Open Access

Recent Progress in Nutrition

LIDSEN Publishing Inc.

Review

The Potential Role of Commensal Microbes in Optimizing Nutrition Care Delivery and Nutrient Metabolism

Anikka M. Swaby, Luis B. Agellon *

School of Human Nutrition, McGill University, Ste. Anne de Bellevue, QC, H9X 3V9, Canada; E-Mails: anikka.swaby@mail.mcgill.ca; luis.agellon@mcgill.ca

* **Correspondence:** Luis B. Agellon; E-Mail: luis.agellon@mcgill.ca

Academic Editor: Jennifer Keogh

Special Issue: Feature Papers of Recent Progress in Nutrition 2021

Recent Progress in Nutrition
2022, volume 2, issue 2
doi:10.21926/rpn.2202014

Received: December 20, 2021
Accepted: May 20, 2022
Published: May 26, 2022

Abstract

Microbes have been part of the diet throughout human history. In the evolution of food preservation practices, some techniques inadvertently leveraged microbial activity not only to extend the storage life but also to enhance the properties and nutritive value of foods. In the last century, a variety of bacterial species (referred to as probiotics) were found to confer health benefits to the host. The advent of high-throughput sequencing methods facilitated improved surveillance of conventional probiotics within gut microbial communities as well as fueled the deep exploration of the human gut microbiota. Metagenomic analyses along with improvements in microbial culture techniques and comprehensive functional characterization of specific microbes both in vitro and in vivo have shed new insights into the intimate relationship of the gut microbiota and its host. Recent findings suggest the potential of conventional and newly identified bacterial species in enhancing nutrient processing and holds promise in improving the efficacy of conventional nutrition intervention strategies in managing diseases as well as in the delivery of personalized nutrition therapy support.

Keywords
Diet; gut microbiota; microbiome; nutrient metabolism; nutrition care; personalized nutrition therapy; probiotics; synbiotics

1. Introduction

Microbes have long-standing symbiotic relationships with humans. Our body is colonized by different classes of microbes including archaea, fungi, viruses and bacteria [1]. Depending on the conditions and nutrient availability, different sets of microbes, collectively called microbiota, thrive in different body sites, and the gut microbiota is the largest and most complex collection [1, 2]. Most of the gut microbial community consists of trillions of bacterial cells that represent thousands of different species of bacteria primarily belonging to one of the two dominant phyla, Firmicutes or Bacteroidetes [2]. As with other species with a gastrointestinal tract, humans have a characteristic gut microbiota composition. Acquired from the mother at birth, the human gut microbiota is shaped by intrinsic factors, such as biological sex, and extrinsic factors, such as infant feeding practices and environment, until a stable functional core population is established by early childhood [3, 4]. Gut microbes actively participate in the maturation of the immune system and contribute to human nutrition by synthesizing essential vitamins (e.g., vitamin B12, vitamin K), processing the components of food and inhibiting the growth of pathogens [5-7]. The gut microbiota can be viewed as an accessory organ that processes both the nutrient and non-nutrient components of food and produces bioactive metabolites that play critical roles in moderating human nutrition and physiological processes [5, 7, 8].

The relationship between gut microbes and humans is complex and dynamic. The human gastrointestinal tract provides habitat and resources for microbes allowing a diverse community to thrive and execute functions that benefit both itself and its host. On the other hand, the host must regulate the microbial load and composition of this community which is partly accomplished through innate immunity that was programmed shortly after birth [9, 10]. Some metabolites produced and secreted by the host (e.g., bile acids, hydrogen peroxide) can kill or inhibit the growth of microbes to help control the size of the microbial community and to maintain greater proportions of commensal members than pathogenic ones [11]. However, the composition of the community is also susceptible to alteration by host dietary habits which can result in either beneficial or pathogenic effects on the host. This intimate and bidirectional relationship can be manipulated to optimize the beneficial contributions of the gut microbiota to the host.

The study of human-associated microbes has yielded many important milestones in understanding the direct and indirect impacts of gut microbes on human heath [1, 5]. Here we focus our discussion on the relationship among humans, nutrients and gut microbes and highlight recent research that demonstrates the important roles of specific commensal gut microbes in supporting human health. We also discuss recent developments in gut microbiota-targeted therapies and provide an outlook on how these approaches can potentially be leveraged to optimize nutrition care delivery and nutrient metabolism.

2. A Brief History of Probiotics

Microbes have been an integral part of the human diet. The need to process and preserve foods gave rise to early practices such as salting, drying and, notably, fermentation. During the fermentation process, microbes grow and metabolize available nutrients, producing a spectrum of metabolites [12]. Controlled fermentation renders foods more digestible since macronutrients are pre-processed by the microbes. The process also generates an array of compounds that impart new flavors which can enhance food palatability [13]. On the other hand, uncontrolled fermentation can spoil foods or induce illness and even death [14]. Interestingly, early humans inadvertently benefitted from the consumption of live microbes in a variety of fermented foods [12, 15]. However, the concept of intentional administration of live microbes for health benefits, only emerged in the early 1900's and credited to Elie Metchnikoff who proposed an association between the consumption of fermented foods and health [16, 17]. Some scholars have disputed this attribution since Józef Brudziński performed earlier experiments using *Bacillus lactis aërogenes* to treat children with acute infectious diarrhea [17, 18]. Around the same time, Henry Tissier also observed low bifidobacteria in the stool of children with diarrhea compared to those without and suggested that providing high amounts of this bacterium to affected children could alleviate the condition [19-21]. Both lactobacilli and bifidobacteria were postulated to be "beneficial" bacteria which drew the attention of researchers aiming to further study these organisms. The term probiotic is now used to describe microbes that, when ingested in sufficient amounts, confers a health benefit to the host [19, 22].

Pioneering research to identify and characterize conventional probiotic candidates primarily relied on knowledge of how to grow these microorganisms in the laboratory. This entailed the use of nutrient-rich growth media that could ensure the growth of the microbe of interest in culture. Today, advanced tools and techniques such as high throughput sequencing platforms, advanced *in vitro* culturing systems and germ-free animals facilitate the deep exploration of the human gut microbiota. Metagenomic analysis enables the determination of the microbe genomes (including those that cannot be cultured outside the host) that make up the microbiota and the assembly of their collective genomes (the microbiome) [23-25]. Advances in *in vitro* culturing systems and methods have enabled the growth of single or collection of gut microbes outside of the host [26-28]. Germ-free animals (largely mice and rats), which are bred and raised free of all microbes, can be inoculated with a selected microbe or a collection of microbes to provide information on microbe-host interactions [29]. The use of these tools has advanced our understanding of the nature of the gut microbiota and its relationship with its hosts, as well as enabled the identification and characterization of new probiotic candidates and the nutrients that support or inhibit their growth. Recent studies have coupled these tools with genetic engineering of microbes (e.g., bacteria or yeast), demonstrating that some commensal microbes can be genetically customized and returned to the host where they impart new functions to the gut microbial community for the benefit of the host. These recent developments provide insights on potential ways to leverage commensal microbes (i.e., probiotics), specific nutrient formulations (prebiotics) or the combination of both (synbiotics) to optimize nutrition, provide therapy for certain metabolic conditions or avert onset of certain diseases in otherwise healthy people.

