REVIEW-SYMPOSIUM

From human to superhuman: the impact of the microbiome on physiology

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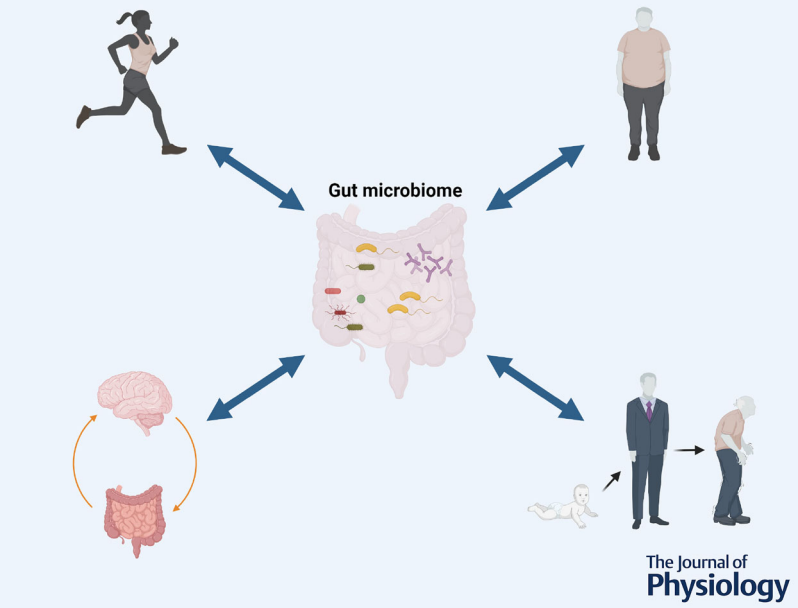

Abstract figure legend The complex microbial community residing in the human gut has long been understood to regulate gastrointestinal physiology and to participate in digestive diseases, but its extraintestinal actions and influences are increasingly recognized. This article summarizes work presented by P.D.C., A.W., H.S. and D.W. at a symposium sponsored by the Physiological Society at its meeting in 2022, and discusses bidirectional interactions between the gut microbiome and (clockwise from top left) athletic performance, metabolism, longevity and the ability of the gut–brain axis to influence cognitive function and mental health. Created in BioRender (Barrett, 2024, https://BioRender.com/f94c524).

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Abstract The complex microbial community residing in the human gut has long been understood to regulate gastrointestinal physiology and to participate in digestive diseases, but its extraintestinal actions and influences are increasingly recognized. This article discusses bidirectional interactions between the gut microbiome and athletic performance, metabolism, longevity and the ability of the gut–brain axis to influence cognitive function and mental health.

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Introduction

Living multicellular organisms, including humans, are not typically comprised solely of cells of a single species but rather are a composite of the cells of the host and those of its associated microbiomes. Notably, the fact that the number of microbial cells associated with the human body far exceeds the number of human cells has led some to refer to the human 'superorganism'. A microbiome encompasses the collection of microbes found within a given niche, as well as its associated genetic material, metabolic capabilities and environmental influences. Humans harbour distinct microbiomes in various niches of the body, of which that in the gut has now been recognized for at least two decades to be the largest. In this article we will focus predominantly on this human gut microbiome, where an explosion of research has shown an association of this specific microbiome with changes in the function of not only the gastrointestinal system but also other organs and/or systems, or with pathological states. However functional information on the basis for these associations, their directionality and their implications for health and disease is still relatively sparse. This is particularly true for information directly pertinent to human subjects, where the complexity and diversity of the microbiome between individuals also make studies challenging. Specifically, much still needs to be understood about the mechanisms by which the specific components of the 'microbial fingerprint' of each person act individually and in concert, and how the human microbiome can be manipulated to treat and prevent disease states, improve health and even slow ageing.

In an effort to spur additional research into the precise mechanism(s) by which microbiomes and their constituents influence human health, we organized a symposium at the 2022 Europhysiology conference held in Copenhagen, Denmark, supported in part by *The Journal*. The research presented by P.D.C., A.W., H.S. and D.W. in the symposium, and now summarized here, describes several complementary approaches to overcome the challenges to linking microbiomes causally with physiological function. Moreover these studies and others like them are working towards increased understanding of the microbiome and methods to manipulate it in ways that are beneficial to human physiology. We intentionally selected topics and speakers that would broaden our horizons beyond the well-established roles of the gut microbiome in regulating digestion and intestinal function, and the association with specific digestive diseases, to encompass how our co-evolution with gut microbes has positively impacted many important aspects of our physiology, including metabolism, athleticism, mental health and longevity. These presentations also illustrated how unexpected and illuminating findings can arise from research that takes different perspectives. Each presentation will be discussed in turn, with a concluding discussion highlighting how there might be synergies between different approaches.

