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The path towards microbiome-based metabolite treatment

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The increasing evidence pointing towards the involvement of the gut microbiome in multiple diseases, as well as its plasticity, renders it a desirable potential therapeutic target. Nevertheless, classical therapies based on the consumption of live probiotic bacteria, or their enrichment by prebiotics, exhibit limited efficacy. Recently, a novel therapeutic approach has been suggested based on metabolites secreted, modulated or degraded by the microbiome. As many of the host–microorganism interactions pertaining to human health are mediated by metabolites, this approach may be able to provide therapeutic efficacy while overcoming caveats of current microbiome-targeting therapies, such as colonization resistance and inter-individual variation in microbial composition. In this Perspective, we will discuss the evidence that supports pursuing the metabolite-based therapeutic approach as well as issues critical for its implementation. In a broader context, we will discuss how recent advances in microbiome research may improve and refine current treatment modalities, and the potential of combining them with metabolite-based interventions as a means of achieving a person-specific, integrated and efficient therapy.

The last decade has seen the emergence of a tremendous amount of research focusing on the population of commensal microorganisms, collectively termed the microbiome. This ecosystem resides throughout the body's mucosal surfaces and cavities, and is potentially associated with a variety of common multifactorial human disorders. Innovative high-throughput genomic and metabolomics technologies, some of which were developed as part of the human genome project[1], now enable an affordable in-depth description of microbial composition, growth dynamics[2], genetic makeup and secreted metabolites. These are complemented by works in germ-free mice and clinical trials that feature associations with multiple aspects of human health.

The interest in curing human diseases using beneficial microorganisms significantly predates these recent discoveries, with an origin in the 1910 publication by Nobel laureate Elie Metchnikoff, *The Prolongation of Life*, which suggested that the consumption of "friendly bacteria" from yoghurt may enhance health and delay age-associated pathologies. But more than a century after Metchnikoff's visionary publication, and almost three decades after Roy Fuller defined probiotics as "a live microbial feed supplement which beneficially affects the host animal by improving its intestinal microbial balance"[3], consumption of so-called health-promoting bacteria fails to live up to its expectations. While some studies have suggested mechanistic insights into how probiotic bacteria may mediate beneficial effects, these were mostly done in cell culture and animal models[4,5]. As such, insufficient evidence supports the efficacy of the current probiotics approach (one bacterial mix is beneficial to all conditions) in most indications, while their human health benefits remain controversial. Consequently, probiotics consumption is currently not recommended by the US Food and Drug Administration (FDA) for the treatment of any medical condition[6].

With the currently limited efficacy of probiotics usage in human diseases notwithstanding, it can serve as an opportunity to study central and currently enigmatic host–microbiome interaction principles that may drive stability and resilience of this ecosystem in different physiological contexts. One such important factor is colonization resistance of the indigenous well-entrenched commensal microbial populations upon encounter with exogenously introduced species. In addition, inter-individual variation in microbiome composition and function, as well as strain-level differences[7,8], may also result in differential responsiveness to probiotics[9] or dietary interventions[10], limiting the efficacy of a 'one strain fits all' therapeutic approach.

Testimony to the potential efficacy of microbiome-based intervention in modulating important human diseases is evident by faecal microbiome transplantation (FMT), in which the microbiome of a healthy donor is transplanted into a patient in an attempt to replace or correct the pathology-associated microbiome. This treatment modality, already approved for recurrent *Clostridium difficile* infections, has shown promising preliminary results in treating insulin resistance[11] and ulcerative colitis[12] in humans, and is currently being tested in multiple clinical trials for treating a myriad of conditions, ranging from metabolic and neoplastic to autoimmune disorders. However, transplanting an entire microbial community comprises its own risks. These include the transfer of pathogens/pathobionts, unwanted effects of the transplanted microbiome on unrelated conditions[13], and the potentially limited long-term stabilization of a foreign microbial configuration when introduced into a new host that harbours a unique genetic, immune, metabolic and nutritional milieu. An additional challenge is identifying the optimal FMT donor for a given condition, as donor selection is increasingly recognized to substantially affect the FMT outcome[14]. Some of these challenges may be addressed by limiting the number of the transplanted organisms to a selected consortium of cultured bacteria from a healthy donor. This approach demonstrated promising results in patients with *C. difficile*[15], suggesting that carefully designed probiotics may overcome the limitations of both FMT and 'one mix fits all' probiotics. Further elimination of risks associated with the administration of live bacteria (while maintaining therapeutic efficiency) can be achieved through faecal filtrate transfer, in which intact cells are removed from the donated sample while maintaining bacterial components, their secretions and bacteriophages[16].