3. Relevance of Gut Microbiota to Human Health

A diverse gut microbiota is important for host health and maintenance of this community can be promoted by the consumption of foods that provide the large constellation of nutrients to support the growth of a wide variety of commensal microbial species [30]. The concerted effort of gut microbes is responsible for the processing of food components which yields new substrates for some members of the community through cross-feeding and also influences nutrient assimilation by the host (Figure 1)[31]. The importance of nutrient formulation in promoting the growth of specific microbes is exemplified by *in vitro* studies where pioneering researchers successfully cultured single species of bacteria, notably conventional probiotic lactobacilli, using a growth medium containing nutrients thought to be sufficient and easily metabolized [32]. However, it turns out that it is exceedingly difficult to culture the majority of resident gut microbiota *in vitro* primarily because the unique nutrient requirements of many of its members are not known [27, 32]. Moreover, the physical environment (e.g., substratum, pH, atmosphere) and other factors that impact the growth of bacteria *in vivo* are difficult to replicate *in vitro*. Indeed, even the different segments of the mammalian host gut are inhabited by characteristic subsets of microbes that make up the entire gut microbiota [27]. Moreover, greater gut microbial diversity is characteristic of individuals that consume diets with high nutrient diversity and low energy density, and these individuals typically present a healthy metabolic profile [1, 33]. On the other hand, suboptimal nutrition (low nutrient diversity and high energy density) promotes a dysbiotic bacterial profile (reduced diversity and a high Firmicutes to Bacteroidetes ratio) and contributes to a variety of host pathologies [33, 34]. Early evidence of this strong influence of gut microbiota on host metabolism emerged in a study showing that transplantation of cecal microbiota from obese or lean mice to the gut of germ-free mice reproduces the obese or lean phenotype of the donor in the recipient animals [35]. A subsequent study recapitulated the findings using fecal microbiota from human twin donors discordant for the obesity phenotype; this study also demonstrated that the microbiota-induced obesity phenotype can be attenuated by feeding recipient animals with a low-fat high-fiber diet [36]. Gut microbiota-induced phenotypes have since been observed for other metabolic diseases including diabetes and cardiovascular disease as well as neurodegenerative diseases and cancers [37-40]. Given the apparent causal effect of gut microbiota composition on host health status, it is favorable to maintain a highly diverse population of commensal gut microbiota to preserve its beneficial contributions to the nutrition and health of the host.

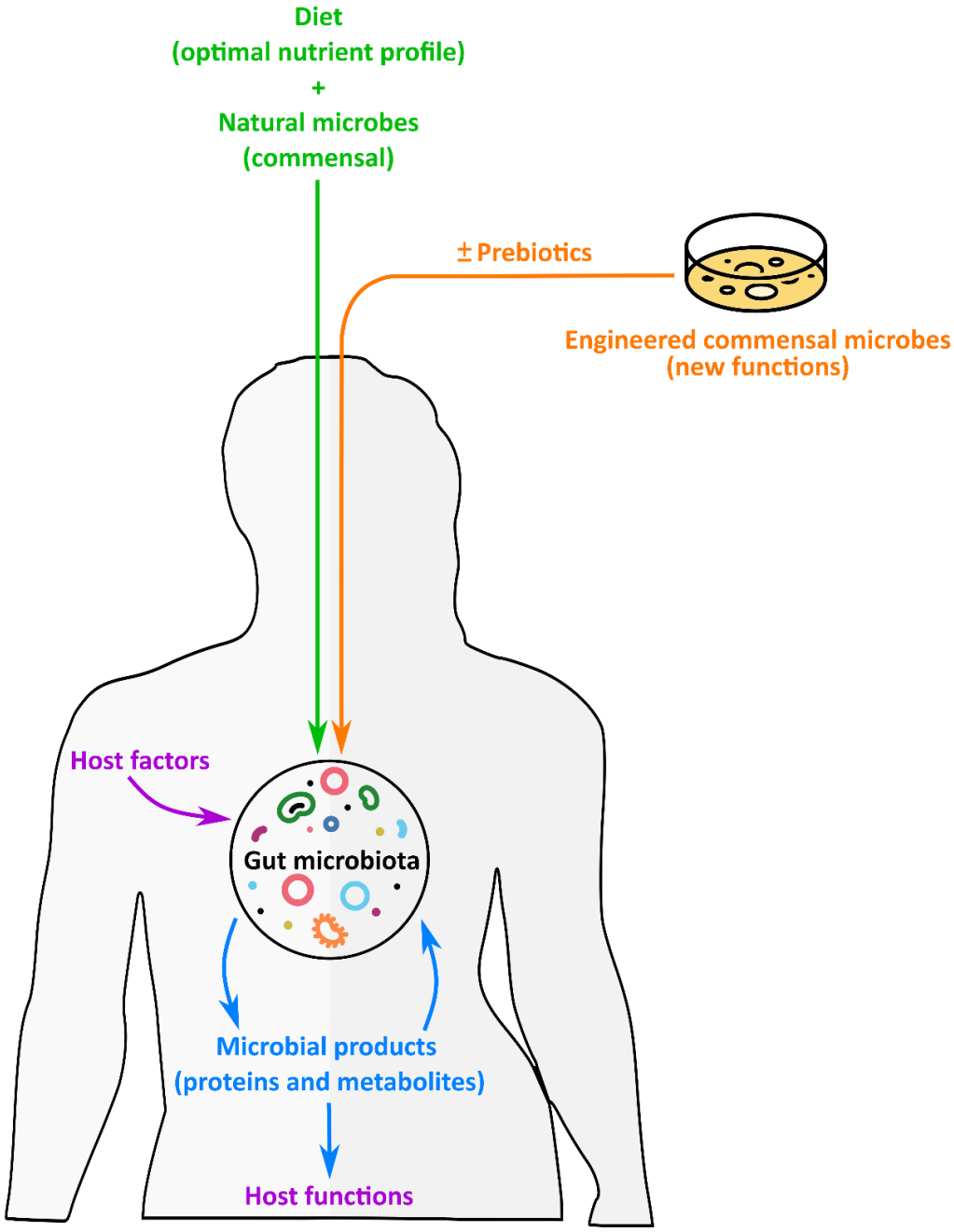

Figure 1 Interaction of the gut microbiota with its host. Dietary components and host factors influence the composition and diversity of the gut microbiota. Microbial proteins and microbe-produced metabolites provide substrates and signalling molecules that impact both the gut microbial community and its host. Some host factors modulate the growth and metabolic capacity of the gut microbial community. Administration of exogenous commensal microbes, as single species or as a collection of species, can augment the metabolic capacity of the resident gut microbial community. Alternatively, administration of engineered microbes without or with special prebiotics can reconstitute missing functions.

