MICROBIOTA

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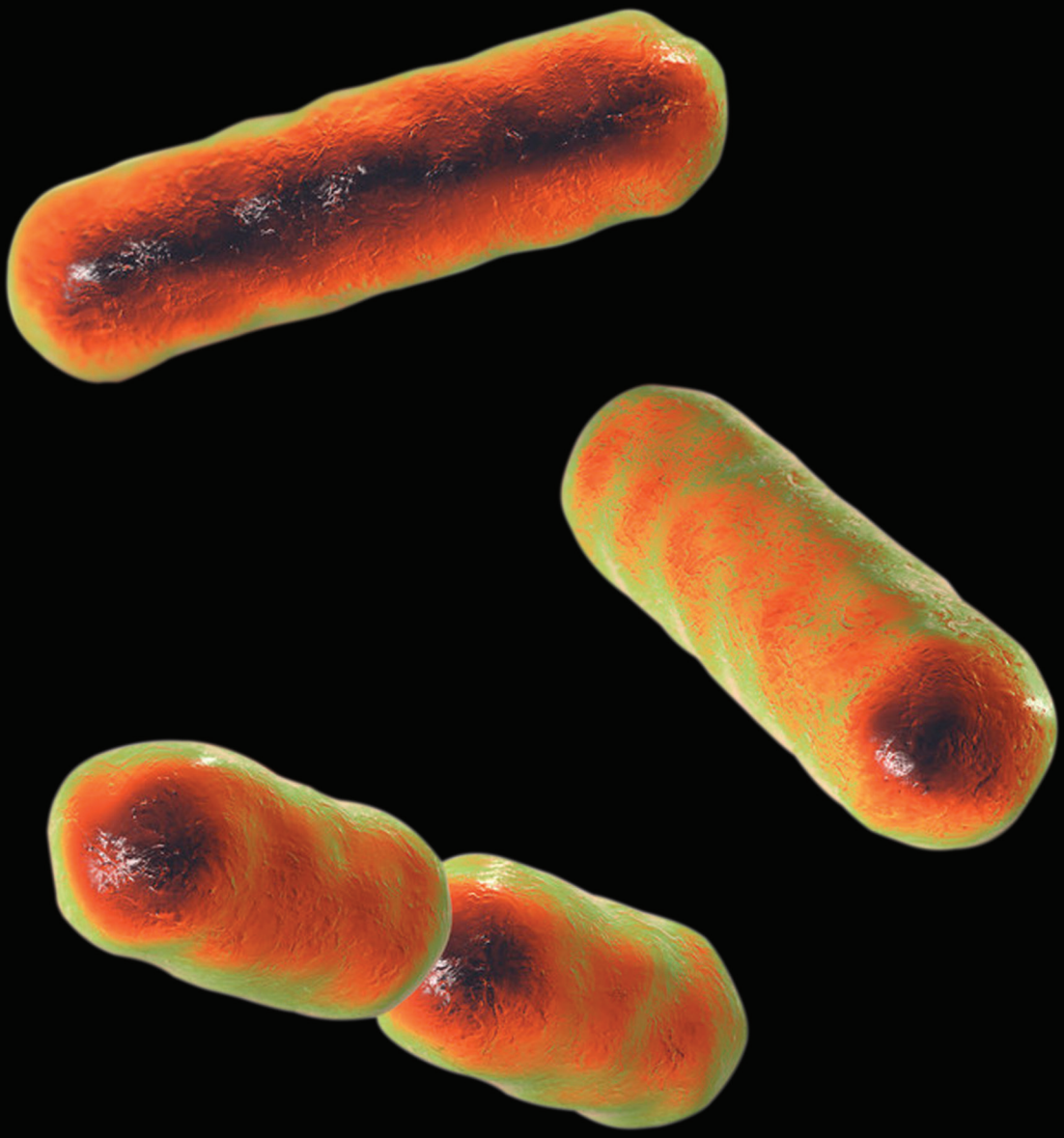

BIOCODEX
Microbiota Institute

SUMMARY

EDITO

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Dear readers,

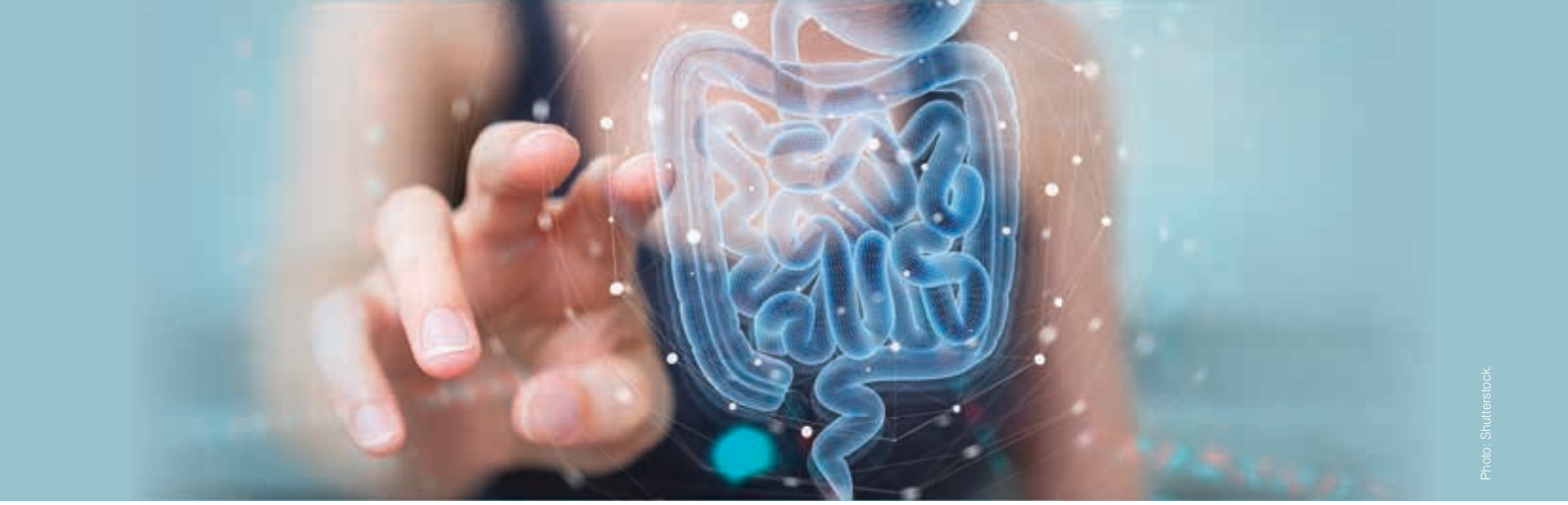
for more than a year now, our news has constantly revolved around a two-syllable word to which a number has been added: Covid-19. There is not a day that goes by without a press article, a news flash, a radio or television programme devoted to this global pandemic. The Google search engine is a good indicator: 5.6 billion queries for “Covid-19”, 43 million for “Covid-19 symptoms”, 10 million for “microbiota and Covid-19”. Medical news is not to be outdone. Try typing “Covid-19 microbiota” into the PubMed search engine and nearly 300 publications come up!

This scientific emulation is good news: research is progressing. Quickly. It is enabling a better understanding of the pandemic: mode of transmission, symptoms, prevention, treatments... So much advances in barely a year! But many questions remain, notably about the link between Covid-19 and the microbiota. Does this virus affect humans via a perturbation of their microbiota? Or are the changes in the microbiota the consequence of the infection by the virus? Some publications show that intestinal dysbiosis persists for a long time after the symptoms have disappeared, but until when? What about the role of the microbiota in cases of long Covid? Professor Tao Zuo’s article gives some clues.

> “THERE IS NO DOUBT THAT IN THE COMING MONTHS, NEW PUBLICATIONS WILL SHED MORE LIGHT ON THIS ‘YOUNG’ PANDEMIC AND ITS INTERACTIONS WITH THE INTESTINAL MICROBIOTA.”

Other questions remain, notably on the involvement of the intestinal microbiota in the immune response to the virus infection and on the severity of the symptoms. This is an opportunity to go back to the basics of the dialogue between the microbiota and intestinal immunity, which begins in foetal life. There is no doubt that in the coming months, new publications will shed more light on this ‘young’ pandemic and its interactions with the intestinal microbiota. And who knows, potential means of prevention may emerge. New knowledge to be discovered in the next issues of *Microbiota*!

Enjoy your reading.



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OVERVIEW

CROSSTALK BETWEEN THE GUT MICROBIOTA AND THE HOST'S IMMUNE RESPONSE TO COMBAT INFECTIONS

The fact that living beings have evolved over millions of years in complex environments occupied by microbial ecosystems has shaped symbiotic relationships regulated by the immune system. The new sequencing techniques have revolutionised our knowledge and have shown that each individual hosts a microbiota which is unique to him, as is its role in the physiology of the host and in numerous diseases such as infections. The interaction between the gut microbiota and the immune system starts during foetal life. Their mutual and constant exchanges shape both the immunity of the host and also the gut microbiota resulting in protection from infection and numerous diseases. Indeed, the specific organisation of the microbiota - separated from the host by a single layer of cells - constitutes a particular challenge for the immune system, the role of which is to recognise "non-self" as a potential sign of infection and thus trigger the immune system cascades. For this reason, the continuous exchanges with the microbiota have a significant impact on the immune system of the host. The immune response, which must be tolerant towards the microbiota, also has an impact on the composition and function of this microbiota.

