10TH ANNIVERSARY SERIES

# Transforming medicine with the microbiome

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**Advances in microbiome research are spurring the development of new therapeutics for a variety of diseases, but translational challenges remain.**

The study of microorganisms has been revolutionized by complementing the centuries-old art of microbiology with next-generation sequencing of complex bacterial communities (collectively termed "the microbiome") within and around the eukaryotic host. Microbiome research initially focused on associations between certain microbial compositional features and human medical conditions. The field has quickly evolved, unraveling causative links between distinct microbial consortia, their collective functions, and impacts on host pathophysiology. In addition to the microbiome's emerging role as an orchestrator of biological processes, it also has plasticity in its composition and function, thereby constituting an attractive target for therapeutic intervention. In this Focus, the first in a special series to celebrate the 10th anniversary of *Science Translational Medicine*, we introduce a paper published in the journal a decade ago and discuss progress in developing translational approaches involving the host-microbiome interface (Fig. 1).

## HOST-MICROBIOME MODULATION BY DIET

For decades, nutritional research focused on seeking direct links between dietary constituents and human health, aiming to establish universal guidelines to combat disease. However, a large body of research has not resulted in conclusive findings, contributing to various unsubstantiated nutritional trends and unsupported practices. Gut microbiome studies have added an important facet to nutritional research by incorporating the microbiome as a major contributor to host metabolic phenotypes, thus clarifying some of the unresolved questions in the field. In their pioneering work published a decade ago, Turnbaugh *et al.* (*1*) showed that host adiposity could be modulated by the gut microbiome's ability to harvest energy from food; transplantation of microbiome consortia obtained from lean or genetically obese mice into germ-free mice transferred the donor's phenotype to the recipient animal. In subsequent work published in *Science Translational Medicine* (*2*), these investigators demonstrated in germ-free mice transplanted with fecal microbiomes from human volunteers that microbiome composition and function could be rapidly and reproducibly altered by diet. These discoveries have led to potential approaches to treat cardiometabolic disease, and attempts have been made to find prebiotic dietary components to shape the microbiome and confer health benefits on the host. An example of such prebiotic intervention was described by Zhao *et al.* (*3*); they showed that dietary fiber intake improved glycemic control in patients with type 2 diabetes mellitus to a greater extent than standard care through modulation of the microbiome. With these examples of "one size fits all" nutritional interventions notwithstanding, heterogeneity among individuals in gut microbiome composition and function is increasingly appreciated to hamper universal food-based interventions. Accordingly, Zeevi *et al.* (*4*) showed that glycemic responses to food were person specific and dictated by a combination of clinical, laboratory, and microbiome characteristics. Individual postprandial glycemic responses became predictable with a machine-learning algorithm, enabling personalized diets that maintained normoglycemia.

In the next decade, microbiome-based dietary and prebiotic interventions may emerge as essential tools for health care and dietary planning, enabling precision therapies, for example, as a complementary preventive treatment of uncontrolled inflammation in inflammatory bowel disease (IBD). Fecal microbiome profiling could become a component of medical evaluation, leading to tailor-made diets or ad hoc medications. However, conclusive evidence of prebiotic and personalized diets as inducers of sustained metabolic improvements in humans still remains to be determined. Future studies should concentrate on long-term impacts and safety of such therapies and on their potential extension to health conditions beyond obesity and its metabolic complications, such as malnutrition, dietary constituent deficiencies, inflammatory states, and neoplastic diseases.

## HOST-MICROBIOME MODULATION BY PROBIOTICS

Bacterial supplements, termed probiotics, have been used to promote health for more than a century, yet their efficacy remains inconclusive. Gut microbiome research offers an opportunity to study live microbial interventions in terms of colonization, interactions with the indigenous microbiome, and impact on the host. Recent work (*5*) suggests that some inconsistencies regarding live microbial effects on the human host might stem from inter-individual differences in probiotic gut colonization patterns and their impact on the indigenous microbiome. As "resistance" and "permissiveness" to probiotic gut mucosal colonization could be predicted by baseline host and microbiome features, an opportunity emerges for context-specific tailoring of distinct probiotic strains to optimize gut colonization and downstream activity.

There are still major obstacles to implementing live microbial therapy in clinical practice. These challenges include the need to develop noninvasive approaches for direct sampling of the gut mucosa and technologies to enable reliable characterization of the microbiome in different regions of the gut. In addition, we need to determine mechanisms of activities of probiotic strains in vivo, thereby enabling the prediction of alterations in the microbiome after treatment. Last, we need to generate high-quality and conclusive clinical data in the form of large multicenter randomized, placebo-controlled trials in different clinical scenarios and human subpopulations.