Pathogenic microbes naturally comprise a very small part of the gut microbial community and are normally outcompeted by the much greater abundance of commensal beneficial microbes [1, 5]. Various factors can induce dysbiosis and the expansion of pathogenic microbes which may cause

infection and other pathologies in the host. For example, use of antibiotics generally inhibits the growth of microbes, collaterally including commensal species, which creates a niche for antibiotic-resistant pathogenic microbes such as virulent strains of *Clostridioides* (formerly *Clostridium*) *difficile* to thrive [41]. It has been suggested that a virulent strain of *C. difficile* arose because it was unintentionally selected for by an ingredient used in the formulation of prepared food products [42]. Toxins produced by this bacterium act on intestinal cells and trigger host responses that lead to intestinal cell death and tissue injury [43]. Fortunately, oral administration of conventional probiotics, such as *Lactobacillus rhamnosus GG*, *Bifidobacterium lactis BB-12* and selected mixtures along with the prescribed antibiotics has been shown to be effective in reducing the overall damage accrued during *C. difficile* infection giving the dysbiotic gut microbiota a chance to repair itself [44, 45]. Another approach that has been shown to be highly effective in restoring heavily damaged gut microbiota is the transplantation of microbes from the stool of healthy human donors to individuals suffering from *C. difficile* infection [46, 47]. This demonstrates the importance of a diversity of commensal microbes in promoting host health as well as reprogramming of dysbiosis.

The contributions of single commensal species within the gut microbial community to metabolic diseases are apparent from comprehensive studies assessing gut microbiota profiles of individuals at different disease states [37, 48]. Follow-up studies to determine both gut microbiota and host responses to different therapeutic interventions highlight the combined efficacy of probiotic and dietary interventions in eliciting improvements in host metabolic status [49, 50]. One prominent microbe of interest is *Akkermansia muciniphila*, a bacterial species that is inversely associated with gut barrier dysfunction, enhanced adiposity and glucose intolerance [51, 52]. Supplementation with this microbe has been shown to improve gut barrier integrity, reduce adiposity and enhance insulin sensitivity not only in mice but also in humans [53-55]. Interestingly, administration of heat-killed preparation of *A. muciniphila* or its isolated Amuc_1100 protein can reproduce the observed therapeutic effect on the host, indicating that a specific protein encoded by this bacterium was responsible, at least in part, for the beneficial outcome [55]. This also exemplifies the potential of inactivated probiotics, their cellular components or products of their metabolic activity (collectively referred to as postbiotics) to contribute to beneficial health outcomes [56]. Other examples of prominent commensal bacteria include *Faecalibacterium prausnitzii* which is inversely associated with type 2 diabetes, as well as *Parabacteroides distasonis* which is inversely associated with obesity, in humans [49, 57, 58]. In these studies, the administration of live cultures of the respective microbe reduced the severity of metabolic disease and thus demonstrates that purposeful manipulation of the gut microbiota can contribute to the recovery of metabolic functions. Together, these findings highlight the crucial role that commensal species can have on host metabolism, reveal new probiotic candidates and how they can potentially be used in the design of probiotic-based therapies.

4. Gut Microbes Generate Products that Regulate Host Function

The diet is the major source of substrates that can be utilized by gut microbes, making it a critical determinant of the composition and function of the gut microbial community which, in turn, contributes to host metabolism (Figure 1). Amid the bioactive metabolites produced from gut microbial activity, short-chain fatty acids (SCFAs), including acetate, butyrate and propionate, are among the most abundant [59, 60]. These SFCAs are produced in the gut predominantly through microbial fermentation of undigested dietary fibre but may also be generated from catabolism of

amino acids [59, 60]. Butyrate is the main energy source for intestinal cells and plays an important role in the stimulation of immune cell differentiation and maturation [61]. Interaction of SCFAs with free fatty acid receptors (members of the G protein-coupled receptor family) on enteroendocrine cells control release of gut peptide hormones (glucagon-like peptide 1, peptide YY) involved in appetite regulation and glucose homeostasis [62]. Furthermore, downstream effects of SCFA signalling such as the activation of the transcription factor peroxisome proliferator-activated receptor γ, can induce transcription of genes involved in fat oxidation in adipose tissue [63, 64]. Studies also show that SCFAs can influence gene expression through epigenetic modifications by inhibiting histone deacetylases [64-66] which illuminates another strategy through which microbially-produced metabolites regulate host cellular functions. Intriguingly, these functions can be modulated by altering the dietary substrates that are accessible to gut microbiota [67-69], and illustrates how the tight interplay between the nutrient composition of the diet and gut microbiota metabolism regulates nutrient and energy metabolism of the host.

Gut microbiota can also transform dietary components into pathogenic metabolites. One example is the gut microbiota-initiated conversion of choline, phosphatidylcholine, betaine or L-carnitine, which are rich in animal-derived foods such as eggs, milk, red meat and seafood, into the pro-atherogenic metabolite trimethylamine *N*-oxide (TMAO) [70]. The process starts with microbial enzymatic conversion of dietary substrates to the gas, trimethylamine (TMA) which is then easily absorbed by the host and transported in blood to tissues including the liver where it is oxidized to TMAO by the hepatic enzyme flavin-containing monooxygenase 3 [71]. TMAO is thought to promote atherosclerosis by reducing reverse cholesterol transport and encourage macrophage recruitment to atherosclerotic plaques [72]. A high concentration of TMAO in human circulation is correlated with the development of cardiovascular disease [73, 74]. A recent study showed that TMAO can bind to protein kinase R-like endoplasmic reticulum kinase or PERK [75] (an important intracellular protein involved in a cellular stress coping mechanism [76]), causing the induction of endoplasmic reticulum stress which is thought to be an integral part of the pathogenesis of many diseases [76-78]. Fortunately, our expanding understanding of the mechanisms through which microbially-produced metabolites contribute to human pathology allows the development of mitigation strategies such as the targeted inhibition of the microbial enzymes required for metabolite production and dietary modifications designed to reduce the production of harmful substrates.

