

Role of the intestinal microbiota in contributing to weight disorders and associated comorbidities

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SUMMARY The gut microbiota is a major factor contributing to the regulation of energy homeostasis and has been linked to both excessive body weight and accumulation of fat mass (i.e., overweight, obesity) or body weight loss, weakness, muscle atrophy, and fat depletion (i.e., cachexia). These syndromes are characterized by multiple metabolic dysfunctions including abnormal regulation of food reward and intake, energy storage, and low-grade inflammation. Given the increasing worldwide prevalence of obesity, cachexia, and associated metabolic disorders, novel therapeutic strategies are needed. Among the different mechanisms explaining how the gut microbiota is capable of influencing host metabolism and energy balance, numerous studies have investigated the complex interactions existing between nutrition, gut microbes, and their metabolites. In this review, we discuss how gut microbes and different microbiota-derived metabolites regulate host metabolism. We describe the role of the gut barrier function in the onset of inflammation in this context. We explore the importance of the gut-to-brain axis in the regulation of energy homeostasis and glucose metabolism but also the key

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role played by the liver. Finally, we present specific key examples of how using targeted approaches such as prebiotics and probiotics might affect specific metabolites, their signaling pathways, and their interactions with the host and reflect on the challenges to move from bench to bedside.

KEYWORDS gut microbiota, obesity, gut barrier, cancer cachexia, nutrition, probiotics, prebiotics, inflammation

INTRODUCTION

The gut microbiota

The gut microbiota is a complex and dynamic community of microorganisms that inhabit the gastrointestinal tract. It is an extraordinarily diverse and intricate ecosystem comprising trillions of microorganisms that encompass bacteria, viruses, fungi, archaea, and protozoa. The microbial inhabitants residing within our gut significantly outnumber our human cells. In terms of genetic diversity, the collective genome of these microbes, known as the microbiome, vastly exceeds human genome. The ratio of microbial genes to human genes is often estimated to be around 100:1 (1, 2). This staggering difference highlights the immense potential influence that these microbial communities could exert on their host. Indeed, this microbial consortium is far from dormant; it actively engages with its host through various mechanisms, including the metabolization/fermentation of different compounds leading to the production of bioactive metabolites, the regulation of the gut barrier function, and the modulation of immune responsiveness (3). Because of these functions, the gut microbiota plays a vital role in various aspects of health and disease, such as digestion, immunity, metabolism, inflammation, and behavior. The composition and function of the gut microbiota varies greatly among individuals and can be influenced by many factors, such as diet, genetics, age, lifestyle, environment, and medication. So far, research has predominantly focused on gut bacteria due to their culturability, genome size and complexity, functional diversity, and therapeutic potential. Therefore, the term “microbiota” will be used to denote gut bacteria in the rest of this review to reflect the current state of research in the field. Nevertheless, it is essential to note that the other microorganisms in the gut microbiota, such as archaea, fungi, viruses, and protozoa, also play a significant role in gut health and disease and are justly gaining increasing attention from researchers.

The gut microbiota interacts with other organs and systems in the body, such as the brain, the liver, and the adipose tissue (Box 1), profoundly impacting on host physiology and homeostasis. Thus, this vast microbial universe, firmly nestled in our gut, should be considered a key modulator of our health and well-being.

BOX 1. BRIEF DESCRIPTION OF THE INTERACTION OF THE GUT MICROBIOTA WITH VARIOUS KEY ORGANS

Intestine

The symbiotic relationship between the gut microbiota and the host intestine is pivotal for maintaining intestinal homeostasis. This relationship aids nutrient absorption, intestinal epithelial health, barrier function, and immune modulation. Through various mechanisms, the gut microbiota can regulate the proliferation and differentiation of intestinal epithelial cells, ensuring the integrity of the gut barrier.

Adipose tissue

The gut microbiota has been linked to the regulation of fat storage and the function of the different types of adipose tissues. Microbial populations can influence adipose tissue development and function by altering the efficiency of calorie extraction from food, modulating dietary short-chain fatty acid (SCFA) production,

and influencing pathways related to adipose tissue metabolic capacities, inflammation, and energy homeostasis (4, 5).

Brain

Often referred to as the “gut-brain axis,” the bidirectional communication between the gut and the brain plays a vital role in mental health and neurological functions. Microbial metabolites, immune modulators, and neural signals are just some of the communicative pathways through which the gut microbiota can influence appetite, behavior, mood, and neurodevelopmental disorders.

Liver

The liver, directly connected to the gut *via* the portal vein, is continuously exposed to microbial metabolites. This close interaction can influence liver functions, including bile acid synthesis, lipid metabolism, and detoxification/clearance processes. An imbalance in the gut microbiota can lead to various liver conditions, including metabolic dysfunction-associated steatotic liver disease (MASLD) and cirrhosis.

Muscles

Emerging research suggests a potential connection between the gut microbiota and muscle health. Changes in microbial populations might influence muscle mass, strength, and function, potentially through pathways related to energy metabolism, inflammation, and insulin sensitivity.

Gut bacteria metabolites and by-products

The gut bacteria can transform, decompose, and produce compounds resulting in a plethora of microbial metabolites, such as short-chain fatty acids (SCFAs), bile acids (BA), bioactive lipids, amino acids (AA), indoles, and vitamins (Box 2 to 7). The human microbiome is believed to produce or process over 55,000 different compounds (6), many of which can modulate host physiology and pathophysiology in some way. Some of the main actors will be briefly described in boxes throughout the text (Box 2 to 7).

BOX 2. MICROBIAL METABOLITES: SHORT-CHAIN FATTY ACIDS (SCFAs)

These organic acids with 1–6 carbon atoms are produced by gut bacteria through the fermentation of dietary fibers, referred to as microbiota-accessible carbohydrates (MACs) (7, 8). The amount and type of MACs consumed substantially affect the diversity and composition of the gut microbiota and the production of SCFAs (9). SCFAs, particularly acetate, propionate, and butyrate, are among the most well-studied microbial metabolites and play a critical role in regulating host metabolism. They act as energy sources for the host intestinal epithelial cells but also regulate various physiological functions such as insulin signaling, lipid metabolism, and immune cell differentiation.

Acetate is the most abundant SCFA produced in the gut, and it is primarily used by peripheral tissues, such as muscle and adipose tissue, as an energy substrate. Propionate is mainly taken up by the liver, where it is metabolized into glucose, and also plays a role in cholesterol metabolism. Butyrate, on the other hand, is primarily used by the colonocytes as an energy source and has been linked to maintaining barrier function, anti-inflammatory effects, and reduced risk of colorectal cancer. The beneficial effects of SCFAs on host metabolism have been well documented, with studies suggesting that they can improve glucose homeostasis, insulin sensitivity, and lipid metabolism. In addition, SCFAs have been shown to have immunomodulatory effects, such as promoting the differentiation of regulatory T cells and inhibiting the production of pro-inflammatory cytokines (10, 11).

BOX 3. MICROBIAL METABOLITES: GASES

Between 10 and 46 liters of gas passes through the intestines every day. This gas is a mixture of swallowed air and gas produced by bacteria in the colon during the digestion of food. Due to (re-)absorption and utilization of gas within the gut, the average net output per day in terms of flatus is limited to 0.5–1.5 liters (12). Their levels can be influenced by factors like diet and gut health, and imbalances may be linked to specific gastrointestinal disorders (13).

Microbial-driven fermentation contributes to produce gases as by-products. The primary gases produced by gut bacteria include hydrogen (H_2), a direct result of fiber degradation; methane (CH_4), generated by archaea called methanogens using hydrogen; and carbon dioxide (CO_2), a universal metabolic by-product. These gases, while natural outcomes of digestion, also play roles in the gut's anaerobic environment, such as modulating luminal acidity. Depending on their type, concentration, and volume, these gases can either cause or alleviate abdominal symptoms and have a range of effects that are physiological, pathogenic, or therapeutic (14). For instance, CH_4 is linked to slower colon motility and constipation (15) and exhibits antioxidant and antiapoptotic properties in animal models of ischemia-reperfusion injury (16). Hydrogen sulfide (H_2S), on the other hand, can have both beneficial and harmful effects. It's potentially toxic to human tissues, especially when combined with nitric oxide (NO), impairing β -oxidation and the synthesis of lipids and proteins (17), yet it is crucial for cell signaling (18). In the colon, H_2S might regulate arterial blood pressure and, as a gasotransmitter, influence various cellular processes in the gut like inflammation, motility, epithelial secretion, nociception, neurodegeneration, and cancer (19–21).

BOX 4. MICROBIAL METABOLITES: TRIMETHYLAMINE (TMA) AND TRIMETHYLAMINE-N-OXIDE (TMAO)

TMA, a gas with a distinct fishy odor, is produced by certain gut microbes from dietary choline, carnitine, and betaine—nutrients found in red meat, eggs, dairy products, and some seafood. Once TMA is produced in the gut, it enters the bloodstream and is transported to the liver. In the liver, TMA is oxidized by the enzyme flavin-containing monooxygenase 3 (FMO3) to form TMAO. This conversion is a critical step that implicates the gut-liver axis in the regulation of systemic TMAO levels. High levels of TMAO have been associated with an increased risk of cardiovascular disease and may contribute to the development of atherosclerosis (22). TMAO has been shown to alter cholesterol and bile acid metabolism, leading to increased cholesterol deposition in arterial walls (23, 24). In addition, TMAO can promote inflammation and endothelial dysfunction, further contributing to atherogenesis. Moreover, TMAO levels have been linked to other cardiovascular risk factors, such as insulin resistance and hypertension, thereby broadening the scope of its potential impact on cardiovascular health.

BOX 5. MICROBIAL METABOLITES: AMINO-ACID-DERIVED METABOLITES

Amino-acid-derived metabolites are a diverse group of compounds that play essential roles in various physiological processes within the human body. These metabolites originate from the catabolism of essential amino acids like tryptophan, phenylalanine, and tyrosine, which are primarily acquired through dietary sources.

Tryptophan (Trp), a notable amino acid in this context, can be metabolized by both gut bacteria and tissue cells along the kynurenine, serotonin, and indole pathway into a range of bioactive compounds, such as indole, indole-3-aldehyde, indole

propionic acid, tryptamine, kynurenic acid (KYNA), and serotonin. These metabolites can have anti-inflammatory, antioxidant, and neuroprotective effects and may play a role in mood regulation, gut motility, and immune function.

Gut microbiota-derived tryptophan metabolites can influence fat development via the aryl hydrocarbon receptor (AHR) signaling pathway, which regulates fat cell development and metabolism. Indoles like indole-3-propionate (IPA) have been found in lower concentrations in the blood of obese individuals compared to their normal-weight counterparts (25–27). By contrast, kynurenine (KYN) levels are elevated in obesity, possibly due to the increased activity of the enzyme indoleamine 2,3-dioxygenase 1 (IDO1), considered to be the rate-limiting enzyme in the degradation of Trp via the kynurenine pathway. KYNA, a tryptophan derivative, has been shown to promote fatty acid oxidation, thermogenesis, and anti-inflammatory actions in adipose tissue (28). This activity reduces weight gain in high-fat diet-fed mice and enhances glucose tolerance. While an enhanced activity of IDO1 in obesity is recognized (29), its precise role in metabolic diseases is not clear. A shift in tryptophan metabolism, from producing indoles to kynurenine, has been linked to obesity-related issues (30). Research has shown that inhibiting IDO1 can counteract various obesity-induced problems. In addition, adipose tissue is believed to be a major source of KYN, with its accumulation potentially contributing to obesity (25–27). Lastly, gut microbiota-driven tryptophan metabolites were found to regulate energy expenditure and insulin sensitivity through the microRNA-181 family in mouse adipocytes (31). This pathway's disturbance contributes to obesity and related complications.