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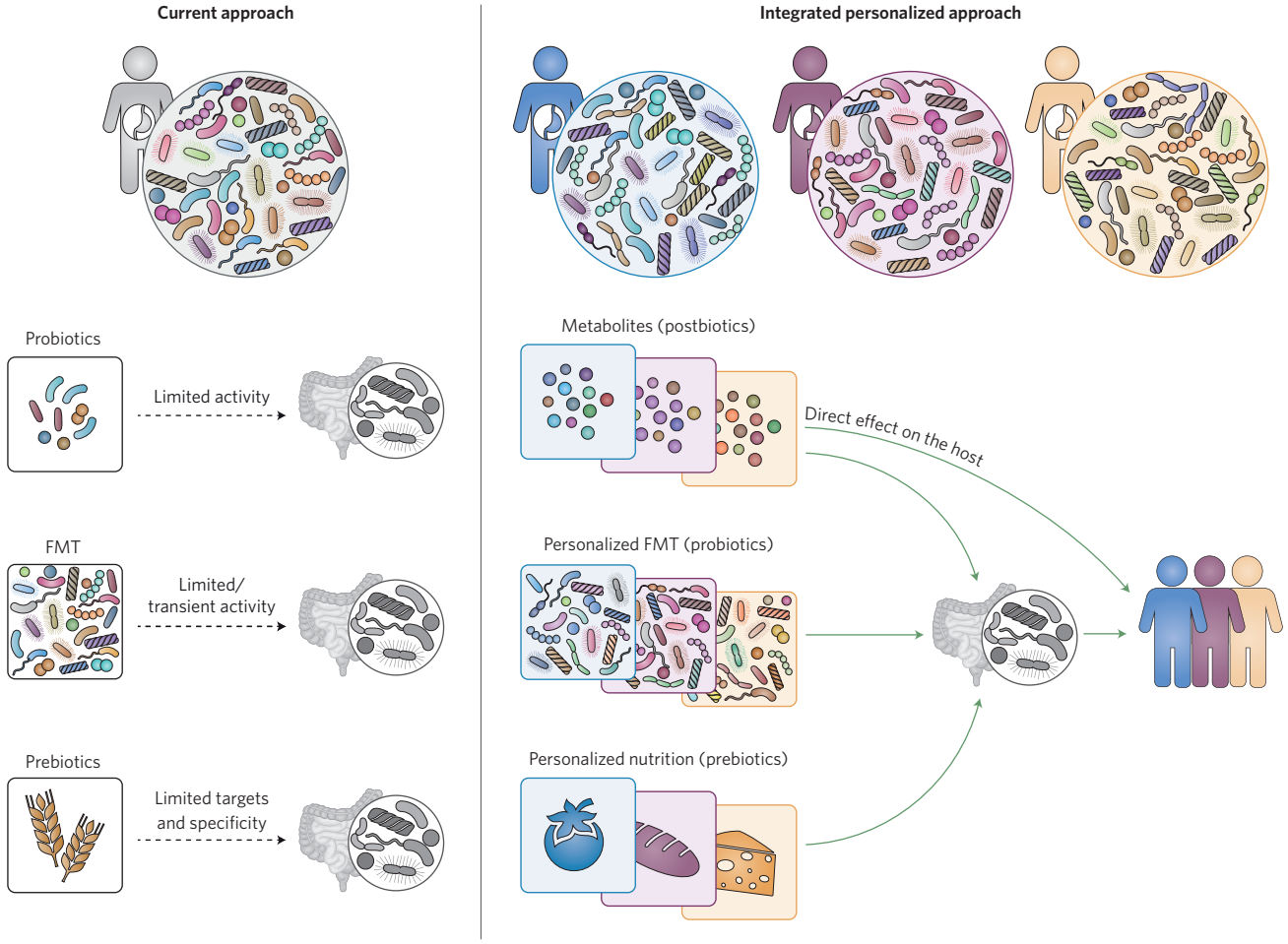

Figure 1 | An integrated approach to microbiome-based therapeutics. Current generalized 'one treatment fits all' approaches (left panel) may suffer from limited efficacy due to an inability of the exogenous bacteria to colonize a host that harbours a discordant microbiome configuration, or from lack of targets for prebiotics. Microbiome-modulated metabolites may surpass these limitations by exerting a beneficial host effect downstream of the microbiome, or by stabilizing the transferred microbial configurations (right panel). As such, metabolite treatment may enable an improved efficacy when coupled with other microbiome-based treatments, such as probiotics and nutritional interventions. All such approaches will be optimized when personally tailored to the individual's physiology and microbiome configuration.

