UC San Diego
UC San Diego Previously Published Works

Title

Gut microbiota through an evolutionary lens

Permalink

Journal

ISSN

Authors

Carmody, Rachel N
Sarkar, Amar
Reese, Aspen T

Publication Date

DOI

Peer reviewed

MICROBIOLOGY

Gut microbiota through an evolutionary lens

Reversing some industrialization-related changes in the human gut microbiota may be risky

By **Rachel N. Carmody**[1], **Amar Sarkar**[1], **Aspen T. Reese**[2]

Although the human genome adapts on slow time scales, there is mounting evidence that industrialized lifestyles have rapidly changed the human gut microbiome (*1*, *2*). Conceptions of health-diminishing biological incompatibility ("mismatch") arising from the disruption of human-microbe relationships negotiated over evolutionary time have led to proposals that the altered microbiota contributes to high rates of noncommunicable disease (*3–6*) and related calls to restore aspects of the ancestral gut microbiota through "rewilding" (*4*). However, appropriate applications of rewilding remain uncertain because the idea does not easily reconcile with present evidence or predictions rooted in evolutionary theory. In particular, high microbial plasticity may underpin an industrialized gut microbiota that is reasonably well adapted to the industrialized environment, even if it is then less well matched with the host. Complex tripartite human-microbiota-environment interactions present an unsolved puzzle for human health: When is it better for the gut microbiota to track versus resist environmental change?

Certain aspects of industrialized lifestyles, such as antibiotic use, have doubtless exerted strong pressure on human-microbe interactions. Although humans have always been exposed to environmental and diet-derived antimicrobial compounds, the nature and doses of antimicrobials encountered today in industrialized societies can contribute to chronic disease (*6*). However, although an altered microbiota may foster disease, it does not necessarily follow that health will improve upon restoring a preindustrial (ancestral) microbial state through interventions such as replacing lost gut microbial taxa, engineering microbes to perform depleted functions,

or transplanting whole gut microbial communities from donors in nonindustrial societies.

Implicit in the concept of ancestral microbiota restoration are the assumptions that the ancestral microbiota can be accurately characterized, that it promotes health, and that microbial manipulations have predictable phenotypic effects. In addition, the underlying premise that digression from evolutionarily relevant conditions compromises health assumes that natural selec-

tion elicits health, that human-microbiota mismatch has net-negative consequences, and that efforts to reestablish an ancestral microbiota in industrialized populations would reduce mismatch. The present lack of theoretical or empirical consensus on these points highlights the uncertainties involved in ancestral gut microbiota restoration.

A practical problem for restoration efforts lies in defining an ancestral microbiota. Direct assessment of historic gut microbiotas from mummies or coprolites is becoming increasingly feasible (*7*), but insights to date have been limited by low data quality. As an alternative, modern hunter-gatherers and other rural, nonindustrialized populations have been used as ancestral stand-ins (*1*, *3*). However, it remains unclear whether the gut microbiotas of these living populations mimic ancestral profiles. All of the best-studied populations, including the Hadza of Tanzania, have routine access to agricultural and pharmaceutical products and are visited year-round by researchers from industrialized populations. Additionally, gut microbiotas could potentially vary between different nonindustrialized populations as much as, if not more than, they vary between industrialized and nonindustrialized populations (*1*). The same may have been true of ancestral microbiotas, making it difficult to define a target restoration community.

There is minimal evidence that microbial traits typically associated with nonindustrialized populations (and thus assumed to be present in an ancestral microbiota) promote health. For example, the relatively low numeric diversity of taxa and functions observed in many industrialized microbiotas has been argued to reflect a disease-associated imbalance. Although lower diversity has been observed in several disease states (*8*), causality remains unclear, and evidence that high diversity is beneficial is also lacking. Indeed, high diversity is theoretically predicted to be destabilizing (*9*). Taxon-level signatures also fail to uphold nonindustrialized profiles as uniformly healthier. For example, bifidobacteria, which are abundant in industrialized infant guts, appear to

Industrialized gut microbiota

Industrialization could affect human-microbiota-environment interactions in several ways, leading to different hypothetical effects on human health with downstream implications for rewilding the gut through ancestral microbiota restoration. Outcomes may differ based on the degree to which humans can direct (canalize) microbiota plasticity and changes in the industrialized environment to promote health.