Gut bacteria can also convert phenylalanine and tyrosine into various metabolites, such as phenylpropionic acid (PPA), phenylethylamine, phenyllactic acid, p-cresol, p-hydroxyphenylacetic acid, and dopamine. These metabolites can affect host health by regulating oxidative stress, inflammation, neurotransmission, and behavior.

BOX 6. MICROBIAL METABOLITES: BILE ACIDS

Primarily produced by the liver, bile acids play a crucial role in digesting and absorbing dietary fats. Their production is significantly influenced by the microbiota. Bile acids, besides aiding in the digestion and absorption of cholesterol, triglycerides, and fat-soluble vitamins, also act as signaling molecules or hormones, influencing glucose, lipid, and energy metabolism. A specialized receptor, G-protein-coupled bile acid receptor-1 (TGR5), present in various tissues, particularly in brown adipose tissue, facilitates these signaling functions. TGR5 activation impacts lipid and carbohydrate metabolism, energy expenditure, and inflammation (5, 32). Studies on mice and human cells indicate that bile acid mimetics can enhance mitochondrial biogenesis and function, promoting energy expenditure. In humans, oral supplementation of primary bile acid has shown potential in increasing brown adipose tissue activity and whole-body energy expenditure (32, 33). Moreover, TGR5 receptors in the gut influence the release of hormones crucial for energy and metabolic balance, such as PYY and GLP-1, thus indirectly affecting food intake.

BOX 7. MICROBIAL METABOLITES: POLYPHENOLIC METABOLITES

Gut bacteria can metabolize dietary polyphenols into a range of pleiotropic bioactive compounds with antioxidant and anti-inflammatory properties that have been shown to reduce the risk of cardiovascular disease and certain cancers (34–36).

Some examples of phenolic metabolites produced by gut microbes include the following:

- Phenylpropionic acid (PPA): PPA has been shown to have anti-inflammatory properties, to promote epithelial barrier function *via* AhR (37) and may help protect against colorectal cancer.
- Hydroxyphenylacetic acid (HPAA): HPAA is known for its antioxidant properties and may contribute to cardiovascular disease prevention.
- 4-Hydroxyphenylacetic acid (4-HPAA): 4-HPAA exhibits both anti-inflammatory and antioxidant properties, potentially aiding in the protection against certain cancers.
- Phenolic acids: Gut microbes can also produce a variety of phenolic acids from dietary polyphenols, including caffeic acid, ferulic acid, and gallic acid that possess health protective effects against several pathogenic conditions, including cancer, cardiovascular, liver, and neurodegenerative diseases, as well as microbial infections (38).

The gut barrier

The gastrointestinal (GI) tract is the largest interface in the body in direct contact with the external environment and the microbial inhabitants. Consequently, it represents the first line of defense against any potentially harmful agents that have been ingested with food and is crucial to protect and maintain overall health (39). The gut barrier is a complex, multilayered system that consists of physical, chemical, immunological, and microbial components that protect the host from harmful substances and pathogens, while still allowing the absorption of water, electrolytes, nutrients, and metabolites (Fig. 1). The gut barrier is essential in maintaining homeostasis and intestinal microbiota function while protecting against pathogens. Disruptions in this barrier can lead to increased intestinal permeability, which has been increasingly recognized as a potential precursor to a variety of metabolic disorders and can contribute to the pathogenesis of weight disorders and their associated comorbidities (39).

The key components maintaining the integrity of the barrier are as follows:

The epithelium

A single layer of epithelial cells that lines the gut and forms the physical barrier. The cells are tightly joined together to prevent the passage of larger substances while regulating the movement of water and electrolytes. There are different types of epithelial cells with specialized functions:

1. Enterocytes: Enterocytes are the most abundant cells in the intestinal epithelium. They form a tightly packed monolayer and are responsible for nutrient absorption and secretion of digestive enzymes. Enterocytes have microvilli on their apical surface, which increases the surface area available for absorption (Fig. 1).
2. Goblet cells: Goblet cells are specialized epithelial cells that secrete mucus. The mucus layer acts as a physical barrier and helps protect the underlying epithelium from pathogens, toxins, and mechanical damage. Goblet cells are primarily found in the small and large intestines (40) (Fig. 1).
3. Paneth cells: Paneth cells are primarily located in the small intestine, particularly in the crypts of Lieberkühn. They also exhibit profound immunomodulatory function since they secrete various antimicrobial peptides, such as defensins and lysozyme, which help to control the gut microbial population and protect against bacterial infections.
4. Enteroendocrine cells: Enteroendocrine cells are subdivided into 12 types according to their location and main secretory hormones (41). Collectively, enteroendocrine cells produce about 30 different hormones and neurotransmitters that control a wide range of metabolic processes (42). These hormones

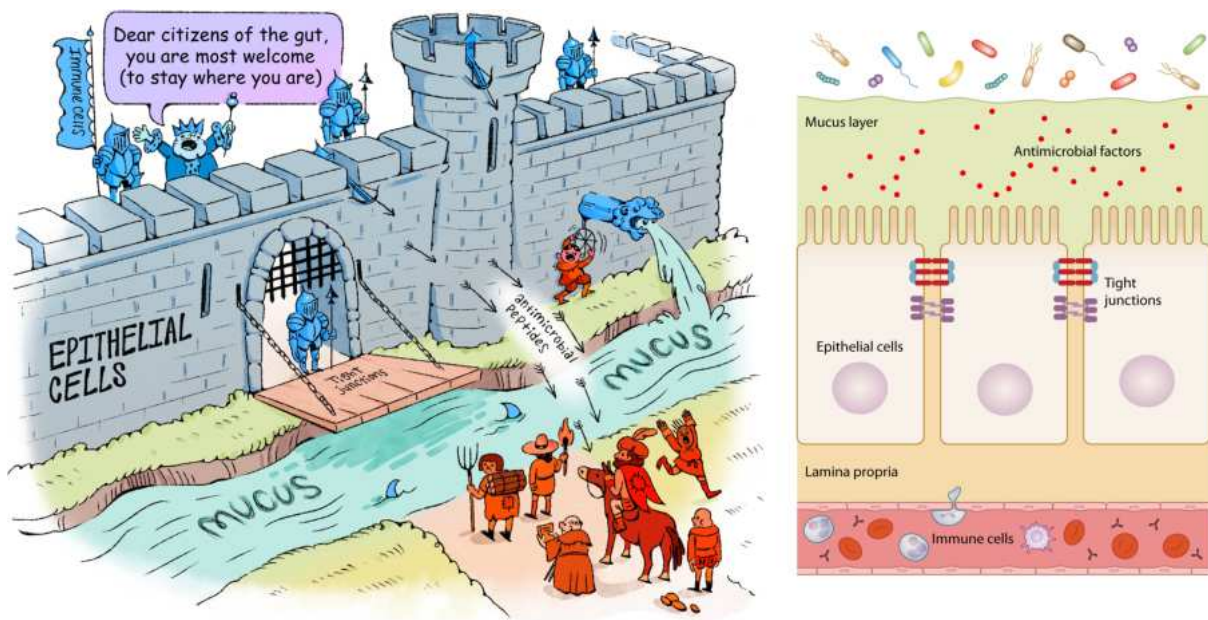


FIG 1 Gut barrier function viewed as a castle. The gut barrier can be compared to a great wall, with a moat and guarded by soldiers. The walls are our epithelial cells that only allows for certain nutrients and selected metabolites to enter. These cells are holding on to each other *via* tight junction proteins. The moat is a mucus layer on top of these cells that is impregnated with antimicrobial peptides, making sure that the bacteria are kept at a certain distance. The soldiers are our immunity cells that patrol our bloodstream and can come into action if needed. In the mucus, a specific mucus specialist the bacterium *Akkermansia muciniphila* is dialoguing with the different partners involved in the gut barrier function.

regulate various functions in the gastrointestinal tract, including digestion, nutrient absorption, and satiety.

5. **Microfold (M) cells:** M cells are specialized epithelial cells found in the follicle-associated epithelium covering Peyer's patches, which are part of the gut-associated lymphoid tissue (GALT). M cells play a critical role in immune surveillance by facilitating the uptake and transport of antigens and pathogens from the gut lumen to immune cells within Peyer's patches.
6. **Stem cells:** The intestinal epithelium has a high rate of turnover, and stem cells located within the crypts of Lieberkühn continuously replenish the epithelial cells. These stem cells can differentiate into various cell types, including enterocytes, goblet cells, and Paneth cells, ensuring the maintenance and repair of the gut barrier.
7. **Tuft cells,** also known as brush cells or caveolated cells, are specialized epithelial cells found in the gastrointestinal tract. They possess microvilli on their surface, giving them a tufted or brush-like appearance. Tuft cells function as chemosensory cells, detecting and responding to various luminal stimuli in the gut. They secrete cytokines, chemokines, and other signaling molecules upon activation, influencing immune responses and tissue repair. Tuft cells play a role in parasite defense, gut homeostasis, and interactions with immune cells, contributing to the overall function of the gut.

Tight junction proteins (TJPs)

These are protein complexes that connect the epithelial cells together and regulate the paracellular permeability of the intestinal epithelium. The main tight junction proteins of the gut barrier include claudins, occludins, and junctional adhesion molecules (JAMs). Tight junction proteins interact with each other to regulate the size of the paracellular pathway, but they also act as ligands for leukocyte integrins, allowing immune cells to cross the epithelial barrier (43) (Fig. 1).

Mucus layer

A thick gel-like substance that is secreted by goblet cells. It acts as a lubricant to ease the passage of food through the gut and also provides a barrier to pathogens. The mucus layer also contains antimicrobial peptides that help to kill off harmful bacteria (40) (Fig. 1).

Antimicrobial peptides (AMPs)

These are small protein molecules that are produced by enterocytes and Paneth cells and are important for maintaining the balance of the gut microbiota and protecting the host from harmful pathogens (44). Some of the main AMPs produced in the gut include the following: defensins that act by disrupting bacterial cell membranes (e.g., alpha-defensins), lysozymes that hydrolyze the peptidoglycan layer of bacterial cell walls (e.g., lysozyme C), cathelicidins that have broad-spectrum antimicrobial activity and can also modulate the immune response by recruiting immune cells, phospholipases, C-type lectin, and regenerating islet-derived 3-gamma (RegIIIγ) which is a secreted C-type lectin that binds the bacterial cell wall and is particularly effective against Gram-positive bacteria (44–46).

Immune cells

The gut is home to a large number of immune cells, including dendritic cells, T cells, B cells, and macrophages. These cells and the gut-associated lymphoid tissue (GALT) play a critical role in detecting and responding to potential threats, such as pathogens and toxins (Fig. 1).