Some host produced metabolites that can influence the composition of the gut microbiota are also substrates for microbial metabolism. One example is mucin, a host-produced glycoprotein that forms a protective barrier for the gut epithelium but also serves as an energy source for mucin-degrading species like *Akkermansia muciniphila* [79]. Bile acids are another class of host-derived metabolites that can either promote or inhibit the growth of gut microbes depending on the metabolic potential of the species. Bile acid metabolizing bacteria (e.g., *Lactobacillus spp.*, *Bacteroides spp.*) secrete enzymes that can convert primary bile acids (produced in the liver) into secondary bile acids (products of microbial metabolism of primary bile acids) [80]. Notably, in humans, microbial enzymes catalyze the deconjugation and epimerization of the primary bile acid chenodeoxycholic acid to ursodeoxycholic acid (UDCA) which, on one hand, benefits the microbial community, and on the other hand, also has beneficial properties for the host [81]. Since UDCA is more hydrophilic than its precursor, it is less toxic to bacteria. Conversely, UDCA is a signalling molecule sensed by the host through the cell surface G-protein-coupled bile acid receptor TGR5 and nuclear receptor farnesoid X receptor, both involved in regulating glucose and energy homeostasis

[82, 83]. Additionally, recent studies demonstrate that UDCA is a proteostasis promoter that can alleviate endoplasmic reticulum stress [84, 85]. This demonstrates that host-derived metabolites also offer new avenues for targeted modulation of the gut microbial composition to program the microbial production of metabolites that benefit the host.

5. Opportunities to Leverage Commensal Microbes in Nutrition Care Delivery

The intentional use of live commensal microbes for human health purposes has a long history of safety and acceptance which has recently been acknowledged in some modern nutrition therapies, particularly for gastrointestinal disorders [86, 87]. For example, in the traditional management of lactose intolerance, a condition caused by gut bacterial fermentation of undigested, unabsorbed lactose, the diet is tailored to restrict or eliminate intake of lactose in order to circumvent the gastrointestinal discomfort caused by bacterially-produced gas and the osmotic diarrhea caused by the presence of lactose in the lumen [88, 89]. It is also recommended to opt for fermented dairy products such as some yogurts that contain lactose-metabolizing bacteria and aged cheeses which have low lactose content [89]. Recent analyses recognize conventional probiotic species of the *Lactobacillus* and *Bifidobacterium* genera for the feature of lactase activity, emphasize advantages of supplementation in lactose intolerant individuals, and suggest potential use for improving the efficacy of the traditional nutritional management of lactose intolerance [90, 91]. Other organisms currently accepted and used as probiotics include select strains of *Saccharomyces* and non-pathogenic strains of *Escherichia coli* typically used in treatment of diarrhea [87, 92, 93]. Although studies continue to evaluate the safety and therapeutic efficacy of existing probiotics, promising new organisms have emerged bearing probiotic features that can be used in disease-oriented nutrition-based interventions.

Personalized diet is an essential principle in the provision of modern nutrition care and considers health status, nutritional needs, food preferences and other influences on the efficacy of recommendations. Given the influence of gut microbiota on individual response to interventions, an important clinical question is whether the efficacy of dietary interventions can be optimized by accounting for individual gut microbial profiles in addition to host genetic composition. Intriguingly, a recent clinical trial compared the efficacy of a personalized diet with the Mediterranean diet in controlling postprandial glucose response in prediabetic individuals. Researchers demonstrated that dietary recommendations based on personalized predictions (including information about participant gut microbiota composition) led to greater improvement in glycemic control compared to the standard Mediterranean diet [94]. This suggests potential advantages of tailoring dietary recommendations based on physiological and gut microbiota characteristics. Although many challenges lie ahead in testing, optimizing, and standardizing the use of microbiota inclusive of dietary strategies in clinical practice, there are exciting opportunities for use in predicting response to nutrition intervention and personalized diet.

Behavioural changes are critical to the success of therapeutic interventions for metabolic diseases such as obesity, cardiovascular disease and diabetes. This includes adjustments to the nutrient quality of foods consumed and physical activity level. Recent evidence indicates that in addition to the effect of gut microbiota on host hunger and satiety, which affects the amount of food consumed, the gut microbiota could also influence host appetite for foods rich in specific nutrients [95, 96]. Conversely, a recent study found an association between exercise intervention

and gut microbiota fermentation in prediabetic individuals [97] while another study found that high abundance of some bacterial species, such as *Veillonella spp.*, is associated with improved physical performance [98], suggesting that microbes contribute to mechanisms that determine host capacity for physical activity. These findings raise the question of whether specific organisms can be prudently leveraged to nudge host behaviours encompassed in food intake and physical performance.

The available technological capabilities for the isolation, *in vitro* culture and genetic programming of commensal microbes presents additional opportunities to refine the metabolic capacity of the microbiota itself (Table 1). In the case of phenylketonuria (PKU), affected individuals lack functional phenylalanine hydrolase and are highly susceptible to adverse neurological outcomes due to toxicity caused by accumulation of phenylalanine in the blood. Hence, the standard treatment of individuals with PKU features a diet restricted in phenylalanine and supplemented with tyrosine. Intriguingly, a group of researchers recently engineered a strain of *Escherichia coli Nissle* 1917, called SYNB1618, to metabolize phenylalanine in the lumen of the gut [99] and subsequently demonstrated the clinical safety and efficacy of this organism in humans [100] thereby showing how specific microbes can provide functions originally missing in the host. Other studies have demonstrated the programming of commensal microbes for surveillance of specific pathogens [101], removal of pathogenic metabolites [102, 103] and reinforcement of natural host metabolic functions [104, 105]. As well, prokaryotic viruses (e.g., bacteriophages) may be useful in specifically targeting certain species of bacteria for genetic modification (e.g., as stable prophages) or eradication [106, 107]. The use of these strategies for therapies will likely be in the form of synbiotics whereby microbes are administered along with the nutrients required for their growth in the host (Figure 1). Overall, cautious and targeted application of engineered probiotics presents an exciting new avenue for the treatment of some genetic and acquired metabolic diseases.