Prebiotic therapy may serve as an alternative approach to FMT[17]. According to common definition, prebiotics are dietary supplements, such as resistant starch, β-glucans, pectin, inulin and other oligosaccharides, that are consumed to increase the abundance of supposedly beneficial bacteria (mainly bifidobacteria and lactic-acid-producing bacteria). However, advances in microbiome research call for a broader definition, in which prebiotics are any compound that, upon bacterial metabolism, affects the composition or the function of the microbiome to exert a beneficial effect on the host[18]. Several meta-analyses suggest a promising therapeutic role for prebiotics in conditions such as metabolic syndrome[19] or irritable bowel syndrome[20], yet their mode of action and their effects on different microbiome compositions requires further study. The response to these dietary supplements also displays inter-individual variation, pertaining in part to the microbiome composition[21,22]. Complementing the concept of prebiotics, a more comprehensive dietary approach termed personalized nutrition[10] utilizes a large person-specific metadata (including a rich person-based dataset of microbiome features) and machine learning techniques in personalizing dietary interventions that modulate the microbiome, thereby impacting metabolic homeostasis. The long-term efficacy of this approach and its applicability across a wide range of microbiome-associated diseases merit further study.

A central role for microbial products

In recent years, our understanding of host–microbiome interactions has been evolving from descriptive, associative studies, towards ones aiming for mechanistic deciphering of the molecular nature of these trans-kingdom interactions. An important insight stemming from these studies is that many host–commensal interactions are mediated by various metabolites that are secreted, degraded or modified by the gut microbiome and/or the host, thereby constituting a rich network of signalling moieties that impact the host, microbiome and their inter-dependent functions. Among these metabolites are short- and long-chain fatty acids, amino acids, bile acids, vitamins and polysaccharides. These insights resulted in the development of an additional microbiome-based therapeutic approach involving administration or inhibition of bioactive microbiome-modulated molecules. By administering or inhibiting microbiome-associated metabolites, this therapy aims at impacting their downstream signalling pathways when relevant to disease pathogenesis while overcoming the need of transplanting an entire or restricted microbial community (through FMT or probiotics). Thus, microbiome-based metabolite treatment may act directly on host pathways that have been damaged by microbial activity; alternatively, the metabolites' effects on the host may alter the pathways that dictate or enable the formation of a pathogenic microbiome, thus supporting a shift

towards a non-pathogenic microbial composition; or the treatment may synergistically affect both processes. In addition, while compositional analysis of the microbiome as a means of identifying potential beneficial commensals or pathobionts is rarely achievable on a strain level specificity, administrating metabolites rather than the bacteria may enable to overcome this difficulty by aiming downstream of the microorganisms, thereby overcoming inter-individual strain-level differences in microbiome composition. Importantly, microbial molecules of therapeutic potential are not limited to secreted metabolites, but may also include bacterial cellular components, such as membrane proteins[16]. In one such example, feeding obese mice with a membrane protein purified from the species *Akkermansia muciniphila* recapitulated the positive metabolic effects previously associated with the live bacterium[23].

Microbiome-based metabolite treatment

One exciting potential indication of this new therapeutic approach involves the enhancement of the ability of an exogenous microbiome to colonize the host by outcompeting an indigenous, pathogenic microbiome, thereby modifying colonization resistance and contributing to treatment of conditions mediated by pathobionts or pathogens. For example, during recurrent infections with *C. difficile*, the pathogen possesses a colonization advantage over the indigenous microbiome, as the latter is depleted by antibiotics treatment. Efficient clearing of such opportunistic infection can be achieved by restoring colonization resistance through FMT[24]. Interestingly, Buffie *et al.* recently demonstrated that resistance could be achieved by administration of a fraction of the microbiome as precise as just one species, *Clostridium scindens*. This commensal possesses a complete secondary bile acid biosynthesis pathway, which inhibits the growth of *C. difficile*[25]. This suggests that supplementation of secondary bile acids may be considered as a metabolite-based alternative or supplement to FMT in treating *C. difficile* infections.

