UCDAVIS
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THE IMPACT OF FOOD ON THE MICROBIOTA-GUT-BRAIN AXIS

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CONTENT

INTRODUCTION

Our gut and our brain are deeply interconnected. A nauseous feeling before an important exam, a knotted stomach while about to skydive — whenever we face a stressful situation our emotions and anxiety can translate into “gut-wrenching” experiences. While the way our brain controls our gut is relatively well documented, insight into the feedback the gut can exert on the brain is only starting to emerge.

Our brain sends information and controls the way our gastrointestinal tract operates, and our gut, often depicted as our body’s “second brain” is in turn able to affect our mood, mental health, and beyond [1], [2]. This bi-directional mind-gut connection relies on a vast web of neuronal circuitry and a plethora of neurotransmitters, hormones, and still-to-discover chemicals constantly providing updates on the state affairs from both ends, through the so-called gut brain axis (GBA).

What if this crosstalk would go beyond these two protagonists' actions and be orchestrated by a third entity, the largest colony of residents inside our bodies: our gut microbiota? These trillions of microorganisms, including bacteria, fungi, protists, archaea, and viruses that colonize every corner of our gastrointestinal (GI) tract deeply impact our daily lives [3]. It has become increasingly clear that the gut microbiota is a key regulator of host physiology and a critical determinant of human health and disease. Indeed, these microbes not only provide essential capacities for the fermentation of non-digestible food substrates like dietary fibers, but they also play an essential role in the development and function of the GI tract, the immune system and the nervous system, by controlling the metabolic state of the body through the gut brain axis [3], [4].

Our gut microbiota's diversity and composition tightly influence hundreds if not thousands of metabolic processes. Gut microbial communities are dynamic entities that can change both in composition and activity throughout our lives. They respond to a myriad of factors, including age, genetics, hygiene, drugs, and, more importantly, diet [5]. Therefore, a careful consideration of the specific nutrients and dietary habits promoting a healthy gut microbiota offers the opportunity to extensively act upon our health and prevent the onset of a wide range of adverse conditions.

Through this paper, we provide insights on how food can impact our health and diseases through the influence that our gut microbiota plays on the intricate and crucial connections taking place between the gut and the brain.

THE MICROBIOTA-GUT-BRAIN CONNECTION

The gut and the brain communicate in tandem both physically and biochemically through the gut brain axis. This complex circuitry involves three main communication channels: the nervous system, the endocrine system, and the immune system, all connected in one way or another to the microbiota and its metabolites [3], [4], [6], [7] (Figure 1).