Table 1 Examples of conventional, candidate probiotics and engineered commensal microbes.

Microbe	Features	Refs.
Conventional probiotics		
Lactobacillus acidophilus	Lactase activity; BA deconjugation and epimerization; produces antimicrobial compounds	[86]
Bifidobacterium animalis subsp. lactis	Competitive exclusion of pathogens; immunomodulating properties; promote epithelial barrier function	[45]
Escherichia coli Nissle 1917	Produces antimicrobial compounds; competitive exclusion of pathogens; immunomodulating properties; thought to improve ion transport activity of epithelial cells	[93]
Saccharomyces boulardii	Produces compounds that neutralize toxins; thought to inhibit proinflammatory pathways	[92]
Candidate probiotics		
Akkermansia muciniphila	Promotes intestinal barrier integrity; Amuc_1100 peptide; immunomodulation	[79]
Faecalibacterium prausnitzii	Butyrate producer	[58]

Roseburia intestinalis	Butyrate producer	[108]
Parabacteroides distasonis	Succinate producer; BA epimerization produces UDCA	[57]
Veillonella atypica	Metabolizes lactate; propionate producer	[98]
Engineered commensal microbes		
Escherichia coli Nissle 1917 (SYNB1618)	Engineered to metabolize phenylalanine	[99]
Escherichia coli Nissle 1917 (unnamed derivative)	Engineered to secrete antimicrobial metabolites specifically against *Pseudomonas aeruginosa* pathogen	[101]
Saccharomyces cerevisiae (unnamed derivative)	Engineered to secrete apyrase in response to detection of ATP; removal of pro-inflammatory metabolite	[102]
Lactobacillus gasseri ATCC 33323	Engineered to secrete GLP-1; support of natural host function	[104]

BA, bile acid; UDCA, ursodeoxycholic acid; GLP-1, glucagon-like peptide 1

6. Summary

Humans have co-evolved complex relationships with microbes and have historically benefitted from the consumption of microbes in fermented foods. Progression in our understanding of the gut microbiota-host relationship has revealed different ways that microbes may confer benefit or cause harm to its host. Recent progress suggests it is not only possible to shape the composition and metabolic capacity of the gut microbiota to a more desirable profile with probiotics and prebiotics, but also impart special functions using engineered commensal microbes. Newly identified beneficial and engineered microbes indicate promising avenues for improving nutrition and developing nutrition-based therapies for metabolic disorders. Even though single species that appear to be therapeutic have been identified, the most effective strategy to restore gut microbial health is likely a collection of probiotic microbes together with the nutrients they require to thrive in the gut. Equipped with knowledge about gut microbiota composition and metabolic potential, it is possible to design diets or specific nutrition interventions that either supply the nutrients (prebiotics) required to alter the composition of the gut microbiota or supplement individuals with specific probiotics or even postbiotics to impart a desired health benefit.

Author Contributions

AMS and LBA conceived, wrote, and edited the manuscript.

Funding

Research in our laboratory is funded by grants from the Natural Sciences and Engineering Research Council of Canada and the Canadian Institutes of Health Research.

Competing Interests

The authors have declared that no competing interests exist.

References

1. Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. Nature. 2012; 486: 207-214.
2. Lozupone CA, Stombaugh JI, Gordon JI, Jansson JK, Knight R. Diversity, stability and resilience of the human gut microbiota. Nature. 2012; 489: 220-230.
3. Rodríguez JM, Murphy K, Stanton C, Ross RP, Kober OI, Juge N, et al. The composition of the gut microbiota throughout life, with an emphasis on early life. Microb Ecol Health Dis. 2015; 26: 26050.
4. Stewart CJ, Ajami NJ, O'Brien JL, Hutchinson DS, Smith DP, Wong MC, et al. Temporal development of the gut microbiome in early childhood from the teddy study. Nature. 2018; 562: 583-588.
5. Lynch SV, Pedersen O. The human intestinal microbiome in health and disease. N Engl J Med. 2016; 375: 2369-2379.
6. Pickard JM, Zeng MY, Caruso R, Núñez G. Gut microbiota: Role in pathogen colonization, immune responses, and inflammatory disease. Immunol Rev. 2017; 279: 70-89.
7. Valdes AM, Walter J, Segal E, Spector TD. Role of the gut microbiota in nutrition and health. BMJ. 2018; 361: k2179.
8. Swaby AM, Agellon LB. 3.52 - Nutrient quality and diversity in foods for optimal nutrition. In: Comprehensive foodomics. Oxford: Elsevier; 2021. pp.689-696.
9. Slack E, Hapfelmeier S, Stecher B, Velykoredko Y, Stoel M, Lawson MAE, et al. Innate and adaptive immunity cooperate flexibly to maintain host-microbiota mutualism. Science. 2009; 325: 617-620.
10. Thaiss CA, Zmora N, Levy M, Elinav E. The microbiome and innate immunity. Nature. 2016; 535: 65-74.
11. Zheng D, Liwinski T, Elinav E. Interaction between microbiota and immunity in health and disease. Cell Res. 2020; 30: 492-506.
12. Kwon DY, Nyakudya E, Jeong YS. Fermentation: Food products. In: Encyclopedia of agriculture and food systems. Oxford: Academic Press; 2014. pp.113-123.
13. Waché Y, Dijon A. 8 - Microbial production of food flavours. In: Microbial production of food ingredients, enzymes and nutraceuticals. Woodhead Publishing; 2013. pp.175-193.
14. Hald T, Aspinall W, Devleesschauwer B, Cooke R, Corrigan T, Havelaar AH, et al. World health organization estimates of the relative contributions of food to the burden of disease due to selected foodborne hazards: A structured expert elicitation. PloS one. 2016; 11: e0145839.
15. Vernon K. Milk and dairy products. In: The cambridge world history of food. Cambridge: Cambridge University Press; 2000. pp.692-702.
16. Metchnikoff E. Lactic acid as inhibiting putrefaction. In: The prolongation of life: Optimistic studies. New York: Putnam; 1908. pp.116-129.
17. O'Toole PW, Marchesi JR, Hill C. Next-generation probiotics: The spectrum from probiotics to live biotherapeutics. Nat Microbiol. 2017; 2: 17057.
18. Krawczyk RT, Banaszkiewicz A. Dr. Józef brudziński - The true 'father of probiotics'. Benef Microbes. 2021; 12: 211-213.

