectancy, are highly comorbid, and exhibit variable response to first line pharmacotherapy. There are no clinically actionable biomarkers for these disorders, further complicating their diagnosis and treatment. To facilitate the development of novel therapeutic strategies and potential interventions, it is imperative that we gain deeper insight into the biological mechanisms underlying these disorders.

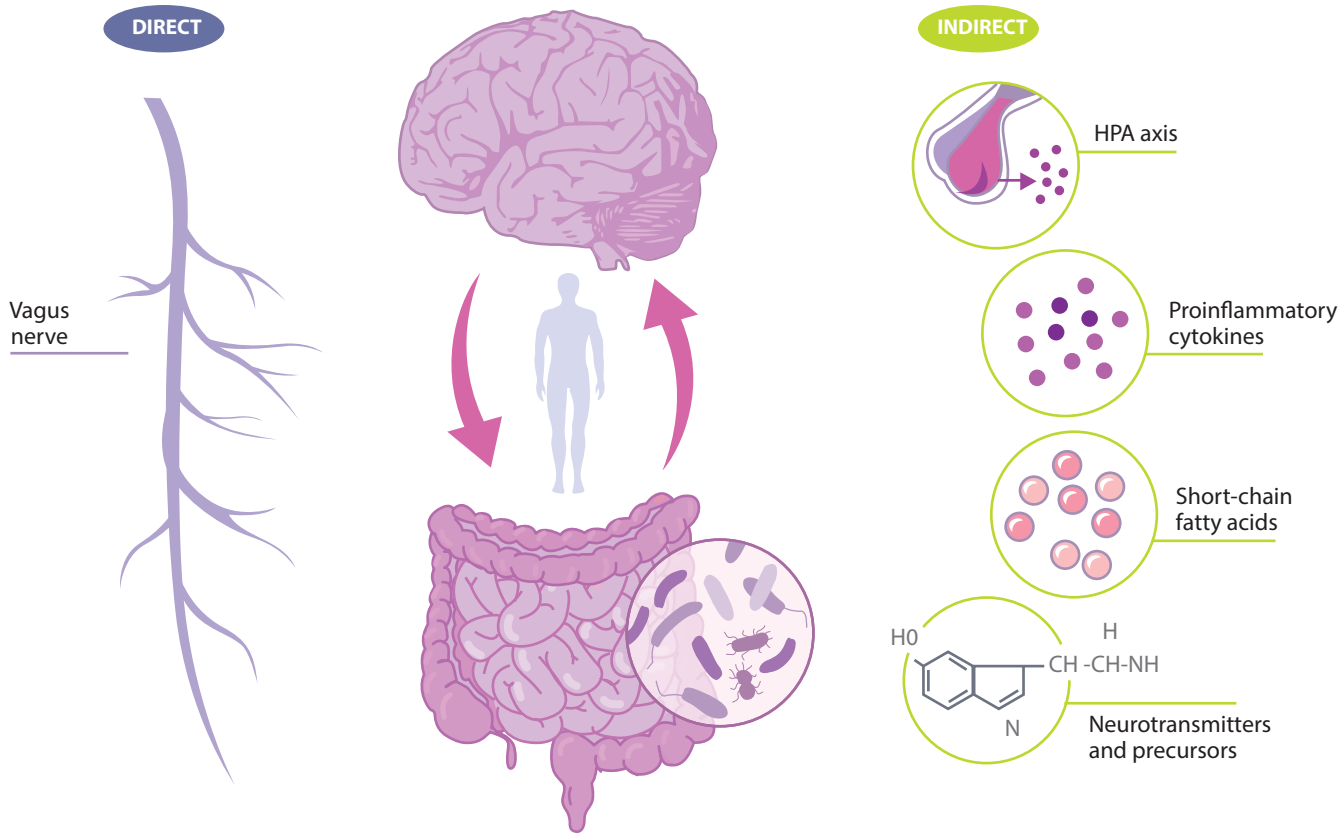
THE MICROBIOME-GUT-BRAIN (MGB) AXIS

"Microbiota" is the term referring to the trillions of microorganisms that live in and on us. The complete catalogue of these microbes and their genes constitutes the human microbiome. The gut microbiome, crucial in maintaining numerous aspects of our physiological functioning, is a dynamic system, the composition of which is affected by numerous factors including host genetics, age, diet and ethnicity [4-6]. The microbiome-gut-brain (MGB) axis is a complex, bidirectional system of communication between the gut microbiome, the gut, and the central nervous system (CNS), facilitated by direct and indirect communication pathways (**Figure 1**).

The vagus nerve, the major parasympathetic nerve of the autonomic nervous system, represents a direct link between the gut and

▼ FIGURE 1

Direct and indirect means of communication in the microbiome-gut-brain axis. HPA, hypothalamic pituitary adrenal axis. HPA axis, proinflammatory cytokines, short-chain fatty acids, neurotransmitters and their precursors.



the brain, with vagal afferents and efferents facilitating reciprocal interaction between the enteric nervous system and the brain. Indirect communication within the MGB axis takes on many forms. Microbiota produce several microbial-derived molecules, including neurotransmitters and metabolites, which act at multiple locations in the body. Many of these molecules, including serotonin (5-HT) have been found to regulate behaviour, brain function and health. As much as 95% of the 5-HT in the body is produced in the enterochromaffin cells lining the intestine, and 5-HT levels in the gut are influenced by microbial metabolites including indole, bile acids and short-chain fatty acids (SCFAs). 5-HT produced in the gut cannot bypass the blood-brain barrier (BBB), and therefore cannot affect 5-HT levels in the brain. However, animal studies provide evidence to suggest that levels of the 5-HT precursor, tryptophan, modulated by certain gut bacteria, are associated the regulation of 5-HT neurotransmission in the brain [7].

Alterations in SCFAs, a product of bacterial fermentation of host-undigestible polysaccharides, have been found to be associated with exposure to chronic stress and depressive-like behaviour in animal studies. SCFAs are involved in a number of regulatory functions, including modulation of gut activity and intestinal integrity, and activation of microglia (innate immune cells in the brain, which play an important role in regulating neuronal survival and responses). SCFAs are capable of crossing the BBB, and in doing so, may affect brain function.

It is well established that the gut microbiome plays an important role in the development of both the peripheral and central immune systems, and accumulating evidence suggests that increased inflammation is associated with stress-related disorders. An imbalance in gut microbial composition can compromise the integrity of the intestinal epithelium [8], increasing intestinal permeability and facilitating translocation of bacteria, or bacterial components, across the epithelial barrier into systemic circulation. This promotes low-grade inflammation, which stimulates increased expression of proinflammatory

Systemic administration of lipopolysaccharides (LPS), a major component of the outer membrane of gram-negative bacteria, has been found to result in acute anxiety and increased depressive-like symptoms, as well as cognitive deficits, and LPS-induced increase in proinflammatory cytokine levels have been found to alter neuronal activity in limbic areas of the brain. LPS has also been found to induce increased cytokine production in the CNS, compromising the integrity of the BBB, resulting in a "leaky brain".


Photo: Shutterstock

A. muciniphila is a gram-negative anaerobic bacterium, found primarily in the intestinal mucosa. It plays a role in maintenance of intestinal barrier integrity as well as in immune and metabolic regulation.

cytokines. Proinflammatory cytokines can stimulate the hypothalamic-pituitary adrenal (HPA) axis to secrete cortisol, which may further increase intestinal permeability. Indeed, evidence of gut and brain barrier dysfunction has been reported in stress-related disorders.

INVESTIGATING THE GUT MICROBIOME IN STRESS-RELATED DISORDERS: PRECLINICAL AND CLINICAL FINDINGS

Several preclinical investigations support the idea that the gut microbiome composition is associated with stress-related disorders. Investigations using germ-free (GF, microbiologically sterile) animals have played a crucial role in our understanding of the MGB axis. In their seminal investigation, Sudo and colleagues [9] observed an exaggerated stress response, evidenced by increased levels of corticosterone, in GF mice compared to controls, following acute restraint stress. This exaggerated HPA axis response to stress was normalised upon mono-colonisation of the GF mice with *Bifidobacterium infantum*. Studies have also shown that it is possible to transfer anxiety-like behavioural phenotypes between two mouse strains, by means of fecal microbiota transplant (FMT) [10]. Similarly, several studies have reported on the development of depressive- and anxiety-like behaviour, and altered neuroendocrine-immune pathways, in microbiota-depleted rodents following FMT from humans diagnosed with MDD, suggesting a causal role for gut microbiota in depressive-like behaviour [11-13]. Animal studies have also shown that exposure to stress can cause long-lasting alterations in the gut microbiome – two recent studies reported on decreased relative abundance of *Akkermansia muciniphila* in the gut microbiome of stressed animals over time, compared to control animals [14, 15]. *A. muciniphila* and the outer membrane coat of the bacteria (Amuc_1100) have been found to ameliorate depressive-like behaviour, and increase circulatory levels of 5-HT.