By Dr. Dorota Czerucka
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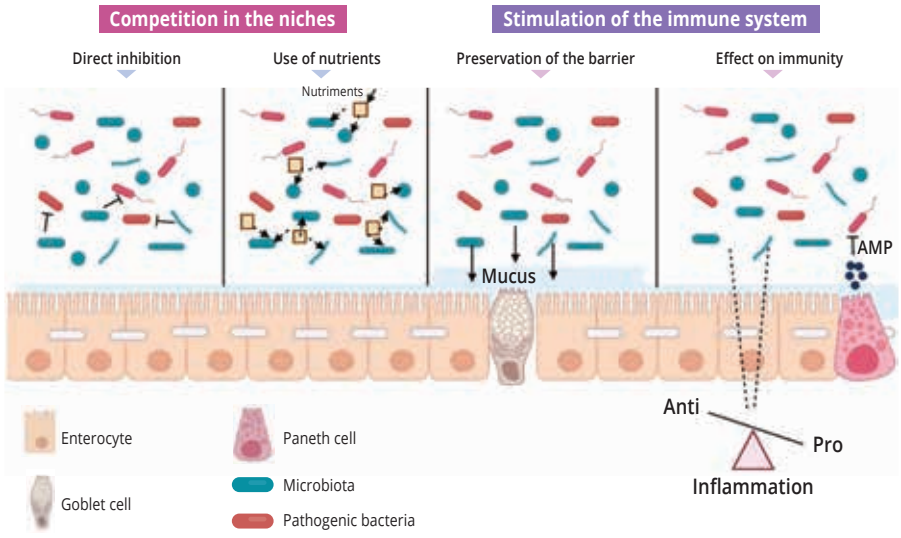
GUT MICROBIOTA AND THE INTESTINAL BARRIER

The gut microbiota is an initial barrier protecting the intestinal mucosa from pathogens. This complex ecosystem inhabits the gastrointestinal tract where it remains stable and limits access to the intestinal niches and to the nutrients required for the multiplication of exogenous bacteria by the phenomenon called "colonisation resistance" [1] (**Figure 1**). The enterocytes, which provide a physical barrier between the intestinal lumen and the host, absorb water and nutrients and secrete antimicrobial peptides, AMPs (RegIIIγ, β-defensins and cathelicidin) [2]. By the recognition of microbe-associated molecular patterns, (MAMPs) by specific receptors (including the Toll-Like-Receptors, TLR), these cells will be able to transduce the signal to cytokines and chemokines thus signalling infection and recruiting immune cells (**Figure 2**). Paneth cells also participate in colonisation resistance by secreting AMPs (lysosyme, α-defensins, RegIIIγ) [2].

The goblet cells – mucus-secreting – and the M cells have gatekeeping action, transporting antigens, intact and captured at

▼ FIGURE 1

Functions of the gut microbiota which contribute to colonisation resistance



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random in the intestinal lumen arising from commensal bacteria or pathogens or dietary antigens. These will then be prepared by the dendritic cells (DC) and presented to the adaptive immune system. This function is vital to intestinal tolerance and the induction of mucosal immune responses [2]: there therefore is a constant balance between pro- and anti- inflammatory responses (**Figure 2**). In particular, this was demonstrated in mice models of induced colitis and in TLR receptor-deficient mice: the absence of microbiota or recognition of this reduces the proliferation of intestinal epithelial cells or barrier repair [2]. Lastly, the mucus also provides protection by capturing AMPs, which act to prevent the pathogens from reaching the epithelium. In the model of Muc2-deficient mice (Muc2 is the gene coding for one of the proteins making up the mucus), an increase in the translocation of commensal bacteria is observed and these animals develop intestinal inflammatory diseases [3].

CROSSTALK BETWEEN THE GUT MICROBIOTA AND THE INNATE IMMUNE SYSTEM

Among the players of the innate immune system which participate in intestinal homeostasis, antigen-presenting cells (APC), such as the macrophages (Mφ) and the DCs have a major role. The Mφ and the DCs synthesise IL-10 and thus promote differentiation of Treg [4] and the maturation of the Th17 lymphocytes via the implication of commensal bacteria: the segmented filamentous bacteria (SFB). These have the particular ability to adhere to the intestinal epithelial cells causing active stimulation of the immune system [5] (**Figure 3**). A study shows that colonisation of mice by these SFB, induces the differentiation of Th17 thus resulting in protection from *Citrobacter rodentium* (the murine equivalent of EPEC and EHEC). It has been suggested that this protection is due to the capacity of the SFB to cause Th17 to stimulate the synthesis of IL-22, a cytokine known to stimulate the synthesis of AMPs [6]. To come back to the DCs, these, by extending their dendrites between the epithelial cells, are able to phagocyte the bacteria present in the intestinal lumen. These commensal bacteria are then transported to the mesenteric lymph nodes to induce the production of IgA secreted by the plasma cells [1].

The innate lymphoid cells (ILC) also play an important role in intestinal homoeostasis; this is related to their capacity to initiate and direct intestinal immune responses. More specifically, the type 3 ILCs (ILC3) have a unique place in the interaction with the gut microbiota. By synthesising IL-22, these cells stimulate the production of mucus, AMPs and the secretion of chemokines and recruitment of polymorphonuclear (PMN) cells (**Figure 2**) [1].

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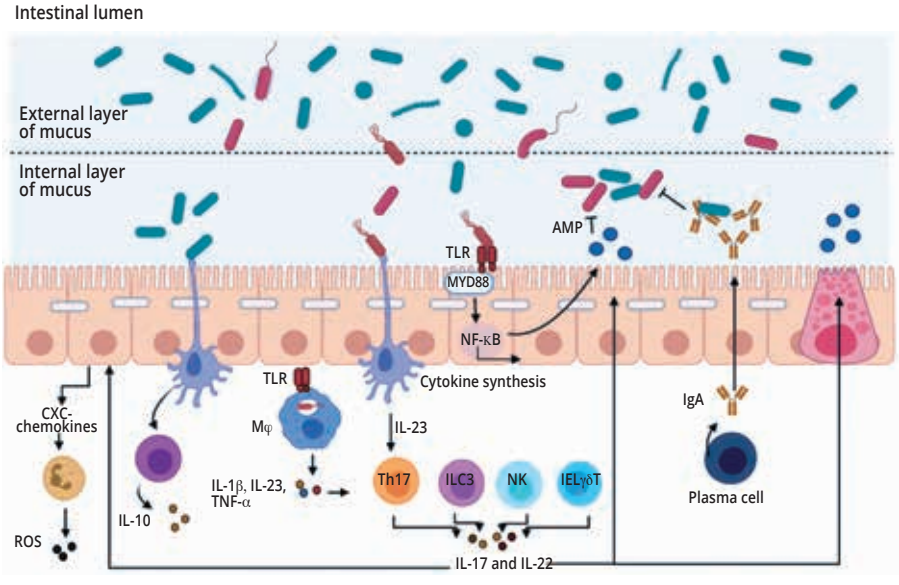
▼ FIGURE 2

Response of the immune system to infections



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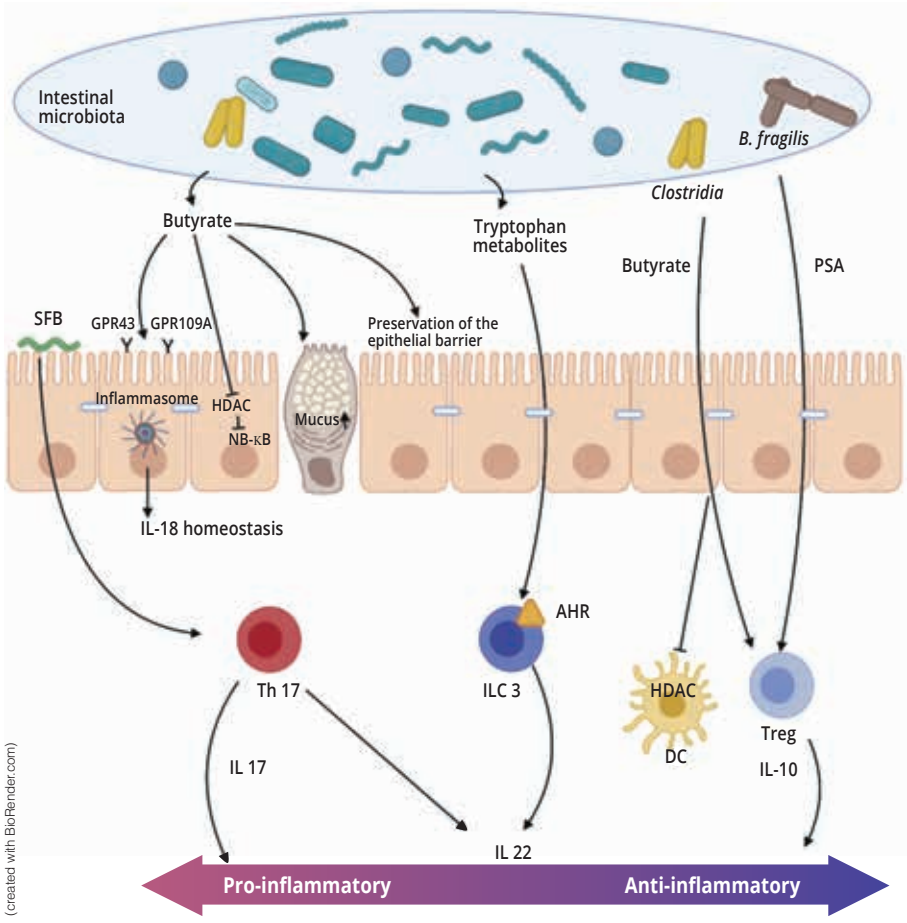
▼ FIGURE 3