19. Health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria. Joint FAO/WHO Expert Consultation; 2001. Available from: http://pc.ilele.hk/public/pdf/20190225/bd3689dfc2fd663bb36def1b672ce0a4.pdf.
20. Dobrogosz WJ, Peacock TJ, Hassan HM. Evolution of the probiotic concept: From conception to validation and acceptance in medical science. Adv Appl Microbiol. 2010; 72: 1-41.
21. Tissier H. Traitement des infections intestinales par la methode de transformation de la flore bacterienne de l'intestin. CRSoc Biol. 1907: 359-361.
22. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, et al. The international scientific association for probiotics and prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol. 2014; 11: 506-514.
23. Almeida A, Mitchell AL, Boland M, Forster SC, Gloor GB, Tarkowska A, et al. A new genomic blueprint of the human gut microbiota. Nature. 2019; 568: 499-504.
24. Nayfach S, Shi ZJ, Seshadri R, Pollard KS, Kyrpides NC. New insights from uncultivated genomes of the global human gut microbiome. Nature. 2019; 568: 505-510.
25. Pasolli E, Asnicar F, Manara S, Zolfo M, Karcher N, Armanini F, et al. Extensive unexplored human microbiome diversity revealed by over 150,000 genomes from metagenomes spanning age, geography, and lifestyle. Cell. 2019; 176: 649-662.e620.
26. Vrancken G, Gregory AC, Huys GRB, Faust K, Raes J. Synthetic ecology of the human gut microbiota. Nat Rev Microbiol. 2019; 17: 754-763.
27. Habib S, Swaby AM, Gaisawat MB, Kubow S, Agellon LB. A novel, scalable, and modular bioreactor design for dynamic simulation of the digestive tract. Biotechnol Bioeng. 2021; 118: 4338-4346.
28. Tidjani Alou M, Naud S, Khelaifia S, Bonnet M, Lagier JC, Raoult D. State of the art in the culture of the human microbiota: New interests and strategies. Clin Microbiol Rev. 2020; 34.
29. Park JC, Im SH. Of men in mice: The development and application of a humanized gnotobiotic mouse model for microbiome therapeutics. Exp Mol Med. 2020; 52: 1383-1396.
30. Le Chatelier E, Nielsen T, Qin J, Prifti E, Hildebrand F, Falony G, et al. Richness of human gut microbiome correlates with metabolic markers. Nature. 2013; 500: 541-546.
31. Rowland I, Gibson G, Heinken A, Scott K, Swann J, Thiele I, et al. Gut microbiota functions: Metabolism of nutrients and other food components. Eur J Nutr. 2018; 57: 1-24.
32. Bonnet M, Lagier JC, Raoult D, Khelaifia S. Bacterial culture through selective and non-selective conditions: The evolution of culture media in clinical microbiology. New Microbes New Infect. 2020; 34: 100622.
33. Chen Y, Michalak M, Agellon LB. Importance of nutrients and nutrient metabolism on human health. Yale J Biol Med. 2018; 91: 95-103.
34. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006; 444: 1027-1031.
35. Bäckhed F, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, et al. The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci U S A. 2004; 101: 15718-15723.
36. Ridaura VK, Faith JJ, Rey FE, Cheng J, Duncan AE, Kau AL, et al. Gut microbiota from twins discordant for obesity modulate metabolism in mice. Science. 2013; 341.
37. Gilbert JA, Quinn RA, Debelius J, Xu ZZ, Morton J, Garg N, et al. Microbiome-wide association studies link dynamic microbial consortia to disease. Nature. 2016; 535: 94-103.

38. Sarkar SR, Banerjee S. Gut microbiota in neurodegenerative disorders. J Neuroimmunol. 2019; 328: 98-104.
39. Witkowski M, Weeks TL, Hazen SL. Gut microbiota and cardiovascular disease. Circ Res. 2020; 127: 553-570.
40. Wong SH, Yu J. Gut microbiota in colorectal cancer: Mechanisms of action and clinical applications. Nat Rev Gastroenterol Hepatol. 2019; 16: 690-704.
41. Kim S, Covington A, Pamer EG. The intestinal microbiota: Antibiotics, colonization resistance, and enteric pathogens. Immunol Rev. 2017; 279: 90-105.
42. Collins J, Robinson C, Danhof H, Knetsch CW, van Leeuwen HC, Lawley TD, et al. Dietary trehalose enhances virulence of epidemic clostridium difficile. Nature. 2018; 553: 291.
43. Leffler DA, Lamont JT. Clostridium difficile infection. N Engl J Med. 2015; 372: 1539-1548.
44. Ekmekciu I, von Klitzing E, Fiebiger U, Neumann C, Bacher P, Scheffold A, et al. The probiotic compound VSL# 3 modulates mucosal, peripheral, and systemic immunity following murine broad-spectrum antibiotic treatment. Front Cell Infect Microbiol. 2017; 7: 167.
45. Jungersen M, Wind A, Johansen E, Christensen JE, Stuer-Lauridsen B, Eskesen D. The science behind the probiotic strain bifidobacterium animalis subsp. Lactis BB-12(®). Microorganisms. 2014; 2: 92-110.
46. Van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, et al. Duodenal infusion of donor feces for recurrent clostridium difficile. N Engl J Med. 2013; 368: 407-415.
47. Borody TJ, Khoruts A. Fecal microbiota transplantation and emerging applications. Nat Rev Gastroenterol Hepatol. 2012; 9: 88-96.
48. Qin J, Li Y, Cai Z, Li S, Zhu J, Zhang F, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature. 2012; 490: 55-60.
49. Haro C, Montes-Borrego M, Rangel-Zúñiga OA, Alcalá-Díaz JF, Gómez-Delgado F, Pérez-Martínez P, et al. Two healthy diets modulate gut microbial community improving insulin sensitivity in a human obese population. J Clin Endocrinol Metab. 2016; 101: 233-242.
50. Roager HM, Vogt JK, Kristensen M, Hansen LBS, Ibrügger S, Mærkedahl RB, et al. Whole grain-rich diet reduces body weight and systemic low-grade inflammation without inducing major changes of the gut microbiome: A randomised cross-over trial. Gut. 2019; 68: 83-93.
51. Schneeberger M, Everard A, Gómez-Valadés AG, Matamoros S, Ramírez S, Delzenne NM, et al. Akkermansia muciniphila inversely correlates with the onset of inflammation, altered adipose tissue metabolism and metabolic disorders during obesity in mice. Sci Rep. 2015; 5: 1-14.
52. Everard A, Belzer C, Geurts L, Ouwerkerk JP, Druart C, Bindels LB, et al. Cross-talk between akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. Proc Natl Acad Sci U S A. 2013; 110: 9066-9071.
53. Depommier C, Everard A, Druart C, Plovier H, Van Hul M, Vieira-Silva S, et al. Supplementation with akkermansia muciniphila in overweight and obese human volunteers: A proof-of-concept exploratory study. Nat Med. 2019; 25: 1096-1103.
54. Dao MC, Everard A, Aron-Wisnewsky J, Sokolovska N, Prifti E, Verger EO, et al. Akkermansia muciniphila and improved metabolic health during a dietary intervention in obesity: Relationship with gut microbiome richness and ecology. Gut. 2016; 65: 426-436.
55. Plovier H, Everard A, Druart C, Depommier C, Van Hul M, Geurts L, et al. A purified membrane protein from akkermansia muciniphila or the pasteurized bacterium improves metabolism in obese and diabetic mice. Nat Med. 2017; 23: 107-113.

