PHOTO: TOM MANGELSEN/MINDEN PICTURES

Sampling 585 yellow baboons across 14 years in the Amboseli National Park, Kenya, demonstrates that most gut microbiota traits exhibit some degree of heritability.

GENOMICS

Host genetics influence the gut microbiome

Longitudinal data from nonhuman primates reveal widespread gut microbiome heritability

By **Liliana Cortes-Ortiz**[1] *and* **Katherine R. Amato**[2]

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 microbi-

[1]Department of Ecology and Evolutionary Biology, University of Michigan, Ann Arbor, MI, USA. [2]Department of Anthropology, Northwestern University, Evanston, IL, USA. Email: katherine.amato@northwestern.edu

ome variation. These results highlight the plastic nature of the gut microbiota, which could allow it to play a role in facilitating rapid, local adaptation in hosts. However, the mechanisms by which these interactions occur remain unclear. The resolution of data for a single time point or individual precluded Grieneisen *et al*. from empirically identifying which environmental factors or host behaviors were driving temporal patterns in heritability.

A key next step will be to improve host genomic resolution to identify the specific genomic regions and mechanisms through which associations between host genetics and the microbiota occur. Although some of these types of studies are being conducted for humans (*7*), studies of natural populations of other mammalian taxa would help identify generalizable principles that underlie host genetic-microbiota associations. For example, in hybrid zones of genetically and microbially divergent host species (*8, 9*), the study of paired microbiome and host genomic data for individuals with a range of admixed genotypes could help identify specific associations. Knowledge of the mechanisms shaping interactions between host genetics and gut bacterial communities will be critical for generating testable hypotheses for other body sites (e.g. skin, mouth, urogenital tract) and other microbial community members (e.g., microscopic eukaryotes, viruses). Similarly, improving resolution of data describing the microbiota will allow testing of the taxonomic specificity at which these interactions occur as well as the extent to which microbial taxonomy or functions are more strongly associated with host genetics. Technological advances are making it easier and more affordable to generate microbial whole-metagenome data. Together with the development of analytical tools to study the dual genomic composition of hosts and their microbiota in nonmodel organisms, these data will shift explorations of microbial influences on host evolution from correlation and theory to causation and mechanism. ■

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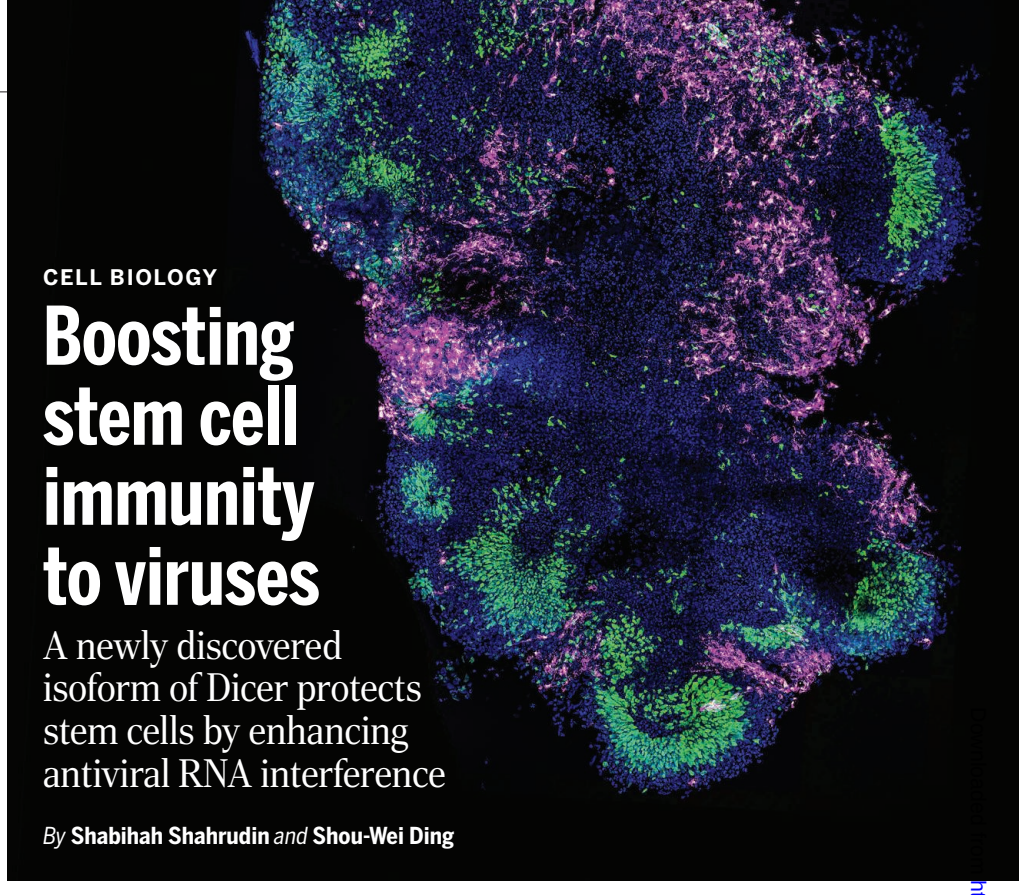

CELL BIOLOGY

Boosting stem cell immunity to viruses

A newly discovered isoform of Dicer protects stem cells by enhancing antiviral RNA interference

By **Shabihah Shahrudin** *and* **Shou-Wei Ding**

In the absence of antiviral Dicer, neural stem cells (green) in mouse brain organoids are more susceptible to SARS-CoV-2 infection (magenta).

PHOTO: POIRIER *ET AL*. (*12*)

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-I)–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

Department of Microbiology and Plant Pathology, College of Natural and Agricultural Sciences, University of California, Riverside, CA, USA. Email: shou-wei.ding@ucr.edu

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