Metabolites produced or synthesised by the gut microbiota and their impacts on immune responses

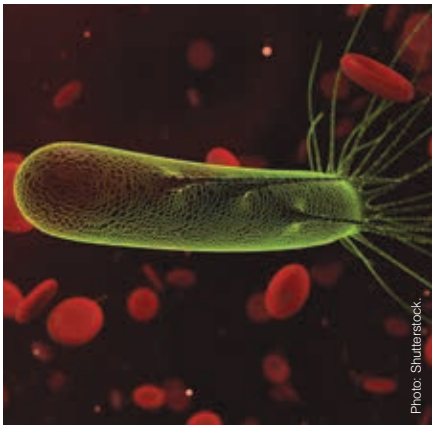


CROSSTALK BETWEEN THE MICROBIOTA AND THE ADAPTIVE IMMUNE SYSTEM

The final maturation of the adaptive immune system is characterised by the colonisation of the intestinal mucosa by mature effector T-lymphocytes with inflammatory properties (Th17), T-lymphocytes with anti-inflammatory properties (Treg) and B-lymphocytes (**Figure 2**). Besides effects on the macrophages and the differentiation of the Th17 cells, the SFB also stimulate the development of the lymphoid follicles and participate in the differentiation of the B-lymphocytes to IgA-producing plasma cells the action of which is the containment of pathogenic bacteria in the mucus [5]. Other commensal bacteria can stimulate adaptive immune responses: a mixture of 17 *Clostridia* strains isolated from a human faecal sample and introduced in mice induced an anti-inflammatory response by stimulating the Treg [7]. *Faecalibacterium prausnitzii* has also been identified for its anti-inflammatory action *in vitro* and *in vivo* by acting on the NF-κB factor, DCs and Mφ which secrete IL-10 and enhance differentiation of Treg to the detriment of Th17 [8]. Of the Bacteroidetes, *Bacteroides fragilis* and *B. thetaiotaomicron* have also been described as exerting anti-inflammatory activity. *B fragilis* synthetises a polysaccharide A (PSA) that prevents pro-inflammatory IL-17 production and stimulates the anti-inflammatory of secretion IL-10 (**Figure 3**). In a specific model of *Helicobacter hepaticus*-induced colitis, PSA stimulated the development of lymphoid follicles, stimulated Treg lymphocyte cells and protected the mice [9].

MICROBIAL METABOLITES: IMPORTANT MEDIATORS IN THE CROSSTALK BETWEEN THE MICROBIOTA AND ADAPTIVE IMMUNITY

Short-chain fatty acids (SCFAs), tryptophan metabolites and bile salts are the principal metabolites produced by the gut microbiota which exert a protective effect against infections [9, 10]. Butyrate, propionate and succinate are known to act on intestinal homoeostasis, on mucus secretion, but also on the various cells of the immune system. Among other effects, butyrate has anti-inflammatory and anti-microbial effects. This action is exerted via the G-coupled protein receptors (GPR) found on the epithelial cells and the macrophages [9]. *F prausnitzii* produces large quantities of butyrate, which may partly explain its anti-inflammatory effect. It inactivates NF-κB and thus suppresses synthesis of the pro-inflammatory cytokines IFN-γ, TNF-α, IL-1β, IL-8 by the enterocytes [8] (**Figure 3**) . It also induces metabolic and epigenetic modifications (via histone deacetylases, HDACs) macrophages in mice, thus amplifying their anti-microbial activities *in vitro* and *in vivo* [11]. Commensal bacteria can also metabolise tryptophan and produce antimicrobial substances. An example is the *Lactobacilli*, which utilise it as an energy source to synthesise an indole that binds to aryl hydrocarbon receptors (AhR) present on the ILC3. AhR triggers IL-22 secretion by the ILCs and this further drives the secretion of AMPs and protects against infections [9].



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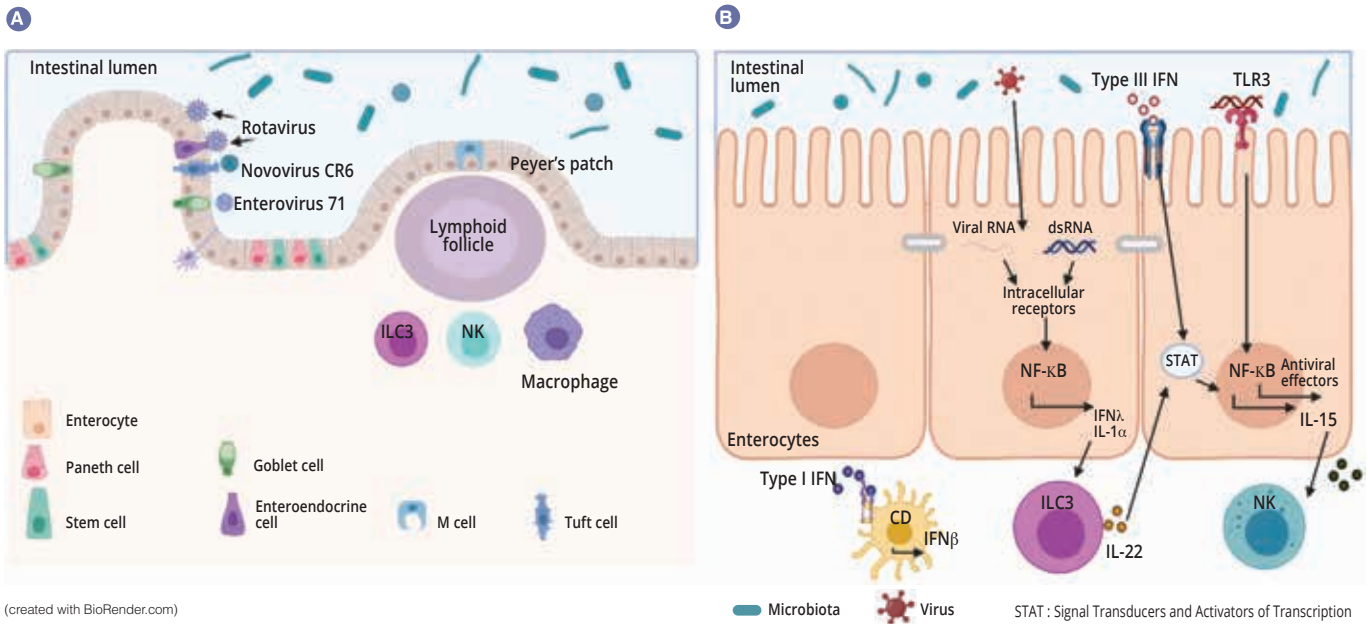
▼ FIGURE 4

A: Various cell types for enteric virus adhesion, B: Antiviral responses in the intestinal epithelial cells in case of infection



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MICROBIOTA – INTESTINAL IMMUNE SYSTEM CROSSTALK FOR PROTECTION AGAINST VIRAL INFECTIONS

Among the enteric viruses, norovirus and rotavirus are the main causes of gastroenteritis [12]. The enteric viruses infect various cell types: enterovirus 71 specifically infect the goblet cells, whereas the rotavirus has a preferential tropism for the enterocytes [13] (**Figure 4A**). The gut microbiota acts as a barrier against enteric viral infections. The viruses have evolved and become adapted to their host, implementing mechanisms that enable them to cross the intestinal barrier and escape barrier immunity: it is in fact difficult to infect mice effectively with human enteric viruses by the oral route [13]. Virus penetration into the enterocyte triggers the secretion of type III interferon (IFN). Detection of a virus can induce IL-lα, which activates the ILC3 to produce IL-22. This IL protects against enteric viral infections and acts synergistically with type III IFN to induce the expression of antiviral effectors and IL-15. Recognition of a virus by TLR-3 leads to the activation of the NF-κB pathway and to the production of IL-15 also. IL-15 activates the cytotoxic lymphocytes (NK cells). Those viruses, which have traversed the intestinal barrier, trigger the production of type I IFN by the macrophages of the lamina propria (**Figure 4B**). Some enteric viruses (rotavirus, reovirus, enterovirus) are able to adhere to the intestinal bacteria, enhancing penetration into the intestinal epithelial cells [13]. The SFB, which accelerate epithelial cell turnover produce protection against rotavirus infection in mice by expulsing infected cells [14]. The bile acids metabolised by the gut microbiota also act to protect the small intestine (but not the colon) from acute infection by norovirus in mice by enhancing the production of type III IFN in the small intestine [15].