Another example of the niche-modulating capability of a metabolite-based therapy is featured in the dysbiotic microbiome (a disrupted community with pathogenic potential) of mice deficient in the nod-like receptor NLRP6 (NOD-like receptor family pyrin domain-containing 6)[26]. In this setting, the aberrant microbiome creates a metabolite milieu that is characterized by over-abundance of histamine and spermine, and reduced levels of taurine. When this dysbiotic microbiome is transferred into a naïve host, its altered metabolite balance drives suppression of the invaded host's NLRP6 signalling. This results in reduced levels of interleukin-18, which leads to inhibition of normal production of antimicrobial peptides, collectively conferring preferential colonization of the invading microbiome over the indigenous microbial configuration[26]. Overcoming this metabolite-driven 'hijacking' of the host homeostatic pathways by taurine supplementation restores its homeostatic levels and reverts normal immune signalling and antimicrobial peptide balance, thereby reversing dysbiosis and ameliorating the severity of dysbiosis-driven intestinal inflammation. Conversely, supplementing naïve mice with a combination of histamine and spermine inhibits homeostatic innate immune signalling downstream of the microbiome, resulting in alteration of the anti-microbial landscape towards a configuration that enhances the formation of dysbiosis and associated inflammatory potential.

Collectively, these findings highlight the role of microbial metabolites in induction or repression of colonization resistance, and suggest that tailoring the correct combination of metabolites for different microbiome compositions may be potentially utilized for subverting pathology-associated microbiome configurations and for improving the efficacy of treatment based on microbial supplementation or whole microbiome transplantation. Applying this concept in humans suffering from microbiome-associated disorders such as inflammatory bowel disease (IBD) requires the identification of bioactive, microbial-associated metabolites that are altered in humans suffering from IBD[27,28]. One such early example of metabolite-based therapy to IBD involves the infusion of short-chain fatty acids (SCFA), which show preliminary promising results in animal models[29] and clinical trials[30]. As SCFA are recognized as one of the major modulators of host–microbiome interactions, it is not surprising that supplementation with SCFA is associated with improvement of different conditions, including cancer[31,32] and metabolic health[33–35]. SCFA act through activation of G-coupled-receptors and inhibition of histone deacetylases, and can also serve as energy substrates, thereby modulating multiple pathways that impact energy metabolism in the intestine[36], inducing immune homeostasis by regulating the quantity and function of regulatory T cells[37–39], and even affecting the gut–brain axis[33,40].

Flavonoids comprise an additional group of compounds that may be considered for microbiome-based metabolite therapy. Multiple studies have attributed beneficial outcomes for flavonoid supplementation, though a considerable inter-individual variability in the magnitude of the effect is often observed[41]. This may be in part due to flavonoid metabolism by members of the microbiome, which also differ in their abundance across the human population. Importantly, while current literature suggests a clear association between the microbiome and the health effects of flavonoids, the mechanisms involved require further research. We have recently demonstrated a role for flavonoids as microbiome-based metabolite therapy in the context of recurrent obesity; the high-fat diet (HFD) that characterizes many overweight and obese humans and is utilized in obesity-promoting experimental animal models is significantly depleted of flavonoids. In mice consuming a HFD, low levels of flavonoids are achieved both by their low dietary levels and by a massive expansion of flavonoid-degrading bacteria during the induction of obesogenic conditions. Interestingly, after a successful weight-reduction diet, the levels of flavonoids are not normalized even when all other metabolic parameters return to normality, and when mice are reintroduced with an obesogenic diet, weight regain and associated metabolic disorders become more pronounced as compared with mice exposed to HFD for the first time. This exaggerated 'cycling obesity' in mice, a common phenomenon among repeatedly dieting humans, suggests that a microbiome-based 'metabolite memory' contributes to exaggerated post-dieting weight regain. Importantly, when flavonoids are reintroduced to the dieting mice as means of a metabolite replenishment therapy, the exacerbated weight gain associated with a previous exposure to HFD is prevented, possibly through metabolite modulation of host adipose tissue energy expenditure[42]. Collectively, these findings support a therapeutic approach that is based on supplementing the host with metabolites downstream of the microbiome, which acts directly on host-related metabolic pathways. The nature and efficacy of such potentially bioactive metabolites in humans featuring cycling obesity merits further studies.