The diet–exercise–gut microbiota triad. The study of the gut microbiome as it pertains to athletic performance has become an increasingly popular area of focus. The possibility of a relationship between exercise and gut microbiome composition and function (both functional potential and metabolome) was first investigated in elite athletes (Clarke et al., 2014). This approach stemmed from the logic that if such a relationship existed, it would be most apparent in these highly trained individuals. Differences between the gut microbiome of elite athletes and other members of society were indeed evident, manifesting as a number of instances in the form of differences in overall α diversity, the relative abundance of particular taxa and/or functional potential (Barton et al., 2018; Clarke et al., 2014; Petri et al., 2024). Changes in functional potential have been seen to be consistent, with, in at least some cases, differences in faecal metabolites, that is, metabolites reflective of the activity of particular microbes in the gut (Barton et al., 2018; Clarke et al., 2014). Differences in the abundance of short-chain fatty acids (SCFAs), generally regarded as beneficial metabolites, are among the most notable (Barton et al., 2018). The specific differences observed have been found to vary across studies and, indeed, in one instance, were evident between athletes from different sports classification groups (Li et al., 2023; O'Donovan, Connor et al., 2020), with

differences being most evident among samples collected from athletes who competed in sports with high dynamic and high static components, respectively (O'Donovan, Madigan et al., 2020). Although it is tempting to ascribe these differences as, at least partially, being driven by specific exercise regimes, it is evident that elite athletes generally have very different diets compared to members of the general public and, given that diet is an important modulator of the gut microbiome, it is difficult to discern the relative roles of diet and exercise in cross-sectional studies. However correlations between creatine kinase (an indirect marker of exercise intensity), protein intake and microbial diversity have been observed (Clarke et al., 2014). Despite these observations that link diet, exercise and the gut microbiome, only modest changes to the gut microbiome were observed after longitudinal studies involving 8-week interventions that required the consumption of whey protein, engagement in an exercise programme or both (Cronin et al., 2018), suggesting that longer-term interventions may be necessary to bring about significant changes.

Other insights have been gained through frequent, repeated serial profiling of the gut microbiome of individuals who have undertaken new fitness challenges, such as completing a marathon or triathlon (Barton et al., 2021), following periodized training (Akazawa et al., 2023) or engaging in extensive travel (with associated changes in diet and exposure to different pathogens; O'Donovan, Madigan et al., 2020). Approaches such as these provide valuable insights, including those related to the potential impact of illness or medications on the gut microbiome, and help to develop new hypotheses for future consideration.

Although research to date relates more specifically, although not exclusively, to elite athletes, it is notable that a recent meta-analysis of studies investigating associations between physical activity, sedentary behaviour and the gut microbiome noted a trend towards a higher microbial richness in athletes relative to non-athletes, as well as greater relative abundances of SCFA-producing taxa (including *Akkermansia*, *Faecalibacterium*, *Veillonella* or *Roseburia*) in individuals who were more physically active (Perez-Prieto et al., 2024). That such effects have the potential to be harnessed for therapeutic purposes is supported by studies showing that moderate exercise, when used as a non-pharmacological intervention, improves symptoms in irritable bowel syndrome (IBS) patients in association with an increase in the abundance of SCFA-producing microbial strains (Li et al., 2024). On the contrary, exercise-induced changes in the microbiome, particularly in strains associated with lactic acid metabolism, have been linked to enhanced athletic performance (Scheiman et al., 2019). Thus although there is still much to be learned of the particular bacterial strains and metabolites involved in the bidirectional interactions between physical activity and the microbiome, there is great promise in this research area for the development of interventions, whether they be intended to prevent disease or promote athletic performance. In this regard it is of interest to note that experiments in mice recently revealed that specific gut microbial species, as well as the endocannabinoids they produce, can enhance the motivation to exercise (Dohnalová et al., 2022). This occurs via a mechanism that involves the activation of TRPV1-expressing sensory neurons and elevation of dopamine levels in the ventral striatum during exercise, thereby improving running performance.