Secretory IgA

These are antibodies that are produced by the gut-associated lymphoid tissue (GALT) and are secreted into the gut lumen. They play a key role in preventing the attachment and invasion of pathogens to the gut epithelial cells (47, 48).

The microbiota

The commensal microorganisms themselves help to maintain the integrity of the gut barrier by regulating/stimulating the immune system, producing metabolites that nourish the gut epithelium, and preventing the colonization of harmful pathogens (by producing antimicrobial peptides and competing with pathogenic bacteria for resources and colonization sites) (Fig. 1).

All these components work together to form the gut barrier and protect the gut and overall body from harmful substances. The gut barrier can become compromised due to a variety of factors, such as chronic inflammation, antibiotic use, poor diet, and stress. A compromised gut barrier can lead to health issues for the host, including food allergies, autoimmune diseases, inflammatory bowel disease, and even some types of cancer.

Dysbiosis, leaky gut, and metabolic endotoxemia

The human gut microbiota is an incredibly diverse ecosystem, hosting over a thousand identified bacterial species. However, in any individual, only around 150 of these species are typically predominant leading to important diversity between individuals (49). This diversity is primarily driven by the interplay of various factors unique to each individual, such as dietary and lifestyle choices, environmental exposures, medication use, and the distinct genetic makeup of every person. This complex variability underlines why it is not feasible to specify a “healthy” gut microbiota in terms of bacterial composition and emphasizes the need for personalized considerations in understanding and maintaining gut health (50).

However, recent advancements in scientific research have demonstrated that certain gut microbial patterns are associated with a multitude of disease states including

obesity, diabetes, inflammatory bowel disease, irritable bowel syndrome, non-alcoholic fatty liver disease, cardiovascular disease, and cancer (4, 10, 51, 52). Though controversial because of its vague definition and limitations, the term “dysbiosis” is often used to describe an imbalance in the gut’s microbial community, where there might be a decrease in beneficial microbes, an increase in harmful microbes, or both. This is often characterized by reduced biodiversity and presumed to be an abnormal composition of the gut microbiota with compromised microbial functions.

Dysbiosis can compromise the integrity of the gut barrier (39). If the gut barrier is compromised, the permeability of the gut can increase, allowing unwanted substances to enter the bloodstream, potentially leading to a range of gastrointestinal and systemic health issues. This intestinal hyperpermeability is referred to as gut barrier dysfunction or “leaky gut.”

Dysbiosis has been linked to metabolic endotoxemia (53). This condition is defined by heightened levels of lipopolysaccharide (LPS) in the plasma (53). LPS, a significant component of the outer membrane of Gram-negative bacteria, can penetrate the bloodstream in larger amounts under certain conditions. One primary route is *via* increased intestinal permeability, which allows for the translocation of LPS from the intestinal lumen into the circulatory system (54). Alternatively, the liver’s compromised ability to clear LPS can also contribute to its accumulation in the bloodstream. The presence of elevated LPS can act as a catalyst for systemic inflammation. Furthermore, it has been found to disrupt normal insulin signaling, leading to insulin resistance—a key player in the development of several metabolic disorders (53). Consequently, metabolic endotoxemia has been intricately linked with conditions like obesity and diabetes, underscoring the intricate relationship between gut health and systemic metabolic function (10, 55) (Fig. 1).

GUT MICROBIOTA AND METABOLIC DISORDERS

Body weight homeostasis is the ability of the body to maintain a stable weight over time, despite fluctuations in food intake and energy expenditure. The body achieves this balance by regulating various physiological processes, such as appetite, metabolism, thermogenesis, and fat storage. When body weight homeostasis is disrupted, it can lead to obesity or underweight, which are associated with an increased risk of various health problems. Body weight homeostasis is influenced by both genetic and environmental factors, but the gut microbiota has also emerged a key player (56).

Gut microbiota and obesity

The intricate relationship between gut microbiota and obesity has been progressively unearthed through a series of pioneering studies. Backhed et al. (57) underscored the pivotal role of gut microbiota in weight regulation by demonstrating that germ-free mice had lower body fat than conventionally raised counterparts, and the transplantation of gut microbiota led to increased fat accumulation (57). In a seminal study by Ley et al. (58), it was revealed that obese individuals exhibited a distinct gut microbiota composition, particularly a different ratio of the bacterial phyla Firmicutes and Bacteroidetes, hinting at the microbiota’s influence on energy metabolism (58). Echoing these findings, Turnbaugh et al. (59) illustrated that the microbiome of obese mice was more adept at energy extraction from food, a phenomenon further emphasized when the obese microbiota was transferred to germ-free mice, leading to fat deposition (59). Cani et al. (2007) ventured into the therapeutic potential of prebiotics, showing that they could modulate the gut environment, enhance glucose tolerance, and reduce fat and inflammation in obese mice (53, 60). Jumpertz et al. (61) expanded the discussion to humans, associating gut microbial composition with caloric intake and nutrient absorption (61). Ridaura’s 2013 study provided compelling evidence of the microbiota’s influence on obesity by transplanting fecal material from lean and obese humans into germ-free mice, observing that those with obese donors’ microbiota exhibited increased fat accumulation (62).

However, as the field matured, some critiques emerged. For example, the Firmicutes over Bacteroidetes ratio as a putative universal characteristic of obesity did not hold long. A 2008 study did not find the proportions of Bacteroidetes and Firmicutes to be different between fecal samples of individuals who were lean or with obesity, even after weight loss, and the concept was challenged as potentially not universally applicable (63), and later meta-analyses were unable to find consistent and reproducible microbial taxonomic signatures of obesity in humans (64–66). Similarly, the dogma that the absence of gut microbiota is associated with reduced body weight and protection against diet-induced obesity has repeatedly been challenged by studies that could not replicate previous findings and argue that the gut microbiota may not be such an essential factor in the onset of obesity and metabolic dysfunction (67). In 2016, Sze and Schloss highlighted the need for rigorous methodologies, suggesting that not all prior conclusions might hold (66). In 2020, Walter et al. further underscored the complexities and challenges in unequivocally establishing causality between gut microbiota and obesity, particularly in rodent models (68).

Collectively, these studies both illuminate the impact of the gut environment on obesity and metabolic health while emphasizing the complex relationship between the gut microbiota and its host and cautioning for the intricacies that researchers must navigate.

Gut microbiota and regulation of energy intake

Dysregulation of energy intake is one of the main drivers of obesity and metabolic disorders. Inappropriate food behavior combined with an increased availability of energy-dense foods has significantly contributed to the emerging worldwide obesity epidemic (69).

Food intake regulation is a multifaceted process intricately orchestrated by the central nervous system, which integrates signals from peripheral organs, including the gut (70).

This regulatory mechanism encompasses the sensations of appetite, satiety (i.e., the feelings of fullness between meals), and satiation (i.e., feelings of fullness during ingestion of a meal). These sensations are mainly consolidated in the hypothalamus, involving complex interactions among several nuclei, a process termed homeostatic feeding (71).

Key to this regulation is the arcuate nucleus, which receives hormonal and neural (*via* the vagus nerve) inputs from peripheral organs like the gut and the adipose tissues. Within the arcuate nucleus, there are two main types of neurons: orexigenic neurons, which produce appetite-stimulating peptides such as neuropeptide Y (NPY) and agouti-related peptide (AgRP), and anorexigenic neurons, which synthesize appetite-suppressing peptides like pro-opiomelanocortin (POMC), a precursor of α -melanocyte stimulating hormone (α -MSH), and cocaine- and amphetamine-related transcript (CART) (72). These neuropeptides then target specific receptors in the paraventricular nucleus (PVN) and the lateral hypothalamus (LH), which are centers of satiety and hunger, respectively, to either stimulate appetite or inhibit food intake (73) (Fig. 2).

However, this hypothalamic mechanism can be overridden by non-homeostatic or hedonic factors, such as the sensory perception or pleasure associated with food. The hedonic properties of food can stimulate feeding behavior through the reward system involving the abrupt release of dopamine in the mesocorticolimbic pathway (74, 75). This reward pathway consists of dopaminergic neurons in the ventral tegmental area of the midbrain, which projects to areas of the limbic forebrain, notably the striatum, nucleus accumbens, and prefrontal cortex (76) (Fig. 2).

Thus, the regulation of food intake is a complex interplay between homeostatic needs and hedonic desires, mediated by a network of hormonal and neural pathways and signals.

The gut-brain axis is a bidirectional communication network between the gut and the brain and plays an important role in the regulation of both homeostatic and hedonic aspects of feeding. Central to this gut-to-brain communication is the vagus nerve, which

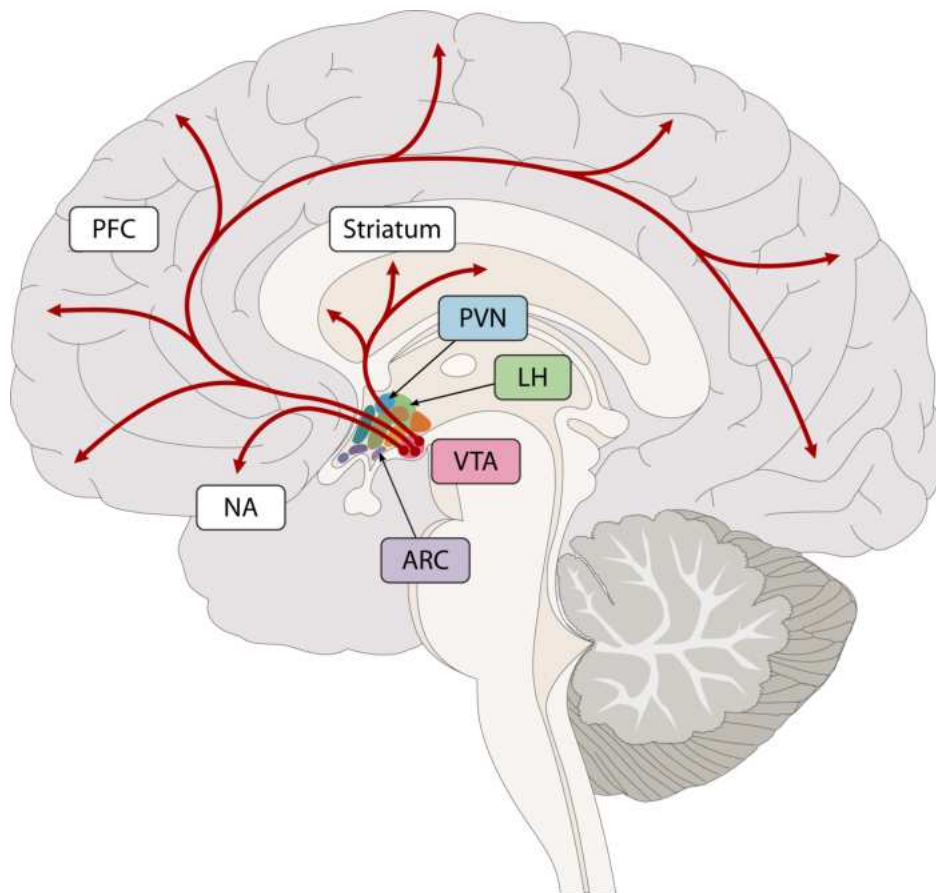


FIG 2 Main brain areas involved in homeostatic and hedonic feeding. Homeostatic feeding: ARC (arcuate nucleus), PVN (paraventricular nucleus), and LH (lateral hypothalamus). Hedonic feeding: VTA (ventral tegmental area), NA (nucleus accumbens), and striatum and PFC (prefrontal cortex). Created with BioRender.com

conveys signals from intestinal vagal afferents to the nucleus tractus solitarius (NTS) and subsequently to the hypothalamus. This neural pathway enables the brain to receive critical information regarding the body's energy status from the periphery (77). Moreover, the key role of the vagus nerve in the functional pathway linking the gut to the brain reward system has also been demonstrated (78), underscoring its significance in feeding behavior.

