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The microbiota-gut-brain axis in functional gastrointestinal disorders

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Abbreviations: GI, gastrointestinal; FGIDs, functional gastrointestinal disorders; IBS, irritable bowel syndrome, FD, functional dyspepsia; IBS-C, IBS-constipation; IBS-D, IBS-diarrhea; ENS, enteric nervous system; HPA-axis, hypothalamus-pituitary-adrenal axis; CRH, corticotrophin-releasing hormone; CRF, corticotrophin-releasing factor; SIBO, small intestinal bowel overgrowth; PI-IBS, post-infectious IBS

Functional gastrointestinal disorders (FGIDs) are highly prevalent and pose a significant burden on health care and society, and impact patients' quality of life. FGIDs comprise a heterogeneous group of disorders, with unclear underlying pathophysiology. They are considered to result from the interaction of altered gut physiology and psychological factors via the gut-brain axis, where brain and gut symptoms are reciprocally influencing each other's expression. Intestinal microbiota, as a part of the gut-brain axis, plays a central role in FGIDs. Patients with Irritable Bowel Syndrome, a prototype of FGIDs, display altered composition of the gut microbiota compared with healthy controls and benefit, at the gastrointestinal and psychological levels, from the use of probiotics and antibiotics. This review aims to recapitulate the available literature on FGIDs and microbiota-gut-brain axis.

Functional Gastrointestinal Disorders

For the last few decades physicians have struggled to understand functional gastrointestinal disorders that escape the objective diagnosis of organic pathology and are characterized by non-structural symptoms that undermine patients' quality of life. The following statement describes a functional gastrointestinal (GI) disorder: There is no evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the patient's symptoms.[1] FGIDs rise from the combination of genetic[2] and environmental factors, including exposure to infections, use of antibiotics, sexual or physical abuse, and also family influences on illness expression, that synergistically shape one's psychological development and susceptibility to gut dysfunctions.[1,3-6] Therefore a FGID is the clinical product of the interaction of altered gut physiology and psychological factors via the gut-brain axis, where brain and gut symptoms are reciprocally influencing each other's expression. The communication between the "GI brain" (the enteric-nervous system; ENS), and the central nervous system (CNS) is key in the pathophysiology of FGIDs.[7] The latest FGIDs classification is the Rome III criteria system, which groups FGIDs into 6 categories: esophageal, gastroduodenal, bowel, functional abdominal pain syndrome, biliary, and anorectal.[1] In order to ascribe reported gut symptoms to FGID, the symptoms must have occurred for the first time ≥6 months before the patient presents to the physician practice and their presence had to be ≥3 days a month during the last 3 months.[8] However the adoption of Rome III criteria is still matter of debate due to inadequate validation of the criteria and consequent low utilization,[9] but also due to low sensitivity of the criteria to diagnose FGIDs and in particular IBS.[10-12] FGIDs include irritable bowel syndrome (IBS), functional dyspepsia (FD), functional bloating, functional constipation, and functional diarrhea.[1,13] For purposes of simplification this review will focus on IBS and FD.

IBS is the most common functional bowel disorder worldwide that affects between 7 to 10% of population.[14] Its prevalence varies across the world according the diagnostic criteria (Manning, Rome II, Rome III, self-diagnosed), the population selected, the access to health care, and culture.[15] IBS is one of the most common reasons of healthcare seeking with significant impacts on health care expenses,[4,16] and the most studied FGID.[15,17] IBS classifies into 4 different categories according to bowel habits and stool form using the Bristol Stool Scale:[8] IBS-constipation (IBS-C), IBS-diarrhea (IBS-D), Mixed IBS, and Unsubtyped IBS.[8] IBS affects patients across the lifespan but there is an overall strong female predominance.[15] Men are more likely to suffer from IBS-D while women from IBS-C.[18,19] Moreover, sex hormones are likely to affect GI function and the severity of IBS symptoms.[19] IBS has been associated with abnormal gut motor function, enhanced visceral perception, abnormalities in central pain processing, and altered gut microbiota, besides psychosocial and genetic factors.