The microbiome and metabolism. Changes in gut microbial composition have been implicated in many physiological and pathological conditions, including metabolic diseases such as obesity and type 2 diabetes (T2D). On the flip side, perturbations in the normal post-natal development of the gut microbiome can render infants susceptible to wasting and stunting (Barratt et al., 2022). Indeed the transfer of gut microbes deficient in particular metabolic capabilities from undernourished mothers to their infants can set the stage for multigenerational growth impairment. Supplementation with growth-promoting bacteria at an appropriate stage of development, or combining supplementary food with components that promote a healthy microbiota, might be methods to interrupt this vicious cycle (Hartman et al., 2024; Mostafa et al., 2024).

A valuable tool to study interactions between the gut microbiome and host metabolism is to use germ-free mice and colonize them with bacteria, and then evaluate changes in physiology and metabolic parameters. It has been shown that germ-free mice have reduced adiposity compared to conventionally raised mice and that they are protected against diet-induced obesity (Bäckhed et al., 2004, 2007; Rabot et al., 2010). Several human studies have also shown that the gut microbiota is altered in metabolic disease, but the large variation in microbial composition between individuals, as well as intra-individual variations between samples from the same individual at different timepoints, makes this type of research challenging (Olsson et al., 2022). Despite difficulties in reaching a clear consensus, one consistent finding seems to be decreased gene richness in the microbiome of individuals with metabolic disease (Le Chatelier et al., 2013; Olofsson & Bäckhed, 2022). Some associations have also been demonstrated between specific gut bacteria and altered metabolism, but additional studies will be needed to understand mechanisms and causality (Wu et al., 2020).

One strategy to study causality is to focus on microbial metabolites, which can affect host metabolic function in various ways. By using human cohorts we can detect microbial metabolites that are either enriched

or decreased in individuals with metabolic disease. Simplified communities of bacteria producing the specific metabolites can then be designed and studied *in vitro*. Subsequently the designed communities can be transferred into germ-free mice, and their impact on metabolic parameters can be evaluated. However one challenge with this strategy is that environmental factors, such as oxygen, pH, nutrient availability and interactions between different strains within a community, can influence the capacity of bacteria to carry out metabolic reactions. Another challenge is that some bacterial species in the gut microbiome can be present at very low abundance but still have a significant impact on metabolic output. This adds to the complexity of studying the function of specific bacteria and may jeopardize translation from human cohorts to *in vitro* and *in vivo* models and then back to a human setting.

Some microbial metabolites relevant to the control of metabolism, for example, SCFAs and trimethylamine *N*-oxide, have been extensively studied, whereas others, such as the amino acid-derived product, imidazole propionate, have more recently been described (Koh et al., 2018). These latter authors showed that imidazole propionate is microbially produced from histidine and enriched in subjects with T2D. They also showed that administration of imidazole propionate resulted in impaired glucose tolerance and insulin signalling in both germ-free and conventionally raised mice via the mTORC1 pathway.

Another group of relevant microbially produced metabolites that have been studied since the 1960s comprises the secondary bile acids. Primary bile acids (cholic acid and chenodeoxycholic acid in humans) are endogenously produced from cholesterol in the liver and amidated (conjugated) with either glycine or taurine before they are released into the bile and stored in the gall-bladder. After ingestion of a meal, bile acids are excreted from the gall-bladder into the duodenum where they mix with ingested food to facilitate the uptake of lipids and fat-soluble vitamins. Bacteria in the gut can modify bile acids by deconjugation, but also by dehydroxylation, dehydrogenation and epimerization, which converts them into secondary bile acids. The two major secondary bile acids in humans are deoxycholic acid and lithocholic acid, which are produced by microbial 7α-dehydroxylation of cholic acid and chenodeoxycholic acid, respectively, but additional microbial modifications can produce a wide range of additional bile acid metabolites with different characteristics. Bacteria with bile salt hydrolase (BSH) activity, which is required for the ability to deconjugate bile acids, have been identified throughout various bacterial phyla, but bacteria with the capability to carry out 7α-dehydroxylation seem to be limited to far fewer bacterial species. Bile acid research regained a major focus two decades ago when the nuclear bile acid receptor, farnesoid X receptor (FXR), was identified. FXR is activated by bile acids and influences host metabolism by regulating glucose-, lipid- and bile acid homeostasis. In addition to FXR there are other receptors that can be activated by bile acids, such as the G protein-coupled receptor 5 (TGR5), vitamin D receptor, pregnane X receptor and liver X receptor, and these can also influence host metabolism (Cai et al., 2022). Individual bile acids have different affinities for these receptors; some are agonists, whereas others can be antagonists. Therefore the composition of the bile acid pool is crucial for signalling via a diverse collection of receptors, and a potential strategy to influence host metabolism and treat metabolic disease might be to target gut microbiome–bile acid interactions and thereby change the composition of bile acids and their signalling properties. Alterations in the bile acid profile have been reported in relation to obesity and T2D, but there are some inconsistencies, and further studies are needed.