The endocrine system is another key component of the gut-brain-axis communication. Gut hormones such as ghrelin, cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), and peptide YY (PYY), as well as leptin and insulin, are released in the blood and/or activate the vagal afferents nerves, thereby targeting the hypothalamus, exerting either anorexigenic (appetite suppressing) or orexigenic (appetite stimulating) effects. (Fig. 3 and 4). Importantly, these hormones also directly influence the activity of the dopaminergic system and, consequently, hedonic feeding (79, 80).

Recent research has highlighted the significant role of gut microbiota in the gut-brain axis, particularly in controlling food intake. Studies, including our contributions, have demonstrated that gut microbes profoundly impact the regulation of appetite, satiety, satiation, and energy expenditure (56). Mechanistically, different elements have been described to be involved in the effects of gut microbes on homeostatic regulation of energy intake. For instance, SCFAs can activate specific G-protein-coupled receptors 41 (GPR41) and 43 (GPR43), thereby stimulating GLP-1 and PYY secretion and inducing anorexigenic effects. Moreover, certain SCFAs (e.g., acetate) and bacterial components [e.g., caseinolytic peptidase B (ClpB)] can directly reach the hypothalamus and modulate appetite (81) (Fig. 3 and 4). [For more details, see (82)].

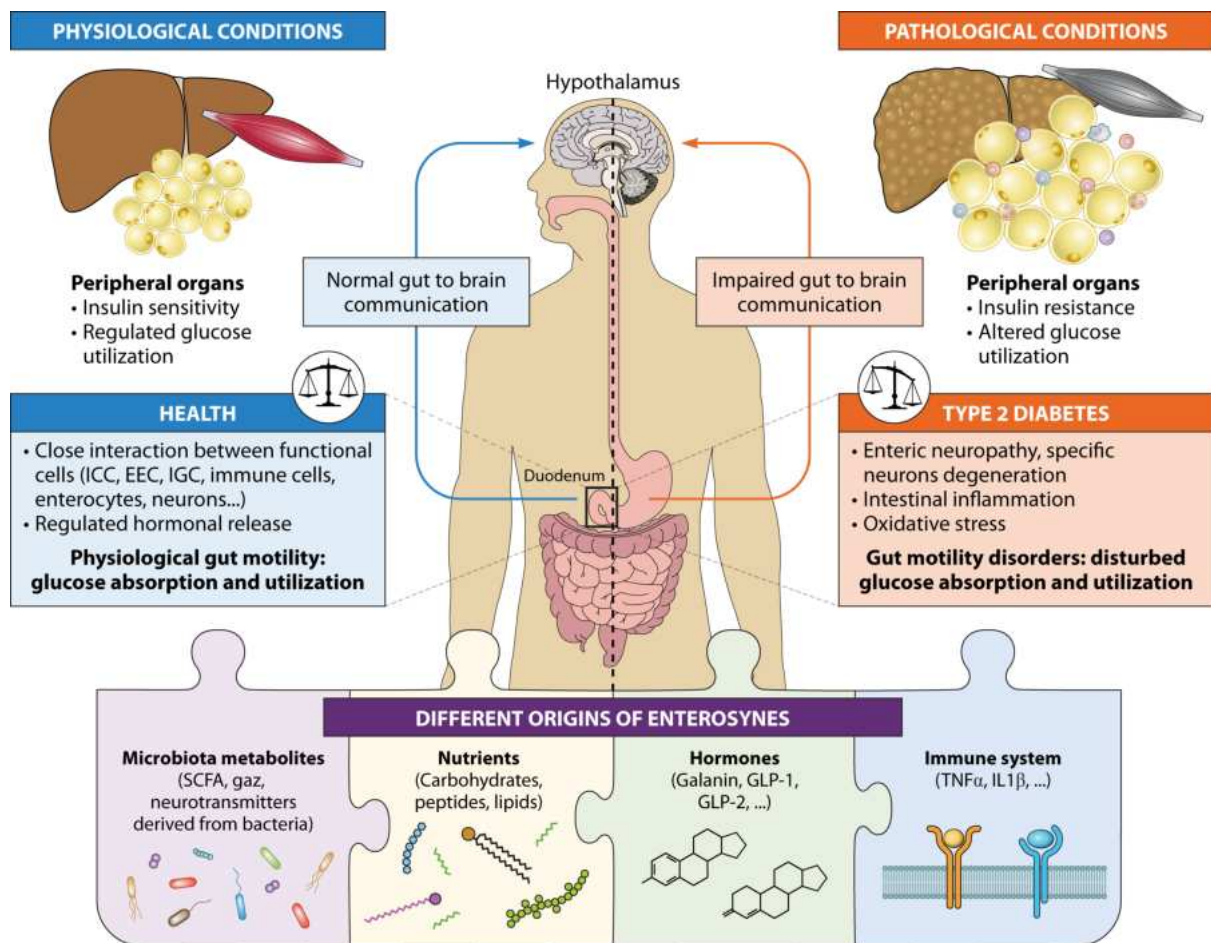


FIG 3 The enterosyne concept: roles and effects of enterosynes on health and diseases. Enterosynes may have various origins (gut microbiota, food, enteroendocrine, or immune cells). By targeting enteric neurons, some of them could decrease the duodenal motility to (i) favor a decrease in glucose absorption and (ii) restore the gut-to-brain-to periphery axis and insulin sensitivity during type 2 diabetes. Created with Biorender.com.

Our recent research has yielded pioneering findings, revealing that microbes can influence hedonic and reward-driven aspects of food intake, thereby affecting the host's food preferences and food consumption patterns (83–85). In our study, we exposed both control mice and mice with depleted gut microbiota, achieved through the administration of broad-spectrum antibiotics, to a food preference test where they were given a choice between a control diet and a high-fat high-sugar diet. Interestingly, antibiotic-treated mice showed a marked preference for the high-fat, high-sugar diet compared to their control counterparts. This outcome suggests that gut microbes play a significant role in regulating the hedonic aspects of food intake. These data have been recently corroborated in another study (86). Moreover, research involving germ-free mice also showed that these mice have an increased preference for lipid solution and consume higher amounts of highly concentrated sucrose solution compared to control mice with normal gut microbiota (87, 88).

During obesity, there is a notable alteration in the hedonic responses to food intake, which can lead to an abnormal increase in energy consumption (89–93). Prolonged excessive food intake has been shown to cause a downregulation of the dopaminergic pathway. Consequently, greater amounts of dopamine are required to achieve the same level of stimulation. This feeds a vicious circle of increased reward-seeking behavior. This often manifests as compulsive eating and an escalated consumption of palatable food to compensate for the diminished reward response (94).

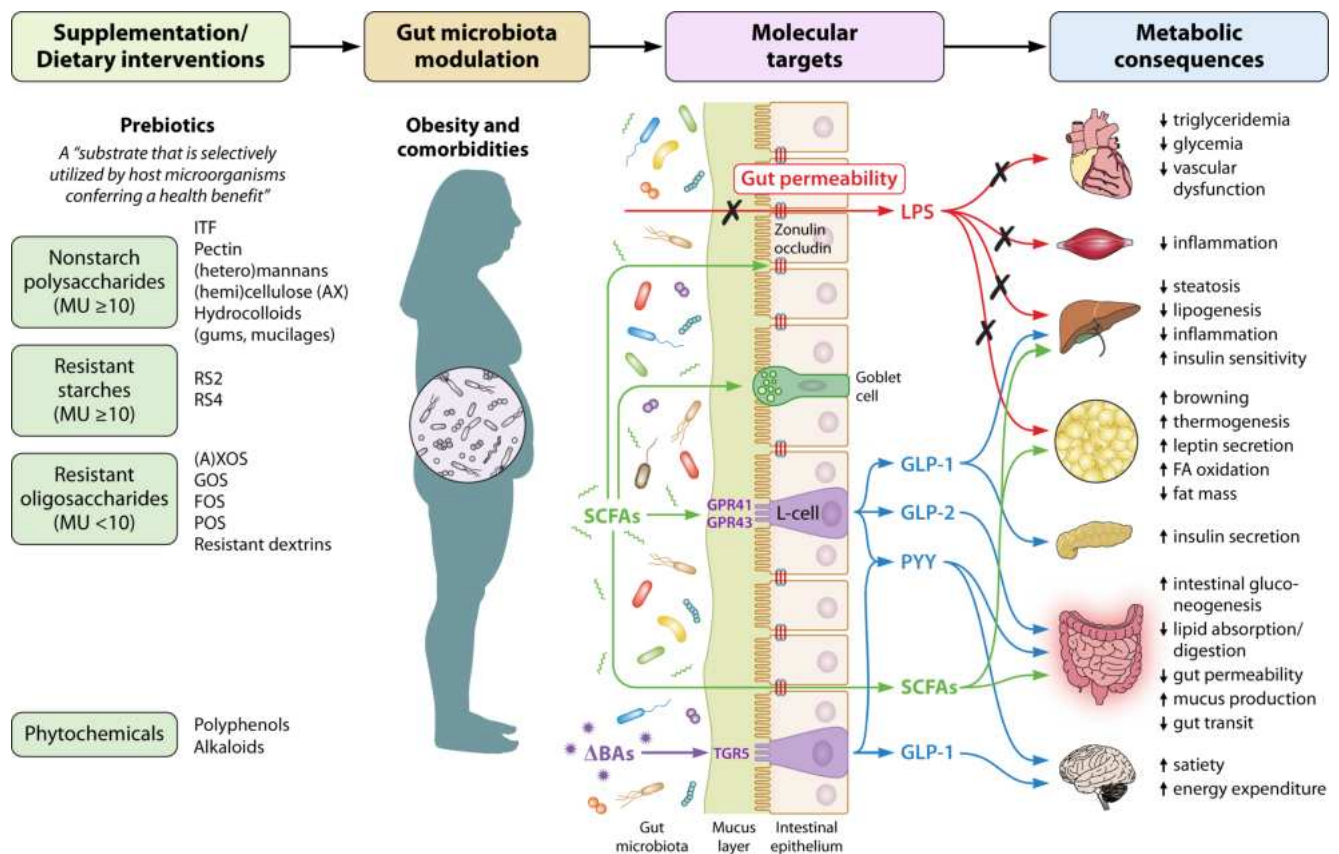


FIG 4 Mechanisms evoked to understand the biological effect of gut microbes and metabolites in the context of obesity and related co-morbidities. In animal models of obesity, prebiotics changes the composition and/or activity of the intestinal microbiota (production of bacterial metabolites). Some bacterial metabolites (SCFA) are metabolized by host cells in the colon or in the liver and, therefore, mainly affect local gut and liver function. Some can bind and activate G protein-coupled receptors leading to the production of the gut hormones, thereby beneficially regulating energy homeostasis and gut barrier function. AX, arabinoolans; (A) XOS, (arabino)xylo-oligosaccharides; FOS, fructo-oligosaccharides; GOS, galacto-oligosaccharides; ITF, inulin-type fructans; MU, monomeric units; POS, pecto-oligosaccharides. SCFAs, short-chain fatty acids; BAs, bile acids; GPR, G protein-coupled receptors; GLP, glucagon-like peptide; PYY, peptide YY; LPS, lipopolysaccharides; RS, resistant starches; TGR-5, G-protein-coupled bile acid receptor-1.