56. Salminen S, Collado MC, Endo A, Hill C, Lebeer S, Quigley EMM, et al. The international scientific association of probiotics and prebiotics (ISAPP) consensus statement on the definition and scope of postbiotics. Nat Rev Gastroenterol Hepatol. 2021; 18: 649-667.
57. Wang K, Liao M, Zhou N, Bao L, Ma K, Zheng Z, et al. Parabacteroides distasonis alleviates obesity and metabolic dysfunctions via production of succinate and secondary bile acids. Cell Rep. 2019; 26: 222-235.e225.
58. Martín R, Miquel S, Benevides L, Bridonneau C, Robert V, Hudault S, et al. Functional characterization of novel faecalibacterium prausnitzii strains isolated from healthy volunteers: A step forward in the use of F. Prausnitzii as a next-generation probiotic. Front Microbiol. 2017; 8.
59. Koh A, De Vadder F, Kovatcheva-Datchary P, Backhed F. From dietary fiber to host physiology: Short-chain fatty acids as key bacterial metabolites. Cell. 2016; 165: 1332-1345.
60. Macfarlane GT, Macfarlane S. Bacteria, colonic fermentation, and gastrointestinal health. J AOAC Int. 2012; 95: 50-60.
61. Donohoe DR, Garge N, Zhang X, Sun W, O'Connell TM, Bunger MK, et al. The microbiome and butyrate regulate energy metabolism and autophagy in the mammalian colon. Cell Metab. 2011; 13: 517-526.
62. Chambers ES, Morrison DJ, Frost G. Control of appetite and energy intake by scfa: What are the potential underlying mechanisms? Proc Nutr Soc. 2015; 74: 328-336.
63. Den Besten G, Bleeker A, Gerding A, van Eunen K, Havinga R, van Dijk TH, et al. Short-chain fatty acids protect against high-fat diet-induced obesity via a pparγ-dependent switch from lipogenesis to fat oxidation. Diabetes. 2015; 64: 2398-2408.
64. Koh A, Bäckhed F. From association to causality: The role of the gut microbiota and its functional products on host metabolism. Mol Cell. 2020; 78: 584-596.
65. Johnstone RW. Histone-deacetylase inhibitors: Novel drugs for the treatment of cancer. Nat Rev Drug Discov. 2002; 1: 287-299.
66. Sabari BR, Zhang D, Allis CD, Zhao Y. Metabolic regulation of gene expression through histone acylations. Nat Rev Mol Cell Biol. 2017; 18: 90-101.
67. Chambers ES, Preston T, Frost G, Morrison DJ. Role of gut microbiota-generated short-chain fatty acids in metabolic and cardiovascular health. Curr Nutr Rep. 2018; 7: 198-206.
68. Liu F, Prabhakar M, Ju J, Long H, Zhou HW. Effect of inulin-type fructans on blood lipid profile and glucose level: A systematic review and meta-analysis of randomized controlled trials. Eur J Clin Nutr. 2017; 71: 9-20.
69. Wastyk HC, Fragiadakis GK, Perelman D, Dahan D, Merrill BD, Yu FB, et al. Gut-microbiota-targeted diets modulate human immune status. Cell. 2021; 184: 4137-4153.e4114.
70. Wang Z, Klipfell E, Bennett BJ, Koeth R, Levison BS, DuGar B, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature. 2011; 472: 57-63.
71. Zhu W, Buffa JA, Wang Z, Warrier M, Schugar R, Shih DM, et al. Flavin monooxygenase 3, the host hepatic enzyme in the metaorganismal trimethylamine N-oxide-generating pathway, modulates platelet responsiveness and thrombosis risk. J Thromb Haemost. 2018; 16: 1857-1872.
72. Warrier M, Shih Diana M, Burrows Amy C, Ferguson D, Gromovsky Anthony D, Brown Amanda L, et al. The TMAO-generating enzyme flavin monooxygenase 3 is a central regulator of cholesterol balance. Cell Rep. 2015; 10: 326-338.