One of the most important factors that shape the microbiota is the diet, and it is evident that dietary components can influence the function of the gut microbiota not only as substrates for the production of microbial metabolites but also by changing the environment in the gut and/or the microbial composition. Recently it was shown that supplementation with the dietary fibre oligofructose can influence microbial production of 6α-hydroxylated bile acids in mice and protect against diet-induced obesity (Makki et al., 2023). Further experiments showed that the effect was mediated through signalling via the bile acid receptor, TGR5, and induction of Glucagon-like peptide-1 receptor activity. One caveat when interpreting and translating bile acid findings from mouse models into humans is that humans lack some of the primary bile acids found in mice; therefore the interactions between bile acids and gut bacteria might be different between the species. To address such differences, mouse models with a human-like bile acid pool have recently been developed. These will be an important tool in driving future research aimed at understanding how we can manipulate the microbiome, and therefore the metabolites it produces, to treat and prevent metabolic diseases (de Boer et al., 2021; Honda et al., 2020).

Microbial regulation of the interplay between metabolic and mental health. It is now understood that gastrointestinal microbes play a crucial role in regulating host physiology through the gut–brain axis (Cryan et al., 2019; Schellekens et al., 2022). Moreover significant advances into how the microbiome influences human metabolism, energy extraction from food, and energy expenditure (Boscaini et al., 2022; Schellekens et al., 2021; Turnbaugh et al., 2009) underpin the emergence of probiotics as potential strategies for weight loss and glucose regulation

in clinical trials (Déchelotte et al., 2021; Depommier et al., 2019; Hibberd et al., 2019; Jung et al., 2013; Kim et al., 2018; Perraudeau et al., 2020; Rajkumar et al., 2014; Sabico et al., 2017; Stenman et al., 2016; Zarrati et al., 2014). However in addition there has been an increasing appreciation that the gut microbiome can also influence brain and behaviour, even though our mechanistic understanding of this phenomenon as yet remains incomplete (Schellekens et al., 2022).