Hypothetical "perfect" match
Area of triangle = 0
No incompatibility with respect to human health
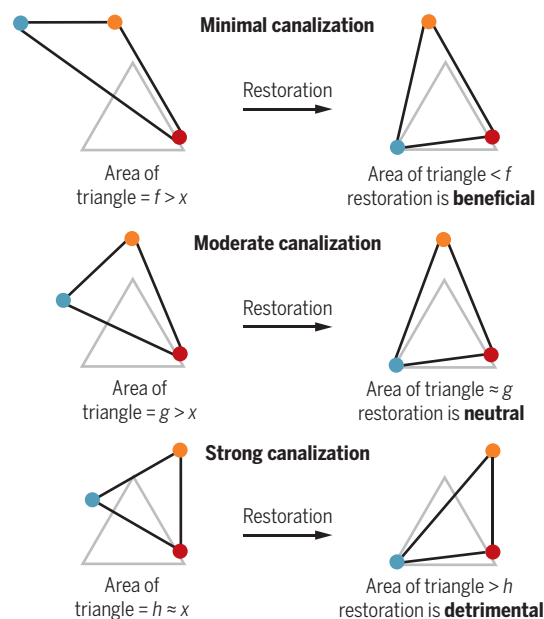
Hypothetical ancestral state
Area of triangle = $x > 0$
Geometry unknown, shown here as equilateral

● Microbiota   ● Environment   ● Humans

Effects of industrialization on human health | **Implications of ancestral microbiota restoration**

Minimal canalization
Restoration
Area of triangle = $f > x$
Area of triangle $< f$ restoration is **beneficial**

Moderate canalization
Restoration
Area of triangle = $g > x$
Area of triangle $\approx g$ restoration is **neutral**

Strong canalization
Restoration
Area of triangle = $h \approx x$
Area of triangle $> h$ restoration is **detrimental**

The sides of the triangle represent the degree of health-relevant incompatibility. The area of the triangle represents the overall degree of systemic mismatch.

[1]Department of Human Evolutionary Biology, Harvard University, Cambridge, MA, USA. [2]Division of Biological Sciences, Section of Ecology, Behavior, and Evolution, University of California, San Diego, La Jolla, CA, USA. Email: carmody@fas.harvard.edu; areese@ucsd.edu

be absent among infants in some nonindustrialized populations (10). Bifidobacteria also appear to be less abundant in nonindustrialized populations after infancy (1). Whether their prevalence in industrialized populations results from reduced exclusion by environmental microbes or adaptive enrichment (10), bifidobacteria are widely regarded as beneficial for immunity, prompting their current exploitation as probiotics.

A substantial problem facing all microbiota-targeted health interventions is that the phenotypic effects of the microbiota may be beneficial in one environment or individual but detrimental in others. For example, *Prevotella copri*, a fiber-degrader enriched in gut microbiotas from nonindustrialized populations, has shown both benefits for glucose tolerance and the propensity to exacerbate chronic inflammatory conditions, depending on context (11). In addition, although nonindustrialized microbiotas are generally enriched in the capacity to ferment fiber into short-chain fatty acids (SCFAs) that confer diverse metabolic and immune benefits (3), SCFAs can lead to context-specific developmental trade-offs with anticipated pleiotropic effects (12), promote weight gain through increased energy salvage, and contribute to the progression of Parkinson's disease (13). Similarly, two individuals could exhibit divergent responses to rewilding the gut microbiota depending on idiosyncratic factors such as parasite and viral burden, immune training, and various other gene-environment interactions.

Rewilding proposals embrace the idea that there was a time in our evolutionary past when humans were better matched to the combination of environmental and microbial conditions, but this is not necessarily the case (see the figure). Increases in both population growth and longevity with industrialization challenge this idea, and industrialization itself arose from human-directed niche construction that may be beneficial, on balance. The extent to which humans have been able to canalize (or, direct and entrain) the manifold environmental changes of industrialization to promote health remains unknown, but the burden of infectious diseases has generally decreased while the burden of noncommunicable disease has increased.

Likewise, it is unknown to what extent humans have been able to control industrialization-related changes in the microbiota. Human-microbiota interactions reflect a dynamic balance between the competing fitness interests of myriad microbial taxa and the host. Industrialization is expected to have forced gut microbes into a new state that balances fresh inputs from the host and environment while humans have presumably responded by canalizing these plastic microbial changes to the extent possible to minimize any negative consequences for fitness, as has been illustrated in many animal models (14). Humans certainly possess mechanisms to beneficially control the microbiota: For example, the encroachment of gut microbes into the small intestine is restricted by pH gradients, breast milk oligosaccharides shape microbial inputs to the infant immune system, and immunological responses are mounted to specific microbial products. If humans are able to exert some degree of control over changes in the microbiota, then host-microbe interactions in industrialized populations may be less detrimental than is often assumed.

Indeed, where the human capacity to canalize microbiota responses is substantial, the ability of the gut microbiota to adapt rapidly to environmental change raises the distinct possibility that, in industrialized populations, existing gut microbial profiles could allow health to a greater degree than nonindustrialized ones (see the figure). In such cases, restoring the gut microbiota to an ancestral-like state could inadvertently prove detrimental rather than beneficial.