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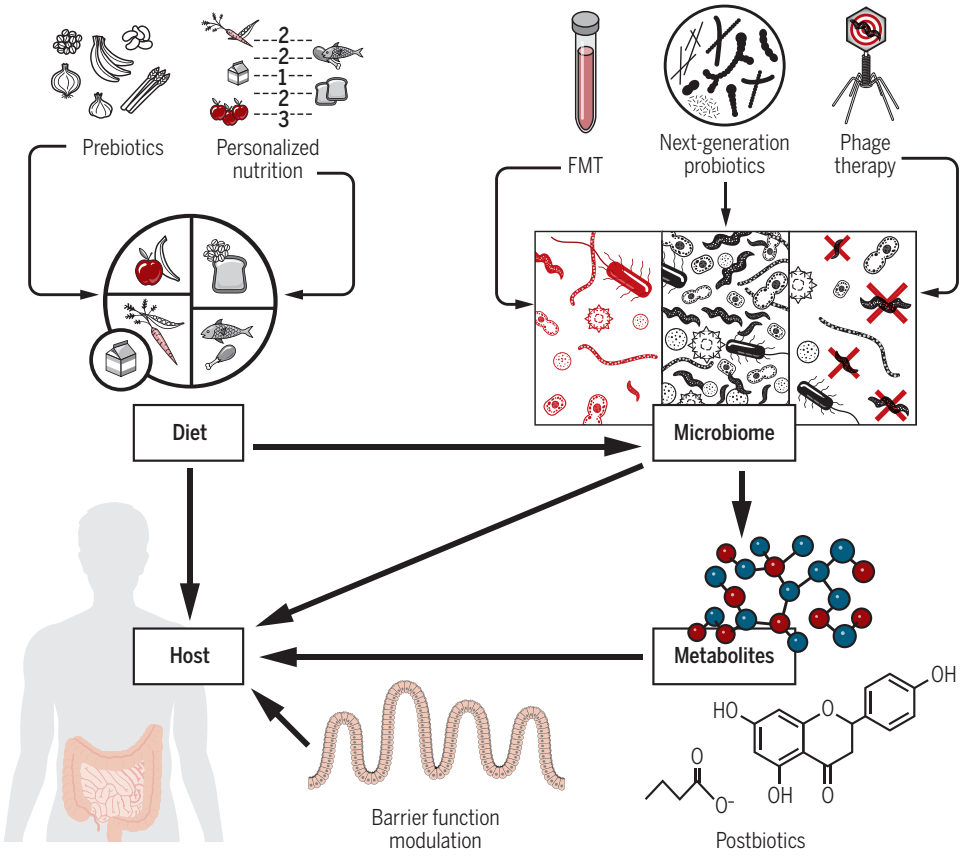


**Fig. 1. Gut microbiome–based therapeutic approaches.** Recent research has elucidated gut microbiome interventions for promoting human health and for combating disease. These approaches include microbiome modulation or direct impact on the host through nutritional intervention, either by prebiotics or by individualized diets (top left). Strategies to affect the gut microbiome or directly impact the host through live bacteria supplementation or exclusion include fecal microbiome transplantation (FMT), treatment with custom-made probiotics, or targeted elimination of bacterial members of the microbiome (top right). The host and potentially its microbiome can also be modulated by administration, reduction, or activity blocking of bacteria-derived metabolites through treatment with or inhibition of postbiotics (bottom right) or by manipulation of host gut barrier function (bottom left). Collectively, these modalities, when used alone or in combinations, will affect the host-microbiome interface.

## HOST-MICROBIOME MODULATION BY BACTERIAL METABOLITES

Another strategy for microbiome-based therapies is to use supplements of bacteria-derived metabolites or to block their generation, rather than attempting to enrich or deplete the bacteria that produce them. One example of these so-called "postbiotics" was described by Maslowski *et al.* (*6*). They showed that short-chain fatty acids produced by fermentation of dietary fiber by the gut microbiome or those administered exogenously could attenuate gut inflammation in mouse models of colitis. In animal models of recurrent obesity, diminished flavonoids from an altered microbiome drove exaggerated weight regain after successful dieting (*7*). Postbiotic replenishment of the depleted metabolites mitigated the accelerated weight regain by affecting adipocyte energy expenditure. Similarly, Koeth *et al.* (*8*) revealed that the gut microbiome metabolizes L-carnitine, a compound abundant in red meat, into the proatherogenic molecule trimethylamine N-oxide. Follow-up studies have tested inhibitors targeting a gut microbial enzyme in this pathway to combat platelet hyperreactivity and to decrease the risk of atherothrombotic events, such as myocardial infarction and stroke. Together, these findings highlight the potential of postbiotic therapy with microbiome-derived molecules in animal models. Additional studies are warranted to shed light on the intended and off-target effects of such compounds and to examine their long-term safety in humans.

## HOST-MICROBIOME MODULATION BY FMT

One of the oldest microbiome-based interventions in humans, which dates back to the fourth century, is fecal microbiome transplantation (FMT). In a landmark study, van Nood *et al.* (*9*) found that intraduodenal infusion of a healthy fecal microbiome administered to patients suffering from recurrent *Clostridium difficile* infection decreased the rate of infection recurrence within 10 weeks of follow-up compared to treatment with the antibiotic vancomycin. Since then, FMT has been studied in other disease contexts, such as cardiometabolic disease and IBD. One emerging limitation of FMT is that efficacy varies between fecal donors because of unknown factors. Another concern involves the risk of transmission of communicable diseases or other microbiome-mediated traits from donor to recipient.

