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REVIEW

# The remedy within: will the microbiome fulfill its therapeutic promise?

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**Abstract** The last decade of research has witnessed a tremendous upsurge in our understanding of the intestinal microbiome and its role in a large range of human diseases, which has incited hopes for a rapid clinical utilization of the new insights for the development of microbiome-based therapies. Nonetheless, only a single microbiome-targeted therapy has so far found its way into clinical routine: fecal microbiota transplantation for patients suffering from recurrent *Clostridium difficile* infections. Herein, we discuss the current hopes, advances, challenges, and obstacles for translating basic microbiome research into therapeutic applications for a larger number of diseases and provide an outline of how such clinical applications might emerge.

**Keywords** Microbiome · Therapy · Metabolites · Fecal microbiome transplantation · Postbiotics

## What is past is prologue: the neglected microbial organ

Despite Ilya Metchnikoff's visionary work about the importance of intestinal bacteria for the physiology of the host more than 100 years ago, for most of the twentieth century, the entirety of microorganisms colonizing the gastrointestinal tract—now called the intestinal microbiota—has been primarily appreciated for assisting in the digestion of dietary nutrients, while any physiological or pathophysiological role beyond this function was largely ignored. The advent of two branches of new technology have rapidly changed our perception of the microbiome, the entirety of microbial genes, over the last 10 years: the metagenomic sequencing of the DNA and RNA repertoires present in the intestinal ecosystem and the re-emergence of gnotobiotic approaches enabling controlled microbial colonization of a mammalian intestine [1]. As a result, it now appears that there is hardly any aspect of host physiology that is completely independent from the impact of intestinal microorganisms and their products. Indeed, the effect of the intestinal microbiome does not only manifest in its classical digestive function in the gastrointestinal tract but also reaches as far as modulating the physiology of other organ systems, such as the liver, adipose tissue, lung, and brain [2]. For instance, intestinal microbial colonization impacts hematopoiesis and immune cell maturation [3, 4], regulates the level of thermogenesis in brown adipose tissue [5, 6], programs circadian gene expression [7], and influences the status of the blood-brain barrier [8], among many others. Consequently, the microbiome also affects pathophysiological processes beyond local bowel inflammation, including metabolic syndrome [9], autoimmunity [10], and neurodegeneration [11]. These local and systemic effects of the microbiome are mediated through immune system modulation and by secretion of structural elements of the microbial cell, such as cell wall components and nucleic acids [12], as well as products of microbial metabolism, including metabolites and proteins [13]. Thereby, the microbiome is involved into a highly connective network of communication with multiple other organ systems.

## Thought is free: therapeutic promises of the microbiome

Interestingly, many of those diseases whose pathophysiology was suggested to involve a microbiome contribution share a

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common feature, namely a sharp increase in global incidence over the last five decades. Furthermore, while auto-inflammatory, autoimmune, neurodegenerative, and metabolic diseases have been linked to genetic susceptibility loci in large genome-wide association studies, the genetic predisposition typically accounts for less than 20% of the clinical cases of these diseases, while the majority of cases often remain of idiopathic etiology [14–17]. The rapid rise in the incidence of these diseases within one generation time also suggests that host genetics are not the sole contributor, as genetic evolution in humans requires much longer time scales. Instead, changes in environmental factors and lifestyle are typically associated with the above modern diseases, including diet, hygiene, lack of exercise, longevity, exposure to xenobiotics (substances that are foreign to the organism), control of environmental temperature, and alterations in the light-dark cycle [18–20]. Remarkably, many of these environmental influences have been shown to shape the ecology of the microbiota, such as its taxonomic composition and functional capacities, leading to the hypothesis that certain environmental factors may exert their impact on host physiology and disease via the microbial community located at the body's surface [18]. This hypothesis provokes three major conclusions: (1) In addition to the human genome, the microbial metagenome needs to be considered when evaluating the genetic and environmental influence on the manifestation of a particular disease. Indeed, metagenome-wide association studies have started to link particular microbial taxa and their genomic functions to disease outcomes [21]. (2) In contrast to the host's genome, the microbial metagenome is highly dynamic and amenable to change over an individual's lifetime [22]. Thus, assuming a metagenomic contribution to disease susceptibility, this contribution is not stable but rather undergoes fluctuations over time and depends on various environmental inputs that modulate its constitution. (3) As a corollary, the therapeutic modulation of the microbiome might be harnessed to alter an individual's risk for the manifestation of a certain disease. If the conditions and factors that control the longitudinal development of microbiota composition are sufficiently understood, then it should be possible to design dietary or biotic interventions to minimize an individual's microbiome-mediated disease risk. This hope has fueled numerous investigations into the identity of microbiome-altering stimuli and the nature of microbial contributions to human health and disease.

