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Note

Home-Field Advantage: Why Host-Specificity is Important for Therapeutic Microbial Engraftment

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Among certain animals, gut microbiomes demonstrate species-specific patterns of beta diversity. This host-specificity is a potent driver of exogenous microbial exclusion. To overcome persistent translational limitations, translational microbiome research and therapeutic development must account for host-specific patterns of microbial engraftment. This commentary seeks to highlight the important implications of host-specificity for microbial ecology, Fecal Microbiota Transplantation (FMT), next-generation probiotics, and translational microbiota research.

Keywords: **Microbiome, probiotics, microbial engraftment, host-specificity, phylosymbiosis**

The gut microbiota is a morphofunctional ecosystem composed of an estimated 10^{14} commensal microbes surrounded by the tissues of the gastrointestinal tract [1]. Recent research highlighted host species-specific patterns of microbiome beta diversity, which play important roles in the health and fitness of their hosts. Within a given species, an individual organism's alpha diversity falls within the boundaries set by its host-specific microbiome. Some host species maintain a microbiome as simple as a single bacterial species, while others develop a complex microbial network [2, 3]. This commentary explores the importance of host-specificity for microbiome research and probiotic development. When paired with mechanistic discussions of microbial ecology and phylosymbiosis (**Box 1**), host-specificity can provide powerful insights into the fundamental processes by which hosts control their gut microbiota, opening new avenues for microbiome research and therapeutic strategies.

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Box 1. Definition of key terms

- Host-specific microbiota: Consistent and unique microbial community patterns associated with the microbiome of a particular host species, stabilized over time and generations.
- Co-speciation: Instance in which the adaptive speciation of a host species dictates the speciation of a symbiotic species.
- Co-evolution: Reciprocal genetic changes and adaptations between interacting organisms which result from selective pressures that each imposes on the other.
- Phylosymbiosis: Concordance between host-specific microbial community structure and the phylogenetic relationships of their hosts, where microbial community structures parallel the phylogeny of their host species.

Phylosymbiosis: Co-evolution or Co-speciation?

The phenomenon of host-specificity was first demon-

strated in a 2013 *Science* paper. Studying *Nasonia* wasps, Brucker and Bordenstein (2013) demonstrated that different species foster unique gut microbiomes. These host-specific microbiomes experience rapid dysbiosis when transferred to another species, producing observable impacts on host health [4]. Host specificity has been observed across a wide variety of animal species, including sponges, insects, and mammals [3]. To understand microbial host-specificity, studies have explored the connections between the host-specific microbiota and the phylogeny of their hosts. These findings have demonstrated that microbiome community structure parallels host phylogeny (**Box 1**) [3, 5].

While studies agree that host-specificity mirrors phylogeny, there is disagreement whether phylosymbiosis is the result of co-evolution or co-speciation (**Box 1**) [6]. Co-evolution would require the existence of mutual pressures between host and microbe. Under co-evolution, both the host and microbe would benefit from promoting adaptation through a mutualistic relationship. However, the microbes which compose the microbiome do not act out of intelligence or benevolence. Microbes seek to grow and reproduce in an advantageous environment. It is the responsibility of the host to modulate their own internal environments, shaping the ecological forces which control microbiome composition. In this way, phylosymbiosis is best considered the result of co-speciation. As adaptive pressures alter the internal environment of hosts, the composition of the microbiome follows suit.

The adaptive origin of host-specificity explains why microbiomes cannot be easily transferred between species. Under standard conditions, exogenous (i.e., non-host-specific) bacteria which attempt to enter the gut microbiome will encounter significant resistance from endogenous microbes, specifically adapted to colonize the gut environment of the host. Since they are not best suited for the host gut environment, exogenous microbes are eliminated [7]. Certain exogenous pathogens have acquired an array of factors (including effector proteins, toxins, and virulence factors of pathogens) to bypass engraftment barriers, overcoming defensive mechanisms of microbial selection [8, 9]. However, even pathogens are limited by host-specificity [10]. The virulence factors which allow pathogenic engraftment are only able to target a limited range of host species. Under co-speciation, pathogens demonstrate that exogenous microbes must possess a targeted engraftment advantage in order to overcome colonization resistance [11]. Host-specificity also shapes the prevalence and activity of opportunistic pathogens - commensal microbes who can negatively impact host wellness under certain gut environmental conditions [12]. Thus, the factors driving host-specificity directly shape pathogen susceptibility and health outcomes [6].