CONCLUSION

The study of the relationship between the gut microbiota and intestinal immune response represents significant progress in gastroenterology research. Intestinal homeostasis is maintained due to the recognition of commensal bacteria by the cells of the innate system and the cells of the intestinal epithelium, either by direct contact (in the case of SFB), or *via* the synthesis of metabolites by the microbiota. The loss of homeostasis (intestinal dysbiosis, infections etc.) causes stimulation of the innate responses and an activation of the adaptive system. Poor "management" of inflammation can result in the onset of disease, such as post infectious irritable bowel syndrome.

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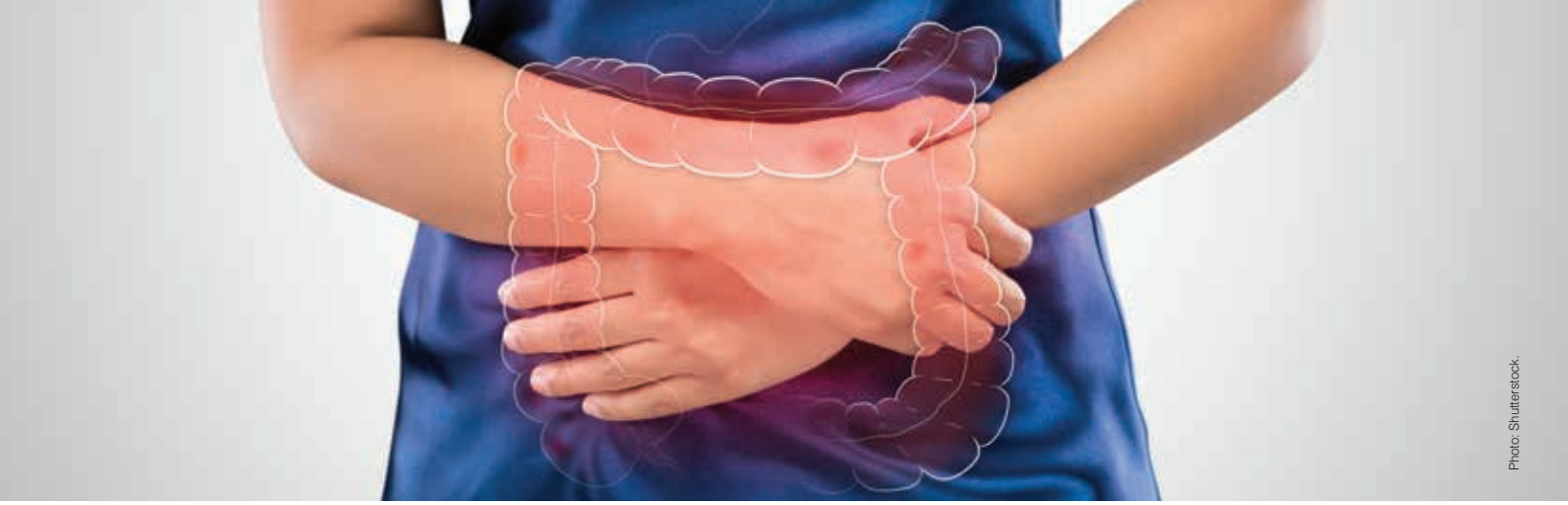

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COMMENTED ARTICLE
ADULTS' SECTION

By Prof. Harry Sokol
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LONGITUDINAL MULTI-OMICS ANALYSIS REVEALS SUBSET-SPECIFIC MECHANISMS UNDERLYING IRRITABLE BOWEL SYNDROME

Commentary on the original article by Mars et al. Cell 2020 [1]

The gut microbiome is implicated in numerous chronic gastro-intestinal disorders in humans. Determining its role however has been rendered difficult due to the lack of correlation between animal and human studies as well as that of an integrated multi-omics view of disease-specific physiological changes. The authors integrated longitudinal multi-omics data from the intestinal microbiome, the metabolome, the host epigenome and the transcriptome in the context of irritable bowel syndrome (IBS) host physiology. They have identified IBS sub-type specific and symptom-related variations in microbial composition and function. A sub-group of changes identified in microbial metabolites corresponds to host physiological mechanisms which are relevant to IBS. By compiling multiple data layers, the authors identified purine metabolism to be a new host-microbiota metabolic pathway in IBS with potential for therapeutic application. This study highlights the value of longitudinal sampling and the integration of complementary multi-omics data in the identification of functional mechanisms which may be future therapeutic targets in a global treatment strategy for chronic intestinal diseases.

WHAT DO WE ALREADY KNOW ABOUT THIS SUBJECT?

Irritable bowel syndrome (IBS) is a disorder observed in patients all over the world, characterised by recurrent abdominal pain or discomfort. Occurring mainly in women, IBS is associated with changes in the form or frequency of stools and it is the form of the latter which defines the IBS subsets: IBS with constipation (IBS-C), IBS with diarrhoea (IBS-D) or IBS with mixed bowel habits (IBS-M). The pathogenesis of IBS involves changes in gastro-intestinal motility, intestinal secretion, visceral hypersensitivity and intestinal permeability, all of which can be modified by the gut microbiome [2]. Moreover, IBS symptoms are influenced by the diet, host genetics and the environment, which are also known to modulate the human gut microbiome [2].

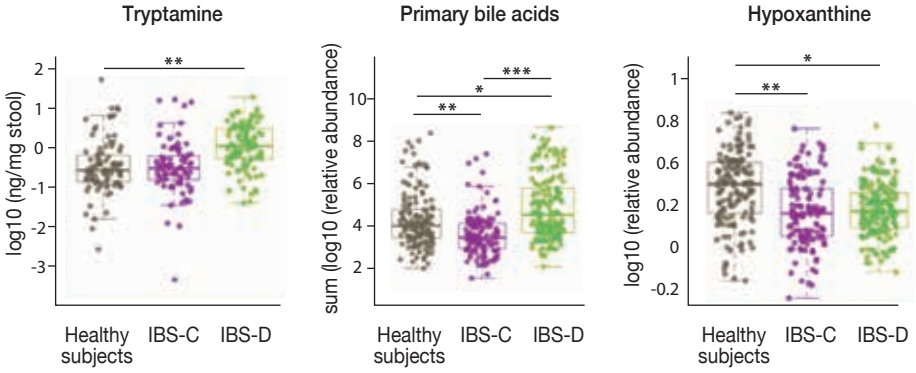
Experimental evidence supporting the role of the gut microbiome in IBS are based on patient-to-gnotobiotic mouse transplantation studies which reproduced certain symptoms associated with IBS-C and IBS-D (transit time, sensation of pain, intestinal permeability…) [3]. However, in the absence of robust animal models of IBS, studies in humans are needed to determine the interactions between the gut microbiome and the pathological pathways specific to humans. Human IBS studies are limited in general by the use of transversal sampling and a failure to stratify into patient subsets, which is reflected in the lack of agreement in the results obtained in the large number of studies on the microbiome [4]. The well-described influence of gastro-intestinal transit on the intestinal microbiome increases the variability of the studies even more. In addition, IBS, in common with other chronic gastro-intestinal disorders, is characterised by periods of remission and flare up of the symptoms, and transversal sampling therefore fails to take into account the fluctuations of the disease over time. Lastly, the inherent differences in host physiology between humans and animals have been an obstacle to progress in our understanding of the mechanistic roles of the gut microbiome in IBS. The authors performed a longitudinal study in

KEY POINTS

- The functions of the gut microbiota are impaired in IBS and there are differences between IBS-C and IBS-D
- The increase in the production of tryptamine and the reduction in transformation of bile acids may be implicated in IBS-D
- Over-consumption of hypoxanthine by the microbiota and host cells may be implicated in IBS by altering the energy level of the intestinal mucosal epithelium cells.

▼ FIGURE 1

Changes in microbial metabolites during IBS: Levels of tryptamine, primary bile acids and hypoxanthine in stools



subsets of patients with IBS, integrating multi-omics measurements, including the microbial metagenome, host transcriptome and the methylome with assessment of host cell functions. This revealed mechanisms specific to the IBS subset induced by impaired microbial metabolism, which corresponded to simultaneous changes in the host physiology.

WHAT ARE THE MAIN INSIGHTS FROM THIS STUDY?

Here, the authors conducted a prospective observational longitudinal study with multi-omics analysis of the gut microbiome and the host cells. Healthy subjects were compared with patients with IBS-C and IBS-D. A total of 77 participants supplied at least one stool sample (a total of 474 stool samples were obtained), and 42 participants received a sigmoidoscopy which provided colon biopsies. In order to identify the microbial factors causing the symptoms specific to each of the IBS subsets, metagenomic sequencing and a metabolomic analysis were performed on the stool samples. A metabolomic analysis and cytokine assays were performed on serum samples. Lastly, 16S sequencing, and metabolomic, transcriptomic and methylomic analyses were performed on the colon biopsies.

The authors identified differences in the composition and diversity of the gut microbiota between healthy subjects and IBS-C or IBS-D patients.