## As good luck would have it: fecal microbiota transplantation

One prototypical microbiome-based intervention that has recently been introduced into routine clinical practice serves as a reference point for the continued hope that microbiome science may ultimately establish new approaches for the rational therapy of a multitude of diseases: fecal microbiota transplantation (FMT) in cases of recurrent intestinal infection with antibiotic-resistant *Clostridium difficile* [23]. FMT is the most radical form of microbiome-based therapy, as it describes the attempt to replace the entire microbial ecosystem in the intestine with the fecal matter of a healthy donor. The first account of FMT dates back to the fourth century, where Chinese physicians used the procedure for the treatment of diarrhea. About 50 years ago, FMT was introduced as a clinical procedure for patients suffering from *C. difficile*-induced pseudomembranous colitis [24]. However, only in the last 5 years has FMT become a widespread and broadly recommended approach in the treatment of recurrent *C. difficile* infections. Although standardization efforts are still underway, the procedure typically involves a certain level of donor screening [25], sample homogenization, and filtration, followed by administration via retention enema, endoscopy, nasogastic, or nasojejunal tubing. Several hundred cases of successful FMT have been reported to date, with cure rates of up to 90% [26]. Despite the success and clinical effectiveness, the procedure remains poorly controlled. FMT involves the transfer of a large number of bacteria, viruses, and unicellular and multicellular eukaryotes, the individual functions of which is largely unknown [27]. Such functions can manifest in phenotypic consequences, as witnessed in a case of unexpected weight gain reported after familial FMT [28]. In addition, in some cases, it might be the non-bacterial rather than the bacterial content that mediates the efficacy of FMT. This has been exemplified by filtrated fecal transfer, in which only bacterial cell components, bacterial-derived molecules, and viruses are retained [29]. Thus, more precise knowledge about interventions through specific microorganisms that mediate the beneficial effect of FMT is critical.

## We have seen better days: vagaries of microbiome-based therapies

The uncertainties inherent to the procedure notwithstanding, the spectacular success of FMT in treating recurrent pseudomembranous colitis have given rise to the hope that a similar procedure might prove effective against other intestinal or even extra-intestinal diseases. Indeed, cases of FMT trials have since been reported not only for gastrointestinal and infectious conditions but also for metabolic, autoimmune, hematologic, and even neurologic conditions [30]. However, in contrast to recurrent *C. difficile* infections, the data from these trials is not sufficiently conclusive to recommend the immediate inclusion of FMT into standard clinical practice [31]. For instance, in the case of inflammatory bowel disease (IBD), FMT has not yet proven to be the "magic bullet" in the form of a long-awaited efficient therapy across different manifestations of the disease, despite the fact that the microbiome is clearly involved in disease etiology. The reasons why simple FMT is likely to be insufficient when considering possible

microbiome-based therapies for a multitude of diseases are manifold and reflect fundamental principles involved in the translation of microbiome research into the therapeutic world.

First, the intestinal microbial ecosystem shows remarkable resistance and resilience properties [32]. While high ecosystem stability is generally desirable for the host, as in the case of colonization resistance against invading pathogens, this presents a problem when the introduction of new species into the microbiome is part of a therapeutic strategy. In the case of *C. difficile* infection, the microbial community is already dramatically disrupted, either through prior antibiotics use or through pathogen expansion, such that FMT can reach its maximal effect. In contrast, in most other conditions, the impact on intestinal microbial composition achieved by FMT is likely to be more temporal, necessitating either repeated FMTs or deliberate ecosystem evacuation by antibiotics, neither of which is clinically desirable.