As described in the literature, our research found that diet-induced obese mice consumed less high-fat/high-sugar diet during their initial exposure to such food compared to control mice. This supports the notion that there is a reduction in the pleasure derived from previously unknown palatable food, reflecting alterations in the "liking" component of food intake (83).

While counterintuitive at first, this phenomenon often leads to overconsumption of palatable food in humans to compensate for the loss of pleasure, especially since such foods were previously typically associated with rewarding experiences.

Our studies also demonstrated that transferring gut microbiota associated with obesity can reproduce the phenotype. Mice receiving gut microbiota from diet-induced obese donor mice showed a reduced intake of high-fat/high-sugar diet compared to those receiving gut microbiota from control mice (83). This finding suggests that gut microbes can influence the host's food preferences and consumption behaviors.

In another set of experiments, we observed obese-microbiota recipient mice displayed excessive motivation to obtain sucrose pellets, thus establishing a link between gut microbes and compulsivity related to hedonic feeding (85). Through untargeted metabolomic analysis, we identified two phenolic metabolites produced by gut microbes, namely 3-(3'-Hydroxyphenyl)propanoic acid (33HPP) and 3-(4'-Hydroxyphenyl) propanoic acid (34HPP), that were particularly increased in both plasma and cecal content of mice transplanted with obese gut microbiota and that correlated

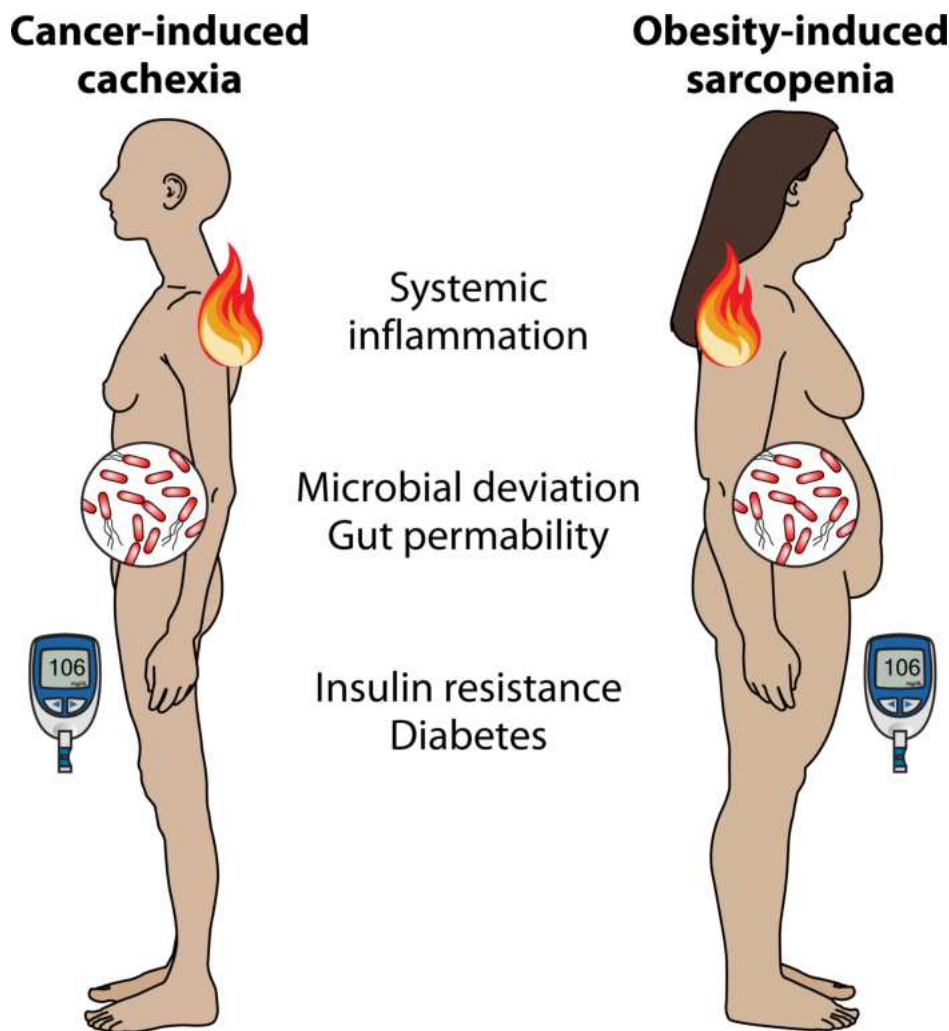


FIG 5 Paradoxical similarities between obesity-induced and cancer-induced cachexia. Created with Biorender.com.

positively with the mice's motivation to obtain food rewards (85). The most abundant metabolite of 33HPP was also increased in the brain of mice transplanted with obese gut microbiota, suggesting its potential to reach circulation, cross the blood-brain barrier, and directly influence brain function. Our research further revealed that 33HPP administration modulates the expression of dopaminergic and opioid markers in reward-related brain areas, which is associated with impacts on memory and learning processes within the reward system (85).

Altogether, these data support that gut microbiota shifts associated with obesity are causally involved in alterations of the hedonic and motivation components associated with food intake. Some gut microbiota metabolites (e.g., 33HPP) could reach the circulation and cross the blood-brain barrier to act on the reward brain areas. Moreover, the vagus nerve has recently been identified as a mediator of bacterial-driven modulation of reward signaling during high-fat feeding (95). That said, other mechanisms of crosstalk between the gut microbiome and hedonic feeding still need to be uncovered.

The concept that supplementation with beneficial bacteria can positively influence the regulation of hedonic feeding in the host has been supported by findings from preclinical models. For instance, supplementation with *Bifidobacterium pseudocatenulatum* has been shown to influence hedonic food behavior by reversing the reduction in sucrose preference that is typically induced by a high-fat diet (96). Moreover, our research demonstrated that *Akkermansia muciniphila* can ameliorate dysregulated food reward

behaviors associated with obesity. The mechanism behind this effect appears to involve a reduction in the activation of inflammatory pathways and lipid-sensing ability in the striatum (84).

The implications of such research are far-reaching, offering potential new avenues for addressing obesity and related eating disorders through microbiome-targeted therapies.

Gut microbiota and diabetes

The gut microbiota of diabetic patients displays a higher prevalence of pathogenic and opportunistic gram-negative species, replacing commensal bacteria. Notably, there is an increase in pathogenic bacteria such as Enterobacteriaceae, various Clostridiales, *Escherichia coli*, *Bacteroides caccae*, alongside *Prevotella copri* and *Bacteroides vulgatus* in the microbiota of these patients (97). Furthermore, research from both animal models and human studies indicates a significant reduction in butyrate-producing species like *Faecalibacterium prausnitzii* and *Roseburia intestinalis*. This reduction has been suggested as a key microbiota-related factor contributing to the onset and progression of type 2 diabetes (98).

Intriguingly, obese subjects treated with vancomycin, which inhibits the growth of butyrate-producing bacteria, consistently develop insulin resistance (99). Conversely, a study in mice found that propionate induces the production of glucagon and fatty acid-binding protein 4 (FABP4), impairing insulin signaling. Similarly, in humans, propionate is associated with a post-prandial increase in norepinephrine, glucagon, and FABP4 plasma levels, thereby promoting insulin resistance (100).

The evaluation of microbiota deviations (dysbiosis) in diabetes reveals some contradictory findings, which may be influenced by the effects of antidiabetic therapies. Meanwhile, several ongoing trials are investigating the therapeutic efficacy of probiotic administration in managing diabetes and its complications (97).

In addition to gut microbiota modifications, type 2 diabetes (T2D) is also associated with alterations in the enteric nervous system (ENS), leading to gut dysmotility issues. The ENS includes enteric neurons and glial cells that closely interact with other intestinal cells such as interstitial cells of Cajal, enterocytes, enteroendocrine cells, immune cells, and smooth muscle cells. This interaction facilitates key “local” functions such as the release of gut hormones and gut motility, but it also engages in “central” communication with the hypothalamus through hormonal and afferent neuronal pathways (101).

In T2D, enteric neuropathy is observed across the digestive tract and is associated with multiple problematic symptoms such as nausea, delayed gastric emptying, and constipation (102).

This neuropathy disrupts the function of enteric motoneurons, particularly affecting those that release neurotransmitters like acetylcholine and Nitric Oxide (NO), which control gut contraction.

From a cellular perspective, the gut motility issues observed are due to impaired communication between intestinal smooth muscle cells and enteric motoneurons. These motoneurons are primarily of two types: those expressing choline-acetyl transferase (ChAT), which releases acetylcholine to stimulate muscle contraction, and those expressing neuronal nitric oxide synthase (nNOS), which produces NO, a neurotransmitter that inhibits gut contraction (103). In T2D, intestinal inflammation and oxidative stress lead to neurodegeneration altering the ChAT/nNOS ratio in the myenteric plexus (104–106) in favor of ChAT-expressing neurons (106) (Fig. 3).

We have recently discovered that duodenal contractions participate in the control of glucose homeostasis through a gut-brain axis. After feeding, increased duodenal contractions causing segmental waves correlate with enhanced glucose absorption (107) due to expanded surface area for exchange between the gut lumen and the intestinal epithelium (108).

Our studies using a mRNA approach show that in diabetic humans and mice, the ratio of ChAT to nNOS neurons in the duodenum increases (104), leading to hypermotility and local over-absorption of glucose, exacerbating postprandial hyperglycemia, an

important aspect of glycemic management for diabetic patient (108, 109). Surprisingly, duodenal hypermotility also disrupts gut-brain communication by blocking the release of hypothalamic NO, which typically improves insulin sensitivity (110). Consequently, duodenal hypermotility participates *via* a “central” action to the development of an insulin-resistant state (111).

To modulate and restore normal contraction in the duodenum and treat metabolic disorders, we proposed the “enterosynes concept” involving gut-derived molecules like peptides (112, 113), lipids (104), or carbohydrates (114) that can modulate enteric neurons to reduce duodenal contraction, thereby normalizing glucose absorption and enhancing insulin sensitivity (111) (Fig. 3). Enterosynes could be synthesized by enterocytes (112) and enteric neurons (113), or have a nutritional origin like glucose (114) and certain components of human milk, such as apelin or GLP-1 (115).