Challenges in microbiome-based metabolite therapy

Consuming microbial products may overcome the challenge of colonization resistance that hampers probiotics, FMT or even compositional changes induced by prebiotics. As such, human implementation of the approach will necessitate devising standardized computational and experimental methods to identify the metabolites that play a role in various pathologies. Even so, it is reasonable to assume that supplementing such microbial products may not always be sufficient in treating microbiome-associated pathologies, with a number of challenges meriting consideration. First, the microbiome may not be inert to the supplemented metabolites. As such, unexpected interactions of these molecules with members of the microbiome may lead to dysbiosis, or to biochemical transformation of the metabolite by the bacteria to an inactive or even toxic form. Thus, the identification of metabolite-resident microbiome interactions is crucial prior to their utilization. Altering the levels

of a metabolite in the gut may also change the balance of a feedback loop, thereby interfering with regulated production of the metabolites. Alternatively, chronic exposure to a given metabolite may promote resistance mechanisms of the host or its microbiome to alter the therapeutic target to these metabolites.

Importantly, identifying low levels of a given metabolite in a faecal sample reveals little of its physiological levels at an upstream biogeographical locality in which it exerts its beneficial role. Thus, it is important to verify that a metabolite supplemented orally can reach its site of action while not being absorbed in more proximal regions of the gastrointestinal tract. This holds true even more in cases in which metabolites are systemically bioactive. Indeed, serum metabolites have recently been highlighted to be greatly impacted by metabolites that are produced in the gut by the microbiome, and to feature physiological effects far outside the gastrointestinal tract in remote organs such as the liver[43]. Disruption of a normally functioning microbiome by antibiotic treatment of mice led to altered drug detoxification in the liver, highlighting the importance of studying the pharmacokinetics and pharmacodynamics of any metabolite considered for treatment and its potential systemic effects.

Furthermore, commercialization requires reproducible production of the therapy that is stable and can be easily administered. However, many of the small molecules produced by bacteria have a complex chemical structure[44], which may be difficult to replicate under industrial settings, especially in cases of bioactive volatile metabolites. For all of the above reasons, and despite a growing number of bacterial metabolites featuring a promising activity, transforming them into an actual therapy is associated with multiple fundamental challenges that are to be experimentally explored.

An integrated approach to microbiome-based therapeutics

In order to benefit from the advantages of metabolite therapy while addressing some of the above challenges, an integrated microbiome-based therapeutic approach may be considered (Fig. 1). This approach should combine lessons learned from probiotics, prebiotics, FMT and metabolites. While probiotics have the advantage over FMT of being comprised only of a selected highly defined number of strains, they may act differently, if at all, in each individual. As such, probiotics may only act efficiently when tailored to the individual's microbiome composition[9]. Adding a combination of niche-stabilizing metabolites to such individualized probiotic treatment may overcome colonization resistance to the newly introduced strains and enhance their long-term efficacy.

Even when personally tailored, an additional important challenge to probiotics therapy is the long-term preservation of the newly introduced microorganisms, should they be featured to be of clinical importance. To this aim, dietary modifications should be considered in parallel to microbiome-based therapies as means of providing continuous support to the newly introduced or modulated microbial strains. Here too, inter-individual variability in response to dietary supplementation largely depends on person-specific microbiome composition[22,45], with the response to virtually any food ingredients being highly variable and affected by the microbiome[10,46]. In this scenario, also, metabolites can serve as a complimentary fast-acting 'bridging' therapy that supports microbial stabilization while the effects of prebiotics are generated and assessed.

In summary, metabolite-based therapy constitutes a promising field of microbiome-related intervention. As this approach is in its infancy, only several potential therapeutic compounds have been recognized. Identifying additional bioactive small molecules from the human microbiome will merit extensive computational and experimental screening and validation. One such approach is high-throughput metabolomics analysis of microbiome samples that are associated with various conditions in the presence or absence of antibiotics treatment[47]. It is clear that optimization of metabolite treatment for clinical use may be associated with conceptual and technical hurdles. Nevertheless, such treatment, when applied alone or in combination with other interventions, may impact a variety of microbiome-associated disorders.