FD is the second most common FGID with a great impact on the quality of life of the patients,[20,21] although it often remains unreported to physicians. Pathophysiological mechanisms underlying FD include delayed gastric emptying,[13,20,22] impaired gastric accommodation to a meal, visceral hypersensitivity, and

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duodenal sensitivity to acids,[20,23] as well as psychosocial and genetic factors.[20]

The Role of the CNS in Functional GI Disorders

Psychological and psychosocial factors are important in the understanding of the pathophysiology of FGIDs. Psychiatric disorders such as anxiety, depressive disorder, and neuroticism, are common comorbidities in patients with FGIDs.[24-33] However, it is unclear whether the brain abnormalities drive the gut symptoms or the changes in the gut alter brain function through vagal and sympathetic afferents. A recent 12-year prospective study aimed at determining the role of the brain-gut mechanism in IBS and FD and concluded that the brain-gut pathway is bidirectional, as brain-gut and gut-brain dysfunctions both occur in FGIDs.[34] FGID patients are also characterized by abnormalities in autonomic nervous system, neuroendocrine and immune functions, which are influenced by psychological distress[35] in the model of emotional motor system (EMS), which reacts to interoceptive and exteroceptive stress. Specific brain structures involved in the EMS, including the anterior cingulate cortex (ACC), amygdala, hippocampus, hypothalamus, and periaqueductal gray, communicate to the gastrointestinal tract through the hypothalamus-pituitary-adrenal (HPA) axis, autonomic nervous system, the endogenous pain modulation system, and ascending aminergic pathways.[36]

An important player in the EMS is corticotrophin-releasing hormone (CRH) located in effector neurons of the paraventricular nucleus (PVN) of the hypothalamus, the amygdala, and the locus coeruleus complex that activate both the autonomic nervous system and HPA axis.[36] Activation of the HPA axis followed by secretion of corticosteroid hormones from the adrenal cortex (i.e., cortisol in humans and corticosterone in rodents) is considered a physiological response to stress.[37,38] Patients with FGID display dysregulation of the HPA-axis response to stress and changes in free cortisol secretion, which correlate with the gastrointestinal symptoms.[39] Moreover, in response to a visceral stressor, IBS patients' basal cortisol levels positively correlate with anxiety symptoms scores.[40,41] HPA axis alterations and stress have also been related to abnormalities in gut motor function.[42] Indeed, psychological stress appears to be a sensitive and specific predictor of symptoms in FD patients.[31,43]

Studies in animal models have shown that acute stress alters intestinal permeability through mechanisms involving CRH,[44] while chronic stress induces low-grade inflammation and can lead to visceral hyperalgesia.[45] Enhanced stress responsiveness has been implicated as a potential mechanism contributing to the pathophysiology of IBS, as stress reactivates previous enteric inflammation and enhances the response to subsequent inflammatory stimuli.[46] Early life stress can permanently affect the development of the HPA-axis, contributing to altered visceral pain modulation, and behavioral changes associated with stress-related disorders.[47] Corticotrophin-releasing factor (CRF) has thus been proposed as a possible mediator in IBS, as central CRF administration mimics acute stress-induced colonic responses and enhances colorectal distension-induced visceral pain, whereas peripheral CRF alters neuromotor gut function.[48-50]

Neuroimaging research has allowed for the investigation of underlying mechanisms of altered visceral perception in patients with IBS. Abnormal brain activation in response to visceral stimuli and dysregulation of the CNS has been found in FGIDs patients compared with healthy controls.[51-54] However, it is unclear whether the reported abdominal pain reflects an abnormal afferent input to the brain, or central alterations in the signals from the gut or both. IBS patients have greater engagement of regions associated with emotional arousal and endogenous pain modulation, but similar activation of regions involved in processing of visceral afferent information, whereas controls have greater engagement of cognitive modulatory regions.[52] Another study showed that upregulated emotional arousal circuitry and altered serotonergic modulation of this circuitry may play a role in centrally mediated visceral hypersensitivity in female patients with IBS.[52,55] Indeed, these patients seem to present altered engagement of descending pain modulation systems that increases the excitability of the dorsal horn resulting in increased ascending input to brain regions processing interoceptive input.[56] Inhibition of neurokinin-1 receptor, which is involved in augmented nociceptive response and behavioral and autonomic responses to stress, reduced central pain amplification during an acute experimental stimulus in women with IBS.[57] A recent study has suggested that changes in gray matter density in regions involved in cognitive and/or evaluative functions are specifically observed in patients with IBS, whereas changes in other brain areas are associated with levels of anxiety and depression.[58] These functional and gray matter abnormalities in IBS patients are also accompanied by white matter changes, which are possibly responsible for the emotional aspect of pain in IBS.[59] Similarly, abnormalities in brain activity in response to visceral stimuli as well as during the resting state have been reported in patients with FD,[60-65] and very recently abnormalities in white matter microstructure have been reported in patients with FD.[66]