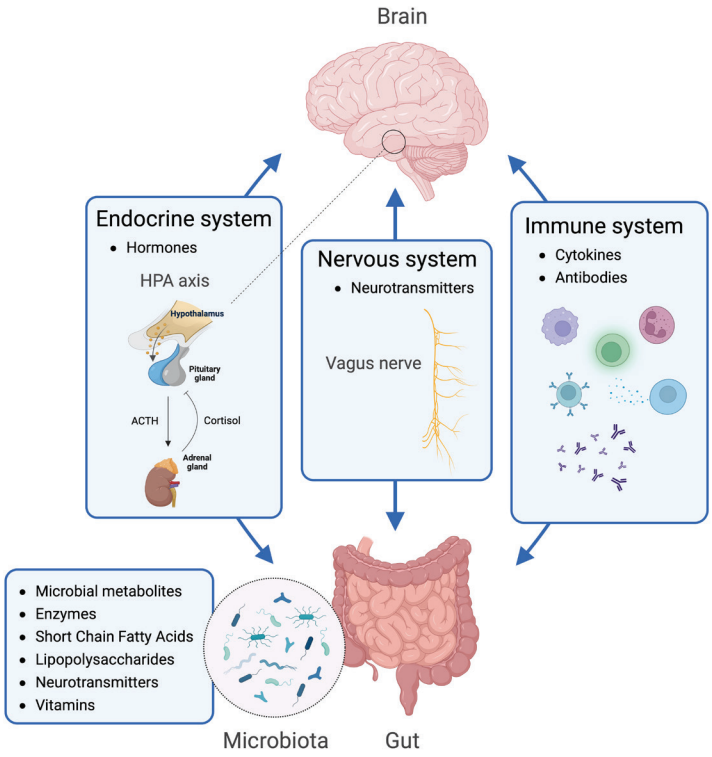

Figure 1. The bidirectional communication between the gut microbiota and the brain is mediated by direct and indirect pathways involving the endocrine system, the nervous system, and the immune system. These pathways use various effectors including, hormones, neurotransmitters, microbial metabolites, peptides, enzymes, immune factors further influencing our metabolism and overall health. The activation of the hypothalamic–pituitary–adrenal (HPA) axis is associated with the occurrence of stress factors or dysbiosis. Under the influence of the adrenocorticotropic hormone (ACTH), the adrenal gland begins to produce and secrete the stress hormone (cortisol), which is responsible for the modulation of intestinal immune and barrier functions. *Created in BioRender.com.*

The Nervous System

Our brain and spinal cord connect to our peripheral nervous system, in particular to the enteric nervous system — a mesh-like system of neurons that governs the function of the gastrointestinal tract considered as our second brain — via the vagus nerve through the use of neurotransmitters. The enteric nervous system controls numerous processes related to the digestive functions such as the speed at which the food transit through the gut, the secretion of acid in our stomach, and the production of mucus on the intestinal lining; and also modulates immune and endocrine function.

As mentioned earlier the gut-brain connection is bidirectional, meaning that beyond its extensive role in monitoring our digestive tract and satiety, the brain can also receive information and feedback from the gut. Indeed, in the past decade, the gut brain axis has been increasingly recognized for its importance in regulating higher-order cognitive and psychological processes. For example, several mood disorders, such as anxiety, depression, and autism spectrum disorders, are correlated to functional GI disruptions [1], [5], [8]–[10]. Moreover, early life gastrointestinal infection with bacterial pathogens such as enteropathogenic Escherichia coli, can have dramatic consequences on the GBA communication and cognitive function in adulthood through the impairment of key neurodevelopmental processes [11], [12].

Indeed, a large proportion of the most potent neurotransmitters, including Dopamine and Serotonin (5-HT), which contribute to our feelings of happiness, as well as gamma-aminobutyric acid (GABA) and Glutamate (Glu), which help control feelings of fear and anxiety, are produced by our gut cells and the trillions of microbes inhabiting our digestive tract [13], [14]. This led to the emerging concept of “microbial endocrinology,” which considers these neurochemicals as a common shared language that enables the communication between the gut microbiota and their host [14]–[16].

Interestingly, theories suggest that microbes are using these neurotransmitters to their advantage to control our cravings and coerce us into delivering specific foods to them. For example, some sugar-hungry bacteria fed with sweets will secrete dopamine, further reinforcing our feeling of happiness and craving for that candy bar staring at us.

The role that the gut microbiota may play in the modulation the vagal pathway to control our feeding behavior and reward signaling is also supported by animal studies in which overeating and/or obesity phenotype can be transmitted to germ-free animal via the transfer of the GI microbiota from individuals fed with high-fat diet [17], [18].

The Endocrine System

In addition to neurotransmitters, communication along the GBA involves the action of hormones such as cortisol through a major channel known as the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis constitutes the primary neuroendocrine coordinator of the stress response but also regulates different body processes, including bowel function during digestion, immunity, emotions, and mood [19].

Not surprisingly, the activation of stress responses or dysregulation of the HPA axis is often linked to gastrointestinal disorders such as inflammatory bowel disease (IBD) or colitis [9]. Several lines of evidence, including studies using deep-sequencing methods, suggest that stress in early life can have long-term effects on the composition of the gut microbiota and mood disorders [20]–[22]. Stress can induce increased permeability, allowing bacteria and bacterial-by-product antigens to cross the intestinal epithelial barrier, and activate inflammatory responses susceptible to altering gut microbiota composition and GI function both locally and distally in the brain [23]. Interestingly, in animals, probiotic treatment can prevent chronic stress through its beneficial effect on the intestinal barrier function [24].