Although ancestral gut microbiota restoration has been proposed as a possible preventative measure or treatment for noncommunicable disease (3–6), an evolutionary lens suggests fundamental challenges. For example, even in ancestral states, the capacity of humans to control the microbiota and microbiota-environment interactions to sustain health is expected to have weakened over the life course. This is because natural selection favors health only to the extent that health increases reproductive success, which declines with age. Indeed, natural selection will favor traits that exacerbate morbidity and mortality later in life if those same traits enhance fertility earlier in life, a legacy that may contribute to explaining associations between early menarche and breast cancer or between the lifetime number of viable pregnancies and metabolic disease (15). Thus, even if ancestral human-microbiota relationships are effectively restored, they may have limited power to ameliorate noncommunicable diseases that reach highest prevalence at older ages.

An evolutionary lens can also illuminate complementary hypotheses that advance our understanding of why human-microbe interactions have responded to industrialization as they have. For example, microbial genes for metabolizing complex carbohydrates are waning in the industrialized microbiome (3–5). This phenomenon could be viewed as an unfortunate loss of host-adapted microbes (3–5), or this loss might be viewed as metagenomic streamlining in which underutilized functions are lost while those more important in the current environment are retained. Notably, the microbes driven seasonally to undetectable levels in the Hadza were those most likely to be rare in industrialized populations, implying that ecology contributes to these differences (1).

Even problematic host-microbiota interactions can be appreciated as adaptive responses. For example, in the case of early-life antibiotic exposure and obesity (6), an evolutionary lens suggests that early-life microbiota disruption could falsely signal a volatile or resource-poor environment. Like early-life malnutrition or chronic stress, gut microbiota disruption might be expected to initiate developmental trade-offs favoring resource sparing that then contribute to obesity in resource-rich environments (12).

Competing fitness interests and the higher plasticity of the gut microbiota versus the human host establishes human-microbiota-environment mismatch as an omnipresent condition, both in the past and today, with variable and sometimes unpredictable effects on human health. To most effectively manipulate the gut microbiota in the service of health, the challenge is to disentangle which aspects of health are promoted by matching the microbiota more closely to the host, to the environment, or, to a lesser extent, to both. It is clear that restoration will require a scalpel, not sledgehammer, approach. Advances will be accelerated by basic research addressing the human capacity to canalize microbial and environmental change, coupled with efforts to catalog, characterize, and preserve human-associated microbes both outside industrialized contexts (2, 5) and within them.

There will doubtless be scenarios where gut microbiota restoration will improve health in industrialized populations, but consideration of the sources of mismatch and their complex dynamics is necessary before pursuing targets for intervention. ∎

REFERENCES AND NOTES

1. S. A. Smits *et al.*, *Science* **357**, 802 (2017).
2. M. Groussin *et al.*, *Cell* **184**, 2053 (2021).
3. E. D. Sonnenburg, J. L. Sonnenburg, *Nat. Rev. Microbiol.* **17**, 383 (2019).
4. J. L. Sonnenburg, E. D. Sonnenburg, *Science* **366**, eaaw9255 (2019).
5. M. G. Dominguez Bello *et al.*, *Science* **362**, 33 (2018).
6. M. J. Blaser, *Science* **352**, 544 (2016).
7. C. Warinner *et al.*, *Annu. Rev. Genomics Hum. Genet.* **18**, 321 (2017).
8. C. Duvallet *et al.*, *Nat. Commun.* **8**, 1784 (2017).
9. K. Z. Coyte *et al.*, *Science* **350**, 663 (2015).
10. F. A. Ayeni *et al.*, *Cell Rep.* **23**, 3056 (2018).
11. R. E. Ley, *Nat. Rev. Gastroenterol. Hepatol.* **13**, 69 (2016).
12. I. Kimura *et al.*, *Science* **367**, eaaw8429 (2020).
13. T. R. Sampson *et al.*, *Cell* **167**, 1469 (2016).
14. K. R. Foster *et al.*, *Nature* **548**, 43 (2017).
15. G. Jasienska *et al.*, *Lancet* **390**, 510 (2017).

Science

Gut microbiota through an evolutionary lens

Rachel N. Carmody, Amar Sarkar and Aspen T. Reese

ARTICLE TOOLS	http://science.sciencemag.org/content/372/6541/462
REFERENCES	This article cites 15 articles, 6 of which you can access for free http://science.sciencemag.org/content/372/6541/462#BIBL
PERMISSIONS	http://www.sciencemag.org/help/reprints-and-permissions