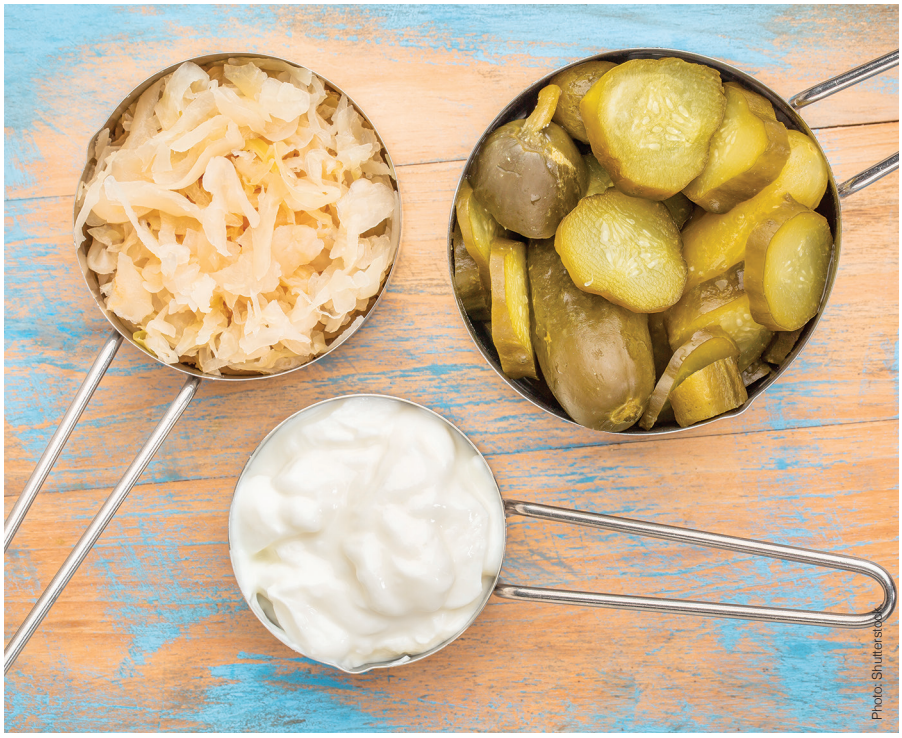
Comparatively few clinical studies have been conducted to determine the association between the gut microbiome and stress-related disorders. Thus far, the only published data on the gut microbiome in PTSD emanates from our research group [16], where a consortium of four bacterial genera was found to predict PTSD status with 66.4% accuracy. In addition, MDD diagnosis in the sample was found to be associated with increased relative abundance of the phylum *Bacteroidetes*. Other studies indicate that bacterial taxa associated with both depression and anxiety disorders are characterised by a higher relative abundance of taxa that induce a proinflammatory environment and a reduced abundance of SCFA-producing bacteria [17].

This field of research is, however, still in its infancy, currently limited by the lack of standardisation in gut microbiome analysis, from sample collection to the analytical pipeline. In many cases, factors that may confound results, including diet, medication use, ethnicity and host genetics, were not accounted for in the studies reviewed

above. Moreover, most of the studies conducted have been cross-sectional in design, limiting our ability to disentangle cause from consequence, and very few have investigated potential mechanisms underlying the associations.

MODULATION OF THE MGB AXIS: PROBIOTICS

The gut microbiome is tractable and has the potential to be modulated, making the search for gut microbiome markers associated with stress-related disorders particularly attractive. *Probiotics* are defined as living microorganisms which, when administered in adequate amounts, confer a health benefit on the host; *psychobiotics* refer to probiotics which confer a benefit on mental health, cognition and behaviour. Recent publications have indicated moderate beneficial effects of psychobiotics in alleviating depressive and anxiety symptoms in both healthy and clinically-defined cohorts [18]. It is, however, important to remain cautious when interpreting results from current studies, as they are variable with regards to probiotic formulation and dosage, sample characteristics (clinical phenotype and severity of depression/anxiety), and follow-up time. In addition, the benefit of psychobiotics over, and interactions with, antidepressant medication has not yet been extensively investigated, although some intriguing results from preclinical studies suggest that certain probiotics, when administered in multi-strain format, possess antidepressant effects similar to, and sometimes with larger effect than, current first-line antidepressants [19]. Such psychobiotics, when used in conjunction with antidepressants, may have particular use in individuals with treatment-resistant depression.



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CONCLUSION

Evidence to suggest that the gut microbiome is altered in stress-related disorders continues to grow, and while much work remains to be done in the field, delineating a specific gut microbial profile associated with the development of stress-related disorders may facilitate identification of reliable biomarkers of *disease-associated risk and predict predisposition to develop these disorders*. The gut microbiome can easily be manipulated and could, therefore, offer a simple and sustainable treatment option to alleviate symptoms of PTSD, MDD and anxiety disorders.

Sources

• **1**. GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Psychiatry 2022; 9: 137-50. • **2**. van Praag HM. Can stress cause depression? Prog Neuropsychopharmacol Biol Psychiatry 2004; 28: 891-907. • **3**. Shin LM, Liberzon I. The neurocircuitry of fear, stress, and anxiety disorders. Neuropsychopharmacol 2010; 35: 169-91. • **4**. De Filippo C, Cavalieri D, Di Paola M, Ramazzotti M, Poullet JB, Massart S, *et al.* Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. Proc Natl Acad Sci USA 2010; 107: 14691-6. • **5**. Schnorr SL, Candela M, Rampelli S, Centanni M, Consolandi C, Basaglia G. Gut microbiome of the Hadza hunter-gatherers. Nat Commun 2014; 5: 3564. • **6**. Ayeni FA, Biagi E, Rampelli S, *et al.* Infant and Adult Gut Microbiome and Metabolome in Rural Bassa and Urban Settlers from Nigeria. Cell Rep 2018; 23: 3056-67. • **7**. Clarke G, Grenham S, Scully P, *et al.* The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner. Molecular Psychiatry 2013; 18: 666-73. • **8**. Desbonnet L, Garrett L, Clarke G, Kiely B, Cryan JF, Dinan TG. Effects of the probiotic Bifidobacterium infantis in the maternal separation model of depression. Neuroscience 2010; 170: 1179-88. • **9**. Sudo N, Chida Y, Aiba Y, Sonoda J, Oyama N, Yu XN. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. J Physiol 2004; 558: 263-75.• **10**. Bercik P, Denou E, Collins J, *et al.* The intestinal microbiota affect central levels of brain-derived neurotropic factor and behavior in mice. Gastroenterology 2011; 141: 599-609. • **11**. Kelly JR, Borre Y, O' Brien C, Patterson E, El Aidy S, Deane J, *et al.* Transferring the blues: Depression-associated gut microbiota induces neurobehavioural changes in the rat. J Psychiatr Res 2016; 82: 109-18. • **12**. Liu S, Guo R, Liu F, Yuan Q, Yu Y, Ren F. Gut microbiota regulates depression-like behavior in rats through the neuroendocrine-immune-mitochondrial pathway. Neuropsychiatr Dis Treat 2020; 16: 859-69. • **13**. Zheng P, Zeng B, Zhou C, *et al.* Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism. Mol Psychiatry 2016; 21: 786-96. • **14**. Hoke A, Chakraborty N, Gautam A, Hammamieh R, Jett M. Acute and delayed effects of stress eliciting post-traumatic stress-like disorder differentially alters fecal microbiota composition in a male mouse model. Front Cell Infect Microbiol 2022; 12: 810815. • **15**. Pascual Cuadrado D, Todorov H, Lerner R, *et al.* Long-term molecular differences between resilient and susceptible mice after a single traumatic exposure. Br J Pharmacol 2022; 179: 4161-80. • **16**. Malan-Muller S, Valles-Colomer M, Foxx CL, *et al.* Exploring the relationship between the gut microbiome and mental health outcomes in a posttraumatic stress disorder cohort relative to trauma-exposed controls. Eur Neuropsychopharmacol 2022; 56: 24-38. • **17**. Simpson CA, Diaz-Arteche C, Eliby D, Schwartz OS, Simmons JG, Cowan CSM. The gut microbiota in anxiety and depression - A systematic review. Clin Psychol Rev 2021;83: 101943. • **18**. Alli SR, Gorbovskaya I, Liu JCW, Kolla NJ, Brown L, Müller DJ. The gut microbiome in depression and potential benefit of prebiotics, probiotics and synbiotics: a systematic review of clinical trials and observational studies. Int J Mol Sciences 2022; 23: 4494. • **19**. Ra Y, Eu P, Ev V, Mv O, Mv M, Gi K, *et al.* A Multi-strain potential probiotic formulation of GABA-producing Lactobacillus plantarum 90sk and Bifidobacterium adolescentis 150 with antidepressant effects. Probiotics and Antimicrobial Proteins 2020; 12: 973-9.