The gut microbiota contributes to the enterosynes concept primarily through its influence on glucose homeostasis *via* biological molecules like apelin (112) or GLP-1 (115) which have receptors on enteric neurons (112, 116). Stimulating the apelin pathway reduces duodenal contractions, thereby lowering postprandial hyperglycemia through both local and central actions (111). This “indirect” action of gut microbiota on enteric neurons has a positive impact on the whole-body *via* the gut-brain axis, as seen in mice where apelin injections improve the sequence from duodenal contraction to hypothalamic NO release, and then muscle glucose uptake (112).

GLP-1 receptors have been located in myenteric neurons, but not in muscles of humans (117). Its stimulation generates enteric NO release that participates in the inhibition of prandial gastrointestinal motility (117). In addition, GPR41, a receptor for SCFAs has been found in enteric neurons (118). Although these SCFAs do not affect gut contraction directly in cultured intact duodenal muscularis externa, their potential role as enterosynes *in vivo* needs further exploration (119).

Conversely, the gut microbiota can negatively impact enteric neurons through LPS/TLR4 signaling, which induces nitrergic myenteric neuronal degeneration and colonic dysmotility in high-fat-fed mice (120). In addition, injection of a low dose of LPS in pig affects the number of enteric neurons such as vasoactive intestinal peptide or substance P expressing in the duodenum (119). Here, the mechanisms implicated are unknown, but the authors suggest a connection between the phenotype and the proinflammatory and neurotoxic activities of LPS.

Identifying novel enterosynes, either produced by the gut microbiota or the host represents a promising therapeutic avenue (111). For instance, Abot et al. demonstrated that the prebiotic oligofructose modulates the gut microbiota to reduce duodenum hypermotility in a high-fat diet mouse model (104). This intervention led to the discovery of 12-hydroxyeicosatetraenoic acid (12-HETE) as a potential enterosyne. This lipid has been associated with both pro-inflammatory (121) and neuroprotective actions (122).

In mice experiments, 12-HETE not only reduced duodenal hypermotility but also improved diabetic outcomes (104), acting possibly through mechanisms like PPAR γ activation. In midbrain neurons, 12-HETE is considered a second messenger of mu-opioid receptor activation (123), a receptor for enkephalin. Enkephalins are synthesized from a precursor named proenkephalin. The mRNA expression of proenkephalin is significantly reduced in the duodenum of diabetic patients and mice (104). Reduced duodenal hypermotility in diabetic mice was observed with a synthetic mu-opioid receptor ligand, suggesting that prebiotics can influence the synthesis of beneficial compounds like enterosynes.

The role of probiotics and postbiotics in affecting the ENS in the duodenum remains less understood, highlighting the need for further research to explore how these elements can act as enterosynes to address metabolic disorders.

Probiotics are recognized for influencing colonic motility and related disorders (124, 125), but their effects on the ENS in the duodenum are not known. Similarly, the impact of postbiotics with anti-diabetic properties, like Amuc_1100 (126) or P9 (127, 128), on the ENS in the duodenum and their potential as enterosynes remain unexplored. A recent

study shows that the duodenal administration of *Anaerobutyricum soehngenii*, a gut commensal producing butyrate, markedly changes the duodenal expression of 73 genes. Strikingly, duodenal *A. soehngenii* stimulated GLP-1 secretion and decreased peripheral glucose (129) (Fig. 3). Whether this effect involves the ENS remains to be proven. These gaps highlight the need for further research to establish how the gut connects with the brain to manage metabolic disorders effectively (124–128)

Gut microbiota and cardiovascular diseases

Increased body weight and body weight fluctuation are associated with increased risk for cardiovascular disease (130). The gut microbiota has been increasingly recognized for its connection to heart failure (HF), atherosclerosis, and major cardiovascular (CV) events like heart attacks and strokes (131). This emerging body of evidence suggests a complex relationship where gut microbiota and their metabolic by-products contribute significantly to the risk for cardiovascular diseases.

Central to understanding this connection is the role of inflammation, the body's innate response to injury or foreign substances, which serves as a common thread linking gut health to cardiovascular conditions. Remarkably, about 70% of the body's inflammatory cells are found within gut-associated lymphoid tissue, highlighting the gut's critical role in immune regulation. When harmful substances produced by gut bacteria enter the bloodstream, they can trigger a systemic inflammatory response (metabolic endotoxemia) (53). This is particularly detrimental to the cardiovascular system, where inflammation can lead to compromised vessel elasticity and endothelial function, ultimately precipitating the development of atherosclerosis (132, 133).

One of the key microbial metabolites implicated in this process is trimethylamine N-oxide (TMAO), generated from dietary nutrients like choline and L-carnitine through gut microbial metabolism (22, 134). Elevated levels of TMAO have been linked with an increased risk of major CV events and mortality, findings that underscore the metabolite's role in promoting inflammation and atherosclerosis (134). Notably, these associations persist even after accounting for traditional cardiovascular risk factors, such as differences in blood pressure, cholesterol, or triglycerides, suggesting that TMAO levels may independently predict cardiovascular events (23, 24).

The significance of these findings is further emphasized by interventional studies targeting gut microbiota composition. For instance, experimental models have demonstrated that targeting the enzyme produced by gut bacteria and capable of synthesizing TMAO can lead to reduced blood levels of this metabolite and a decrease in atherosclerotic plaque formation, offering a glimpse into potential therapeutic avenues (135).

This exploration into the gut-heart axis represents a paradigm shift in our understanding of cardiovascular disease pathogenesis. By highlighting the role of gut microbiota and the inflammatory processes, it opens new avenues for the prevention and management of heart disease. While much remains to be learned about the mechanisms at play and the optimal strategies for modulating gut microbiota to improve cardiovascular outcomes, the evidence to date underscores the potential of targeting gut health as part of a holistic approach to cardiovascular disease prevention and treatment. As research continues to unravel the complex interactions between gut microbes and heart health, it holds the promise of novel therapeutic interventions and a deeper understanding of cardiovascular disease mechanisms.

Gut microbiota and undernutrition

While most research has focused on the role of the microbiota in overweight and obesity and their metabolic disorders, there is an emerging body of evidence highlighting the gut microbes' significance in another facet of malnutrition: undernutrition and being underweight. Research has identified variations in the gut microbiota associated with

eating disorders like anorexia nervosa (136–139) and severe acute malnutrition types like kwashiorkor (140).

A pivotal study published in *Science* in 2013 uncovered a critical link between gut microbiota and kwashiorkor, a form of severe acute childhood malnutrition in Malawi, sub-Saharan Africa (140). By examining Malawian twin pairs over their first 3 years of life, allowing a unique comparative opportunity due to their genetic similarities and shared environments, the study highlighted the significant role of the gut microbiome in the development and potential treatment of kwashiorkor. The research utilized a longitudinal approach, tracking changes in the gut microbiomes of both monozygotic (MZ) and dizygotic (DZ) twins. Those discordant for kwashiorkor were treated with a ready-to-use therapeutic food (RUTF), a peanut-based supplement fortified with essential nutrients. This treatment allowed the researchers to assess microbiome changes during and after RUTF intervention. Notably, RUTF initially improved metabolic functions in the kwashiorkor microbiomes, but these improvements were not sustained after stopping the treatment.

Further investigation using gnotobiotic mice, which received fecal microbiota transplants from the discordant twin pairs, demonstrated that the microbiome from kwashiorkor-affected twins induced significant metabolic disruptions when combined with a Malawian diet. These disruptions included abnormal sulfur metabolism and selective inhibition of the tricarboxylic acid (TCA) cycle, critical for energy production (140). The same group also demonstrated how the immaturity of gut microbiota affects the malnourished condition. These researchers transferred the underdeveloped gut microbiota from sick children into GF mice that were fed a typical Malawian diet. The results showed that these mice had lower body weight and lean mass increases compared to mice with a healthy, mature microbiota. In addition, cohousing experiments revealed that a healthy microbiota can partly mitigate the growth deficiencies seen in mice with an immature microbiota. Like findings in obesity studies, bacteria from the healthy microbiota were capable of infiltrating the unhealthy microbiota. Moreover, giving mice a specific microbial consortium selected for their invasive properties led to increased body weight and lean mass in these animals (141). The research provides valuable insights into the microbial contributions to malnutrition and suggests that managing microbiome health could be crucial in addressing such severe malnutrition. This approach not only sheds light on the underlying mechanisms of kwashiorkor (or malnourished conditions) but also underscores the potential of microbiome-targeted interventions in therapeutic strategies.

Gut microbiota and cachexia

Besides underweight caused by malnutrition, research has recently also begun to delve into the contribution of the gut microbiota to metabolic and inflammatory disorders associated to body wasting, particularly within the contexts of sarcopenia and cachexia.

Sarcopenia is a progressive and generalized skeletal muscle disorder that is associated with an increased likelihood of adverse outcomes including falls, fractures, physical disability, and mortality (142). Cachexia is a complex systemic disease, involving several metabolic pathways in different tissues and organs, and is characterized by systemic inflammation, progressive weight loss, and depletion of adipose tissue and skeletal muscle that cannot be fully reversed by conventional nutritional support (143–146). Sarcopenia shares some key features with cancer cachexia, such as muscle weakness and systemic inflammation (146), and their clinical definitions present overlaps. Here, as indicated in the introduction, we will focus on cancer and associated cachexia.

Clinically, cancer cachexia results in increased morbidity and mortality rates as well as reduced tolerance to anti-cancer treatments (147). The latest available data estimate cancer cachexia prevalence at 1 million people in Europe (148). The prevalence of cachexia varies depending on the cancer type, ranging from 15% in prostate cancer to 45% in colorectal cancer and 70% in pancreatic cancer patients (147). The best option to treat this multifactorial syndrome seems to be a multimodal approach, consisting

of nutritional support, physical exercise, and pharmacological agents (147, 149–151). However, the nature of these pharmacological and nutritional tools remains largely undefined. In this context, the gut microbiota and their metabolites appear as attractive and innovative targets (152–156).

The hypothesis of a contribution of the gut microbiota to cancer cachexia has now been explored for a decade (152, 155). We showed several times that gut microbial alterations occur in mouse models of cancer cachexia (157–159), a finding confirmed by other teams (160–162). Specifically, we highlighted a common, reproducible, anorexia-independent, microbial signature (characterized mainly by an increase in *Enterobacteriaceae*) in preclinical models of cancer cachexia (158, 159, 163, 164). We found an increased gut permeability and an altered intestinal morphology in cachectic mice, in strong association with an increase in *Enterobacteriaceae* and cachectic features (163, 164). In a follow-up study, we identified *Klebsiella oxytoca* as the main *Enterobacteriaceae* species increased in cancer cachexia and we demonstrated that *Klebsiella oxytoca* acts as a gut pathobiont contributing to this intestinal dysfunction (164). Such associations between cachexia and gut permeability were also reported in a genetic mouse model of colorectal cancer (165). In accordance with our preclinical findings, three other studies reported gut microbiota alterations in cancer patients with cachexia (166–168). The discordant microbial signature reported in these papers may be related to the cancer type and geographical origin of the cohorts. Increased gut permeability in cachectic patients versus non-cachectic patients has also been reported in a cohort of 87 patients with advanced gastric cancer. Finally, gut microbiota alterations induced by intensive chemotherapy in patients with acute myeloid leukemia are associated with gut barrier dysfunction and body weight loss (169). Altogether, these pilot studies suggest that the gut microbiota is altered in cancer cachexia.