Second, studies in both animal models and humans suggest that the amenability of the microbiome to change by external influences is not stable over the course of an individual's lifetime but undergoes successive stages of development. The early life from birth until the weaning period and the introduction of solid food present a particularly vulnerable and impactful phase of ecosystem establishment [33]. Aberrations of healthy microbiota development during this phase have been associated with numerous pathological conditions later in life, including metabolic syndrome [34], allergy, and asthma [35], as well as stunted development in the case of undernutrition [36]. On the one hand, this period therefore opens a "window of opportunity" for the sustainable modulation of the microbiome for therapeutic purposes. Indeed, perinatal modulation of the microbiome has shown promise in the first trials of newborns delivered by caesarian section that are lacking the natural colonization during the birth canal passage [37]. On the other hand, this also means that the relative stability of the microbiome later in life likely hampers the ability for sustainable interventions, suggesting that microbiome-based contributions to disease manifestations might have occurred long before the onset of the disease [38, 39].

Third, the microbiome underlies enormous inter-individual taxonomic variation. The broad range of stable microbiome configurations that can be maintained by a healthy human host may not only reflect a person's lifestyle, including dietary habits, but also introduces a large variability with respect to an individual's susceptibility to microbiome intervention. The initial state of the intestinal ecosystem with respect to microbiome composition and function is critically involved in determining the success of microbiome therapies, as has recently been shown in the case of oral probiotic administration [40]. This large inter-individual variability might in part explain why FMT trials in diseases other than pseudomembranous colitis have yielded conflicting results. Efficient microbiome-based approaches are therefore only warranted to succeed if they take into account the pre-treatment state of the intestinal community. In addition to the inter-individual variability in microbiota composition of the FMT recipient, an additional variable that necessitates a thorough understanding is the donor microbiota [25]. As such, donor screening for potentially beneficial microorganisms, as well as their selective enrichment in culture, might be a promising avenue for improving the efficacy of FMT [41].

Fourth, in the case of recurrent *C. difficile* infection, a single infectious agent is associated with disease exacerbation. In contrast, for the majority of human conditions in which the microbiome exerts a modulatory influence on disease severity, the situation might be far more complex. Rather than a single microorganism being sufficient to elicit the disease, it is likely that a complex network of microorganisms and their metabolic activities is involved in the pathogenesis of IBD, aspects of metabolic syndrome, and potentially other diseases [42]. In addition, it is possible that the microbiome triggers that contribute to disease etiology precede the onset of symptoms, collectively suggesting why a simple microbiome replacement at the time of established disease might not contribute to modulation of disease progression.

## Nothing will come of nothing: the rational basis for microbiome-based therapies

Given the above roadblocks, is there any scientific basis to assume that the microbiome will become an integral part of routine therapies in adult individuals? In principle, any patient receiving oral antibiotics for the treatment of an infectious disease undergoes microbiota ablation to a certain extent, usually without any overt signs of physiological repercussions. For instance, in a recent trial of short-term oral antibiotic administration in overweight adults, no meaningful short-term impact on insulin resistance and other metabolic parameters was observable [43]. Thus, the question arises whether the observations made in animal models about the importance of intestinal microbial colonization on a large range of host physiological functions will prove relevant in humans. There are several lines of evidence arguing for this possibility. As early as the 1950s, large-scale human studies were carried out in soldiers receiving broad-spectrum antibiotics. The motivation behind these studies was to test whether prophylactic antibiotic administration would protect them from contracting infections. While the susceptibility to infection was not significantly altered by antibiotic treatment (likely due to the fact that viral infections accounted for the majority of disease cases), a significant weight gain was noted in subjects receiving antibiotics compared to non-treated controls [44]. Around the same time, large-scale antibiotic use was introduced to enhance productivity in livestock, based on the observation that antibiotic treatment in the drinking water greatly increased the weight gain rate at constant food intake [45]. Thus, the link between the commensal microbiome and metabolism has already found

widespread application in mammals, a practice that has only recently been reduced due to concerns about antibiotic resistance development [46]. The conclusion from these observations is that metabolic effects of antibiotic treatments become apparent over long time scales, providing a potential explanation why acute antibiotic trials failed to document any apparent system-wide alterations of metabolism.

