Host genetics influence the gut microbiome

Longitudinal data from nonhuman primates reveal widespread gut microbiome heritability

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The influences of the microbiota on host physiology are so pervasive that the microbiota has been hypothesized to play a critical role in host evolution by shaping key host phenotypes (1). However, to contribute to host evolution, traits must be transmitted across generations. One way to assess whether some or all microbes are influenced by the genetic composition of the host, and therefore conserved across generations, is by measuring heritability. Host species-specific patterns in the composition of the microbiome—the genetic content of the microbiota—suggest there is some degree of heritability in the microbiota (2). However, studies evaluating variation in the microbiota and host genetics within a single host species have generally reported low heritability for a small proportion of microbial taxa (3). On page 181 of this issue, Grieneisen et al. (4) reject this common conclusion by demonstrating that most gut microbiota traits in wild baboons exhibit some degree of heritability.

Grieneisen et al. analyzed fecal samples from 585 yellow baboons (Papio cynocephalus, some of them admixed with anubis baboons, P. anubis) from 10 free-ranging social groups sampled longitudinally across 14 years in Amboseli National Park, Kenya. They determined the microbial composition of each sample and defined 1134 microbiome traits (i.e., relative abundance and presence or absence of microbial taxa, and measures of overall microbiome composition). Then they used kinship data and environmental data, including rainfall, social interactions, and group-level diet, to calculate heritability (the proportion of the variation of a trait attributable to genetic variance as opposed to environmental factors) of each of these microbiome traits with a standard formula used for nonmicrobial traits in livestock and wild animals. The scale of this dataset is currently unmatched in any host-microbe system, which may explain why previous estimates of microbiome heritability have been so low.

Most microbiome studies, including those of humans, analyze a small number of samples or target populations at a single point in time. When Grieneisen et al. subsampled their dataset to simulate smaller sample sizes, or sampling at a single time point, most signals of microbiome heritability were not detected. Without data from multiple time points and a large number of individuals to account for stochasticity as well as temporal variation in host environments and the microbiota, it is difficult to accurately estimate microbiome heritability. Therefore, microbiome heritability is likely higher than reported previously in most host species, including humans.

Estimating heritability of the microbiota under natural conditions is essential to advancing knowledge of the extent to which the microbiota affects host ecology and evolution. However, measuring heritability of the microbiota is difficult because there are many environmental variables at play. As Grieneisen et al. demonstrate, nonhuman primates provide a strong but currently underutilized system for addressing this challenge. In addition to being genetically closely related to humans, the ecology of nonhuman primate populations is extensively studied and several populations, such as the Amboseli baboons, have decades of relevant data.

Such long-term studies that follow known individuals across their lives (5) give primatologists an unmatched ability to collect detailed, longitudinal data describing environment, diet, and individual behavior, as well as noninvasive biological samples. Furthermore, a diversity of physiological and behavioral adaptations to a range of environments exists within the Primates order, allowing targeted testing of specific host-microbe interactions with different primate species and populations. Baboons represent an excellent general model for the human microbiota because previous research has demonstrated that humans share more microbiome traits (e.g., taxonomic and functional profiles) with baboons than chimpanzees (6). However, comparative data collected from a variety of primate taxa could reveal underlying mechanisms that maintain specific associations between host genetic traits and particular components of the primate gut microbiota.

Despite reporting evidence of heritability in the majority of microbiome traits they assessed, Grieneisen et al. also show that a larger proportion of variation in microbiome data is attributable to environmental factors rather than host genetic factors, as has been shown consistently across studies in other systems (3). Furthermore, estimates of microbiome heritability varied between dry and wet seasons, and with diet and host age, as a result of changing environmental contributions to microbiome traits.
REFERENCES AND NOTES
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INSIGHTS | PERSPECTIVES

Boosting stem cell immunity to viruses
A newly discovered isoform of Dicer protects stem cells by enhancing antiviral RNA interference

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Mammalian stem cells exhibit deficiencies in innate immunity regulated by interferons (IFNs), so they rely on constitutive expression of some IFN-stimulated genes (ISGs) (1) and Argonaute 2 (AGO2)–dependent RNA interference (RNAi) (2, 3) for antiviral protection. Mammalian antiviral RNAi is initiated by Dicer, which processes viral double-stranded RNA (dsRNA) replicative intermediates into small interfering RNAs (siRNAs) that act as specificity determinants for viral RNA cleavage by RNA-induced silencing complex ([RISC] which contains AGO2) (2–10). However, it remains unclear how stem cells activate antiviral RNAi because deletion of Dicer paradoxically enhances virus resistance in mouse embryonic stem cells (11). On page 231 of this issue, Poirier et al. (12) show that mouse and human stem cells have a specialized Dicer isoform for virus-derived siRNA (vsiRNA) production to initiate potent antiviral RNAi. This further indicates that siRNA therapeutic strategies may be viable for RNA viruses such as Zika virus (ZIKV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Similar to Caenorhabditis elegans nematodes (13), mammals encode a single Dicer ribonuclease (RNase) that is responsible for the biogenesis of both microRNAs from their stem-loop precursor transcripts and siRNAs from long dsRNA. Dicers have an amino-terminal helicase domain and tandem RNase III domains as well as additional domains between them, such as the RNA-binding PAZ domain (see the figure). Helicase domains of Dicers and mammalian retinoic acid–inducible gene 1 (RIG-1)–like receptors that trigger IFN-regulated immune responses are highly homologous and contain a distinct helicase-insertion subdomain (Hel2i). The study by Poirier et al. began with discovering an alternatively spliced mouse and human Dicer messenger RNA (mRNA) from embryonic, neuronal, and tissue stem cells. These transcripts contain an in-frame deletion of exons 7 and 8 so that Hel2i is absent. Poirier et al. demonstrate that RNAi initiated by this Dicer isoform, designated antiviral Dicer (aviD), protects mouse stem cells from infections with the RNA viruses ZIKV and SARS-CoV-2.

The authors found that the loss of Hel2i enhances avID processing of long dsRNA into siRNAs without impairing its ability to generate microRNAs. Notably, ZIKV and another RNA virus, Sindbis virus, replicated to lower amounts in human cells forced to express avID. Moreover, the antiviral activity of avID was abolished by depletion of AGO2 or ectopic expression of the viral suppressor of RNAi (VSR) encoded by Nodamura
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