The bidirectionality of the gut brain axis applies to our endocrine system too. Evidence suggests that the gut microbiota play a critical role in the regulation of sex hormones, such as estrogens, and that poor gut health increases the risk of estrogen-related diseases such as Polycystic ovary syndrome (PCOS), endometriosis, and even breast cancer in women [25]–[27].

The Immune System

Our immune system constitutes our body's frontline of defense against harmful external agents and endogenous perturbation of homeostasis. It is characterized by two components:

1. The *innate immunity*, a built-in, rapid, and non-specific response to any foreign molecules (e.i.; antigen), and

2. The *adaptive immunity* reacting to specific antigens for a slower but more selective and targeted response to pathogens including those previously unmet.

Although the immune system spreads across all tissues, sites like the gut are particularly rich in immune cells. About three-quarters of all human body immune cells are located in the gastrointestinal tract [28], exposing them to a constant interaction with the gut microbiota. These interactions "teach" our immune system to distinguish and tolerate beneficial bacteria from pathogenic agents amongst trillions of entities [29].

The detection of foreign bacteria, bacterial by-products, or antigens by immune cells antibodies trigger the production of small proteins called cytokines, spreading the signal and coordinating the response to other immune cells. Cytokines and other proinflammatory immune factors, such as Lipopolysaccharides (LPS) can activate microglia cells — the brain-specific type of immune cells — to further fight pathogens but may also lead to mental disorders. The activation threshold for pathogenic stimulation depends on a finely tuned balancing act between anti- and pro-inflammatory cytokines.

Recent evidence reveals that short-chain fatty acids (SCFAs) — the primary metabolites of the intestinal microbiota produced by anaerobic fermentation — exhibit potent immunomodulatory properties on both innate and adaptive response through the modulation of cytokine production, and the induction of regulatory T cell expansion [30]. Therefore, an imbalance of our gut microbial community, known as dysbiosis, can have dramatic consequences on the regulation of immune homeostasis leading to autoimmune and immune-mediated diseases [31], [32].

In addition, the intestinal microbiota strongly influence vitamin metabolism which can in turn have profound consequences on host immunity [33]. Indeed, vitamins are essential for the development, maintenance, and function of the immune system. Since we cannot produce them, vitamins must be acquired either from diet, or through their synthesis by commensal bacteria. This implies that not only compositional changes in gut microbiota can affect immune function but that the immune system can in turn modulate vitamin biosynthesis through its action on the gut microbiota [34].

FEEDING THE GUT

The health of a natural ecosystem is often measured by the richness and diversity of its species community. Our gut microbiota is no different. Estimated at 100 trillions of microbes including bacteria, yeast, protists and viruses, the diversity of microbial species inhabiting our gut is subject to dynamic changes that play a pivotal role in our health and well-being throughout life [35], [36].

The progress in next-generation sequencing technologies has revolutionized the way in which microbes that colonize the GI tract are identified and functionally characterized, allowing the discovery of unculturable species and their metabolic capabilities [37], [38]. Although there are similarities in the microbial phylum commonly found in our GI tract – with *Bacteroidetes* and Firmicutes representing about 90% of our entire flora [39] – the composition of our gut microbiota is a complex entity evolving throughout our life stages, showing an important variability within and between individuals. Indeed, the different anatomical regions of our digestive tract constitute various ecological niches characterized by their own physiology, pH, O_2 tension, and digestive flow rates linked to specific microbial assembly [40], [41]. For instance, while some bacteria thrive in the acidic environment of the small intestine, others requiring an anaerobic (deprived of oxygen) habitat find their optimal conditions in the large intestine [40].

Various factors influence our gut microbiota fingerprint, including genetic, mode of birth delivery, history of infections, use of medications (antibiotics), and arguably one of most important, our diet [3], [42], [43]. In link with these factors, inter-individual variability in gut microbiota composition begins early in life. At birth, neonates' GI tract is colonized by specific sets of microbes inherited from the mother and determined

by the mode of delivery. Unlike naturally delivered babies, newborns delivered by C-section are not exposed to vaginal species (mostly represented by *Lactobacillus spp*.) nor to fecal microbes leading to essential differences in the establishment and composition of their gut microbiota. Studies suggest that these differences have been associated with long-lasting adverse effects on postnatal immune development, predisposing to infections, allergies, and inflammatory disorders through childhood [44]–[47].