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COMMENTED ARTICLE
ADULTS' SECTION

IMMUNE REGULATION BY FUNGAL STRAIN DIVERSITY IN INFLAMMATORY BOWEL DISEASE

Comments on the article by Li XV et al. Nature 2022 [1]

By Pr. Harry Sokol
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The fungal microbiota (mycobiota) is an integral part of the complex microbial community colonising the mammalian gastro-intestinal tract and has an important role in immune regulation. Although changes in the mycobiota have been linked to several diseases, including inflammatory bowel disease (IBD), it is currently unknown whether fungal species identified by sequencing represent living organisms and whether specific fungi have effects on the development of IBD. The authors developed a translational platform for the functional analysis of the mycobiome. By combining high-resolution mycobiota sequencing, fungal culturomics and genomics, a CRISPR-Cas9-based fungal strain editing system, *in vitro* functional immunoreactivity assays and *in vivo* models, this platform enables the examination of host-fungal crosstalk in the human gut. We discovered a rich genetic diversity of opportunistic *Candida albicans* strains that dominate the colonic mucosa of patients with IBD. Among these isolates, strains with high immune-cell-damaging capacity (HD strains) reflect the disease features of patients with ulcerative colitis and aggravate intestinal inflammation i*n vivo* through IL-1β-dependent mechanisms. The inflammatory and antifungal responses of interleukin-17A-producing T helper cells (Th17 cells) induced by the HD strains in the gut were dependent on candidalysin, the peptide toxin secreted by *C. albicans* during the transition from a benign commensal to a pathobiont state. These findings reveal the strain-specific nature of host-fungal interactions in the human gut and highlight new diagnostic and therapeutic targets for IBD.

WHAT DO WE ALREADY KNOW ABOUT THIS SUBJECT?

Studies based on deep sequencing of the gut mycobiota in several cohorts of patients supply coherent evidence that «fungal dysbiosis» is a characteristic of chronic inflammatory bowel disease (IBD) [2], the most widespread forms of which are Crohn's disease (CD) and ulcerative colitis (UC), which affect millions of individuals worldwide. Anti-*Saccharomyces cerevisiae* antibodies (ASCA), directed against the mannans presented by the cell wall of fungi, define sub-types of IBD, because their presence in the serum is associated with CD but not with UC, which establishes an additional link between fungi and IBD. *Candida* is the most widespread fungal genus, and its presence is systematically increased in several cohorts of patients with IBD analysed by sequencing of the faecal microbiota [2].

In particular, *C. albicans* in the gut induces a set of antifungal antibodies and acts as an immunogen for ASCA. *Candida* species associated with the gut mucosa are detected by the macrophages present in the gut and have been shown experimentally to have the potential to induce protective immunity or to trigger inflammation, depending on the context [3]. Despite this evidence, it is currently unknown whether the fungi detected by sequencing technologies in the human gut have an essential role in the orientation of mucosal immunity or in the evolution of inflammatory disease in each individual patient. A lack of correlation has been repeatedly observed between changes in the composition of the mycobiota and the seriousness of the disease in IBD patient cohorts, despite a constant increase in *Candida* species. The authors have therefore emitted the hypothesis that the functional diversity of *Candida* strains determines the host-fungal relationship in human gut mucosa with an effect on intestinal inflammation.

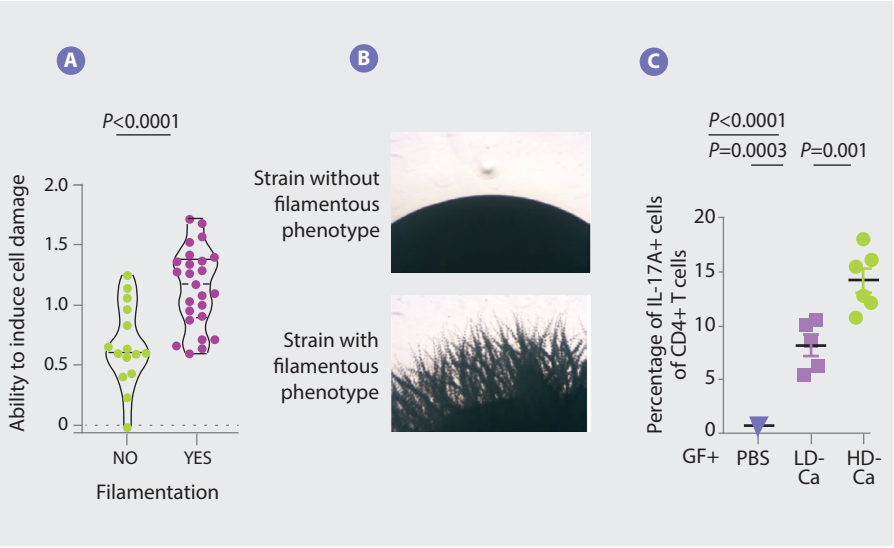
KEY POINTS

- The mycobiota is changed in patients with IBD and *Candida albicans* has pro-inflammatory effects
- The pro-inflammatory effects of *C. albicans* vary from one strain to another and are associated with the capacity to induce cell lesions in the macrophages and to filament
- The pro-inflammatory effects of these strains of *C. albicans* are mediated by the production of candidalysin and the induction of IL-1β production
- *C. albicans*, candidalysin and IL-1β are potential therapeutic targets in UC

▼ FIGURE 1

The pro-inflammatory capacity of *C. albicans* is variable from one strain to another.

A. Strains with filamentation phenotype induce cellular lesions in macrophages
B. Strain without and with filamentation phenotype
C. Mice monocolonized with *C. albicans* with high filamentation abilities induce a Th17 response in the colon



WHAT ARE THE MAIN INSIGHTS FROM THIS STUDY?

In agreement with numerous other studies, the authors first observed that the mycobiota of patients with UC were rich in *Candida albicans* and, in contrast, poor in *Saccharomyces*. In the situation of impaired immune response induced by corticosteroid therapy, *C. albicans* exacerbates the severity of colitis in mice. The authors then isolated several strains of *C. albicans* from the mycobiota of healthy subjects and from patients with UC and observed a wide heterogeneity in terms of pro-inflammatory capacity. In particular, the capacity of causing cell damage to the macrophages, which are a key defence against fungi, varies from one strain to another. The strains able to inflict cell damage to the macrophages have a greater tendency to filament and have pro-inflammatory effects *in vivo* by inducing a Th17 response (**Figure 1**). The authors then showed that a large part of the pro-inflammatory effects were mediated by the secretion of a toxin, candidalysin, and the induction of IL-1β production. Subsequent analyses revealed a strong correlation between the pro-inflammatory capacity of strains isolated from patients with UC and the inflammatory activity of the disease. On the other hand, there was no correlation between the magnitude of intestinal inflammation and the overall abundance of *Candida albicans* in the patients. These results explain why the composition of the mycobiota is poorly correlated to the characteristics of human pathologies and suggest that the functional capacities (pro-inflammatory in this case) may provide a better explanation of the role of the mycobiota in these pathologies.

WHAT ARE THE CONSEQUENCES IN PRACTICE?

This study shows that, in addition to analyses of the composition of the mycobiota, in particular by sequencing, a functional analysis is necessary to understand its contribution to the disease and in particular in IBD. If pro-inflammatory strains of *C. albicans*, candidalysin and IL-1β are confirmed to have a role in UC, we can imagine a therapeutic option which targets one of these elements, especially as several molecules which antagonise the IL-1β pathway are already available.