Despite their great promise the development of functional bacterial strains into effective probiotics for either metabolic disease or promoting mental health has been limited, emphasizing the need for more targeted mechanistic screening approaches across the gut–brain axis. In this regard a pharmaceutical screening approach could be utilized as a targeted and multimodal microbiota mining platform capable of accelerating the discovery of probiotics with defined mechanisms of action (Schellekens, 2024). Indeed a screening approach was recently developed to investigate the therapeutic potential of microbiota-derived metabolites as modulators of the ghrelin receptor [GHSR (growth hormone secretagogue receptor)], which is a G protein-coupled receptor (GPCR), widely expressed along the gut–brain axis (Torres-Fuentes et al., 2019). The physiological effects of GHSR activation have been extensively studied, comprising its central regulation of appetite, metabolic functions, glucose homeostasis, immune modulation, food reward mechanisms and stress response (Bouillon-Minois et al., 2021; Howick et al., 2017; Schellekens et al., 2010, 2012). Additionally the ghrelinergic system is proposed to play crucial roles in stress-induced obesity, mood disorders and psychiatric conditions related to stress (Fritz et al., 2020; van Loenen et al., 2022). Interestingly *Bifidobacteria* and *Lactobacillus*, common bacterial strains in the human gastrointestinal tract, can inhibit internalization of the GHSR in an *in vitro* assay (Torres-Fuentes et al., 2019). Because GHSR is extensively expressed throughout the human gastrointestinal tract (Takeshita et al., 2006), it may be a plausible target for microbiota-derived metabolites (Leeuwendaal et al., 2021). This underscores the potential for gut bacteria to influence the ghrelinergic system (Leeuwendaal et al., 2021), offering promise as a therapeutic avenue for addressing metabolic and stress-related disorders (Bouillon-Minois et al., 2021; Fritz et al., 2020; Howick et al., 2017; Schellekens et al., 2012; van Loenen et al., 2022). *In vitro* screening revealed that *Bifidobacterium longum* APC1472 supernatants were particularly effective in attenuating GHSR-1a constitutive activity and ghrelin-mediated receptor internalization (Torres-Fuentes et al., 2019), and caused a significant increase in ghrelin-mediated recruitment of β-arrestin and downstream phosphorylation of extracellular regulated kinase (ERK) 1/2. These findings suggest that *B. longum* APC1472 may modulate the functional selectivity and bias of ghrelin towards β arrestin-mediated signalling in the GHSR-1a receptor cascade, a phenomenon previously described for small-peptide and non-peptide GHSR ligands (Ramirez et al., 2019). Moreover in diet-induced obese (DIO) mice, APC1472 supplementation significantly mitigated weight gain irrespective of caloric intake, and reduced plasma corticosterone levels, while improving glucose tolerance compared to mice fed a low-fat diet (Schellekens et al., 2021). Furthermore a significant reduction in the accumulation of mesenteric, retroperitoneal and subcutaneous fat depots was observed in mice fed a high-fat diet (HFD) receiving *B. longum* APC1472. Consistent with the decreased adiposity levels of circulating leptin, which correlate with fat mass, were also reduced in DIO mice supplemented with *B. longum* APC1472 (Schellekens et al., 2021). Additionally APC1472 supplementation in HFD mice normalized hypothalamic expression of the anorexigenic genes, *POMC* and *CART* (Schellekens et al., 2021).

Translationally supplementation of APC1472 in overweight and obese individuals led to significant reductions in fasting glucose levels and, in obese individuals, also caused a decreased cortisol awakening response, along with normalization of circulating active ghrelin levels after fasting (Schellekens et al., 2021). These findings reinforce the concept of the link between metabolic disease and mental health, and highlight the potential for functional assays across the gut–brain axis to identify second-generation probiotics with both metabolic potential and the capability to modulate the hypothalamic-pituitary-adrenal (HPA) axis (Schellekens, 2024). Going forward, novel screening tools promise tailored probiotic identification for metabolic and psychiatric disorders, harnessing pharmaceutical approaches and bacterial metabolites that target GPCRs (Cryan et al., 2018). In turn this will likely lead to paradigm shifts in the research field of gut–brain signalling and offer accelerated discovery of bacterial strains that have the capacity to enhance human health and treat disease.

In addition to gut microbial effects on the nexus between metabolic disease, the brain, and behaviour, studies have independently implicated the gut microbiome and its metabolites in specific psychiatric, neurodevelopmental and neurodegenerative disease states, including anxiety, depression, autism and Alzheimer's disease (Rogers et al., 2016; Shoubridge et al, 2022). For example a recently reported multiomic analysis suggested that the presence of *Paraprevotella clara* in the gut was one of several factors that was highly associated with Alzheimer's disease severity (Meng et al., 2024). The gut microbiome may also predict the efficacy of treatments for mental health conditions (Shoubridge et al., 2022).

Importantly there is a notable shift towards understanding mechanisms that link components of the microbiome to mental health, and this ultimately should result in an ability to use such knowledge not only to define associations but also to impact treatment and/or allow for prevention of neurological and psychiatric disorders.