Summary: FGIDs patients present with abnormalities in visceral perception, neuroendocrine and immune functions, which are influenced by psychological distress. Abnormal brain activation in response to visceral stimuli, or altered engagement of descending and ascending pathways, have been implicated in the pathophysiology of FGIDs,

The Gut Microbiota

The gut microbiota is a key player in determining gut health and function.[67] The gut microbiota is composed mainly by bacteria but also by archaea, viruses, and protozoa that roughly reach 10^{14} cells, outnumbering the human cells in our bodies by a factor of ten.[68] The human gut is rapidly colonized at birth and this ecosystem is under constant evolution until adult-like communities stabilize. The microbiota undergoes selective pressure from the host as well as from microbial competitors and once the ecosystem reaches homeostasis, some species will occur in high and others in low abundance.[69-71] However, out of the

numerous phyla described in the literature only 19 are present in the human GI tract,[72] and five of them are predominant (Firmicutes, Bacteroidetes, Proteobacteria, Fusobacteria, and Actinobacteria).[72] Three genera have been used to determine the main "enterotypes" under which humans can be categorized (*Bacteroides*, *Prevotella*, and *Ruminococcus*)[73,74]; however, this categorization has recently become a matter of debate and the term "enterogradients" has been proposed instead, to describe bacterial communities with prevalence of *Bacteroides* or *Prevotella*.[75] These autochthonous genera stably colonize the gastrointestinal tract and are present in a majority of individuals. Even though the gut microbiota still differs greatly between subjects in membership and community structure, the microbiomes appear largely functionally equivalent and necessary for the proper development of the host. Known functions of the gut microbiota include the conversion of non-digestible carbohydrates (dietary fiber) to short-chain fatty acids (SCFAs), transformation of bile acids, the provision of a barrier against pathogenic bacteria, and modulation of the innate and the adaptive immune systems (for review see ref. 69).[69] The importance of the gut microbiota is highlighted by the increasing number of studies performed in germ-free animals, which demonstrate physiologic and metabolic abnormalities compared with conventional animals. Indeed, germ-free mice have an immature and deregulated immune system,[76-80] with abnormal IgA production[81,82] and decreased numbers of intestinal mast cells.[83] Germ-free mice have also impaired capacity for harvesting energy from the diet.[84] The absence of microbiota protects against diet-induced obesity[85,86] and excessive energy storage in the liver and in the skeletal muscle.[86] Interestingly, transplanting the microbiota from obese mice or mice fed high-fat diet induce the same donor phenotype in germ-free recipients,[87-89] meaning that the gut microbiota plays a role in obesity and weight gain. Several studies showed that germ-free animals have an enlarged cecum reflecting abnormal gut motility,[84,90,91] increased expression of genes encoding transporters throughout the gut,[70] as well as altered perception of inflammatory pain.[92]

Summary: Gut microbiota has evolved with its host and plays a pivotal role in host's physiology and homeostasis.

Gut Microbiota and Functional Gastrointestinal Disease

Alterations in the gut microbiota composition have been well described in several functional gastrointestinal disorders and are reviewed exhaustively in a recent report by the Rome Working Team.[93] Multiple studies have shown differences in the composition of the gut microbiota between IBS patients and healthy controls.[94-115] However, the results of these studies are inconsistent and no unique IBS bacterial signature and/or profile has been identified, due in part to different detection methods as well as different patient populations.[94,116] A pair of recent studies confirmed that IBS is associated with a decrease in the stability and biodiversity of the gut microbiota.[117,118] However there is not a clear consensus on what constitutes a healthy microbiota.