73. Senthong V, Wang Z, Li XS, Fan Y, Wu Y, Tang WH, et al. Intestinal microbiota-generated metabolite trimethylamine-N-oxide and 5-year mortality risk in stable coronary artery disease: The contributory role of intestinal microbiota in a courage-like patient cohort. J Am Heart Assoc. 2016; 5: e002816.
74. Roncal C, Martínez-Aguilar E, Orbe J, Ravassa S, Fernandez-Montero A, Saenz-Pipaon G, et al. Trimethylamine-N-oxide (TMAO) predicts cardiovascular mortality in peripheral artery disease. Sci Rep. 2019; 9: 15580.
75. Chen S, Henderson A, Petriello MC, Romano KA, Gearing M, Miao J, et al. Trimethylamine N-oxide binds and activates perk to promote metabolic dysfunction. Cell Metab. 2019; 30: 1141-1151.e1145.
76. Groenendyk J, Agellon LB, Michalak M. Coping with endoplasmic reticulum stress in the cardiovascular system. Annu Rev Physiol. 2013; 75: 49-67.
77. Gao G, Xie A, Zhang J, Herman AM, Jeong EM, Gu L, et al. Unfolded protein response regulates cardiac sodium current in systolic human heart failure. Circ Arrhythm Electrophysiol. 2013; 6: 1018-1024.
78. Hetz C, Chevet E, Harding HP. Targeting the unfolded protein response in disease. Nat Rev Drug Discov. 2013; 12: 703-719.
79. Derrien M, Vaughan EE, Plugge CM, de Vos WM. Akkermansia muciniphila gen. Nov., sp. Nov., a human intestinal mucin-degrading bacterium. Int J Syst Evol Microbiol. 2004; 54: 1469-1476.
80. Agellon LB. Chapter 15 - Metabolism and function of bile acids. In: Biochemistry of lipids, lipoproteins and membranes. San Diego: Elsevier; 2008. pp.423-440.
81. Ridlon JM, Harris SC, Bhowmik S, Kang DJ, Hylemon PB. Consequences of bile salt biotransformations by intestinal bacteria. Gut Microbes. 2016; 7: 22-39.
82. Wahlström A, Sayin Sama I, Marschall HU, Bäckhed F. Intestinal crosstalk between bile acids and microbiota and its impact on host metabolism. Cell Metab. 2016; 24: 41-50.
83. Thomas C, Gioiello A, Noriega L, Strehle A, Oury J, Rizzo G, et al. TGR5-mediated bile acid sensing controls glucose homeostasis. Cell Metab. 2009; 10: 167-177.
84. Groenendyk J, Lee D, Jung J, Dyck JR, Lopaschuk GD, Agellon LB, et al. Inhibition of the unfolded protein response mechanism prevents cardiac fibrosis. PLoS One. 2016; 11: e0159682.
85. Vega H, Agellon LB, Michalak M. The rise of proteostasis promoters. IUBMB Life. 2016; 68: 943-954.
86. Bull M, Plummer S, Marchesi J, Mahenthiralingam E. The life history of lactobacillus acidophilus as a probiotic: A tale of revisionary taxonomy, misidentification and commercial success. FEMS Microbiol Lett. 2013; 349: 77-87.
87. Douglas LC, Sanders ME. Probiotics and prebiotics in dietetics practice. J Am Diet Assoc. 2008; 108: 510-521.
88. Deng Y, Misselwitz B, Dai N, Fox M. Lactose intolerance in adults: Biological mechanism and dietary management. Nutrients. 2015; 7: 8020-8035.
89. Suchy FJ, Brannon PM, Carpenter TO, Fernandez JR, Gilsanz V, Gould JB, et al. Nih consensus development conference statement: Lactose intolerance and health. NIH Consens State Sci Statements. 2010; 27: 1-27.
90. Fassio F, Facioni MS, Guagnini F. Lactose maldigestion, malabsorption, and intolerance: A comprehensive review with a focus on current management and future perspectives. Nutrients. 2018; 10: 1599.

91. Oak SJ, Jha R. The effects of probiotics in lactose intolerance: A systematic review. Crit Rev Food Sci Nutr. 2019; 59: 1675-1683.
92. Czerucka D, Piche T, Rampal P. Review article: Yeast as probiotics—Saccharomyces boulardii. Aliment Pharmacol Ther. 2007; 26: 767-778.
93. Sonnenborn U, Schulze J. The non-pathogenic escherichia coli strain nissle 1917 – Features of a versatile probiotic. Microb Ecol Health Dis. 2009; 21: 122-158.
94. Ben-Yacov O, Godneva A, Rein M, Shilo S, Kolobkov D, Koren N, et al. Personalized postprandial glucose response—Targeting diet versus mediterranean diet for glycemic control in prediabetes. Diabetes Care. 2021: dc210162.
95. Fetissov SO. Role of the gut microbiota in host appetite control: Bacterial growth to animal feeding behaviour. Nat Rev Endocrinol. 2017; 13: 11-25.
96. Leitão-Gonçalves R, Carvalho-Santos Z, Francisco AP, Fioreze GT, Anjos M, Baltazar C, et al. Commensal bacteria and essential amino acids control food choice behavior and reproduction. PLoS Biol. 2017; 15: e2000862.
97. Liu Y, Wang Y, Ni Y, Cheung CKY, Lam KSL, Wang Y, et al. Gut microbiome fermentation determines the efficacy of exercise for diabetes prevention. Cell Metab. 2020; 31: 77-91.e75.
98. Scheiman J, Luber JM, Chavkin TA, MacDonald T, Tung A, Pham LD, et al. Meta-omics analysis of elite athletes identifies a performance-enhancing microbe that functions via lactate metabolism. Nat Med. 2019: 1104–1109.
99. Isabella VM, Ha BN, Castillo MJ, Lubkowicz DJ, Rowe SE, Millet YA, et al. Development of a synthetic live bacterial therapeutic for the human metabolic disease phenylketonuria. Nat Biotechnol. 2018; 36: 857-864.
100. Puurunen MK, Vockley J, Searle SL, Sacharow SJ, Phillips JA, Denney WS, et al. Safety and pharmacodynamics of an engineered E. Coli nissle for the treatment of phenylketonuria: A first-in-human phase 1/2a study. Nat Metab. 2021; 3: 1125-1132.
101. Hwang IY, Koh E, Wong A, March JC, Bentley WE, Lee YS, et al. Engineered probiotic escherichia coli can eliminate and prevent pseudomonas aeruginosa gut infection in animal models. Nat Commun. 2017; 8: 15028.
102. Scott BM, Gutiérrez-Vázquez C, Sanmarco LM, da Silva Pereira JA, Li Z, Plasencia A, et al. Self-tunable engineered yeast probiotics for the treatment of inflammatory bowel disease. Nat Med. 2021; 27: 1212-1222.
103. Mimee M, Nagler CR. Engineered yeast tune down gut inflammation. Nat Med. 2021; 27: 1150-1151.
104. Duan FF, Liu JH, March JC. Engineered commensal bacteria reprogram intestinal cells into glucose-responsive insulin-secreting cells for the treatment of diabetes. Diabetes. 2015; 64: 1794-1803.
105. Holmes D. Genetically engineered lactobacilli reprogram intestinal cells to secrete insulin and ameliorate hyperglycaemia. Nat Rev Endocrinol. 2015; 11: 192-192.
106. Selle K, Fletcher JR, Tuson H, Schmitt DS, McMillan L, Vridhambal GS, et al. *In vivo* targeting of clostridioides difficile using phage-delivered CRISPR-cas3 antimicrobials. mBio. 2020; 11: e00019-00020.
107. Górski A, Bollyky PL, Przybylski M, Borysowski J, Międzybrodzki R, Jończyk-Matysiak E, et al. Perspectives of phage therapy in non-bacterial infections. Front Microbiol. 2019; 9: 3306.

108. Duncan SH, Hold GL, Barcenilla A, Stewart CS, Flint HJ. Roseburia intestinalis sp. Nov., a novel saccharolytic, butyrate-producing bacterium from human faeces. Int J Syst Evol Microbiol. 2002; 52: 1615-1620.