Metabolomic analysis of the stools revealed increased levels of tryptamine, a tryptophan metabolite produced by certain intestinal bacteria, in patients with IBS-D (**Figure 1**). Because tryptamine accelerates transit due to an action on the serotonin receptor, 5-HT4, it is suggested that it could have a role in the phenotype of these patients. Similarly, the proportion of primary bile acids was higher in patients with IBS-D, a sign of impaired transformation of bile acids by the microbiota. *In vitro* experiments suggest that primary bile acids increase secretion in the colon and could also participate in the phenotype.

Lastly, the integration of multi-omics data identified a potential new mechanism in IBS. The results suggest that in IBS patients there is increased degradation of purine nucleotides and of hypoxanthine in particular, by the microbiota and the host cells, which induces stress in the colon. It is suggested that this could lead to a compensatory response with an increase in purine recuperation. The low levels of purine nucleotides could lead to a reduced source of energy to the mucosal epithelium and to a reduced capacity for repair of the gut mucosa, which could partly contribute to IBS physiopathology.

WHAT ARE THE CONSEQUENCES IN PRACTICE?

These data suggest a role of the gut microbiota in the physiopathology of IBS with differences between IBS-C and IBS-D. Moreover, these results point towards the potential role of a deficiency in purine nucleotides, in particular via an over-consumption of hypoxanthine by the microbiota and the host cells. These results point the way to treatments stimulating the production of microbial hypoxanthine or inhibiting xanthine oxidase locally in the intestine.

CONCLUSION

This longitudinal study with integrated multi-omics shows the value of longitudinal studies in humans and highlights functional alterations to the microbiota in IBS which may potentially be implicated in the physiopathology of this disease. The new leads which have been identified may be new therapeutic targets.

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COMMENTED ARTICLE
CHILDREN'S SECTION

DUODENAL MICROBIOTA IN STUNTED UNDERNOURISHED CHILDREN WITH ENTEROPATHY

Comments on the original article of Chen et al. (N Engl J Med 2020) [1]

Environmental enteric dysfunction (EED) is an enigmatic disorder of the small intestine that is postulated to play a role in childhood undernutrition, a pressing global health problem. Defining the incidence of this disorder has been hampered by the difficulty in directly sampling the small intestine mucosa and the microbiota. This study involved 110 young children exhibiting linear growth stunting who lived in an urban slum in Bangladesh, and who had not benefitted from nutritional intervention. The authors performed an endoscopy on 80 children who had biopsy-confirmed EED and for whom samples of plasma and duodenum were available. Of the bacterial strains obtained from the children, the absolute levels of a shared group of 14 taxa (not typically classified as enteropathogens) were negatively correlated with linear growth and positively correlated with duodenal proteins implicated in immuno-inflammatory responses. The representation of these 14 duodenal taxa in the faecal microbiota was significantly different from that of samples obtained from healthy children. Enteropathy of the small intestine developed in gnotobiotic mice that had been colonised with cultured duodenal strains obtained from children with EED.
These results confirm the existence of a relationship between delayed growth and components of the microbiota of the small intestine and enteropathy, and provide a rationale for the development of therapies targeting these microbial contributions to EED.

WHAT DO WE ALREADY KNOW ABOUT THIS SUBJECT?

The proportion of chronic undernourishment with growth stunting is 25 % in infants who have had more than 5 episodes of diarrhoea. These recurrent intestinal infections result in EED, a disorder characterised by villous atrophy combining a reduction in intestinal surface area and absorption capacities, alteration of the intestinal barrier and mucosal inflammation. More recent data suggest that microbiota dysbiosis of the upper gastrointestinal tract may be present in EED.

By Prof. Emmanuel Mas
Gastroenterology and Nutrition Department, Children's Hospital, Toulouse, France

WHAT ARE THE MAIN INSIGHTS FROM THIS STUDY?

This study included 110 infants with a mean age of 18 months, from Dhaka, Bangladesh, who had chronic undernutrition with stunted growth, defined by nutritional intervention. Duodenal biopsies confirmed the presence of EED in 80 of them. The duodenal aspirate microbiota from 36 of these infants was analysed; a group of 14 bacterial taxa was present in over 80% of this population and were negatively correlated with the length/age ratio ($r = -0.049$, $p = 0.003$) (**Figure 1**). The proteomics study of the duodenal biopsies showed a positive correlation between these 14 taxa and 10 proteins including 2 antimicrobial peptides, a marker of intestinal inflammation (LCN2), and a negative correlation with 10 proteins produced by the enterocytes (**Figure 2**).

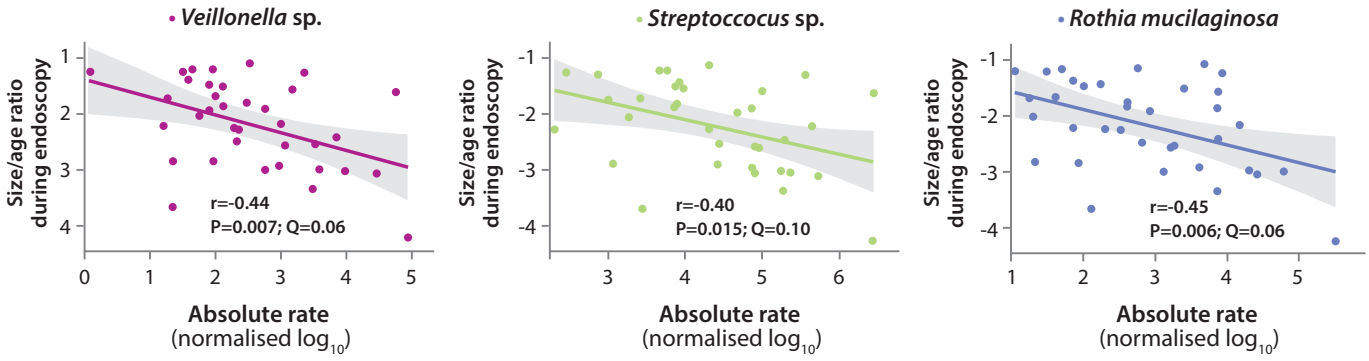
In the 80 infants with demonstrated EED, the plasma proteomics study showed a strong positive correlation with REG3A and LCN2.

Comparison of the faecal microbiota of EED infants with 27 controls revealed a significant increase in *Veillonella* genus bacteria which were the most highly correlated with the duodenal proteins implicated in gastrointestinal inflammation.

After culture of 39 bacterial strains from duodenal aspirates of infants with environmental enteric dysfunction, including 11 of

▼ FIGURE 1

Correlation between chronic undernutrition with stunted growth (z-score of length/age ratio) and the abundances of *Veillonella*, *Streptoccocus* and *Rothia mucilaginosa*.



the 14 taxa, these were administered by oral gavage to mice that had been fed a diet similar to that of an 18-month-old Dhaka infant. Twenty-three of these bacteria were found to be present with a relative abundance > 0.1% in at least one part of the gut. Control mice received the caecal microbiota of conventionally raised mice by oral gavage. In contrast to the control mice, mice receiving "environmental enteric dysfunction" bacteria, exhibited infiltration of inflammatory mononuclear cells in the lamina propria of the small intestine in addition to epithelial abnormalities and architectural distortion with elongated crypts. These abnormalities had a patchy location in the small intestine but did not extend to the colon. From a functional viewpoint, the results showed in these mice an increase in mRNA expression of anti-microbial peptides (Reg3β and Reg3γ), an increase in a metalloproteinase (MMP8) and a reduction in mRNA encoding tight junction proteins. These alterations in the innate immune response and of the mucosal epithelial barrier may explain the systemic bacterial translocation to the spleen (*Escherichia coli* and *Enteroccocus hirae*).

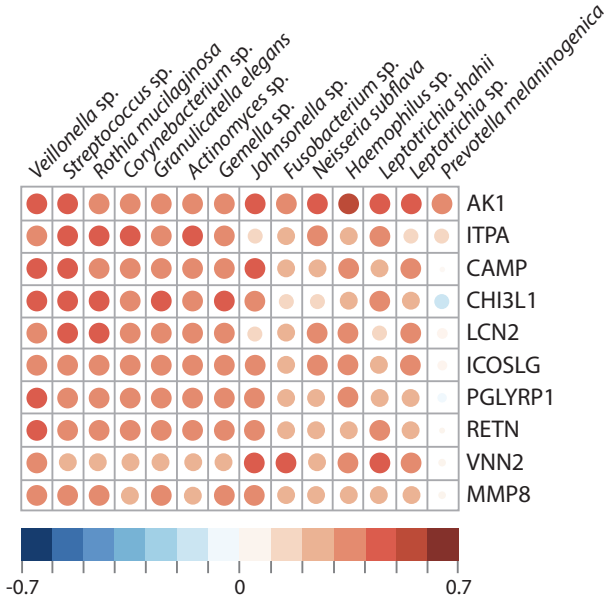
WHAT ARE THE CONSEQUENCES IN PRACTICE?

This study shows the usefulness of an upper gastrointestinal endoscopy with biopsies in confirming the existence of environmental enteric dysfunction.

Nevertheless, it is not yet possible to recommend specific therapeutic treatment.

▼ FIGURE 2

Top 10 of correlations between the 14 core bacterial taxa and duodenal proteins.