The microbiome and ageing. Although interactions between gut microbes and diet clearly have significant implications for human health and well-being, another intriguing question that is only beginning to be addressed by researchers is if interventions that modify the microbiome can also be used to slow ageing and increase the lifespan. For example old age in humans is accompanied by dysbiosis of the gut microbiome as well as systemic low-grade inflammation/immunosenescence, the latter being a phenomenon that has been referred to as 'inflammaging' (Bosco & Noti, 2021). Many have suggested that gut dysbiosis and inflammaging are causally related, perhaps via the diet, although as yet there is a paucity of definitive data to prove this in humans (Di Giosia et al, 2022). Similarly research is ongoing to assess the role of the microbiota in selected dietary interventions that have been suggested to increase longevity. In the nematode worm *Caenorhabditis elegans*, used widely as a model organism to study ageing, ageing can be slowed and lifespan extended by modulating *Escherichia coli* used as a food source for these animals (Weinkove, 2015). Because these are the only bacteria associated with the worms in the laboratory, this model provides a simplified system to study host–microbe interactions that influence health (Weinkove, 2015). A serendipitous discovery using this model showed that the lifespan of *C. elegans* increased when the animals were fed with a spontaneous mutant of *E. coli* (Virk et al., 2012) compared to control bacteria. Furthermore it was found that the underlying mutation disrupted folate synthesis in the bacteria, whereas a drug that directly inhibits *E. coli* folate synthesis, sulfamethoxazole (SMX), mimicked the effects of the mutant bacteria in slowing ageing (Virk et al., 2012).

The questions that stemmed from this work are as follows: was this finding relevant to humans, and were the observed effects on ageing secondary to a decrease in folate uptake by the host? The latter question is important because adequate folate intake is required for human health. However subsequent experimentation revealed that it was not a decrease in folate intake that slowed ageing in *C. elegans* but rather decreased folate synthesis, an effect that in turn prevented the bacteria from producing metabolites that enhance host ageing (Virk et al., 2016). Inhibiting bacterial folate synthesis has not been tested for long-term effects on health in humans, but there are indications that it could be beneficial. For example as long ago as 1958, a study showed that the inhibition of bacterial folate synthesis increased the lifespan of mice, rats and dogs (Hackman, 1958). At that time the researchers did not understand that the effect might be mediated by the microbiome, but their findings were consistent with that conclusion. Furthermore it is interesting to note that many of the gut bacteria associated with disease states are members of the *Proteobacteria* phylum, most of which are strong producers of folate (Shin et al., 2015). Indeed in conditions of small intestine bacterial overgrowth (SIBO), increased plasma folate levels are a known clinical sign of the condition (Camilo et al., 1996), and folate synthesis is likely to be essential for the pathogenic behaviour of the overgrowing microbes. In fact many microbes from other phyla do not produce their own folate, rather relying on folate from the environment (Magnusdottir et al., 2015). All microbes (like all living cells) require folate, but the hypothesis resulting from this work is that folate is required only in small amounts for growth and in larger amounts for the activities of a subset of microbes that can be harmful to the host. Therefore it follows that there may be a way to slow human ageing by modulating the folate-synthetic capacities of gut microbes while at the same time making sure the host has enough folate. In the *C. elegans* model it is possible to decrease bacterial folate synthesis to increase lifespan and health span but without causing folate deficiency (Virk et al., 2016; Zavagno et al., 2024).

Folic acid is the main supplement used to maintain healthy levels of folate, but these studies in *C. elegans* revealed that folic acid can be easily broken down to a product that can be taken up by *E. coli* through the AbgT transporter and used to synthesize new folate (Maynard et al., 2018). Thus when taken as a supplement, folic acid could enhance folate synthesis by the microbiome, which, in turn, may have negative effects on the host. Future studies will need to focus on understanding the exchange of folate between microbes and the downstream effects of folate-dependent metabolism within the microbiome to determine how supplementation may be used to intervene in the ageing process.

Discussion and conclusions

The research presented in the symposium, as elaborated upon here, illuminated different aspects of microbiome research and illustrated a selection of the many different approaches that can be used to understand the microbiome and its roles in physiology and disease. Specifically, the use of longitudinal sampling in human subjects with or without specific interventions (e.g. a new exercise regimen), metabolomic analyses to identify candidate small molecules capable of exerting either beneficial or harmful effects, germ-free animals and humanized mouse

models bearing complex or model human microbiomes and the administration of probiotics all have a role to play in elucidating the functional role of the gut microbiome in humans, as well as disease-associated changes in its structure. Similarly high-throughput screening of human-derived gut microbes and their metabolites based on specific qualities and functional repertoires, and an in-depth knowledge of microbial genetics and metabolism along with ways to manipulate these, may lead to the discovery of more effective and/or targeted probiotics. It is even possible that such studies could lead to an ability to substitute small molecules as 'post-biotics' to reproduce the effects of probiotics, without the need to administer live microorganisms to vulnerable patient populations (with a potential attendant risk if these microbes escape the gut).