CONCLUSION

This study suggests that candidalysin is a key factor in the pro-inflammatory effect of *C. albicans* in the gut and that some highly pro-inflammatory strains act via IL-1β-dependent mechanisms. Patients who are carriers of highly pro-inflammatory strains may represent a target population for a treatment antagonising IL-1 and/or *C. albicans*.

Sources

• **1**. Li XV, Leonardi I, Putzel GG, *et al.* Immune regulation by fungal strain diversity in inflammatory bowel disease. *Nature* 2022 ; 603 : 672-8. • **2**. Sokol H, Leducq V, Aschard H, *et al.* Fungal microbiota dysbiosis in IBD. *Gut* 2017 ; 66 : 1039-48. • **3**. Doron I, Leonardi I, Li XV, *et al.* Human gut mycobiota tune immunity via CARD9-dependent induction of anti-fungal IgG antibodies. *Cell* 2021 ; 184 : 1017-1031.e14.

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COMMENTED ARTICLE
CHILDREN'S SECTION

BACTEROIDOTA AND *LACHNOSPIRACEAE* INTEGRATION INTO THE GUT MICROBIOME AT KEY TIME POINTS IN EARLY LIFE ARE LINKED TO INFANT NEURODEVELOPMENT

Review of the original article of Oliphant K et al. [1]

By Pr. Emmanuel Mas
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The early life gut microbiome plays a critical role in host development and influences brain functioning. This study investigated the association between gut microbiome succession from the first week of life and head circumference growth (HCG). Faecal samples were collected weekly from a preterm infant cohort in order to evaluate gut microbiome composition, in conjunction with clinical data and head circumference measurements. Preterm infants with suboptimal HCG trajectories had a depletion in the abundance/prevalence of *Bacteroidota* and *Lachnospiraceae*, which was unrelated to morbidity and caloric restriction. This article provides evidence that their integration into the gut microbiome needs to occur early for optimal neurodevelopment.

WHAT DO WE ALREADY KNOW ABOUT THIS SUBJECT?

Neurodevelopment disorders are frequent in young children, affecting up to 8.4% of individuals under 5 years of age worldwide. Head circumference growth (HCG) is a marker correlated with early neurodevelopment.

It is important to seek environmental factors which could be modified to reduce neurodevelopment disorders. Interventional nutrition studies have failed to show significant results on neurodevelopment (e.g.: the benefit of breast feeding). The authors investigated the gut microbiome (GM) because its acquisition during the first months of life and the use of antibiotics during the first year are associated with various pathologies including neurodevelopment disorders later in childhood, in particular attention deficit hyperactivity disorder and autism spectrum disorder.
The study objective was to determine whether there is a relationship between the characteristics of the early GM and a suboptimal trajectory of the HCG (SHCGT).

WHAT ARE THE MAIN INSIGHTS FROM THIS STUDY?

Infants of < 37 weeks postmenstrual age (Chicago neonatal care unit) were included between January 2010 and December 2018. HCG trajectory was the difference between head circumference z-scores measured at birth and at 36 weeks postmenstrual age (PMA); 0.5 z-score interval losses were used to define the groups having an appropriate HCG trajectory (AHCGT) or a suboptimal trajectory (mildly, moderately and severely impaired, SHCGT).

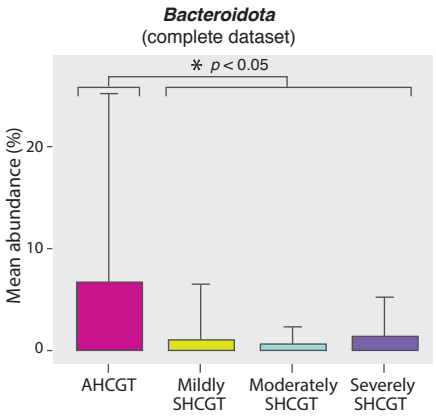
The β diversity of the GM differed significantly between SHCGT and AHCGT infants, as did the change in abundance of the taxa in the stool samples at 30 PMA. The loss in HCG z- score > 0.5 occurred between 31 and 36 weeks PMA in the SHCGT groups. This suggests that an «immature» GM precedes the SHCGT.

SHCGT infants had a significantly decreased abundance of *Bacteroidota* ($p = 0.0009$) (**Figure 1**) and *Lachnospiraceae* ($p = 0.009$), between 31 and 36 weeks PMA, which may result in a reduced carbohydrate utilisation capacity of these taxa. The prevalence of the *Ruminococcaceae* family ($p = 0.007$) was attributed to the species *Faecalibacterium prausnitzii* ($p = 0.004$), 48% in the AHCGT vs 8% in the SHCGT infants. It is to be noted that there was an increase in Firmicutes in the SHCGT groups from 24 to 30 weeks PMA ($p = 0.009$) but without any difference in the sub-taxa.

Analysis of the clinical parameters showed that changes in HCG were not due to caloric restrictions. There were more morbidities in the children of the SHCGT groups than in those with AHCGT: necrotising enterocolitis ($p = 0.0006$), severe neurological injury ($p = 0.01$), sepsis ($p = 0.03$). However, the analytical methods used, such as the random decision forest with permutations, showed that the most

▼ FIGURE 1

Difference in the abundance of *Bacteroidota* according to head circumference growth trajectories.



important factors associated with HCG trajectories were the characteristics of the GM rather than the comorbidities, whether from 24 to 30 PMA or from 31 to 36 PMA (**Figure 2**). In infants free from severe morbidities, the differences in *Bacteroidota* and *Lachnospiraceae* were still present but the abundance of *Actinobacteriota* was significantly greater in the AHCGT and in the mildly SHCGT than in the moderately and severely SHCGT groups.

Delivery mode had more effect on HCG trajectories than factors influencing GM such as enteral nutrition and antibiotic treatments. This is linked to the transmission of the GM at delivery because the abundance of *Bacteroidota* was greater in vaginally delivered infants than in those delivered by caesarean section. Moreover, among the vaginally delivered infants, those with a SHCGT had a fall in the abundance of the taxa described above as related to HCG trajectories, compared with the AHCGT. Moreover, the birth term is an important factor because all the vaginally delivered SHCGT infants were born < 27 weeks postmenstrual age, whereas only 17% of the vaginally delivered AHCGT infants were born < 27 weeks postmenstrual age.

WHAT ARE THE CONSEQUENCES IN PRACTICE?

It is suggested therefore that SHCGT starts with a reduction in the abundance of *Bacteroidota* and *Lachnospiraceae*, and then is exacerbated with the reduction in *Actinobacteriota*.

Vaginal birth enables the vertical transmission of *Bacteroidota*.

One must however be vigilant concerning infants born before 27 weeks PMA because even those delivered vaginally appear to be at a higher risk of SHCGT.

Studies designed to optimise GM from the first days of life in very premature infants may confirm and refine these results.

KEY POINT

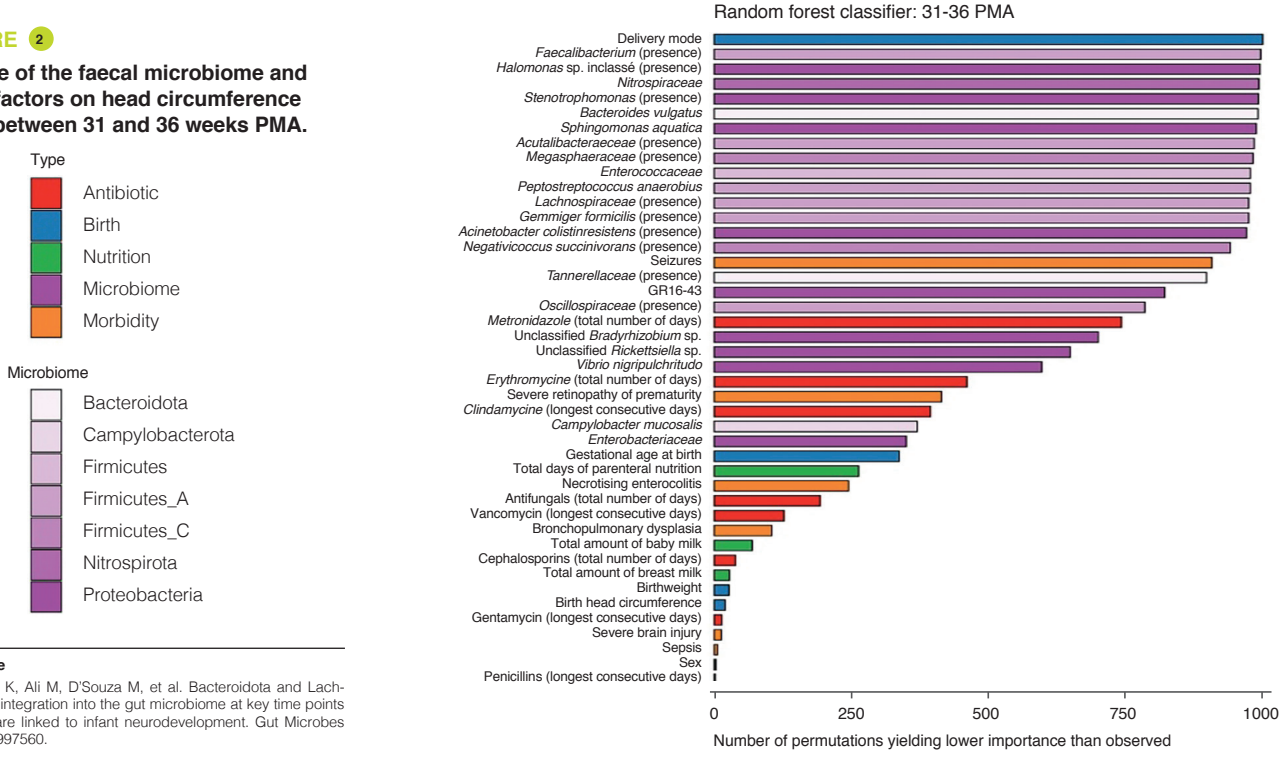
- Early colonisation of the gut by *Bacteroidota* and *Lachnospiraceae* in the premature infant may improve neurodevelopment, via certain metabolic pathways (carbohydrates, amino acids)