The gut microbiota may represent an attractive therapeutic adjuvant option for cancer cachexia. In 2012, we showed that restoring the lactobacilli levels through the administration of rationally selected lactobacilli counteracted muscle atrophy and decreased systemic inflammation in cachectic mice (157). Furthermore, nutritional interventions that target the microbiota, such as prebiotics or probiotics, decreased cancer progression, reduced morbidity and fat mass loss (the latter likely through inhibition of lipolysis), and/or increased survival of cachectic mice (158–160, 170, 171).

Altogether, these studies reveal that the gut microbiota is altered in cancer cachexia and represents an attractive therapeutic target in this context. However, the exact mechanisms underlying the microbiota-host crosstalk in this context remain elusive. One hypothesis is that the gut microbiota modulates cancer-associated inflammatory and metabolic dysregulations through the production of metabolites. SCFAs are reduced in cachectic mice (170, 172) and cachectic patients (167). This observation is particularly attractive considering the impact of SCFA on muscle physiology (173), gut barrier function (4, 10), and host metabolism as a whole (4, 10) (Fig. 4 and 5). However, to date, there is no demonstration that SCFA supplementation would alleviate cachexia. One set of metabolites that have been recently investigated is tryptophan (Trp) derivatives. The bacterial metabolism of tryptophan appears to be reduced in cachectic mice, with a lower production of AHR ligands in the intestine and lower AHR signaling (172, 174). However, such reduction in the AHR pathway does not contribute to the increased gut permeability found in these mice (174). A last set of bacterial metabolites explored in the context of cachexia are bile acids. Bile acid alterations at the fecal and blood levels have been reported in mouse models of cancer cachexia (161, 175, 176) and cachectic cancer patients (166). Mechanistically, systemic inflammation (through IL-6) drives the impairment of the hepatobiliary transport system in cancer cachexia (175, 176). Such alterations are associated with the presence of cachexia and cannot be ascribed to anorexia or the tumor itself (176). Furthermore, reducing the bile acid load using cholestyramine brought the proof-of-concept that bile acids contribute to hepatic inflammation in cachectic mice (175). Altogether, these studies highlight a vicious circle between bile acids and inflammation in cancer cachexia. Of note, whether the gut

microbiome, through its ability to metabolize bile acids (32), contributes to the bile acid dysmetabolism observed in cancer cachexia remains to be investigated.

Additional mechanisms, highlighted in other pathological contexts, may be of interest when considering the gut-muscle axis. Metabolites able to exert an impact on muscle physiology have been identified in the context of chronic kidney diseases (e.g., the uremic toxin indoxyl sulfate (177, 178), reducing cell proliferation and mitochondrial function), in the context of sarcopenia (e.g., urolithin A (179), promoting mitochondrial function and muscle mass) and in the context of obesity (e.g., imidazole propionate (180), reducing insulin signaling). Complementary mechanistic components of the gut-muscle axis include among others a modulation of the gut permeability and associated systemic inflammatory tone and LPS levels, changes in the hepatic production of IGF1, and the intestinal production of FGF19 as well as through the production of quorum sensing molecules, as reviewed here (181).

Paradoxically, obesity-induced and cancer-induced metabolic syndromes share some similarities (Fig. 5). As evoked earlier, both appear to be characterized by systemic inflammation, microbial dysbiosis, and an alteration in the gut barrier function. Other common features may include insulin resistance and diabetes development. The presence of these metabolic alterations is well established in obesity but much less explored in cancer. A meta-analysis published in 2023 suggests that patients with a cancer diagnosis are markedly insulin resistant (182). Along those lines, an analysis of 51,353 incident cancer case subjects revealed an increased likelihood of new-onset type 2 diabetes for all cancers, which, in turn, was associated with increased overall mortality (183). Furthermore, pre-existing diabetes aggravates cancer cachexia and inflammatory status, thereby increasing mortality in patients with colorectal and pancreatic cancer (184). These clinical observations strengthen the links between cancer, glycemic disorders, and cachexia. However, the underlying mechanisms remain unclear and may involve ceramides (185) and AMPK (186).

One last aspect of cancer cachexia that may be triggered or modulated by the gut microbiota is anorexia. Anorexia does not drive cachexia alone, as adequate nutritional intake is not sufficient to counteract cachexia but does contribute to it. Tackling anorexia and reduced nutritional intake is therefore included in the recommended multimodal anti-cachectic treatment (150). As discussed above, gut microbial control of appetite may occur through different pathways and mediators, some of them being already reported as altered in cancer cachexia (e.g., ghrelin, bile acids). Furthermore, the administration of prebiotics delayed anorexia in leukemic mice with cachexia (158), bringing the proof-of-concept that the gut microbiota may modulate anorexia in this context. Altogether, these observations raise the possibility that gut microbiota modulation may be instrumental in tackling cancer-induced appetite reduction.

Targeted modulation of the gut microbiota

Several strategies can be employed to help maintain a balanced gut microbiota and promote a healthy gut barrier. A fundamental aspect is adhering to a diverse and balanced diet that includes a wide variety of fruits, vegetables, whole grains, lean proteins, and fiber-rich foods. In addition, incorporating probiotic-rich foods such as yogurt, sauerkraut, and kefir can introduce beneficial bacteria to support gut health. Equally important is to minimize the consumption of processed foods, artificial sweeteners, and excessive sugar, as these substances can disrupt the delicate balance of the gut microbiota. Furthermore, it is advisable to use antibiotics judiciously and only when medically necessary. In addition to dietary choices, engaging in regular physical activity, striving for adequate sleep, effectively managing stress, and refraining from smoking and excessive alcohol consumption are additional measures that contribute to maintaining a healthy gut. Below, some of these aspects are discussed in greater detail.

Probiotics

Probiotics, live microorganisms offering health benefits when ingested in sufficient quantities, have gained significant attention in metabolic health, including conditions such as obesity, overweight, and diabetes (187).

Notably, certain species within the *Lactobacillus* genus, such as *Lactobacillus rhamnosus*, have been linked to potential weight loss and metabolic enhancements (188). *Lactobacillus gasseri*, in particular, has been associated with a reduction in abdominal fat in certain trials (189). In addition, strains within the *Bifidobacterium* genus, like *Bifidobacterium lactis* and *Bifidobacterium breve*, have demonstrated potential in improving insulin sensitivity and reducing body fat, respectively (190, 191). Emerging evidence points to the non-traditional (next-generation) beneficial bacterium *Akkermansia muciniphila* as a key player in metabolic health, particularly with its ability to boost insulin sensitivity (192). More recently, a novel bacterium named *Dysosmobacter welbionis* has been isolated from the human gut (193). This bacterium is inversely associated with blood glucose and glycated hemoglobin in humans and has been shown to improve type 2 diabetes in high-fat diet-fed mice (194). *D. welbionis* produces several key bioactive lipids that might partially explain the decreased inflammatory tone and the higher mitochondrial function (195). It has been shown that *D. welbionis* is higher in the gut of metformin-treated subjects and in obese subjects responding to a prebiotic-induced body weight loss (196). Another noteworthy bacterium is *Faecalibacterium prausnitzii*, which possesses anti-inflammatory properties and whose abundance is often diminished in individuals with metabolic disorders (197).

Numerous scientific studies have also demonstrated the beneficial impact of specific probiotics on gut barrier integrity. These probiotics include *Lactobacillus rhamnosus*, *Bifidobacterium lactis*, and *Saccharomyces boulardii*. These probiotics are commercially available in supplement form and can also be found in certain fermented foods such as yogurt and kefir. In addition, *Akkermansia muciniphila* has been shown to have a positive effect on gut barrier integrity. Among the proposed mechanisms, this bacterium is thought to improve gut barrier function by increasing the thickness of the mucus layer, which helps to protect the gut lining from harmful substances (55, 198, 199).

While the potential of these probiotics is promising, it is paramount to understand that the relationship between the gut microbiome and metabolic health is intricate, influenced by a mosaic of factors like diet, genetics, and lifestyle (200).

The debate on probiotic colonization

Probiotics generally do not establish a permanent or long-term presence in the digestive tract or other parts of the human body. However, recent discussions have centered on whether probiotics must colonize the gut to provide health benefits. This debate revolves around the concept of “colonization,” which pertains to the enduring establishment of supplemented bacteria in the gut lasting weeks, months, or even years, and potentially resulting in engraftment. A true colonization necessitates probiotics to multiply and form a stably replicating population. Such colonization has the potential to bring about lasting changes in the composition and function of the gut microbiota over an extended period. This outcome is distinct from the more transient, short-term persistence (a few days to a week or so) of probiotics. While transient probiotics can exhibit metabolic activity in the intestine, including growth and division, they are not expected to replicate in substantial numbers or displace members of the native gut microbiota.

This debate has prompted critical questions including “Do probiotics genuinely colonize the gut, and is colonization a prerequisite for their effectiveness?” “If probiotics do not establish colonization, does this imply their ineffectiveness?” and “In scenarios where colonization is absent, should we be exploring novel probiotic strains with colonization capabilities?”

These questions have been debated recently in two papers published in 2018, discussing whether colonization is indeed a key factor for reaping health benefits and even raising concerns about potential harm from probiotic treatment following antibiotic use (201, 202). This brings to the question: can probiotics provide health benefits even without establishing colonization? And could probiotics impair post-antibiotic gut mucosal microbiota restoration?

In reality, probiotics can bring about transformative effects in the digestive tract through alternative mechanisms, sidestepping the need for colonization. These mechanisms include the generation of metabolites that modulate the activity of the gut microbiota or the direct stimulation of the intestinal epithelium (as discussed earlier in this review). As a result, these effects can manifest relatively quickly, ranging from minutes to hours.

Nonetheless, in specific situations, colonization may be deemed preferable or even essential for influencing health, particularly when introducing a microbe that performs vital metabolic functions in the gut, such as the breakdown of complex carbohydrates. However, it is vital to acknowledge that colonization also carries risks of unintended consequences and potential loss of control over factors like dose, frequency, and duration of exposure to the specific microbe. Rather than fixating solely on achieving direct engraftment or worrying about the absence of colonization, a deeper understanding the precise molecular interactions and cause-and-effect consequences of introducing specific probiotics will be instrumental in determining whether colonization is indeed a necessity. As discussed by specialists in the field (203), this will necessitate further investigation and confirmation.

The discussion about whether probiotics should colonize and whether they should be used with antibiotics raises new questions and highlights the importance of further evaluating the potential risks of using probiotics. Nevertheless, the evaluation of the health benefits of probiotics should primarily rely on clinical parameters and be complemented by microbiome data, employing thoroughly characterized probiotic strains or a mix of bacteria.