Post-infectious (PI) FGID represent a category within the general FGID classification.[119,120] The occurrence of infectious gastroenteritis has been well documented by several studies in both IBS and FD, showing that the risk to develop a functional disorder is greater in exposed individuals.[119,121,122] Some studies also reported the incidence of FGIDs after a viral infection.[123,124] The underlying mechanisms involved in PI-FGIDs are still to be fully elucidated, although several studies have shown evidences of low grade "immune activation" in IBS patients.[125] It has been proposed that transient inflammation could lead to subtle but permanent changes in the structure and function of the digestive system, such as in lymphocytes, mast cells, enterochromaffin (EC) cells, and enteric nerves, which, in turn, induce the symptoms.[120] The microbiota is deeply perturbed at the site of the infection[126] and it might act synergistically with ongoing inflammation and increased epithelial permeability, increasing the sensitivity to develop a FGID in prone individuals.[127]

Small intestinal bacterial overgrowth (SIBO) is another condition that has been associated with IBS and that may be responsible for symptom generation in some patients with IBS. SIBO is defined as a quantitative alteration of the small intestinal microbiota.[128] Its role in IBS is controversial, partly as the scientific community has not reached a consensus on the detection method to use: the breath tests are not well validated and the jejunal aspirates are not always accurate.[129-132] Bacterial overgrowth results in unusual fermentation with increases in gas production, abdominal bloating, malabsorption, abdominal pain, diarrhea, and abnormal gastrointestinal motility.[133-135] It remains unclear whether SIBO is actually fundamental to the pathophysiology of IBS, or is just a complicating phenomenon. However, several studies suggested that treatment of SIBO with non-absorbable antibiotics improves gut symptoms in a proportion of patients with IBS.[136-138]

Summary: Patients with IBS have different composition of the gut microbiota but no unique bacterial profile has been identified. It is unclear whether this dysbiosis is a cause or a consequence of gut dysfunction.

Microbiota-Gut-Brain Axis

There is growing evidence that there is a complex interaction between the host and specific bacterial species or their metabolites. Striking examples are found in nature: *Toxoplasma gondii*, an obligate intracellular protozoal parasite is able to convert the natural fear of its intermediate host mice against cat urine into attraction, facilitating the transmission of the parasite from mice to its specific host, the cat.[139,140] It has been shown that tachyzoites and bradyzoites (cysts) of *Toxoplasma gondii* impair neuronal function in a mouse model.[141] Another example comes from clinical practice: laxatives and oral antibiotics are used to treat patients with hepatic encephalopathy, a disorder that likely results from the systemic accumulation of gut-derived neurotoxins in patients with impaired liver function and portosystemic shunting.[142,143] The use of different antibiotics, on the other hand, has been reported to induce acute psychosis with

symptoms resolved after cessation of antibiotics.[144,145] Although controversial, there is some evidence of abnormal microbiota composition and partial improvement in symptoms after treatment with antibiotics in patients with late onset autism (for review see ref. 146).[146] An association between Major Depressive Disorder and altered gut microbiota has been also suggested as carbohydrate malabsorption has been linked with increased risk to develop mental depression.[147-150] The scientific community has begun to accept the concept that gut microbiota is implicated in brain autoimmunity in Multiple Sclerosis (for review see ref. 151).[151] The commensal intestinal bacteria appear to be essential in triggering immune processes, leading to a relapsing-remitting autoimmune disease.[152] Antibiotic treatment effectively reduces the severity of the disease in mouse model of experimental autoimmune encephalomyelitis (EAE) and germ-free mice are more resistant than conventional mice to develop EAE.[153,154]

Germ-free mice display abnormalities within the CNS with a dysregulated HPA stress response,[155] altered level of brain-derived neurotrophic factor in the hippocampus,[155-158] reduced anxiety-like behavior,[157,158] altered expression of genes known to be involved in second messenger pathways and synaptic long-term potentiation,[157] and altered tryptophan availability and metabolism.[156] Non-absorbable antibiotic treatment in conventional BALB/c mice induced changes in intestinal microbiota composition, with increased levels of Firmicutes, phylum dominated by *Lactobacillus* species but including also some species of sulfate-reducing bacteria (SRB), and decreased levels of γ-Proteobacteria and Bacteroidetes.[159] These microbial alterations were accompanied by increased levels of hippocampal BDNF and an autonomic-independent anxiolytic behavior in mice.[159]

Summary: Accumulating data suggest that gut microbiota influences CNS function and host's behavior. Underlying mechanisms are unclear but likely involve immune, humoral, and neural pathways.