An alternative, more personalized approach involves an autologous FMT using fecal samples from the individual that were banked before disease onset. Such an approach would necessitate large-scale fecal banking facilities. However, it still carries underlying risks, as microbiomes from individuals who may appear healthy could harbor causal factors of the condition to be treated, resulting in unforeseen resurgence of the disease. Future studies should investigate the factors that render some FMT donors superior to others, decipher the interactions between the transplanted and host microbiomes, and elucidate gut colonization. New mechanistic insights could enable development of "designer" therapies of custom-made microbiome signatures conferring distinct functions.

## TARGETED ELIMINATION AND GUT BARRIER REGULATION

One unmet need is an intervention that specifically eliminates harmful members of the microbiome (pathobionts) from the ecosystem. Although antibiotics are commonly used against pathogens, they are nonspecific, inflict collateral damage both to commensal bacteria and to the host, and are associated with the emergence of antibiotic-resistant bacterial strains. Bacteriophages are now attracting renewed attention because they can target specific bacteria and result in fewer side effects than antibiotics due to their lack of tropism for eukaryotic cells. Norman *et al.* (*10*) showed that patients with IBD exhibited abnormal enteric viromes with an increased richness of bacteriophages. Exogenous administration of lytic bacteriophage combinations or designer nanomolecular structures that

use bacterial recognition sites and phage-associated membrane penetration machinery could serve as a strain-specific pathobiont-targeting modality. Although having great potential, bacteriophage therapy faces major challenges, including an inability to recapitulate in vitro antibacterial action in vivo. This could be attributable to dosing issues, phage mutagenesis, interaction with the microbiome, neutralization by host antibodies, or the emergence of phage-resistant bacterial strains. Combinations of phages targeting distinct receptors on pathobionts of interest may offer a solution to some of these issues.

Another underexplored methodology to regulate host-microbiome interactions and microbial immunomodulatory products lies in direct targeting of the host intestinal barrier. Emerging regulators of gut barrier function include biophysical factors such as osmotic pressure, microbiome-generated molecules, and host-related modulators. Comprehensive understanding of the repertoire and mechanisms of these barrier-modulating factors is an exciting avenue of future research.

## CHALLENGES AND PROSPECTS

The last decade has witnessed a remarkable leap in microbiome research. In its infancy, such research focused on important but inherently limited descriptive studies, providing a detailed characterization of microbiome alterations during health and disease and in response to distinct dietary regimens. These studies are now being followed by more mechanistic approaches to establish causal links between microbiome assemblages and various phenotypes. A new and exciting aspect of microbiome research focuses on personalization of interventions, as well as harnessing the inherent individualized variability in microbiomes and other physiological features to explain and even predict human health and disease states.

In addition to the specific challenges presented so far, there are some general limitations to be considered when attempting to draw clinical conclusions from gut microbiome research. Conceptual pitfalls include distinguishing between associative and causative relationships, which should be validated by appropriate experimentation. This could be accomplished by ablation of the disease phenotype after antibiotic treatment or by mimicking the phenotype with the administration of a postbiotic compound. The ideal validation would reproduce the phenotype by transplantation of different microbiome configurations into germ-free mice. It is crucial to account for differences between preclinical models and humans in terms of anatomy, physiology, and microbiome composition. Humans tend to have more heterogeneous microbiomes than do animal models because of variations in geographic, ethnic, and nutritional backgrounds and thus manifest a wider spectrum of phenotypes. In addition, nonbacterial members of the microbiome, such as the virome, mycome, and parasitome, are currently understudied but are increasingly recognized to mediate important regulatory functions in the host gut. Furthermore, with the development of techniques to handle low-biomass samples, other organs such as the skin, genitourinary tract, and respiratory tract are being explored as treatment targets. Last, several technical challenges need to be addressed, such as establishing standardized protocols for sample collection, storage, processing, sequencing and analysis, and harmonization of interpretation.

Clinical translation necessitates stringent testing, preferably in the form of randomized placebo-controlled clinical trials. In these trials, feasibility, efficacy, adverse events, and long-term safety issues need to be assessed in large cohorts to ensure that the tested interventions are used responsibly, avoiding unsubstantiated claims and contemporary hype. As part of the process, regulatory authorities, such as the U.S. Food and Drug Administration and the European Food Safety Authority, will have to adapt their procedures to accommodate new data mining techniques such as machine learning and artificial intelligence, while enabling the testing of microbial and metabolite consortia, rather than individual components of consortia. Uniform, rigorous, and unbiased experimental and regulatory approaches, similar to the careful and stringent testing and approval processes practiced in other human interventions, will allow the safe and efficacious long-term integration of microbiome-based therapies into the treatment of a variety of different diseases.

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