Prebiotics

While numerous non-digestible carbohydrates can undergo fermentation by the gut microbiota (204), prebiotics, in particular, are defined as “substrates selectively utilized by host microorganisms that confer a health benefit” (205). For over a decade, significant research has focused on the role of prebiotics in modulating the gut microbiota, particularly in the context of obesity and related metabolic disorders. Insights from *in vivo* studies, predominantly conducted in rodent models, have shed light on the molecular mechanisms by which prebiotics influence energy balance and modulate inflammatory processes associated with obesity. These findings (summarized in Fig. 4) underscore the potential of prebiotics in regulating metabolic health. The foundational aspects of this prebiotic research have been extensively reviewed in earlier literature (206, 207).

Several epidemiological studies have linked diets rich in dietary fiber to lower body weight or BMI, highlighting a consistent trend across multiple research efforts (208–210). Specifically, inulin-type fructans (ITF) have been studied extensively in animal models, showing promising results in reducing energy intake, promoting weight loss, and decreasing fat mass (206, 211–213). The proposed mechanism involves the fermentation of ITFs in the gut, which increases the levels of the appetite-regulating hormones PYY and GLP-1 through the production of SCFA. Dietary ITF have also been shown to increase the number of endocrine L cells in the jejunum and colon of rodents (214, 215), further promoting the production and release of the active forms of GLP-1, thereby decreasing glycemia (216). In humans, a 2-week supplementation with ITF (at a daily dose of 16 g) increased the postprandial release of PYY, glucose-dependent insulinotropic polypeptide (GIP) and GLP-1, resulting in increased satiety and reduced energy intake as well as improved postprandial blood sugar levels (217). A 12-week study using 21 g/day of

fructo-oligosaccharides (FOS) in overweight and obese subjects showed a reduction in energy intake and body weight, attributed to decreased ghrelin levels and increased PYY levels, while GLP-1 levels remained unchanged (218). However, meta-analyses suggest that the beneficial effects of ITF on weight management might not be significant, possibly because many studies did not control for factors like dietary energy intake or intentional weight loss in their analyses (219).

GLP-2 is known to contribute to maintain the gut barrier function and is co-secreted with GLP-1 in response to ITF supplementation. This mechanism has been observed both in preclinical studies with obese mice (60) and in human interventional studies (220).

In a study involving obese or overweight individuals, the first evidence correlating changes in gut microbiota due to ITF supplementation with reduced serum LPS levels was published in 2013 (221). Specifically, a 3-month treatment of obese women with ITF (at a daily dose of 16 g) resulted in an increase in *Faecalibacterium prausnitzii* and bifidobacteria; both of which were negatively correlated with endotoxemia. Although this study did not observe significant changes in body weight, there was a slight reduction in fat mass, coinciding with decreases in *Bacteroides intestinalis*, *Bacteroides vulgatus*, and *Propionibacterium*. In a study conducted a decade later, we demonstrated that the variability in body weight reduction among obese patients receiving ITF supplementation for 3 months could be dependent on factors like the initial composition of the gut microbiome, concurrent drug treatments (in particular metformin) and the level of physical activity (222–224). In the same patient cohorts, ITF-prebiotic intake over the 3-month period led to a decrease in a fecal marker associated with intestinal inflammation (225). However, recent findings from a longitudinal, randomized, cross-over study, in which 38% of participants were insulin resistant, 47% were overweight and 29% were obese, have indicated that long-chain inulin, when consumed in increasing doses over a 3-week period until a high dose of 30 g per day, may lead to inflammation and elevated levels of alanine aminotransferase (ALT) (226).

Exploring the connection between the gut and the brain, preclinical studies have demonstrated that ITF prebiotics can alleviate neuroinflammation in middle-aged (10 months old) mice (227) and in APOE4 mice, a transgenic model for the strongest genetic risk factor for Alzheimer's disease (228). While some studies have assessed the impact of prebiotics on human behavior in healthy populations, elderly subjects, and patients with irritable bowel syndrome (IBS) (229), their potential effects on behavior related to metabolic diseases, including obesity, have been relatively understudied (229). Nonetheless, targeting the gut microbiota with prebiotics for the improvement of psychological health in obese individuals is an intriguing prospect. For example, we have conducted research indicating that inulin supplementation had a moderate beneficial effect on emotional competence and cognitive flexibility in obese subjects (230). Interestingly, patients with specific microbial signatures, such as elevated levels of *Coprococcus*, appeared to derive greater benefits from prebiotic supplementation in terms of mood. In addition, a positive response to inulin intervention in terms of mood was found to be dependent on baseline inflammatory and metabolic features, including elevated levels of IL-8, insulin resistance, and adiposity.

In a more recent study, the effects of inulin supplementation on psychological outcomes and biomarkers related to gut permeability, endotoxemia, inflammation, and brain-derived neurotrophic factor (BDNF) were investigated in women with obesity and depression who were following a calorie-restricted diet (231). However, the results showed that prebiotic supplementation (in the form of inulin, administered at a dose of 10 g per day for 8 weeks) did not yield significant beneficial effects on depressive symptoms, inflammatory biomarkers or gut permeability in obese women with depression.

Besides ITF, there are other nondigestible carbohydrates that are fermented by the gut microbiota. These include glucans, galactans, arabinoxylans (AX), resistant starch (dextrin), hemicellulose, pectins, and various oligosaccharides with FOS, galacto-oligosaccharides (GOS), arabinoxylan oligosaccharides (AXOS), pecto-oligosaccharides, and

xylo-oligosaccharides being among the most prominent examples (232). Numerous reviews have been published summarizing intervention studies that have investigated the effects of supplementing nondigestible carbohydrates on various aspects of health in obese individuals. These studies have explored the impact on the gut microbiota, fat mass, satiety, energy intake, postprandial glucose levels, insulin resistance, and low-grade inflammation (204, 233–235). This body of research highlights the potential benefits of including nondigestible carbohydrates in the diet of individuals dealing with obesity, as depicted in Fig. 4.

In addition, non-carbohydrate phytochemicals, such as polyphenolic compounds, also have the potential to modulate gut microbiota composition in the context of obesity and cardiometabolic risk and are considered as prebiotics. Typically, only a small fraction (approximately 5%–10%) of ingested polyphenols is absorbed in the small intestine due to their glycosidic bonds. The majority of polyphenols continue their journey through the digestive tract, ultimately reaching the large intestine, where they possess the capability to modulate the composition of gut bacteria (34, 236–238).

Animal studies demonstrated that the consumption of polyphenols, particularly those such as catechins, anthocyanins, and proanthocyanidins, decreases body weight, reduces food intake, lowers triglyceride levels, reduces hepatic inflammation and oxidative stress, and maintains gut barrier function while increasing the abundance of certain bacteria such as *Lactobacillus*, *Bifidobacterium*, *Akkermansia*, *Roseburia*, and *Faecalibacterium* spp. (238–240). Their anti-inflammatory and antioxidant properties, the increased production of SCFA, and the reinforcement of the gut barrier have been proposed as the primary mechanisms responsible for the beneficial effects of polyphenols.

In humans, there are few results regarding the effectiveness of polyphenols in body weight management. Some studies showed small, statistically significant weight reductions, but these were often numerically minor and deemed unlikely to contribute significantly to weight management or obesity prevention (219). Several studies have also explored the interactions between dietary polyphenols and gut microbiota, particularly in obese individuals or those at cardiometabolic risk. These studies are summarized in a review published in 2023 and while effects on body weight are limited, these studies advocate for a shift in research focus toward understanding the broader health benefits of polyphenols beyond just weight management (238).

Hence, considering the broadening scope of the prebiotic concept to encompass various nondigestible food components, it becomes increasingly intriguing to investigate their potential role in influencing obesity and related metabolic disorders (Fig. 4). While most studies have been conducted primarily in preclinical settings or controlled intervention trials, there is a pressing need for additional data. Further investigation should not only delve into the effects of prebiotics but also consider their natural dietary sources. This holistic approach is crucial to gain a comprehensive understanding of how prebiotic strategies can be harnessed for the management of obesity and related metabolic conditions.

CHALLENGES AND LIMITATIONS

Despite significant advances in human microbiome research, the field primarily remains in a descriptive phase, with therapeutic applications largely limited to fecal transplantation for *Clostridioides difficile* infections. Establishing a direct causal link between specific microbiota changes and health outcomes remains a challenge. The majority of the current research in the microbiota field is correlational, identifying relationships between microbial signatures and disease states without confirming that these microbes cause the observed effects. To move from correlation to causation, researchers need to employ more rigorous experimental designs. Indeed, there are still many challenges that need to be overcome before translating research into medical interventions (Box 8). Current microbiome-based therapies are typically broad spectrum and do not target specific microbes or pathways. Developing targeted therapies will require a deeper

BOX 8. WHAT ARE THE KEY CHALLENGES?

1. **Understanding the complexity of the human microbiome:** Understanding the functional role of individual microbes and their interactions within a complex and dynamic environment within the host presents a formidable challenge.
2. **Defining what a "healthy" microbiome is:** There is no consensus on what constitutes a "healthy" microbiome, and considerable variability exists among individuals. Determining what changes in the microbiome are relevant to human health is a complex task.
3. **Developing targeted therapies:** Current microbiome-based therapies are typically broad spectrum and lack specificity toward particular specific microbes or pathways. Developing targeted therapies will require a deeper understanding of the functional role of individual microbes and how they contribute to disease.
4. **Standardizing methodologies:** There is a lack of standardization in microbiome research, spanning from sampling methods and sequencing techniques to data analysis. This makes it difficult to compare results across studies and to draw meaningful conclusions.
5. **Conducting rigorous clinical trials:** There is a pressing need for more large-scale, randomized, placebo-controlled clinical trials to evaluate the safety and efficacy of microbiome-based interventions. This is particularly challenging given the variability in the microbiome between individuals and the difficulty in controlling for the many confounding factors.
6. **Regulatory challenges:** There are currently no standardized regulatory pathways for microbiome-based therapies, which makes it challenging for companies to bring new products to market.
7. **Terminological and methodological considerations:**
 - Terminology surrounding "dysbiosis" needs refinement to avoid circular reasoning and instead rely on sound ecological and evolutionary principles.
 - More extensive meta-analyses are required to differentiate consistently from spurious associations between dysbiosis and disease in underpowered case-control studies.
 - To establish causal relationships between the microbiome and diseases, modified Koch's postulates for commensals must be met. However, even advanced statistical analyses only explain a small percentage of the microbiome's variance, suggesting that microbe-microbe interactions and stochastic processes may play a greater role than anticipated. To satisfy Karl Popper's concept of conjectures and refutations in scientific progress, more experiments are necessary to refute the role of the commensal gut microbiota in human health and disease.

understanding of the functional role of individual microbes and how they contribute to disease. However, the human microbiome is a very complex ecosystem consisting of trillions of microorganisms, which not only interact with the host, but also with each other. Disentangling the functional role of each microbe in this large and complex system is a significant challenge in human microbiome research. Add to this, there are practical issues like the considerable variability between individuals and the large numbers of confounding factors. Moreover, there is a lack of consensus on what a "healthy" microbiome looks like. Also, there are many gaps for the standardization from sampling and sequencing to data analysis. Obviously, we lack large-scale randomized, placebo-controlled clinical trials to evaluate the safety and efficacy of microbiome-based interventions. In conclusion, it becomes easy to comprehend why it is so difficult to compare results across studies and to draw meaningful conclusions that could lend themselves to medical and industrial applications.

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