Microbiota-Gut-Brain Interactions in FGIDs

A recent study has shown that IBS-C patients have higher numbers of SRB than healthy controls.[96] These bacteria use lactate and H_2 as substrates for H_2S production, reducing availability of lactate for butyrate and propionate producing bacteria and increasing the levels of H_2S in the gut.[160] Interestingly, luminal H_2S and NaHS (an H_2S donor) have been reported to play pronociceptive roles in mouse colon, through activation of T-type Ca^{2+} channels,[161] but also antinociceptive roles in a rodent model of visceral pain.[162] Bacterial secretion of H_2S has been also shown to alter the effectiveness of many clinically used antibiotics.[163] Thus, it appears that H_2S might affect visceral perception in patients with FGIDs; however the literature is controversial, and further studies are warranted in order to clarify H_2S' role in visceral nociception and inflammation in FGIDs. Several specific bacterial probiotic strains have been shown to improve symptoms severity and abdominal pain in IBS patients,[164-182] although their mechanism of action remains unclear. There are some species that in clinical trials appear to be more effective than others, such as *Bifidobacterium* species (*B.infantis* 3564 and *B.bifidum* MIMBb75)[172,176,178] and *Lactobacillus* species (*Lactobacillus acidophilus*-SDC 2012, 2013, *L. paracasei* B2106, *L. plantarum* 299V, and *L. rhamnosus* GG).[164,170,171,175,177] These probiotics appear to be effective in reducing abdominal pain and discomfort in adults and in children (*L. rhamnosus* GG). Several studies have also suggested that combinations of different probiotic strains, such as VSL3# or mixtures of *Bifidobacterium* and *Lactobacillus* species, are able to decrease abdominal pain and discomfort in patients with IBS.[166,180-183]

As discussed previously, gut bacteria have been shown to affect depression- and anxiety-like behavior in animal models. The first study to suggest psychological benefits of a probiotic supplementation in human involved 132 healthy adults; a subset of the individuals with depressive symptoms at baseline appeared to improve their mood after consuming a *L. casei* fermented product.[184] However, administration of this probiotic seemed to worsen their cognitive performance. Another study in healthy adults found that the combined supplementation with *L. helveticus* R0052 and *B. longum* R0175 for 30 days decreased scores for anxiety, depression, and psychological distress.[185] Moreover, the same group subsequently reported improved well-being (anxiety, depression, and somatization) in those individuals who had the lowest urinary free cortisol.[186] A recent study using fMRI has demonstrated that administration of probiotic mixture, containing *B. lactis* can affect brain regions concerned with the central processing of afferent signals from the gut, and reduce the impact of the brain regions involved in emotional arousal on the central processing of gut afferent signals.[187] However, these studies were performed in healthy volunteers and its relevance to disease remains to be demonstrated.

Summary: Probiotics are widely used in FGIDs patients, either as single species or their mixtures. Probiotics appear to improve gut symptoms, but also affect anxiety, depression, and psychological distress.

Microbiota-Gut-Brain Axis in Animal Models of FGIDs

Animal models of functional bowel disorders have been used extensively to study effects of probiotics. *L paracasei* NCC2461 was found to improve post-infective neuromuscular dysfunction in mice.[188] *B.infantis* 35624 reduced visceral sensitivity to colorectal distension in rats,[189,190] likely through improvement in tissue inflammation. A similar effect was reported with *B. lactis* CNCM I-2494,[103] and VSL3#.[162,191] In another study, *L paracasei* NCC2461 reduced visceral perception via reduction of MPO activity and substance P.[192] In parallel, *L. acidophilus* was shown to induce analgesic receptors[193] which could contribute to visceral pain reduction. Other studies have shown barrier enhancing effects of several probiotics associated with normalization of visceral pain perception.[103,191,194] Thus, the beneficial effects of probiotics in animal models of IBS demonstrate a variety of mechanisms and targets that may be strain dependent.

Maternal separation in rodents is widely used as a model of early life stress that mimics some of the features of IBS.[195-197] Maternally separated mice display long-lasting hyperactivity of the HPA-axis,[196,198,199] anxiety-like behavior,[198,200-202] visceral hypersensitivity,[203-205] and altered cholinergic activity in the gut,[196] accompanied by increased intestinal permeability.[196,201,203,206] The behavioral and physiological changes induced by early life stress are accompanied by altered gut colonization,[205] and the use of probiotics ameliorates the detrimental effects of stress.[162,207-209] Furthermore, the effects of maternal separation on anxiety and depression are absent in mice raised in germ-free conditions,[210] suggesting that intestinal microbiota plays an important role in this animal model of IBS.