The First Meal

Our first encounter with food is instrumental in shaping our gut microbiota. Rich in fats, protein, carbs and other health-promoting compounds, human milk constitutes a complete and nutritious source of food for the baby. However, long-standing questions have been occupying researchers' minds for decades. Why is the third most abundant class of molecules found in breast milk – a collection of complex sugars known as human milk oligosaccharides (HMOs) – undigestible by babies? What's the reason mothers would produce energetically costly compounds if they were not meant to serve babies' needs?

In the first half of the 20th century research on HMOs experienced a breakthrough with their characterization as "*Bifidus* factors". Acting as prebiotics, in other words, substances promoting the growth of intestinal bacteria, such as Bifidobacteria and *Bacteroides* [48], [49], these sugars play a critical role in shaping the infant's gut microbiota further influencing their short and long-term health. With over 200 HMOs identified so far, these complex carbs exhibit an important structural diversity that translates into a wide array of biological functions extending beyond their role in feeding babies gut good guys.

Recent studies are continuously providing new insights regarding HMO's beneficial health impact, including anti-adhesive properties against

pathogens, modulation of the epithelial and mucosal barrier, as well as an extensive effect on immune cell function, brain development, and cognition [50]–[53] (Figure 2A). For example, sialic acid, a sugar group entering in the composition of certain HMOs constitutes an important nutrient for the developing brain and is associated with cognitive benefit as shown in animal studies [54], [55]. These lines of evidence along with our recent ability to synthetize HMOs [56] provide unprecedented opportunities to rethink milk formulas and reduce the discrepancy in health outcomes observed between breast-fed and formula-fed babies.