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KEY POINTS

- Environmental enteric dysfunction is promoted by a disturbance in the intestinal microbiota at the duodenal level
- This duodenal dysbiosis is correlated with chronic undernutrition
- The pathology is transmissible to mice, which could help understanding the physiopathological mechanisms involved (intestinal inflammation, abnormalities of the epithelial barrier and immune alterations of bacterial signalling)

CONCLUSION

The results of this study suggest a causal relationship between the bacteria of the duodenum, environmental enteric dysfunction and chronic undernutrition with stunted growth. It is suggested that these children could therefore benefit from the development of treatments targeting this dysbiosis.

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COVID-19 AND THE GUT MICROBIOTA

By Prof. Tao Zuo
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The gut microbiota, including the bacterial, fungal, and viral fractions, is co-populating the human intestines and regulating the host immunity against pathogen invasions. The largely heterogeneous gut microbiota (GM) compositions across individuals may influence the host's immune responses to SARS-CoV-2 infection, leading to various disease symptoms and outcomes of Covid-19. On the other hand, though SARS-CoV-2 infection primarily causes respiratory symptoms, it deeply dysregulates the host's systemic immunity and impacts the gastrointestinal systems where the gut microbiota might be affected in both short and long term. Here, we review the current evidence on the impact of Covid-19 on the human GM as well as associations between GM composition and Covid-19 severity.

Covid-19 is a respiratory illness caused by a novel coronavirus (SARS-CoV-2) and is still affecting tens of millions of people worldwide today. Although most of Covid-19 patients present respiratory symptoms, up to 20% of them have gastrointestinal (GI) symptoms including diarrhea [1], suggesting that the digestive tract is an extrapulmonary site of disease expression and SARS-CoV-2 infection. In addition, Covid-19 presents a wide spectrum of disease severity, varying from asymptomatic, mild, severe, and up to critical resulting in respiratory failure or even death [2]. The GI tract is the largest immune organ in humans, playing critical roles in host defense against pathogens infections. Trillions of microorganisms live and colonize the human gut – bacteria, fungi, viruses, and other life forms that are collectively known as the microbiota – regulating the host immunity. Therefore, it is of paramount importance to understand if the gut microbiota modulates the host susceptibility to and severity of SARS-CoV-2 infection, as well as the impact of SARS-CoV-2 infection on the host GM and its downstream long-term effect on human health.

THE GUT BACTERIAL MICROBIOTA AND COVID-19

Covid-19 patients had significant alterations in the gut bacterial microbiome compared with healthy individuals, characterized by depletion of beneficial commensals and enrichment of opportunistic pathogens in the gut (**Figure 1**) [3]. Depletion of gut symbionts persisted even after the resolution of Covid-19. The baseline (at hospitalization) abundance of the bacteria *Coprobacillus*, *Clostridium ramosum* and *Clostridium hathewayi* showed positive correlation with Covid-19 severity, whereas there was an inverse correlation between the abundance of *Faecalibacterium prausnitzii* (known as an anti-inflammatory bacteria) and the disease severity.

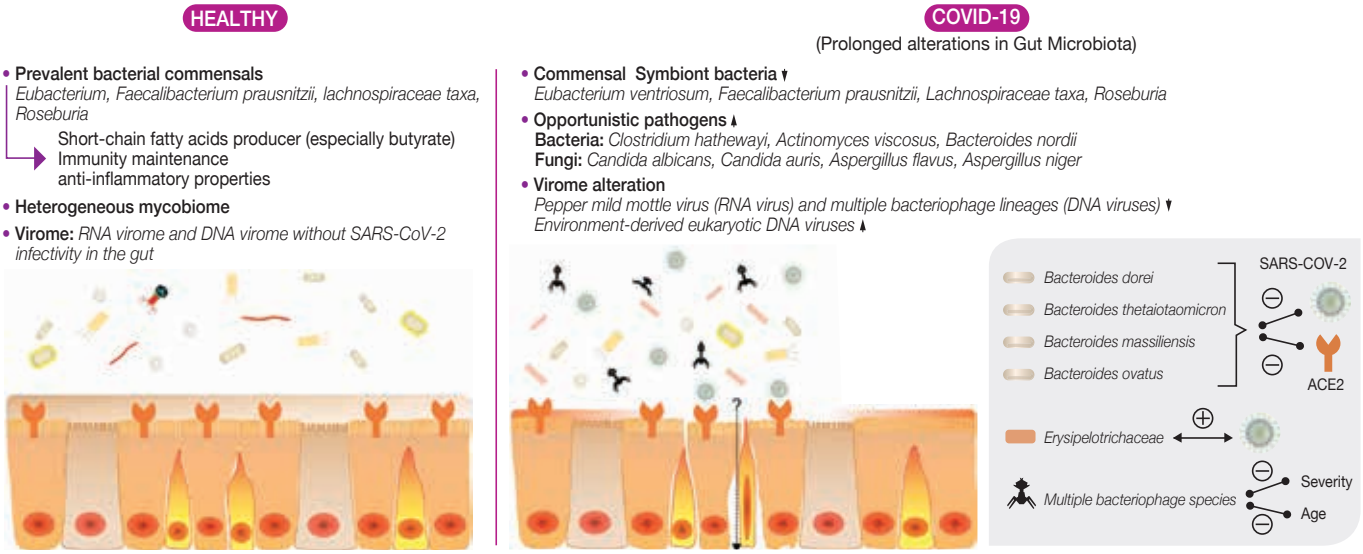
SARS-CoV-2 uses the angiotensin converting enzyme 2 (ACE2) receptor to enter the host and this receptor is highly expressed in both the respiratory and gastrointestinal tracts [4]. ACE2 is important in controlling intestinal inflammation and gut microbial ecology [5]. Four *Bacteroides* species : *B. dorei, B. thetaiotaomicron, B. massiliensis,* and *B. ovatus,* were reported to inversely associate with ACE2 expression in murine gut [6]. Interestingly, their abundances in faecal microbiome also showed inverse correlation with faecal SARS-CoV-2 viral load in Covid-19 patients during the disease course. These findings suggest that the human bacterial GM is affected by Covid-19 and might calibrate the host defense against SARS-CoV-2 infection.

THE FUNGAL MICROBIOME AND COVID-19

The GI tract also harbors a large number of fungi, collectively known as the mycobiome (fungal microbiome), which have been shown to be causally implicated in GM assembly and immune development

▼ **FIGURE 1**

The gut microbiota in Covid-19



[7]. Patients with Covid-19 also had altered gut mycobiomes, characterized by enrichment of *Candida albicans* and highly heterogeneous mycobiome configurations (**Figure 1**) [8]. The diversity of the fecal mycobiome in patients with Covid-19 at discharge was 2.5-fold higher than that in healthy individuals. Opportunistic fungal pathogens, *Candida albicans, C. auris*, and *Aspergillus flavus* were highly present in faeces of Covid-19 patients during the disease course. Two respiratory symptom-associated fungal pathogens, *A.flavus* and *A. niger*, were detected in faecal samples from a subset of patients with Covid-19, even after disease resolution. Unstable gut mycobiomes and prolonged dysbiosis persisted in approximately 30% of patients with Covid-19.

THE GUT VIROME AND COVID-19

Through shotgun RNA viral sequencing, a signature of active gut viral infection were found in 47% of patients with Covid-19, even in the absence of gastrointestinal symptoms and after respiratory clearance of SARS-CoV-2 [9], suggesting "quiescent" SARS-CoV-2 infection in the GI tract and potential faecal-oral transmission risk. Patients with such gastrointestinal SARS-CoV-2 activity harboured abnormal GM compositions and functions, featured by high abundances of opportunistic pathogens and enhanced capacity for biosynthesis of nucleotide and amino acid and carbohydrate metabolism (glycolysis) [9].

The human GI tract also harbours abundant viral/phage members collectively known as the gut virome. Covid-19 patients had under-representation of Pepper mild mottle virus (RNA virus) and multiple bacteriophage lineages (DNA viruses) and enrichment of environment-derived eukaryotic DNA viruses in faecal samples, compared to non-Covid-19 subjects (**Figure 1**) [10]. Faecal virome in SARS-CoV-2 infection showed more stress-, inflammation- and virulence-associated gene encoding capacities. At patient baseline, faecal abundances of the RNA virus, Pepper chlorotic spot virus, and multiple bacteriophage species inversely correlated with Covid-19 severity. These viruses were also inversely associated with blood levels of pro-inflammatory proteins, white cells and neutrophils, indicating gut resident viruses might tune host immune response to SARS-CoV-2 infection. Among Covid-19 severity-associated DNA virus species, 40% species showed inverse correlation with age, which may underlie the observation that elderly subjects are at a higher risk for a more severe Covid-19.

CONCLUSION

In summary, the collection of evidence suggests that the human GM (bacterial microbiota, mycobiome and virome) is impaired in Covid-19. Such dysregulation persists even after the disease resolution, which potentially pose a long-term health threat to the host. Gut microbiota composition is associated with host immune responses and Covid-19 severity to SARS-CoV-2 infection. Further research is needed to explore the long-term effects of Covid-19 and to improve the host GM and immunity to this unprecedented viral pandemic.

