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Review

Engineering Microbiomes to Improve Plant and Animal Health

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Animal and plant microbiomes encompass diverse microbial communities that colonize every accessible host tissue. These microbiomes enhance host functions, contributing to host health and fitness. A novel approach to improve animal and plant fitness is to artificially select upon microbiomes, thus engineering evolved microbiomes with specific effects on host fitness. We call this engineering approach host-mediated microbiome selection, because this method selects upon microbial communities indirectly through the host and leverages host traits that evolved to influence microbiomes. In essence, host phenotypes are used as probes to gauge and manipulate those microbiome functions that impact host fitness. To facilitate research on host-mediated microbiome engineering, we explain and compare the principal methods to impose artificial selection on microbiomes; discuss advantages and potential challenges of each method; offer a skeptical appraisal of each method in light of these potential challenges; and outline experimental strategies to optimize microbiome engineering. Finally, we develop a predictive framework for microbiome engineering that organizes research around principles of artificial selection, quantitative genetics, and microbial community-ecology.

Trends

The microbiome's evolutionary potential is often ignored in medical and agricultural research.

Evolutionary engineering protocols can shape microbiomes that improve animal and plant health.

Microbiome engineering leverages host traits that evolved to control associated microbes.

Microbiome engineering employs basic principles of quantitative genetics and community ecology.

Optimized microbiome engineering could revolutionize research on agriculturally and medically important microbiomes.

Microbiome Engineering

Animals and plants are universally and persistently inhabited by microbes. These host-associated microbial communities (microbiomes) thrive on host surfaces, inhabit multiple tissue types, and colonize both inter- and intracellular host habitats [1,2]. Microbiomes of animals and plants are often dominated by eubacteria, but fungi, protozoa, archaea, and viruses also can play important roles in these communities [1–5]. Microbiomes are not passive players [6,7]; rather, microbes can alter host development, physiology, and systemic defenses [2,8,9], enable toxin production and disease resistance [10,11], increase host tolerance to stress and drought [12–14], modulate niche breadth [15], and change fitness outcomes in host interactions with competitors, predators, and pathogens [6]. Because microbiomes can encompass a hundred-fold more genes than host genomes [16], and because this 'hologenome' of a host–microbiome association can vary over space and time [17,18], microbiomes can function as a phenotypically plastic buffer between the host-genotype's effects and the environmental effects that interact to shape host phenotypes. Expression of virtually any host phenotype thus depends to some extent on the presence and taxonomic makeup of host-associated microbes.

A primary research goal in microbiome research is to elucidate microbiome functions that alter host performance. Several complementary approaches (Box 1) have emerged to differentiate between beneficial, neutral, and detrimental effects on host fitness [19,20]. A common preliminary method is to conduct a microbial phylotyping survey to define a host's **core microbiome**

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Box 1. Principal Approaches to Investigate Microbiome Function

Correlational Analyses

Microbiome functions can be deduced by (i) correlating the presence and abundance of microbial phylotypes with measures of host performance, and (ii) defining a core microbiome associated with healthy hosts [21,22]. ***Advantages***: Correlational analyses are straightforward with next-gen methods that utilize conserved barcoding loci (e.g., 16S rDNA for bacteria; ITS region for fungi). ***Disadvantages***: Phylotype abundances are subject to PCR-biases [81] and must be interpreted cautiously. Although some bacterial metabolic functions can be inferred from 16S phylotypes [82], closely related bacteria can differ significantly at genomic regions that influence function [79,83,84].

Single-cell Genomics, Whole-Community Metagenomics and Metaproteomics

Genomic, transcriptomic, or proteomic data can inform biochemical and metabolic analyses of microbiome–host interactions [2,24,85,86]. ***Advantages***: Network interactions between microbiome components and their potential effects on the host can be elucidated [87]. ***Disadvantages***: Analyses can be costly and time-consuming for whole-community metagenomics because deep sequencing is needed to capture contributions of rare community members, which can have important effects on microbiome function [88]. Reconstruction of individual genomes from metagenomic information is challenging (e.g., for bacteria with similar genomes; for genetic elements that are horizontally transferred between community members). Analyses can also be complicated by genetic or protein contaminations stemming from the host.