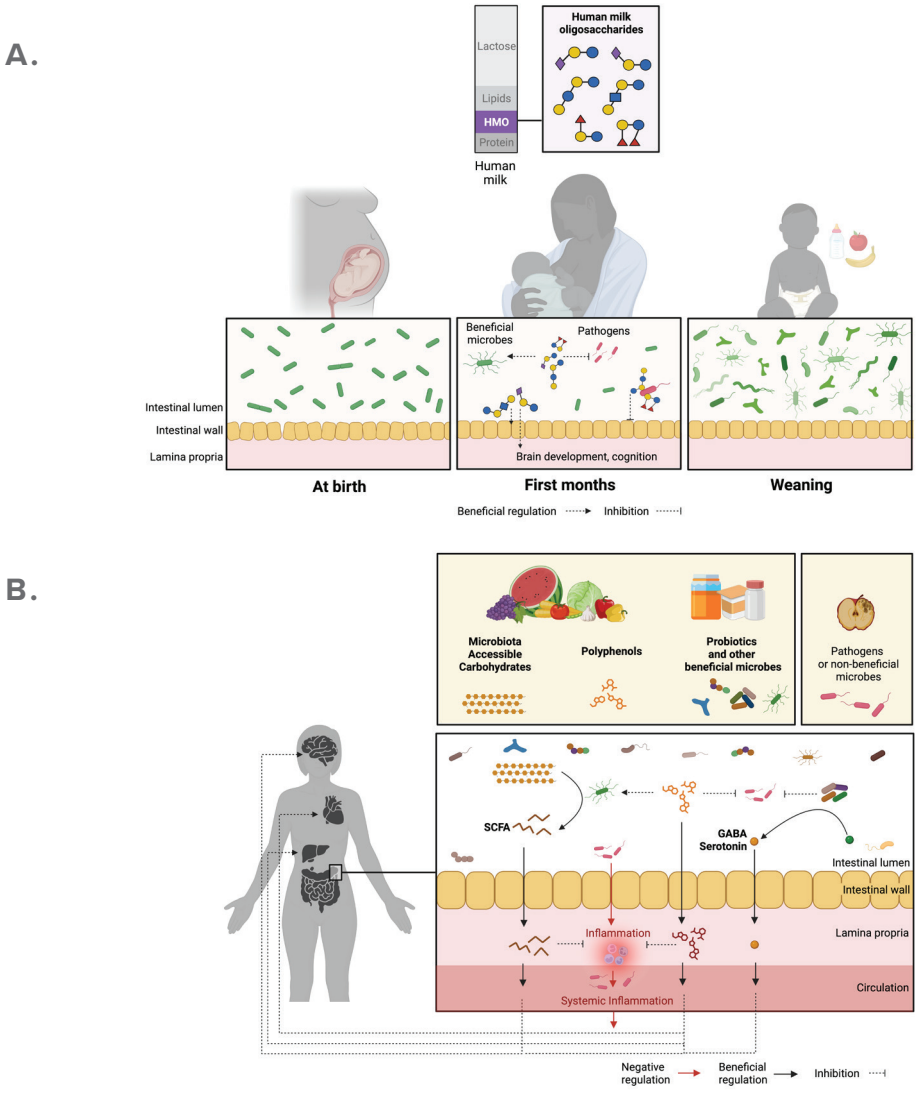

Figure 2. From birth to adulthood our diet plays a pivotal role in the structural and functional capacity of our microbiota. (A) During the first month of life, Human Milk Oligosaccharides (HMOs) promote the growth of beneficial bacteria and positively influence brain development and cognition. As the baby starts transitioning to solid food, its microbiota undergoes drastic changes in composition and function. (B) Later in life, the consumption of food rich in Microbiota Accessible Carbohydrates (MAC), Polyphenols, and Probiotics help build a healthy microbiota and achieve better health outcomes. Along with Polyphenols, the production of Short Chain Fatty Acids (SCFAs) and neurotransmitters such as gamma-aminobutyric acid (GABA) and Serotonin by beneficial bacteria exert a positive impact on various tissues and body systems. *Created in BioRender.com.*

Through the weaning phase the microbiota membership undergoes a radical change as the infant starts transitioning to solid food. This change is characterized by a "bloom" in microbial diversity occurring almost immediately after the introduction of solid food. Studies show that the role of HMOs is instrumental in preparing the ground for the digestion of the baby's first meal by favorizing the early colonization of the gut with the right microbiota [49], [57].

Building a Healthy Microbiota

The establishment of a healthy microbiota during the first years of life is critical in setting the right dialing system between our gut and our brain. Nonetheless, it is never too late to act upon microbiota gut brain (MGB) axis communication. The gut microbiota is a dynamic entity evolving throughout our entire life, deeply influenced by diet, drugs (antibiotics), and supplements including prebiotics and probiotics. Prebiotics refer to non-digestible food ingredients including fibers and polyphenols that promote the growth of resident beneficial bacteria [58]. Probiotics on the other hand represent the live microorganisms contained in food and that confer a health benefit to the host by improving intestinal microbial balance [59]. Although they differ in nature both pre- and probiotics are important to human health and constitute strong drivers shaping the composition and the functional capacity of the gut microbiota [60].

The big MACs

Unlike simple carbs such as glucose, fructose and galactose, complex carbs known as dietary fibers cannot be absorbed by the small intestine due to the lack of digestive enzymes in our body able to degrade them. However dietary fibers and certain types of fermentable fibers called microbiota accessible carbohydrates (MACs) — particularly abundant in fruits, vegetables, and plant-based diets — constitute a favored food source for the microbes living further down in the colon. As these microbes start fermenting MACs, they manufacture a wide diversity of

metabolites such as short chain fatty acids (SCFAs), that are utilized by host intestinal cells (colonocytes) promoting colonic intestinal epithelial integrity and a healthy gut. In addition, SCFAs affect both positively and negatively other gut bacteria and further enrich and modulate the microbial community assembly [60].