Infection models are commonly exploited to study the mechanisms responsible for generation of FGID symptoms. Chronic *H. pylori* infection in mice alters the gastric motility and increases visceral sensitivity, leads to abnormal feeding behavior and altered expression of pro-inflammatory cytokine TNF-α in the hypothalamus and regulatory peptide propiomelanocortin (POMC) in the arcuate nucleus.[211,212] *Citrobacter rodentium* infection in mice has been used to mimic PI-IBS following bout of gastroenteritis by *E. coli*. *C. rodentium* results in a self-limiting colitis that induces chronic hyperexcitability of colonic dorsal root ganglia (DRG) neurons and hyperalgesia, a dominant feature of PI-IBS in humans.[213-215] Combined with stress, *C. rodentium* infection results in increased intestinal permeability,[216] increased levels of epinephrine and corticosterone, exaggerated neuronal excitability, and visceral hyperalgesia and/or allodynia.[217] The ability of *C. rodentium* to colonize the intestine is significantly enhanced by stressor-induced changes in the microbiota.[213] The initial phase of infection with *C. rodentium* also coincides with the development of anxiety-like behavior and the activation of vagal sensory neurons.[218] Similarly, early phase of infection with *Campylobacter jejuni*, known to cause most of the food-borne gastroenteritis in humans,[219] has been reported to induce anxiety-like behavior in mice, in the absence of immune response.[220] The infection with *C. jejuni* activates viscerosensory pathways involved in identification and response to internal challenges, noradrenergic neurons and serotonergic neurons in different portions of the brain.[221,222] Moreover, it affects central viscerosensory pathways that interface with stress-related and "defensive" network nuclei in the hypothalamic PVN, the amygdala, and the bed nucleus of the stria terminalis (BST), previously established as nodal points for the integration of psychological or processive stress with behavioral responses to potential threats or threatening situations.[223] The above described effects of early infection appear to be purely neural in origin, however changes in behavior and brain biochemistry have been also observed in models of chronic low-grade colitis. Chronic infection with a non-invasive parasite, *Trichuris muris*, and mild chemically-induced colitis, induce anxiety-like behavior in mice and decreased levels of hippocampal BDNF expression[224,225] via immune mediated mechanisms, including pro-inflammatory cytokines and altered tryptophan/kynurenine metabolism. Interestingly, probiotic *B. longum,* but not *L. rhamnosus*, was able to revert the abnormal behavior in both studies in a vagal-dependent manner.[224,225] A recent study in healthy mice has demonstrated that administration of probiotic *L. rhamnosus* decreases anxiety and depression-like behaviors and alters expression of GABAergic receptors in the CNS, and this effect was also dependent on the integrity of the vagal nerve.[47] Similarly, treatment with a probiotic combination of *L. rhamnosus* R0011 and *L. helveticus* was able to revert the memory impairment, accompanied by decreased BDNF levels in the hippocampus and c-fos expression, induced by *C. rodentium* infection.[226]

Summary: Animal models have been widely exploited to study the role of bacteria in pathophysiology of FGIDs and beneficial effects of probiotics, and have demonstrated a variety of mechanisms and targets that may be strain dependent.

Conclusions

Despite growing research on the microbiota-gut-brain axis, our knowledge of underlying mechanisms remains rather limited. It is unclear which pathways are involved in the communication between the intestinal microbiota or specific bacterial strains, the gut, and the brain, both in health and disease. Accumulating data suggest that, in a significant percentage of patients, the microbiota plays an important role in the genesis and maintenance of FGIDs. Probiotic supplementation appears to be of therapeutic value, although the clinical data to date remain controversial.[227-229] This may be due to heterogeneity in underlying pathophysiological mechanisms, as well as the use of multiple probiotic bacteria with divergent mechanisms of action, as described in animal models, and which may not directly apply to the human condition. Further research should address whether specific probiotic treatment should be tailored to a particular host's microbiota and whether the administration of a single strain is more effective than strain combinations.

Disclosure of Potential Conflicts of Interest

No potential conflict of interest was disclosed.

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