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References

1. Collins, F. S., Morgan, M. & Patrinos, A. The Human Genome Project: lessons from large-scale biology. *Science* **300,** 286–290 (2003).
2. Korem, T. *et al.* Growth dynamics of gut microbiota in health and disease inferred from single metagenomic samples. *Science* **349,** 1101–1106 (2015).
3. Fuller, R. A review. *J. Appl. Bacteriol.* **66,** 365–378 (1989).
4. von Schillde, M.-A. *et al.* Lactocepin secreted by *Lactobacillus* exerts anti-inflammatory effects by selectively degrading proinflammatory chemokines. *Cell Host Microbe* **11,** 387–396 (2012).
5. Yan, F. *et al.* A *Lactobacillus rhamnosus* GG-derived soluble protein, p40, stimulates ligand release from intestinal epithelial cells to transactivate epidermal growth factor receptor. *J. Biol. Chem.* **288,** 30742–30751 (2013).
6. *Probiotics: In Depth* (NCCIH, 2016); https://nccih.nih.gov/health/probiotics/introduction.htm.
7. Zhu, A., Sunagawa, S., Mende, D. R. & Bork, P. Inter-individual differences in the gene content of human gut bacterial species. *Genome Biol.* **16,** 82 (2015).
8. Nayfach, S., Rodriguez-Mueller, B., Garud, N. & Pollard, K. S. An integrated metagenomics pipeline for strain profiling reveals novel patterns of bacterial transmission and biogeography. *Genome Res.* **26,** 1612–1625 (2016).
9. Maldonado-Gómez, M. X. *et al.* Stable engraftment of *Bifidobacterium longum* AH1206 in the human gut depends on individualized features of the resident microbiome. *Cell Host Microbe* **20,** 515–526 (2016).
10. Zeevi, D. *et al.* Personalized nutrition by prediction of glycemic responses. *Cell* **163,** 1079–1094 (2015).
11. Vrieze, A. *et al.* Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology* **143,** 913–916 (2012).
12. Paramsothy, S. *et al.* Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. *Lancet* **389,** 1218–1228 (2017).
13. Alang, N. & Kelly, C. R. Weight gain after fecal microbiota transplantation. *Open Forum Infect. Dis.* **2,** ofv004 (2015).
14. Moayyedi, P. *et al.* Fecal microbiota transplantation induces remission in patients with active ulcerative colitis in a randomized controlled trial. *Gastroenterology* **149,** 102–109 (2015).
15. Petrof, E. O. *et al.* Stool substitute transplant therapy for the eradication of *Clostridium difficile* infection: 'RePOOPulating' the gut. *Microbiome* **1,** 3 (2013).
16. Ott, S. J. *et al.* Efficacy of sterile fecal filtrate transfer for treating patients with *Clostridium difficile* Infection. *Gastroenterology* (2016).
17. Glenn, G. & Roberfroid, M. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. *J. Nutr.* **125,** 1401–1412 (1995).
18. Bindels, L. B., Delzenne, N. M., Cani, P. D. & Walter, J. Towards a more comprehensive concept for prebiotics. *Nat. Rev. Gastroenterol. Hepatol.* **12,** 303–310 (2015).
19. Beserra, B. T. *et al.* A systematic review and meta-analysis of the prebiotics and synbiotics effects on glycaemia, insulin concentrations and lipid parameters in adult patients with overweight or obesity. *Clin. Nutr.* **34,** 845–858 (2015).
20. Ford, A. C. *et al.* Efficacy of prebiotics, probiotics, and synbiotics in irritable bowel syndrome and chronic idiopathic constipation: systematic review and meta-analysis. *Am. J. Gastroenterol.* **109,** 1547–1561 (2014).
21. Walker, A. W. *et al.* Dominant and diet-responsive groups of bacteria within the human colonic microbiota. *ISME J.* **5,** 220–230 (2011).
22. Kovatcheva-Datchary, P. *et al.* Dietary fiber-induced improvement in glucose metabolism is associated with increased abundance of *Prevotella*. *Cell Metab.* **22,** 971–982 (2015).
23. Plovier, H. *et al.* A purified membrane protein from *Akkermansia muciniphila* or the pasteurized bacterium improves metabolism in obese and diabetic mice. *Nat. Med.* **23,** 107–113 (2017).
24. van Nood, E. *et al.* Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N. Engl. J. Med.* **368,** 407–415 (2013).
25. Buffie, C. G. *et al.* Precision microbiome reconstitution restores bile acid mediated resistance to *Clostridium difficile*. *Nature* **517,** 205–208 (2015).
26. Levy, M. *et al.* Microbiota-modulated metabolites shape the intestinal microenvironment by regulating NLRP6 inflammasome signaling. *Cell* **163,** 1428–1443 (2015).