Although a large number of SCFAs have been identified so far, acetate, propionate, and butyrate are amongst the most abundant [61]. Not only do these metabolites constitute key factors feeding our gut microbes, but they also play an extensive role in our entire physiology through their action in the regulation of immune function, host metabolism and brain homeostasis (more on butyrate's health benefit in our keto paper). Once absorbed SCFAs enter the systemic circulation exerting their beneficial effect in distal organs including the liver, heart, and brain. As major actors of the MGB axis crosstalk, SCFAs interact with a series of receptors located in various cell populations from the gastrointestinal mucosa to the immune and nervous systems, promoting direct and indirect signaling to the brain [62]–[64]. Through their action on brain myelination – a process particularly important during early neurodevelopment to provide the foundation for brain connectivity – SFCAs are able to restore antibiotic induced anxiety in animal models [65]. Alternatively, these metabolites have also been shown to control gene expression through the regulation of the epigenetic landscape, therefore influencing a wide range of biological processes including energy metabolism and innate immune memory [66], [67]. Although more research is still needed to fully understand SFCAs implication in human health and how this could translate into applicable dietary intervention, these metabolites clearly represent promising targets for development of novel therapeutic methods to treat brain disorders and improve cognitive function.

Polyphenols

Along with fibers, polyphenols represent another important class of plant-derived substances known for their potent health benefits through their antioxidant, anti-inflammatory and neuroprotective properties [68]. According to recent studies these effects may be associated with the action that polyphenols exert on our microbiota by selectively inhibiting the growth of pathogenic bacteria and promoting the growth of the beneficial ones including SCFAs' producing bacteria [69], [70]. Reciprocally, the microbiota itself can influence polyphenols bioavailability as well as using them as precursors for the production of beneficial metabolites [71]. Because certain microbes are better than others in processing polyphenols, inter-individual differences in gut microbiota composition can result in significant variation in their bio-transformation and absorption [72], [73]. In addition, the low bioavailability of dietary polyphenols constitutes a serious limitation to their therapeutic potential. To overcome this barrier, innovation in food formulation is critical to improve the way phenolic compounds can be delivered throughout the GI tract and achieve health benefits. Flavonoids for example, a class of polyphenols interacting with the gut microbiota and supporting memory, cardiovascular and brain health, is undergoing extensive research to improve its absorption and how it can be supplemented in food products for dietary intervention [74].

Probiotics

As discussed, eating nutritious and diversified food is arguably an efficient way to nurture a healthy microbiota and prevent dysbiosis associated diseases. However, it is becoming increasingly clear that we all respond differently to diet, which largely stems from the interindividual variability of the microbial community inhabiting our gut. Also, in addition to feeding commensal microbes with food that enhance the production of beneficial metabolites, enriching our microbiota with selected strains of probiotics is another way to improve gut microbiota functional capacity. Therefore, when the integrity of the microbiota

is challenged by diverse factors including stress, poor diet, bacterial infection or antibiotic treatment, probiotics have proven to be helpful to restoring the microbial intestinal balance and recovering from dysbiosis through the reinforcement of the gut barrier [75].

The relationship between probiotics and our microbiota is as old as human history and closely related to the process of fermentation used for centuries to increase food and drink preservation [76]. Probiotic microorganisms present in fermented food such as Kefir, kombucha or kimchi (usually containing lactic acid bacteria and yeast) produce useful metabolites such as organic acids and antimicrobial compounds that inhibit the growth of pathogens and spoilage organisms. Associated with health promoting effects including mitigation of metabolic syndrome [77], [78], probiotic bacteria have become increasingly popular. In combination with prebiotics (termed as synbiotics) or under the newly developed form of postbiotics (isolated bioactives) they are now widely applied to various food products and supplements, as well as animal feed, as an alternative to antibiotic treatment [79].

Whether probiotic treatment can be effective in reshaping our microbiota diversity on the long run is still debated and significant variation in efficacy can not only be observed between probiotic species but also between different strains. Although probiotics are generally regarded as safe, many probiotics sold as dietary supplements don't require approval from the Food and Drug Administration and the benefits being claimed are not always scientifically established. In addition, there are growing concerns associated with the potential implication of probiotic bacteria in antibiotic resistance. Indeed, probiotic bacteria can carry antibiotic resistance genes that may be transferred to opportunistic pathogens sharing the same intestinal habitat [80], [81]. Given the recent and unregulated expansion of the probiotic market it is important to remain conscious of the potential risk associated with an excessive use of probiotics to keep the balance in favor of their beneficial health effects.