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CONGRESS REVIEW

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MICROBIOTA HIGHLIGHTS FROM UEG WEEK VIRTUAL 2020

OCTOBER 2020

Due to the ongoing pandemic UEG Week 2020 was for the first time held as a virtual meeting. Just like previous years, the meeting attracted a large number of abstracts of high quality and of these a substantial number focused on the role of microbes in health and disease.

MICROBIOTA, ENVIRONMENTAL AND HOST FACTORS IN HEALTH AND DISEASE

The gut microbiome has been associated with a large number of diseases, but it is still not clear how a healthy or unhealthy microbiome should be defined. A large Dutch population-based study (*OP178 R Gacesa et al.*) demonstrated common microbial patterns across several diseases (including inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), asthma, diabetes and mental disorders), making it possible to define clusters of health- and disease-linked gut microbes and functions. Specifically, the microbiome associated with diseases was found to be characterized by a significant increase in prevalence and abundance of opportunistic pathogens of genera *Clostridium, Gordonibacter* and *Eggerthella*, by a reduction in carbohydrate catabolism, synthesis of amino-acid and vitamins, and by an increase in synthesis of long-chain fatty acids. On the other hand, the healthy microbiome showed high abundances of butyrate-producing commensals from genera *Alistipes, Roseburia, Faecalibacterium* and *Butyrivibrio*. The authors also showed that the microbiome was primarily shaped by the environment and lifestyle, and therefore concluded that alterations through improving diet, lifestyle and the environment, and use of probiotics can be advocated to improve general health. Furthermore, a longitudinal follow-up study (*OP201 L Chen et al.*) highlighted that microbial changes over time seem to be driven by environmental exposures and can affect the metabolic health of the host.

MICROBIOTA IN INTESTINAL DISEASES

Lactose restriction is the cornerstone of treating gastrointestinal (GI) complaints in subjects with lactose malabsorption due to lactase deficiency. However, the severity of gut symptoms, such as flatulence, bloating and diarrhea, after lactose intake in these subjects varies substantially, and the reason for this remains unclear. Via analyses from the Dutch Microbiome project (*OP177 MDF Brandao Gois et al.*), a plausible mediating role of the gut microbiome between dairy intake and the occurrence of gut symptoms in subjects with lactase deficiency was demonstrated, and in particular the *Bifidobacterium* genus was found to be of potential relevance. Hence, modulating the gut microbiota composition may influence the sensitivity to dairy products in subjects with lactose malabsorption.

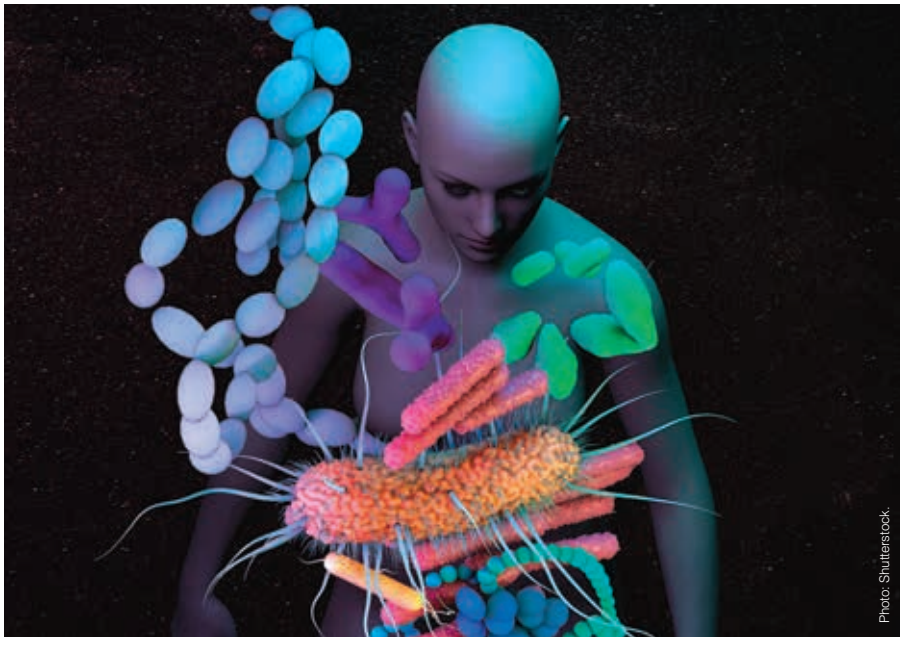
Even though the exact mechanisms that explains food-related GI symptoms in patients with IBS remains unclear, different dietary adjustments improves GI symptoms in subsets of patients. A posthoc analysis of a previously published clinical trial (*P0786 E Colomier et al.*) revealed patterns of psychological, nutritional, and microbial factors that can predict treatment response to both the traditional NICE (National Institute for Health and Care Excellence) diet for IBS and the low fermentable oligo-, di-, monosaccharides, and polyols (FODMAP) diet for specific symptoms. This indicates that individual tailoring of dietary treatment advice in IBS will be possible in the near future.

Gut microbes and their metabolites are involved in the pathophysiology of a number of intestinal diseases, including IBS and IBD, with several abstracts at UEG week 2020 highlighting this. In IBD, a large cohort study nicely confirmed the presence of gut dysbiosis in both ulcerative colitis (UC) and Crohn's disease (CD) (*OP002 A Vich Vila et al.*), and that this was translated into the fecal metabolite profile, which could be used as a potential biomarker to distinguish between IBD and non-IBD and between UC and CD. Specifically, metabolites related to sphingolipid synthesis were increased in IBD, whereas fatty acid metabolites were decreased. Furthermore, in a proof-of-concept study (*OP045 L Oliver et al.*), a combination of four microbiome markers (*Faecalibacterium prausnitzii* and one of its phylogroups (PHG-II), *Ruminococcus* sp., and *Methanobrevibacter smithii*) could predict the treatment response to anti-TNF treatment with a positive predictive value of 100% and negative predictive value of 75%. This indicates that microbiome analyses can be used to personalize treatment in IBD in the near future. The role of gut microbiota in IBS was highlighted in several abstracts, including a study supporting good long-term effects of fecal microbial transplantation in IBS (*OP059 M El-Salhy et al.*), which was associated with changes in the faecal bacterial and short chain fatty acid profile and increase in enteroendocrine cells (*P0783 M El Salhy et al.*). Moreover, another study demonstrated a distinct intestinal microenvironmental profile in IBS with a link to the predominant bowel habit of the patient (*P0651 C Iribarren et al.*), with the separation between IBS and health and among IBS subtypes (IBS with diarrhea *versus* IBS with constipation) being mostly driven by metabolites involved in *e.g.* amino acid metabolism and certain cellular and molecular functions. Hence, it seems to be more important what the microbes do than the composition *per se.* There were also abstracts focusing on animal models of relevance for IBS pathophysiology. These studies highlighted the importance of gut microbiota for the development of abnormal gut-brain interactions (*P0052 M Constante et al.*), as well as the role of stress in inducing gut dysbiosis and visceral hypersensitivity (*OP056 C Petitfils et al.*). These studies are of great relevance for our understanding of gut-brain interactions in IBS and the role of gut microbes and their metabolites in these interactions, and fits well into the concept that IBS and other functional GI disorders are now called disorders of gut-brain interactions.

MICROBIOTA IN EXTRAINTESTINAL DISEASES

Finally, there were also studies focusing on the gut microbiome in extraintestinal diseases. Gut microbiome alterations were demonstrated in both renal and liver transplant recipients (*OP180 JC Swarte et al.,* and *OP112 y Li et al.*). Patients with end stage renal disease were characterized by low gut microbial diversity, increased richness of virulence factors, and antibiotic resistance genes. The microbial diversity decreased further post-renal transplantation and gut microbiota composition was not restored. Furthermore, immunosuppressive agents had a profound effect on gut microbiota composition. The authors concluded that these changes could have far-reaching implications for the outcome of renal transplantation. Similar findings regarding microbial diversity, gut microbiota composition and effect of immunosuppressive agents were noted also in liver transplant recipients, and intriguingly microbial diversity was associated with survival post liver transplantation, therefore revealing a new potential biomarker or therapeutic target.

To summarize, based on the abstracts presented at UEG week 2020 it is obvious that the gut microbiome is of great importance in several different disease states as well as in health. Enhanced understanding of the role of gut microbes and their metabolites in various diseases substantially influences health care today and will do so even more in the near future.



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LITERATURE SELECTION

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GUT MICROBIOTA

FECAL MICROBIOTA TRANSPLANTION (FMT) FOR CESAREAN-SECTION-DELIVERED INFANTS TO RESTORE NORMAL GUT MICROBIOTA


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The gut microbiota of infants born vaginally differs from that of CS born infants since they are not exposed to maternal microbes during delivery. Several studies reported that CS may be associated to short- and long-term consequences, including an increased risk of chronic immune diseases. In this study, the efficacy and safety of fecal microbiota transplant (FMT) has been evaluated as a means of restoring the gut microbiota of babies born by CSD. Seven CSD infants received a stool-transplant from their own mother at the first milk feeding, and the composition of their gut microbiota was compared to that of 82 babies born vaginally or by CS without FMT. During the 3-month follow-up, no adverse effects was reported. One week post-FMT, the gut microbiota of CSD infants was similar to that of vaginally delivered infants while CSD-infants without FMT had lower microbial diversity. FMT corrected the bacterial signature of CSD delivered infants by rapid normalization of *Bacteroidales* which was lower in CSD group and also reduced potential pathogens typical for CSD infants. This proof-of-concept study showed that FMT normalizes gut microbiota development in CSD infants.