The work described also illustrates the panoply of potential mechanisms by which the microbiota can exert its physiological and pathophysiological effects (Fig. 1). These include direct interactions of live bacteria with the host, microbial interactions that either encourage or inhibit the proliferation of other strains (e.g. co-metabolism or the production of bacteriostatic/bacteriocidal products, respectively), the production of small molecules and other compounds that can activate host receptors in the gut or more distantly (e.g. in the brain), microbial conversion of dietary constituents into products that exert effects on the host or the ability of the diet to modify the composition of the microbiome by supporting or inhibiting the growth of specific members. In any event it is clear to the authors that there is still a wealth of information to be gleaned as to how the microbial partners in our collective superorganism encourage or prevent our health, behaviour, metabolism, well-being, longevity and health span. This ancient partnership, where we have co-evolved with our microbiomes over millennia as well as harnessing their power for food preparation and preservation, doubtless will yield new additions to the armamentarium for optimal physiological functioning in the years to come.

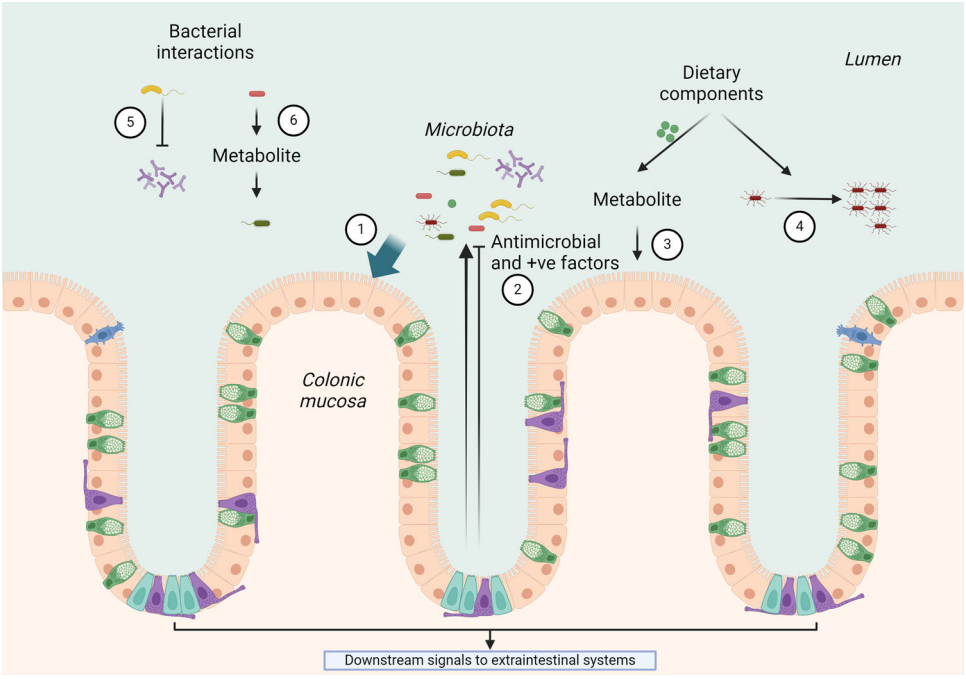

Figure 1. Pathways for interactions within the gut microbiome and its constituents, as well as with the gut mucosa, that ultimately propagate signals to the extraintestinal systems discussed in this article (e.g. those regulating exercise performance, metabolism, central nervous function and longevity)
(1) Components of the microbiome, or substances they produce, can interact directly with the cells of the gut epithelium. (2) The gut reciprocally controls the quantity of microbiome constituents as well as their specific identities via the production of antimicrobial products (e.g. antimicrobial peptides, antibodies). It may also produce positive factors that promote the growth of specific bacterial species. (3) The microbiota can process dietary components into bioactive molecules that signal to the epithelium. (4) Specific dietary components, including non-absorbable products of digestion, may be substrates for the proliferation/colonization of specific microbial species. (5 and 6) Within the microbiota itself, specific components may synthesize products that inhibit the growth of other members or, conversely, may supply specific metabolites that promote growth of other members. This includes mediators of quorum sensing that regulate various aspects of microbial biology, such as biofilm formation. Created using BioRender (Barrett, 2024, BioRender.com/q04c093).

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Additional information

Competing interests

The authors have no competing interests to declare.

Author contributions

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Supporting information

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