Challenges for Fecal Microbiota Transplantation (FMT)

FMTs provide a new microbiome for patients with microbiome dysbiosis, particularly after antibiotic perturbation or enteric infections. Post-infection FMTs for *Clostridium difficile* have been a particularly well-studied and present decreased risk of re-infection in the hospital setting [13]. However, while FMTs have demonstrated therapeutic value, not all FMTs are equally successful. The degree of similarity between host and donor gut environments shapes how dramatically FMT can shape a recipient's microbiome [14]. Important considerations include endogenous commensal populations, pH and oxygen gradients, gut motility, mucus composition, bacteriophage levels, adaptive and innate immunity, diet, medical interventions, and external environment [3, 13]. Each of these factors plays a direct role in shaping niche availability for incoming colonists. While the exact mechanisms controlling FMT engraftment fall outside the aims of this commentary, host-specificity provides helpful guidance for future FMT research studies.

Challenges for Probiotic Development

Probiotics are a billion-dollar industry. Stores are filled with a wide array of probiotic products which broadly claim to promote gut health. Unfortunately, most of these probiotic products utilize microbes which have been sourced from non-human hosts. While human strains of these microbes may have been associated with positive health outcomes, probiotics are composed of exogenous bacterial strains. Since human gut environments eliminate most exogenous microbial colonists, probiotics have consequently demonstrated poor efficacy and longevity [11, 14–16]. While their goal is to promote "healthy" human microbiomes, few probiotics utilize bac-

terial strains which are tailored for engraftment in the human gastrointestinal tract.

Effective microbiome interventions can only be possible in the context of the ecological, microbial, and host-associated mechanisms which control microbial colonization [11]. We believe that the development of microbiome-modulating therapeutics must utilize endogenous rather than exogenous strains of commensals [17]. A recent example is enlightening: Russell *et al.* (2022) engineered an endogenous *E. coli* isolate to promote alternate bile acid processing [18]. This endogenous strain stably engrafted in the host gut after a single treatment, and produced meaningful metabolic changes in a diabetic mouse model. This approach, driven by host-specificity, holds great promise for next-generation probiotics modulating microbial engraftment.

Challenges for Microbiome Models

Translational microbiome research relies on the use of non-human models; yet mice, rats, dogs, and even non-human primates demonstrate significant host-specificity. Any animal model used for translational microbiome research must therefore take into consideration the biases introduced by host-specificity [19]. It is little wonder that many promising microbiome therapies in animal models fail to produce consistent results when introduced to human trials [20, 21]. Host-specificity also calls into question the efficacy of "humanized" animal models in microbiome research [20, 21]. If human microbes are transferred to germ-free mouse gut, most human commensals fail to engraft. The microbiome environment of each host species is uniquely tailored to a specific microbiome. Interactions between a human microbiome and a mouse host, for example, will be fundamentally distinct from a human microbiome in a human host. A deeper understanding of phylosymbiosis and host-specificity will improve the efficacy of translational microbiome research, and pave the way for novel microbiota-modulating therapeutics.

This commentary seeks to highlight a developing trend in microbiome research: how hosts utilize species-specific mechanisms establish specific patterns of microbial engraftment. We call for a novel approach for microbiome research - experimentally isolating the critical influences on gut microbial communities at a host-specific level. This will require interdisciplinary coordination, consideration of multiple influences on host-specificity, and controlled experimental conditions. By shedding light on how microbiotas are shaped by their host environment, we can develop a clearer view of how microbial engraftment occurs and the mechanisms underlying host-specific microbial selection.

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Conflict of Interest

The authors have no financial conflicts of interest to declare.

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