Korpela K, Helve O, Kolho K-L, Saisto T, *et al.* Maternal fecal microbiota transplantation in cesarean-born infants rapidly restores normal gut microbial development: a proof-of-concept study. *Cell* 2020; 183: 324-34.

CESAREAN SECTION AND CHILDHOOD ASTHMA RISK

The authors analyzed the effects of cesarean section (CS) delivery on gut microbiota composition during the first year of life and examined if the perturbations were associated with a risk of developing asthma in the first 6 years of life. They included 700 children from the $COPSAC_{2010}$ (Copenhagen Prospective Studies on Asthma in $Childhood_{2010}$) cohort, of whom 22% (151) were born by CS and 78% (549) by vaginal delivery. Gut microbiota composition varied with delivery mode: CS born babies had lower abundance of Bacteroidetes and Actinobacteria at 1 week of age, but the abundance of Firmicutes and Proteobacteria were higher compared with vaginally born children. At genus level, only 3 genera were different at age 1 year and CS delivery was associated with higher relative abundance of a genus belonging to the family *Enterobacteriaceae* and *Escherichia/Shigella*. A microbial profile was identified that predicted the birth mode at one week, one month, and one year of age. CS delivered children who retained a CS gut microbiota signature at age 1 year had a three times increased risk of developing asthma by age 6. This increased asthma risk was ameliorated in CS-born children whose gut microbiota at the age of 1 year resembled that of vaginally born children. It indicates that healthy maturation of a dysbiotic CS gut microbiota could ameliorate some of the risk of asthma associated with CS delivery.

Stokholm J, Thorsen J, Blaser MJ, *et al.* Delivery mode and gut microbial changes correlate with an increased risk of childhood asthma. **Sci Transl Med** 2020; 12, eaax9929.

SKIN MICROBIOTA

AGE-RELATED SKIN MICROBIOTA PROFILES

Intrinsic skin aging is a natural aging process determined by internal factors while photoaging is the accelerated aging of the skin due to repeated exposure to ultraviolet radiation (UV). Little is known about how the skin microbiota influences the aging process (either natural or photoaging) and on the effects of age-related skin microbes. To answer this question, the authors analyzed 160 skin samples from the cheek and the abdomen of 80 individuals of varying ages to develop age-related microbiota profiles. They found that abundance of Cyanobacteria was higher in the children group and was associated with decreased UV-induced skin damage and pigmentation. In young and middle-aged, *Staphycococcus*, *Cutibacterium* and *Lactobacillus* improved skin barrier and protected from photoaging. *Cutibacterium* may modulate immune responses and suppress inflammation and slow aging processes. In young and middle-aged people, *Staphylococcus* may protect from intrinsic skin aging and maintain skin microbiota homeostasis. The authors suggest that these findings may have great innovation and clinical value, and that the development and use of microbial skin homeostasis regulators may reduce the incidence of age-related skin diseases.

Photo: Shutterstock.

Li Z, Bai X, Peng T, *et al*. New insights into the skin microbial communities and skin aging. *Front Microbiol* 2020: 11: 565549.

SACCHARIDE ISOMERATE MODULATES SKIN MICROBIOTA

Many intrinsic, extrinsic and host-related factors modulate skin microbiota. Skin cleansing products such as bar or liquids soaps and deterge have impact on the skin microbiota. Saccharide isomerate (SI) is a plant-derived moisturizer that resembles the natural carbohydrate fraction of the upper layer of the skin. SI binds to the skin stronger than other moisturizer ingredients and keeps skin hydrated longer than usual. The investigators performed a placebo-controlled, single-blind, and randomized clinical study to investigate how skin cleansing with liquid soap containing SI affects skin microbiota over time. Of potentially beneficial organisms, *Paracoccus marcusii* was positively associated with the active formulation. This bacteria naturally produces astaxanthin, a potent antioxidant carotenoid having potential positive effects on health. *P. mercusii* is also a potentially carcinogenic polyaromatic hydrocarbons degrader and a biosurfactants producer and may have a key role in maintaining healthy skin. SI wash also reduced the abundance of "coryneforms" (*Brevibacterium* casei and *Rothia mucilaginosa*) linked to skin infections and represents uncharacterized benefit of the active wash formulation. These results suggest that skin wash with SI may have beneficial effects on skin microbiota.

Sfriso R, Claypool J. Microbial reference frames reveal distinct shifts in the skin microbiota after cleansing. *Microorganisms* 2020; 8: 1634.

VAGINAL MICROBIOTA

SEVERE PRE-ECLAMPSIA AND MICROBIOTA

Severe preeclampsia (SPE) is a hypertensive disorder of pregnancy that can have serious consequences for both mother and child. It is characterized by hypertension and manifestations of a multisystem disorders. The role the vaginal microbiota may play in the pathogenesis of SPE remains unknown. The present study revealed that women with SPE had increased relative abundance of vaginal *Prevotella bivia* (Pb). Pb is an anaerobic gram-negative bacterial species that was previously associated with pelvic inflammatory disease and bacterial vaginosis. Previous studies have shown that obesity was a risk factor for SPE and that vaginal microbiota of obese women was characterized by increased diversity and predominance of *Prevotella* spp. In this study, the Body Mass Index (BMI) was the strongest SPE predictor and the authors suggest that the higher relative abundance of Pb in the vaginal microbial, which is tightly regulate by BMI, may be involved in the pathogenesis of SPE.

Lin CY, Lin CY, Yeh YM, *et al.* Severe preeclampsia is associated with a higher relative abundance of Prevotella bivia in the vaginal microbiota. *Sci Rep* 2020; 10: 18249.

CERVICAL MUCUS ESSENTIAL FOR FEMALE REPRODUCTIVE HEALTH

Cervical mucus (CM) is key for women health: it protects vaginal epithelium, helps to maintain fertility and fecundity. In this study, the authors assessed its role in both the physiological state and in bacterial vaginosis. Normal vaginal microbiota is characterized by *Lactobacillus* spp dominance. Undisturbed cooperation between vaginal microbiota, CM and host cells is necessary for vaginal health. This includes acidification by lactic acid, production of reactive oxygen species, interaction between mucins and cells, and diffusion of signaling cells. Bacterial vaginosis, which may cause preterm birth, is characterized by depletion of *Lactobacilli* leading to impaired vaginal barrier function. During pregnancy, a cervical mucus plug (CMP) is formed to prevent the vaginal microbes to ascend into the uterus, which protects the fetus from pathogens. CMP contains mucus, antimicrobial compounds and immune cells. A shorter, more permeable and less mucoadhesive CMP has been found in women at high risk for preterm birth compared with those at low risk. In addition to oral or vaginally administered antibiotics, bacterial vaginosis may be treated by restoring vaginal *Lactobacillus* flora. In conclusion, CM is essential for the fertility and protects from bacterial vaginosis and sexually transmitted infections, which increase the risk of infertility and preterm births.

Lacroix G, Gouyer V, Gottrand F, Desseyn JL. The cervicovaginal mucus barrier. *Int J Mol Sci* 2020; 21: 8266.

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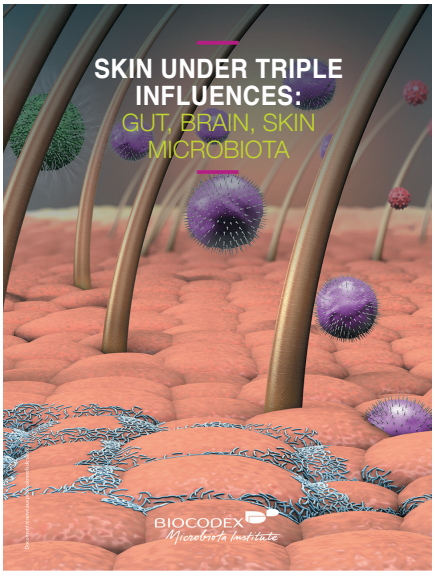
SKIN MICROBIOTA REPORT: THE SKIN FROM EVERY ANGLE

The Microbiota Institute has published a new thematic report on one of the largest organs of the human body: the skin and its microbial ecosystem. The skin has many functions: it separates the body's internal environment from the external environment, protects against UV rays, participates in thermoregulation, confers the sensation of touch, absorbs and synthesises compounds. It also hosts a complex community of micro-organisms. For health professionals, this dossier provides an exhaustive overview of the current state of knowledge about the skin microbiota, questions the microorganisms involved and specifies the mechanisms of action envisaged, which go far beyond the skin environment alone since they could involve the intestinal microbiota and the brain.

https://www.biocodexmicrobiotainstitute.com/en/pro/services/publications/thematic-folder/skin-under-triple-influences-gut-brain-skin-microbiota



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