CONCLUSION

The gut microbiome is an important factor influencing head circumference growth trajectory. The very early acquisition of certain bacteria (*Bacteroidota* and *Lachnospiraceae*), enhanced by a vaginal delivery, may reduce neurodevelopment disorders.

▼ FIGURE 2

Influence of the faecal microbiome and clinical factors on head circumference growth between 31 and 36 weeks PMA.



Source

• **1**. Oliphant K, Ali M, D'Souza M, et al. Bacteroidota and Lachnospiraceae integration into the gut microbiome at key time points in early life are linked to infant neurodevelopment. Gut Microbes 2021 ; 13 : 1997560.

Photo: Shutterstock.

THE INTERACTION BETWEEN THE ORAL MICROBIOTA AND SARS-COV-2 INFECTION

The mouth accommodates a high and diverse bacterial load embedded within extracellular matrices. Poor oral hygiene encourages dysbiotic shifts in these polymicrobial biofilms, fostering increasingly pathogenic bacterial species to colonise and proliferate. While the microbiota is known to mediate inflammation, recent studies suggest that dysbiosis of the oral microbiota could be associated with the severity and duration of Covid-19 symptoms. For these patients, maintaining or enhancing oral hygiene practices may improve clinical outcomes.

By Dr. Jay Patel

Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, United Kingdom

A HISTORY OF VICIOUS PARTNERSHIP

Viral infections are known to precipitate bacterial co-infections. The majority of deaths in the 1918 influenza pandemic were directly attributable to secondary bacterial pneumonia [1]. Furthermore, severe clinical outcomes during the 2009 H1N1 influenza pandemic were associated with bacterial co-infections [2]. The challenge of viral-bacterial copathogenesis during infectious disease outbreaks can significantly complicate the global response, retard recovery, and accelerate antimicrobial resistance. Fortunately, findings from a multicentre cohort study of nearly 50,000 patients revealed that few bacterial infections were reported in patients hospitalised with Covid-19 [3]. However, it should be noted that diagnosing co-infections is complex, as the organisms might present prior to the viral infection; as part of an underlying chronic infection; or may be contracted nosocomially [4].

THE ORAL MICROBIOTA: FROM EUBIOSIS TO DYSBIOSIS

The oral cavity and upper respiratory tract harbour a high and richly diverse bacterial load. In health, the oral microbiome maintains a finely-tuned, harmonious relationship but small changes in routine behaviours can cause substantial ecological shifts in this symbiosis. Poor oral hygiene can render the environment pathogenic, transitioning the microbiome into a state of dysbiosis, where the conditions for disease processes are enhanced [5, 6].

Periodontal disease – chronic inflammation of the gingiva (gums) – is primarily mediated by the inflammatory components within the biofilm and alters the architecture of the gingival tissues to present micro-ulcers. These form a communication between the oral cavity and the blood, which leads to routine activities (*e.g.* chewing, flossing, and tooth brushing) inducing bacteraemia. Oral bacteria and inflammatory mediators are then disseminated widely via the blood, reaching vital organ systems. Evidence shows that exposure to bacteraemia can be significantly damaging and contributes to a low-grade systemic inflammation precipitating inflammatory conditions [5]. Moreover, periodontitis is known to be an aggravating factor in the incidence of type II diabetes and oral microbiota dysbiosis is involved in both periodontal and metabolic disorders (cardiovascular diseases, dyslipidaemia…)[7].

ORAL DYSBIOSIS AND COVID-19 SEVERITY, IS THERE A LINK?

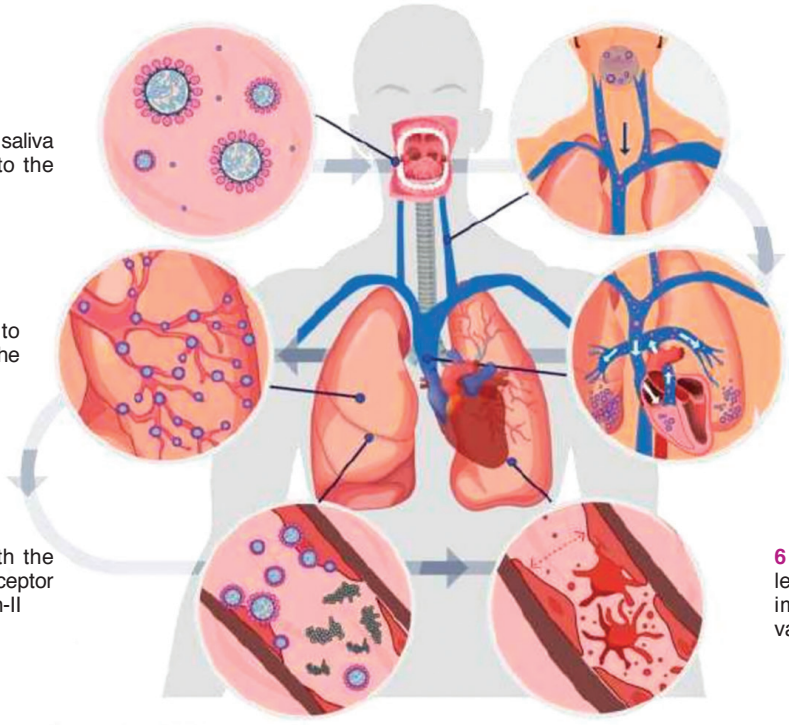
Research on this association is limited, but the few studies that do exist point towards intriguing connections. A double-blinded cross-sectional study of 303 PCR-confirmed Covid-19 patients in Egypt investigated the interplay between three factors: 1) oral hygiene; 2) the severity of Covid-19; and 3) the C-reactive protein (CRP) values. CRP is a marker of hyper-inflammation, hence patients with high levels of CRP were hypothesised to have a poorer prognosis with COVID-19 [8]. The researchers found that poor oral health was correlated to increased values of CRP and delayed recovery period.

A (unmatched) case-control study of 568 patients in Qatar found that periodontitis was associated with severe COVID-19 complications, including a 3.5 times increase in the need for a ventilator; a 4.5 times increase in the risk of intensive care admission; and an 8.8 times increase in the risk of death [9]. Although these results do not suggest causality and other factors may be implicated, the associations are stark and warrant further questions around the true role of oral dysbiosis on Covid-19 outcomes.

This largely hypothesised relationship is based on a number of factors that have shared relevance in the pathophysiology of SARS-CoV-2 infection and periodonti-

▼ **FIGURE 1**

A schematic hypothetical model for an oral-vascular-pulmonary route of infection [10].



tis. For instance, pulmonary radiological evidence of primary vascular pathological processes suggests an oral-vascular-pulmonary axis forming a direct route of infection, in addition to direct vascular delivery to the pulmonary vessels (**Figure 1**) [10]. Secondly, metagenomic analyses have determined that the upper respiratory tract – a key initial anatomical site of infection – is high in bacterial species implicated in oral diseases, and the role of the oral cavity as a natural viral reservoir. Thirdly, adequate viral survival within the sub-gingival biofilm and the ability for viral translocation from saliva to the periodontal pocket – both contributing towards an evasion of the host immune response. Fourthly, the abundance of angiotensin-converting enzyme 2 receptors on key components of the oral-vascular-pulmonary axis.