Potential microbiome-based therapeutic interventions for human disease might therefore be classified according to four conditions (Fig. 1). First, microbiome therapies are useful to treat acute derangements in the ecology of the gastrointestinal community. As discussed above, this is successfully practiced for *C. difficile* infections and might similarly be applicable to other gastrointestinal infections that involve severe aberrations in the structure of the microbiota. Second, systemic metabolic derangements, including inborn errors of metabolism and metabolic complications that are secondary to hepatic and endocrine disorders, might benefit from acute interventions with microbial colonization in the intestine, with the goal of restructuring the metabolic capabilities of the meta-organism [47]. While this may prove efficient in achieving short-term alleviation of symptoms, long-term therapies would require additional strategies to establish persistent establishment of commensals with the desired metabolic capacity. Third, given the neonatal window of opportunity discussed above, microbiome therapies targeted at this temporal phase have the potential to fundamentally impact health at later stages of development, including metabolic diseases, allergy, and asthma [33]. Additional work is required in this area to define the components of the microbiota that are critical for long-term health. Fourth, probably the most challenging and as yet most speculative group of diseases potentially benefiting from microbiome-based treatment are those multifactorial diseases for which a microbiome contribution has been suggested solely based on animal studies. For some of these diseases, the driver microbial species and the metabolites involved in the pathogenesis remain largely unknown, and a causative relationship in humans has not been unequivocally established. This group of diseases includes neurodegeneration [11], metabolic syndrome [42], and inflammatory disease [48]. A potential microbiome involvement in the treatment of these diseases will possibly involve long-term strategies of microbial ecosystem engineering or more targeted pharmacological approaches that are built on but do not directly interfere with microbial colonization. We will elaborate on such strategies below.

## The brave new world: microbiome therapeutics and "postbiotics"

If FMT is not suitable for most microbiome-based therapeutic developments, what are the potential alternatives? One of the approaches under intensive investigation is the refinement of microbiome engineering by more targeted approaches, such as the introduction of a single bacterium that is as powerful as FMT-based community replacement with respect to achieving a clinically desired effect. Such probiotic strategy would greatly improve the safety of microbiome treatments and would facilitate the more precise dosing and administration of the procedure. Indeed, in the case of *C. difficile* infection, this may be possible with only one strain, *Clostridium scindens*, which effectively inhibited *C. difficile* via the production of secondary bile acids in a rodent model [49]. Further developments of this strategy include the biological engineering of biotic interventions through system biology approaches in bacteria in order to enhance their functionality [50]. Proof-of-concept studies in this area indicate that it might be possible to administer engineered bacteria with the goal of achieving local therapeutic actions, but such methods need rigorous assessment with respect to safety and long-term maintenance upon successful administration.

Additionally, targeted interventions with the microbial ecosystem could be achieved through bacteriophages [51], a prominent component of the intestinal microbiome with the capacity to regulate the microbial genepool. Indeed, several clinical trials employing bacteriophage strategies are underway and have so far proven safe in the first phases [52]. However, the establishment of such viral therapies would necessitate an improved understanding of ecological interactions between the bacterial and bacteriophage communities in the intestine [53] and proofs of efficacy [54].

A complementary approach involves the pharmacologic administration of microbiome modulators, rather than biotic interventions. In fact, the realization that microbial metabolic activity is involved in host physiology and pathophysiology opens up an entirely new branch of pharmacology, which instead of targeting host enzymes focuses on modifying biochemical processes in the microbiome. The obvious challenge is that prokaryotic pharmacology is much less developed, but first studies have demonstrated that this might be a feasible approach in certain cases. For instance, interfering with the microbial generation of TMAO, a microbiota-dependent metabolite that enhances atherosclerosis and cardiovascular complications [55], through the pharmacological inhibition of the first enzymatic step in TMAO generation by a structural analog of choline provided protection from atherosclerotic lesion development in preclinical models [56]. While the effectiveness of this molecule in humans awaits further study, this approach may provide a potential blueprint for the development of further small molecules targeted against bacterial enzymatic cascades in order to modulate their metabolic activity.