27. Patel, N. *et al.* Metabolomic analysis of breath volatile organic compounds reveals unique breathprints in children with inflammatory bowel disease: a pilot study. *Ailment. Pharmacol. Ther.* **40,** 498–507 (2014).
28. De Preter, V. *et al.* Faecal metabolite profiling identifies medium-chain fatty acids as discriminating compounds in IBD. *Gut* **64,** 447–458 (2014).
29. Butzner, J., Parmar, R., Bell, C. & Dalal, V. Butyrate enema therapy stimulates mucosal repair in experimental colitis in the rat. *Gut* **38,** 568–573 (1996).
30. Scheppach, W. Treatment of distal ulcerative colitis with short-chain fatty acid enemas a placebo-controlled trial. German-Austrian SCFA Study Group. *Dig. Dis. Sci.* **41,** 2254–2259 (1996).
31. McIntyre, A., Gibson, P. & Young, G. Butyrate production from dietary fibre and protection against large bowel cancer in a rat model. *Gut* **34,** 386–391 (1993).
32. Hinnebusch, B. F., Meng, S., Wu, J. T., Archer, S. Y. & Hodin, R. A. The effects of short-chain fatty acids on human colon cancer cell phenotype are associated with histone hyperacetylation. *J. Nutr.* **132,** 1012–1017 (2002).
33. De Vadder, F. *et al.* Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. *Cell* **156,** 84–96 (2014).
34. Gao, Z. *et al.* Butyrate improves insulin sensitivity and increases energy expenditure in mice. *Diabetes* **58,** 1509–1517 (2009).
35. Lin, H. V. *et al.* Butyrate and propionate protect against diet-induced obesity and regulate gut hormones via free fatty acid receptor 3-independent mechanisms. *PLoS ONE* **7,** e35240 (2012).
36. Donohoe, D. R. *et al.* The microbiome and butyrate regulate energy metabolism and autophagy in the mammalian colon. *Cell Metab.* **13,** 517–526 (2011).
37. Atarashi, K. *et al.* Induction of colonic regulatory T cells by indigenous *Clostridium* species. *Science* **331,** 337–341 (2011).
38. Smith, P. M. *et al.* The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. *Science* **341,** 569–573 (2013).
39. Round, J. L. & Mazmanian, S. K. Inducible Foxp3^{+} regulatory T-cell development by a commensal bacterium of the intestinal microbiota. *Proc. Natl Acad. Sci. USA* **107,** 12204–12209 (2010).
40. Perry, R. J. *et al.* Acetate mediates a microbiome-brain-β-cell axis to promote metabolic syndrome. *Nature* **534,** 213–217 (2016).
41. Cassidy, A. & Minihane, A.-M. The role of metabolism (and the microbiome) in defining the clinical efficacy of dietary flavonoids. *Am. J. Clin. Nutr.* **105,** 10–22 (2017).
42. Thaiss, C. A. *et al.* Persistent microbiome alterations modulate the rate of post-dieting weight regain. *Nature* **540,** 544–551 (2016).
43. Thaiss, C. A. *et al.* Microbiota diurnal rhythmicity programs host transcriptome oscillations. *Cell* **167,** 1495–1510 (2016).
44. Donia, M. S. & Fischbach, M. A. Small molecules from the human microbiota. *Science* **349,** 1254766 (2015).
45. Desai, M. S. *et al.* A dietary fiber-deprived gut microbiota degrades the colonic mucus barrier and enhances pathogen susceptibility. *Cell* **167,** 1339–1353 (2016).
46. Suez, J. *et al.* Artificial sweeteners induce glucose intolerance by altering the gut microbiota. *Nature* **514,** 181–186 (2014).
47. Klemashevich, C. *et al.* Rational identification of diet-derived postbiotics for improving intestinal microbiota function. *Curr. Opin. Biotechnol.* **26,** 85–90 (2014).

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J.S. and E.E. chose the topics for the various sections, reviewed the literature, designed the figure and wrote the manuscript. Both authors contributed equally to the writing.

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Competing interests

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