GOOD ORAL HYGIENE

Regardless of the precise nature of oral microorganisms implicated in the pathophysiology of Covid-19, good oral hygiene should be encouraged for the known benefits to oral and general health. Scrupulous toothbrushing twice daily, interdental cleaning and use of an adjunctive mouthwash are relatively simple measures that will disturb the biofilm, maintain a symbiotic flora and decrease the salivary viral concentration.

CONCLUSION

In summary, the role of poor oral hygiene on the severity of Covid-19 outcomes is understudied and unclear. However, the potential role for a clinically-relevant interplay logically follows. Maintaining or improving oral hygiene practices has clear benefits on oral and general health and during SARS-CoV-2 infections may also improve the prognosis of the disease.

Sources

• **1**. Morens DM, Taubenberger JK, Fauci AS. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. *J Infect Dis* 2008; 198: 962-70. • **2**. MacIntyre CR, Chughtai AA, Barnes M, *et al.* The role of pneumonia and secondary bacterial infection in fatal and serious outcomes of pandemic influenza a(H1N1). *BMC Infect Dis* 2018; 18: 637. • **3**. Russell CD, Fairfield CJ, Drake TM, *et al.* Co-infections, secondary infections, and antimicrobial use in patients hospitalised with COVID-19 during the first pandemic wave from the ISARIC WHO CCP-UK study: a multicentre, prospective cohort study. *Lancet Microbe* 2021; 2: e354-e365. • **4**. Cox MJ, Loman N, Bogaert D, O'Grady J. Co-infections: potentially lethal and unexplored in COVID-19. *Lancet Microbe* 2020; 1: e11. • **5**. Patel J, Sampson V. The role of oral bacteria in COVID-19. *Lancet Microbe* 2020; 1: e105. • **6**. Patel J, Woolley J. Necrotizing periodontal disease: Oral manifestation of COVID-19. *Oral Dis* 2021; 27 (Suppl 3): 768-9. • **7**. Minty M, Canceil T, Serino M, *et al.* Oral microbiota-induced periodontitis: a new risk factor of metabolic diseases. *Rev Endocr Metab Disord* 2019; 20: 449-59. • **8**. Kamel A, Basuoni A, Salem Z, *et al.* The impact of oral health status on Covid-19 severity, recovery period and C-reactive protein values. *Br Dent J* 2021 (online). • **9**. Marouf N, Cai W, Said KN, *et al.* Association between periodontitis and severity of COVID-19 infection: A case-control study. *J Clin Periodontol* 2021; 48: 483-91. • **10**. Lloyd-Jones G, Molayem S, Pontes C, Chapple I. The COVID-19 pathway: A proposed oral-vascular-pulmonary route of SARS-CoV-2 infection and the importance of oral healthcare measures. *J Oral Med and Dent Res* 2021; 2: S1.

ESPGHAN
54th ANNUAL MEETING
of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition

CONGRESS REVIEW

ESPGHAN

HIGHLIGHTS FORM THE 54TH ESPGHAN

By Pr. Koen Huysentruyt
Pediatric gastroenterology, hepatology and nutrition, Brussels Centre for Intestinal Rehabilitation in Children (BCIRC), Belgium

JUNE 2022

The 54th annual ESPGHAN meeting was held from the 22 to the 25th of June 2022 in the beautiful city of Copenhagen. It was the first time that the meeting took place again in real life after two years of limitations due to the Covid pandemic. It was a great opportunity to meet with experts in paediatric gastro-enterology, hepatology and nutrition from all over the world to share knowledge, research and interesting new insights. The aim of this article is to highlight a few of the topics addressed about the microbiome.

THE VIROME

Pr. Dennis Sandris Nielsen introduced us to the virome, a collection of viruses that we carry, which is an emergent research field that appears to play an important role in human health and disease. Faecal sample analysis shows that approximately 6% of the found DNA is not of bacterial, but of viral origin. For every bacteria in the human body, a virus matches it. Like the microbiome, the virome is influenced by pre-, peri- and postnatal factors (diet, environment, siblings, medication, etc.). Those viruses are thus omnipresent in the gut and play a key role in the regulation of the gut microbiome. Bacteriophages are a type of viruses that attack bacteria in a host specific matter. Two different types of interactions are described: “kill-the-winner dynamics” and “piggyback-the-winner dynamics”. In the first, the bacteriophages attack the bacteria, inject its DNA and use the bacteria as a host to create new phage particles after the cell is lysed. The speaker makes an analogy with lions and gazelles in the Savannah, meaning constant-diversity dynamics, destruction of niche competitors, phage shunt and bacterial turnover and pressure on host for diversification of the phage receptor. In the latter, the virus rides with the winner, by integrating its DNA in the genome of the bacteria, altering the host cell and making it more efficient, thus making the winner a winner. A study on faecal samples of a healthy infant population in Denmark identified more than a 10.000 viral species, be-

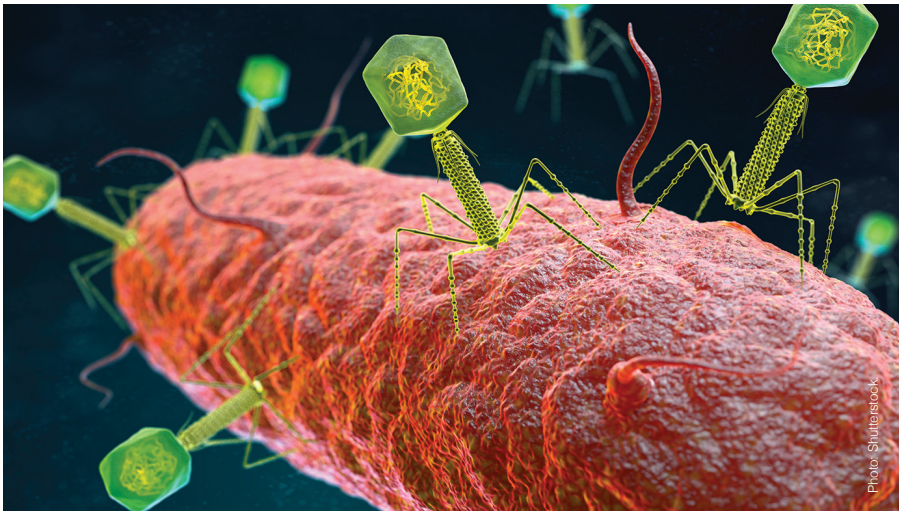


Photo: Shutterstock

longing to 248 viral families. Remarkably, 232 of those families were not previously described, supporting the hypothesis that only the tip of the iceberg has yet been discovered [1]. The questions that are raised is what implication it has on human health, and if it plays a role in immune system maturation. Gut virome imbalance might play a role in disease development (i.e. VEO-IBD, NEC, etc.).

C-SECTION AND MICROBIOME

The mode of delivery at birth plays a key-role in the early shaping of the gut microbiome. Babies that are born vaginally are exposed to different bacterial strains compared to those delivered by C-section, with different colonization as a consequence. In addition, the reason for a C-section is more than often due to a foetal emergency. Those babies are more likely to have a low pH on cord blood, which causes a reduction in tight junction permeability promoting dysbiosis.

Breastfeeding seems to counteract the deleterious effect of C-section on the microbiota and remains the golden standard in infant nutrition. However, women who deliver by C-section are less likely to breastfeed, or delay breastfeed initiation, and infants are then formula fed. For this reason, researchers are constantly looking for the perfect cocktail of pre-, pro-, syn- or postbiotics to mimic the gut microbiome of a breastfed infant.

Dr Eduardo López-Huertas discussed a strain of *Lactobacillus fermentum* and showed promising results in infants delivered by C-section. In a randomized controlled trial (RCT), they analysed the stool samples of infants fed with a symbiotic formula containing *L. fermentum* and GOS and found major resemblances to the samples of breastfed infants (higher bifidobacteria, lower faecal pH) [2]. Furthermore, it is shown in a recent meta-analysis (3 trials) that *L. fermentum* reduces the incidence of gastrointestinal infections with 73% in C-section born infants. More research is needed to investigate possible advantages in potential disease prevention, *i.e.*, gastrointestinal tract or respiratory tract infections, especially in C-section born babies, that have a disadvantageous gut microbiome [3].