Experimental Manipulation

Microbiomes can be manipulated experimentally to test their contributions to host fitness, for example by inoculating gnotobiotic hosts with specific microbial strains, synthetic communities, or natural communities (e.g., experimental substitution of entire microbiome [25–28]), or by manipulating microbiomes (e.g., alteration of pH or other abiotic parameters, addition of amendments, knockout of specific taxa with antibiotics [29]). ***Advantages***: Experimental manipulation can elucidate causal roles of microbiomes in affecting host performance, overcoming the inferential limits of the above correlational analyses. ***Disadvantages***: Experimental manipulations can be disruptive to host fitness (e.g., antibiotics can impair the host). Experimental inoculation with single strains is typically restricted to microbes that can be cultured.

Synthetic Microbiomes

Microbial strains with candidate functions can be combined into simple synthetic microbiomes (containing few to several dozen species) as clinical tools to promote host health or as streamlined models of microbiomes in nature [27,89]. ***Advantages***: Synthetic microbiomes allow increased control over microbiome composition, potentially testing antagonistic versus synergistic effects among strains on host performance [90], uncovering host loci that mediate microbiome taxonomic makeup [91], or to reverse effects of dysbiosis, for instance in cases of *Clostridium* infections in humans [26]. ***Disadvantages***: Only culturable or easily transferable microbes can be used to construct synthetic microbiomes. Microbial combinations and concentrations that can be tested increase exponentially with the number of microbial types per synthetic community; there exists presently no clear strategy to reduce the combinations that need to be tested to explore all regions of the combinatorial 'hyperspace'. The spatial structure within synthetic microbiomes is likely different compared to natural microbiomes.

Microbiome Engineering by Artificial Selection on Host–Microbiome Associations

Artificial selection can be used to engineer microbiomes using methods detailed in Boxes 2 and 3. ***Advantages***: Unlike synthetic microbiomes (see above), a community comprised of both culturable and unculturable microbes can be engineered. Because microbiomes can be engineered to optimize different functions (e.g., enhancing versus degrading host health), microbiome contributions can be deduced in experimental contrasts that compare taxonomic and genetic makeup of diverged microbiomes that received different selection treatments. ***Disadvantages***: Selection experiments can be time-consuming.

(i.e., microbial taxa consistently present in a healthy host; see Glossary [21,22]) and to correlate microbial taxa with specific measures of host performance (e.g., host health [23]). A second approach is to employ metagenomics, metatranscriptomics, or metaproteomics to infer functional properties of the whole microbial community or of focal microbial taxa within it [2,24]. Third, the taxonomic makeup of microbiomes can be experimentally manipulated to test hypotheses about microbiome function. For example, **gnotobiotic** hosts can be maintained with a defined set of microorganisms, and microbiomes can be manipulated with antibiotic treatments or transfer of microbiomes between hosts [25–29]. With any of these approaches, it remains challenging to elucidate specific functional roles of the microbiome in shaping host performance traits (e.g., growth, health, enemy deterrence, mate attraction, fertility, and overall fitness). Central to this challenge is the complexity of microbiome properties, which can be driven by interactions among taxa within the microbiome community and which can vary with both the host genotype and the environment [30].

Glossary

Co-adaptation: state of matched adaptations between members of interacting species, which can arise through co-evolution, but also through preferential acquisition of specific symbiotic partners from environmental and biotic sources. Co-adaptation and co-evolution are frequently confused [77,78]; co-evolution requires reciprocal evolution where adaptations in host and symbiont drive each other's evolution; co-adaptation does not require reciprocal evolution and can arise through other processes (e.g., differential association).

Co-evolution: evolutionary change in two interdependent populations of two species, where each population changes adaptively and reciprocally in response to changes in the population of the other species, such that evolutionary modifications in one population drive modifications in the other population, and vice versa [77,78].

Co-propagation: linked replication of host and microbiome between host generations, for example, when an endophytic fungus is inherited from the mother through a seed, or a gut microbiome is inherited from a parent by a newborn, uninfected offspring. As microbiome symbionts co-propagate with the host, they necessarily co-propagate also with each other.

Core microbiome: set of microbial taxa that are consistently associated with a host taxon. For example, although many bacterial types can be found in the bee gut, a core microbiome of only eight bacterial types is consistently present in bee guts [62,79].

Direct versus indirect artificial selection: direct artificial selection describes a selection regime where the target of selection (phenotypic trait) is measured directly to select individuals for propagation to the next generation. The particular trait can be genetically correlated to other traits that are not measured, and both the directly selected trait and the correlated traits therefore can respond to selection (i.e., both change in average phenotype between generations). The correlated traits responding to selection are said to be indirectly selected. Sometimes it is easier to select indirectly on a trait [58], for example when the trait