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Microbial Evolution: An overlooked biomarker of host diet

Nandita Garud[1,2,*]
[1]Department of Ecology and Evolutionary Biology, University of California, Los Angeles, Los Angeles, CA, USA
[2]Department of Human Genetics, University of California, Los Angeles, Los Angeles, CA, USA
*Correspondence: ngarud@ucla.edu
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The evolutionary dynamics of gut microbiota are still being explored. In this issue of *Cell Host & Microbe*, Dapa et al. conduct an experimental evolution study in mice to track the rapid adaptation of the gut microbiome based on host diet.

We humans have come to depend on the trillions of gut microbes inside of us to perform myriad essential functions, including the digestion of the complex plant fibers (Fehlner-Peach et al., 2019) that we otherwise cannot digest ourselves. At the same time, gut microbes depend on the food we eat for their own survival as well. This dependency is reflected in the fact that daily fluctuations in diet can result in daily fluctuations in microbial composition (Johnson et al., 2019) and that richness in diet can predict richness in taxonomic diversity (Sonnenburg et al., 2016). However, although the impact of diet on taxonomic diversity has been extensively studied, an open question has remained unanswered: can diet induce genetic adaptations in the microbiome on human-relevant timescales?

Recent work has shown us that gut microbiota can evolve novel *de novo* mutations in a matter of months (Garud et al., 2019; Zhao et al., 2019). However, it is unknown what the phenotypic consequences of these within-host adaptations are because these studies were conducted in healthy human hosts without any obvious disease or perturbation. Being able to predict how the microbiome will evolve in response to a changed environment and how these evolutionary changes will affect the host could, in turn, aid in the development of high precision and efficacious microbiome-based therapies.

In this issue of *Cell Host & Microbe*, Dapa et al. (2022) perform an experimental evolution study in mice to show that gut microbiota can indeed rapidly adapt *in vivo* to changes in host diet and that these adaptations can have consequences for host health. The authors tracked the evolutionary trajectory of the common human gut commensal *Bacteroides thetaiotaomicron* over three months in mice experiencing three diet regimes: a standard diet (SD: low fat, high fiber), a Western diet (WD: high fat, low fiber), and an alternating diet (AD) of the two. The authors focused on *B. thetaiotaomicron* in this study because of its strong relevance to human diet; it is known to degrade fiber, but, in the absence of fiber, it consumes elements of the mucosal lining of the gut known as mucin O-glycans (Salyers et al., 1977).

Experimental evolution studies like the one performed by the authors in replicate mice provide the ability to finely control the environment and ecological composition of the microbiome, enabling the statistical resolution to quantify the repeatability and rapidity of evolution that otherwise would be difficult to measure in human microbiomes. In particular, it is possible to perturb each replicate mouse's microbiome in a systematic manner to identify targets of natural selection that evolve repeatedly in parallel across microbiomes.

In the three-month time span studied, the mice evolved 73 parallel mutations. Some of the adaptations were specific to a diet-specific regime, whereas many were found in 2 or more regimes. Upon further investigation, the authors found that two of these adaptations confer a growth advantage in the presence mucin O-glycans, indicating that the nutrient-poor Western diet causes *B. thetaiotaomicron* to adapt to more efficiently to subsist on our gut lining, which could have profound implications for our gut health (Figure 1). This remarkable finding suggests that there is a tight host-microbe connection in which the nutrients provided by the host impact the evolution of microbes, and the evolution of microbes in turn have the potential to impact host physiology.

Among the targets of adaptation identified across treatments were genes in the SusC and D families, which are implicated in polysaccharide utilization. This family of genes intriguingly has also shown up as a target of recurrent positive selection in other recent studies in healthy humans (Zhao et al., 2019; Chen and Garud,

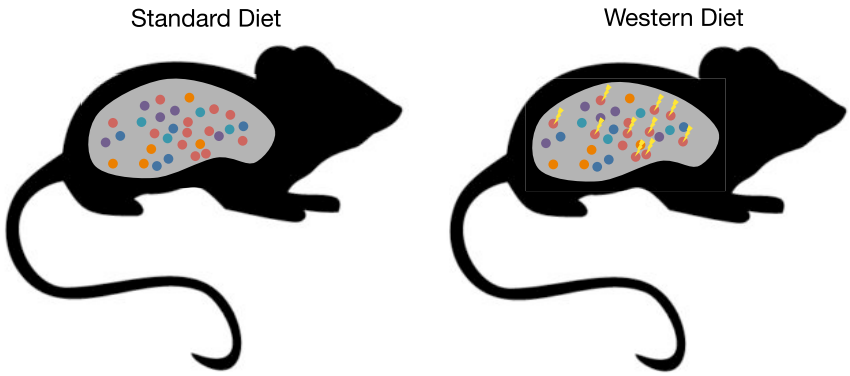

Figure 1. Adaptation of gut microbiota in response to diet
B. thetaiotaomicron (red circles) evolves new genetic adaptations (yellow thunderbolts) in the presence of a high-fat and low-fiber Western diet.

2021), indicating that they could play a central role in responding to rapidly fluctuating nutrient conditions. Interestingly, the AD regime experienced the highest levels of adaptation and, moreover, had the greatest levels of genetic diversity. It is similarly likely that the average human gut experiences variable environments, contributing to high levels of genetic diversity.

The authors perform several analyses to demonstrate the relative importance of the evolutionary adaptations they discovered. In comparison with metabolites and species abundances, changes in allele frequencies are more strongly correlated with fluctuating diets. The authors also show that adaptations have a higher level of association with metabolites than species abundances, further underscoring the higher resolution that genetic variation provides over species.

Intriguingly, the authors found that they could retroactively distinguish between mice undergoing different dietary regimes with the adaptations in their *B. thetaiotaomicron* populations. These adaptations were in fact equally if not more predictive of the dietary regime than were species abundances or metabolites. Thus far, predictive studies of host phenotypes in the microbiome using machine-learning approaches have relied primarily on taxonomic abundances as input features (Pasolli et al., 2016) and have not incorporated microbiome genetic information despite genetic variants having potentially high functional importance. Being able to predict host phenotypes with microbiome genotypes and evolutionary changes could one day help to guide targeted diagnoses and intervention, given that current therapeutics still have variable efficacies and do not incorporate information about the genetic composition of the strains being included in a fecal microbiome transplant.

Dapa et al.'s results are remarkable because they show that the evolutionary adaptations of the gut microbiome are a bona fide biomarker of diet. Now the authors have opened the door to examining connections between microbiome genotypes and other host phenotypes. Can we start to make similar kinds of inferences in humans to understand why we harbor so much diversity at a nucleotide level in our microbiomes (Schloissnig et al., 2013) and how this diversity impacts our health? The answers to these questions in the coming years will enable a deeper understanding at the nucleotide level of the mechanisms by which our microbiomes confer health and disease in human hosts.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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