HMOS IN INFANT FORMULA AND THE MICROBIOME

Dr. Giles Major provided us with his insights in the link between glycans and the gut microbiome. Glycans or human milk oligosaccharides (HMOs) affect the overall gut microbiome composition. Mother milk consists of many different HMOs that vary in concentration in breastmilk depending on the ethnicity of the mother and during the infant's growth. When the gut microbiome at an early age is investigated, we notice a predominance of bifidobacteria in breastfed compared to formula fed infants. These bifidobacteria are important as they take up carbon and produce short-chain fatty acids that modulate the gut barrier permeability. Their carbon-source are HMOs, and the microbiome plays a role in the digestion of those HMOs trough the presence of CAZymes. Thus, the CAZymes you have, will determine which glycans you can digest and the type of glycans a child is fed will steer the microbiome maturation trough early-life.

A RCT is conducted where a control group of formula fed infants was compared to test groups who received a 5-HMO-Blend formula. The trial is still ongoing, but preliminary results show that the overall gut microbial diversity was significantly different in the control group compared to the test group, where in the test group the composition became more similar to the breastfed infants. The speaker suggests this could be the consequence of promotion of bifidobacteria, although this was just a speculation.

Photo: Shutterstock.

Sources

• **1**. Shah SA, Deng L, Thorsen J, *et al.* Hundreds of viral families in the healthy infant gut. bioRxiv 2021: 2021.07.02.450849. • **2**. Maldonado J, Gil-Campos M, Maldonado-Lobón JA, *et al.* Evaluation of the safety, tolerance and efficacy of 1-year consumption of infant formula supplemented with Lactobacillus fermentum CECT5716 Lc40 or Bifidobacterium breve CECT7263: a randomized controlled trial. BMC Pediatr 2019; 19: 361. • **3**. Pastor-Villaescusa B, Blanco-Rojo R, Olivares M. Evaluation of the Effect of Limosilactobacillus fermentum CECT5716 on Gastrointestinal Infections in Infants: A Systematic Review and Meta-Analysis. Microorganisms 2021 ;9(7).

PRESS REVIEW

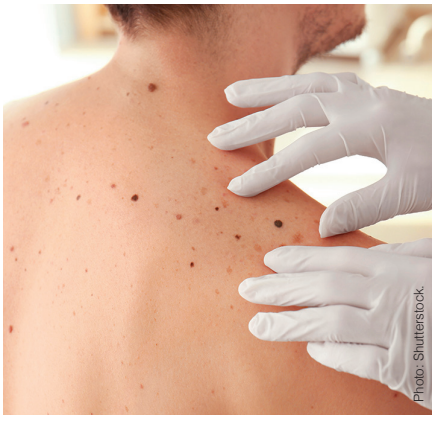
By Pr. Satu Pekkala
Academy of Finland Research Fellow, Faculty of Sport and Health Sciences, University of Jyväskylä, Finland

GUT MICROBIOTA

CROSS-COHORT GUT MICROBIOME ASSOCIATIONS WITH IMMUNE CHECKPOINT INHIBITOR RESPONSE IN ADVANCED MELANOMA

Immune checkpoint inhibitors (ICIs) have significantly improved the treatment of advanced melanoma. However, not all patients respond to the treatment, which has been thought to be linked to the gut microbiota. Lee *et al.* performed metagenome shotgun sequencing of fecal samples from five European ICI-naïve cohorts, with a total of 165 advanced cutaneous melanoma patients. Due to clinical and mutational differences between the cohorts, they were analyzed separately and not pooled. The authors found a significant difference in the gut microbiota composition between responders and non-responders in the PRIMM-UK cohort, but not in the PRIMM-Netherland (NL) cohort. Further, by analyzing publicly available databases (n = 147 metagenomic samples), it became evident that there was limited reproducibility of response predictions across cohorts. No single bacterium was an entirely constant biomarker of response to ICIs across all datasets. However, a panel of microbial species, including *Bifidobacterium pseudocatenulatum, Roseburia* spp. and *Akkermansia muciniphila*, was identified in the study associated with responders. Regarding the functional genes of the microbiota, *e.g.*, DNA adenine methylases were increased in the responders. In conclusion, though a potential panel of microbial biomarkers showing the responsiveness to ICI treatment was identified, future studies in larger cohorts are needed. In addition, several clinical factors should be considered as confounding when evaluating the biomarkers that may be useful in diagnostics

Lee KA, Thomas AM, Bolte LA, *et al.* Cross-cohort gut microbiome associations with immune checkpoint inhibitor response in advanced melanoma. *Nat Med* 2022; 28: 535-44.



INTESTINAL *AKKERMANSIA MUCINIPHILA* PREDICTS CLINICAL RESPONSE TO PD-1 BLOCKADE IN PATIENTS WITH ADVANCED NON-SMALL-CELL LUNG CANCER

Many patients with non-small-cell lung cancer (NSCLC) do not respond to the treatment with immune checkpoint inhibitors (ICIs), such as anti-PD-1. Recent evidence shows that certain members of the gut microbiota, especially *Akkermansia muciniphila*, can influence the efficacy of ICIs in patients with NSCLC. In addition, the treatment resistance has been associated with lower inflammatory tumor microenvironment. Derosa *et al.* prospective, multicentric study included 338 patients with advanced NSCLC treated with ICIs to determine whether the gut microbiota metagenome profiles could explain the treatment response. They show that higher *Akkermansia* abundance in the baseline feces was associated with higher response rate to the ICI treatment, associated with clinical benefit (increase in survival). In addition, the presence of *Akkermansia*

associated with other potentially prognosis-relevant shifts in the gut microbiota. Several differentially expressed tumor genes were linked to the response to PD-1 blockade suggesting that *Akkermansia* could promote migration of T helper cells to the tumor microenvironment. To ultimately show that *Akkermansia* could rescue the ICI resistance, the authors inoculated two different strains of *A. muciniphila* to mice that were previously transplanted with feces of a patient with resistance to PD-1 blockade. Compared to the control mice, the two strains rescued the treatment response. By far, this study is the largest metagenomics prospective analysis that has validated *Akkermansia* as a potential prognostic factor for ICI-treated NSCLC patients and showed the mechanistic potential of *Akkermansia*.

Derosa L, Routy B, Thomas Am *et al.* Intestinal Akkermansia muciniphila predicts clinical response to PD-1 blockade in patients with advanced non-small-cell lung cancer. *Nat Med* 2022; 28: 315-24.


Photo: Shutterstock.

FAECAL MICROBIOTA TRANSPLANTATION FOR BIPOLAR DISORDER: A DETAILED CASE STUDY


Photo: Shutterstock.

The only validated indication for FMT is recurrent *Clostridioides difficile* infection, However, the involvement of gut microbiota in numerous other diseases (Parkinson disease for example) suggests that indications for FMT could soon be expanded.Gut microbiota can also modify numerous depression-associated processes, such as hypothalamic-pituitary-adrenal gland axis. So far, there are no published trials using FMT to treat patients with bipolar conditions. The longitudinal study by Parker *et al.* presents the case of a 28-year-old male with bipolar disorder. At the age of 10, he developed depressive episodes. Symptoms included a severely depressed mood, suicidal thoughts, anergia, impaired concentration, psychomotor retardation, and insomnia. The symptoms were commonly associated with irritability and anxiety. At the age of 15, he developed his first hypomanic episode. For years, he was successfully treated with drugs, but then mood problems occurred again. He voluntarily started taking probiotics (strains of *Lactobacillus and Saccharomyces*. After the probiotics, he self-reported a huge relief of symptoms. Encouraged by the improvements, the patient read on microbiome research and elected to trial FMT. This procedure was performed via colonoscopy by a gastroenterologist. After the FMT, he charted his mood states for 470 consecutive days. He self-reported that mood episodes decreased in frequency and severity over the months. He was also able to reduce the drug treatment significantly. Twelve months after FMT, he stated having distinct highs, virtually no bipolar symptoms, and attention deficit hyperactivity disorder symptoms had improved. Though this is only a case study, FMT was able to reduce the bipolar symptoms, thus warranting the need for FMT studies in larger bipolar cohorts.

Parker G, Spoelma MJ, Rhodes N. Faecal microbiota transplantation for bipolar disorder: A detailed case study. *Bipolar Disord* 2022 (ahead of print).

VAGINAL MICROBIOTA

GONORRHEA IN WOMEN: A LINK BETWEEN VAGINAL MICROBIOTA AND SYMPTOMS?