Psychobiotics

A new class of probiotics of interest for their distinctive role in brain health and psychotropic activity is emerging: the psychobiotic. Psychobiotics represent promising tools to alleviate the symptoms of several brain disorders including autism spectrum disorders, Parkinson's disease, multiple sclerosis, insomnia, depression, diabetic neuropathy and others [82]. Mood disorders and psychiatric conditions such as depression are characterized by an hyperactivation of the HPA, enhanced permeability of the blood-brain barrier and decreased levels of serotonin caused by proinflammatory cytokines. Some *Lactobacillus* and *Bifidobacterium* strains are reported to be effective in ameliorating these symptoms. Indeed, through their anti-inflammatory properties and the natural production of neuroactive metabolites and neurotransmitters such as GABA and Serotonin, they play an extensive role in the regulation of HPA activity leading to a decrease in cortisol levels [83]–[85]. Furthermore, an active area of research is the metabolic/genetic engineering of bacteria to enhance the production of neurotransmitters for microbiome therapy [86], [87]. In mouse model oral administration of bacteria genetically engineered to continuously produce L-DOPA is showing promising results in the mitigation of Parkinson's disease [88].

The development of psychobiotic and microbiome treatments are expected to provide valuable alternatives to the use of conventional anti-depressant and benefit patient suffering from mood disorders and neurodegenerative and neurodevelopmental disorders.

Minimizing the impact of the bad guys

Nurturing a healthy microbiota also means limiting our exposure to factors susceptible to impair its composition and function such as antibiotics, poor diet, or bacterial infection. Xenobiotics constitute a well-documented class of compounds known for their deleterious

impact on gut health. They include a wide range of molecules such as antibiotics, pesticides, air pollutants, polychlorinated biphenyls (PCBs), and heavy metals able to induce profound functional changes to the gut microbiota and induce dysbiosis [89]. In addition, the gut microbiota also contributes to the biotransformation of xenobiotics, affecting their activities, toxicities, and lifetimes within the body making the characterization of their effects on our metabolism challenging [90]. Depending on what they feed on, even good gut microbes can impact our health through the by-products they secrete. Food such as red meat and full-fat dairy products are particularly rich in choline, carnitine, and betaine, used by certain gut bacteria as precursors to produce Trimethylamine (TMA). In the liver circulating TMA is oxidized to form Trimethylamine-N-oxide (TMAO), a key driver of vascular inflammation, recognized as biomarker for atherosclerosis and cardiovascular diseases (CVD) as observed in patient with high TMAO blood level [91]–[94]. On the bright side, the growth of TMA producing bacteria can be inhibited through dietary intervention using bioactive ingredients and phytochemicals in order to reduce TMAO biosynthesis and mitigate CVD [95].

CONCLUSION

Our current understanding of the MGB axis represents a change in paradigm in the way we think about human health and clinical medicine. Although the identity of what constitutes a healthy gut microbiota remains challenging, our comprehension of the relationship between the key members of our gut community and their influence on our physiology is getting deeper than ever [5]. From our immune system, to our endocrine system, to our nervous system, our gut microbiota and its by-products modulate the most important communication centers of our body as illustrated by their central role in the gut-brain axis.

We now know that gut microbiota drive beneficial health development and prevent disease when balanced, whereas a dysbiotic microbiome can create disease and in certain cases, impede recovery. Since historical breakthroughs using germ-free mice or fecal transplant experiments, the recent progress in omics technologies is revolutionizing the field. We can now interpret how food affects the diversity of our gut microbes, promote the growth of beneficial bacteria and decipher the impact of their metabolites on our body.

Science based dietary interventions are key to improving human health and additional research is needed to keep unfolding the effects of gut microbiota in other areas of human health (i.e other organs and systems) as well as at all stages of life (from prenatal "in-utero" development to the elderly). Meanwhile, the development of the next generation of healthy "-biotics", metabolites-based products and therapeutic strategies leveraging the way our microbiota respond to diet and affect brain function, will offer unprecedented opportunities to rethink our relationship with food and achieve better health outcomes.

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ENDNOTES

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