Finally, the quintessential microbial contribution to human health and disease is frequently provided in the form of either structural components of the bacterial cell, as most prominently exemplified by LPS, or in the form of secreted metabolites, such as short-chain fatty acids [13]. The dietary modulation or direct administration of these metabolites is therefore an

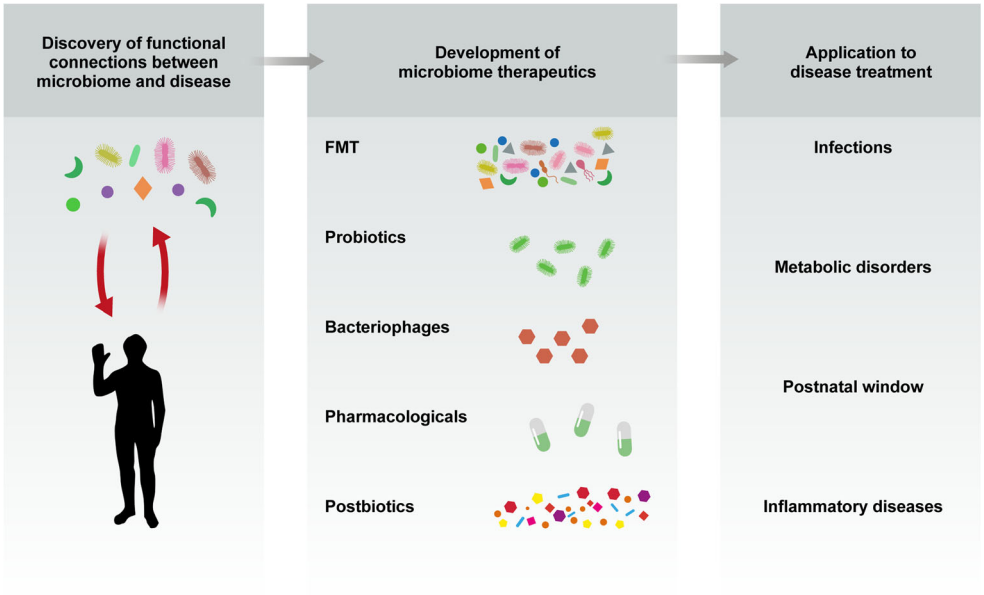


**Fig. 1** From discovery to therapy: the brave new world of microbiome therapeutics. A potential pipeline for the development of microbiome-based therapeutics begins with the causative association of the microbiome with a human disease, followed by the rational design of targeted interventions (FMT, probiotics, bacteriophages, pharmaceuticals, postbiotics), which are ultimately used in trials against infectious diseases, metabolic disorders, perinatal microbiome reconstitution, or against inflammatory diseases

attractive target for therapeutic interventions that harness the newly gained insights into the microbiome contribution to human disease. In contrast to pre- and probiotics, which aim at altering the composition of the microbial community, such "postbiotics" bypass the complex modulation of microbial ecology and directly exert an effect on the host [18]. As such, they might be applicable in a wider range of populations compared to pre- and probiotics, whose effectiveness depends in part on the microbial community present prior to the intervention. Examples for postbiotic interventions have been found, for instance, in animal models of autism [57], colitis [58], recurrent obesity [38], asthma [4], type I diabetes [59], and CNS inflammation [60].

Together, biotic engineering, microbial therapeutics, and postbiotics may present important avenues into the future development of microbiome-based therapies (Fig. 1). Well-controlled clinical trials will then determine whether FMT against recurrent *C. difficile* infections will be joined in the clinical repertoire by a larger arsenal of tools targeting the microbial contribution to a multitude of human diseases. Given the speed of discovery in the field over the last 10 years, it is possible that future generations of physicians will fulfill Ilya Metchnikoff's dream from more than a century ago and will embrace a new perception of the intestinal microbiome: the remedy within.

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