Each year, nearly 90 million cases of gonorrhea are reported worldwide. In women, infection of the lower genital tract by *Neisseria gonorrhoeae* has highly variable consequences, from no symptoms at all to cervicitis. Although the factors behind this variability are not known, the cervico-vaginal microbiota may be involved. In fact, a team has recently shown that the cervico-vaginal microbiota predicts the clinical presentation of gonorrhea in women.

These are the results of a pilot study in the US on 19 patients infected with *N. gonorrhoeae*, 10 of whom were symptomatic and 9 asymptomatic. Most of these patients were African American, a population whose microbiota is more frequently low in lactobacilli than that of Caucasian women. *Neisseria* spp. accounted for only 0.24% of the bacteria present in all 19 patients, whether symptomatic or asymptomatic. Half of the patients in each group also had co-infections with *Chlamydia trachomatis* and/or *Trichomonas vaginalis*.

The cervico-vaginal microbiota of the asymptomatic patients with no co-infection more frequently contained microbial communities dominated by lactobacilli (92.2% of bacteria on average) than that of the symptomatic patients with no co-infection (21.6%).

In contrast, the symptomatic women had microbial communities characterized by more diverse and heterogenous bacterial taxa. They were composed of a mixture of anaerobic bacteria associated with bacterial vaginosis (BV): *Prevotella, Sneathia, Mycoplasma hominis* and *Bacterial Vaginosis-Associated Bacterium-1* (BVAB1) / *Candidatus Lachnocurva vaginae*.

These results are merely those of a pilot study based on a small sample. This is a crucial first step, but further studies are needed to evaluate the potentially protective effect against *N. gonorrhoeae* infection of a Lactobacillus-dominated vaginal microbiota.

Lovett A, Seña AC, Macintyre AN, *et al.* Cervicovaginal Microbiota Predicts Neisseria gonorrhoeae Clinical Presentation. ***Front Microbiol*** 2022; 12: 790531.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EXPERT OPINION

ASSOCIATION BETWEEN IBD AND GREATER AMOUNTS OF MICROPLASTICS IN STOOL

By Dr. Alberto Caminero
Department of Medicine, Farncombe Family Digestive Health Research Institute, McMaster University, Hamilton, Canada

In a recent study [1], scientists reveal that people who had a high concentration of microplastics in their faeces were more likely to have inflammatory bowel disease (IBD). Is this enough to build a causal association?

What is your opinion regarding the hypotheses of researchers, suggesting that microplastic exposure may be related to IBD process or that IBD exacerbates the retention of MPs?

Up to 71% of patients with inflammatory bowel disease (IBD) believe diet affects symptomatology and 81% follow elimination diets while in remission. However, current dietary recommendations are confusing and contradictory. In this study by Dr Yan et al. [1], authors raised the provocative hypothesis that microplastics (MP) may contribute to the development of IBD. MP are small plastic particles (<5 mm diameter) and considered a major environmental problem due to the overuse of plastics nowadays. MP are widely distributed, easily ingested with our diet, or even inhaled, and may accumulate in various organs due to their small sizes and low rate of degradation. Although preclinical studies have suggested the adverse events of MP on metabolic disorders and inflammation, their impact on human health hasn't been fully investigated yet. Here, authors collected feces of healthy and IBD patients and analysed the concentration of MP. Authors showed a higher concentration of fecal MP in IBD than healthy. Intriguingly, the concentration of MP positively correlated with the disease severity, suggesting MP as potential triggers of clinical activation in IBD while providing a potential link between diet and inflammation. Indeed, authors reported that patients with a higher abundance of fecal MP consumed more plastic-packaged products. Although it has been suggested that MP could pass through the intestinal barrier into the circulatory system and potentially impact health, the results are very preliminary and more information is needed before taking premature conclusions affecting patients. Independently of the impact on gastroenterology, this study highlights the global concerns regarding the large use of plastics nowadays, the implications it may have for human health through the food chain but also through commodities and agricultural products, and the pressing need of reducing plastic use.

What would be your advice to patients suffering IBD regarding the microplastic exposure?

Results need to be taken with caution and more research is required to understand the reported increase of faecal MP in IBD and the implications for clinical severity. Although dietary consumption seems to be the most plausible hypothesis, multiple demographic, methodological or clinical factors could be explaining this increase. It would be of interest to see whether these observations apply to countries other than China, where IBD is on the raise. IBD patients also present with an altered gut microbiome, absorption, permeability and motility, as well as different stool consistency, all factors that can influence MP excretion. Indeed, the gut microbiome is a complex and diverse ecosystem presenting microbes with the capacity to digest different components including MP, and IBD patients present an impaired microbiome. In addition, patients frequently consume different drugs or bioproducts (vitamins, probiotic, etc) to manage their symptoms and this could also indirectly affect faecal MP.

Finally, diet affects symptomatology in IBD and there is the wrong impression that ultraclean foods which are frequently plastic-packaged or bottled (*e.g.* the increase use of bottled water in the last decades), are beneficial. Thus, dietary choices by patients could potentially include more plastic-packaged food. My advice to patients is adhering to traditional and well-tolerated diets, preferring home-prepared and natural foods, and avoiding both ultra-processed and plastic-packaged foods. Reduction of plastic is also good for taking care of our planet!

Source

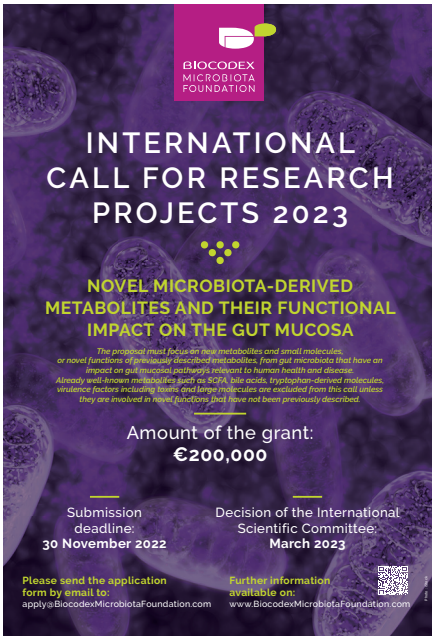
- **1**. Yan Z, Liu Y, Zhang T, Zhang F, Ren H, Zhang Y. Analysis of Microplastics in Human Feces Reveals a Correlation between Fecal Microplastics and Inflammatory Bowel Disease Status. *Environ Sci Technol* 2022; 56: 414-21.

BIOCODEX MICROBIOTA FOUNDATION

INTERNATIONAL GRANT 2023: WHO TO SUCCEED PROFESSOR SØRENSEN?

In April 2022, the international scientific committee of the Biocodex Microbiota Foundation awarded Professor Søren Johannes Sørensen, University of Copenhagen, for his study project: "Linking the early life resistome and microbiome maturation". The Biocodex Microbiota Foundation international research grant for 2022 will allow Pr. Sørensen and his team to follow up on our recent findings of surprisingly many antimicrobial resistance genes (AMRG's) in the gut microbiome of 1-year-old infants.

The call for project for the international research grant 2023 is open. Projects will have to focus on **"Novel microbiota-derived metabolites and their functional impact on the gut mucosa"**. Researchers can apply until 30th November 2022 (apply@BiocodexMicrobiotaFoundation.com). The International scientific committee will announce the awarded project in March 2023.



BIOCODEX MICROBIOTA INSTITUTE

THE INSTITUTE'S NEW LINKEDIN ACCOUNT IS LIVE: SHARING IS CARING!

After Facebook and Twitter, you were all expecting it: Biocodex Microbiota Institute is pleased to announce that it is now on LinkedIn, to promote the importance of microbiota to everyone. The Institute's page will be regularly updated with:

- news on its yearlong initiatives;
- participation to events dedicated to microbiota;
- interviews and portraits of its teams all over the world.

Moreover, it will focus on specific tools created to help healthcare professionals in their everyday practice but also educate Lay Public on the importance of microbiota. Stay tuned!

To sum up the Institute's presence on social media:

LinkedIn: Biocodex Microbiota Institute for news about events, teams and specific tools

Twitter: @microbiota_Inst the feed for HCPs to follow to get the latest information about microbiota

Facebook: "My health, my microbiota" educates a lay public audience to the importance of Microbiota in health

YouTube: Biocodex Microbiota Institute is where all the Institute's videos, testimonies and interviews are posted

Join the microbiota community now!

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