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Review

The Co-evolution of the Human Host and Commensal Microbiota in the Modern World

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Abstract

We comment on the co-evolution of the human host and commensal microbiota in the aspects of the evolutionary foundations and complexities of the holobiont, evolutionary mismatch and the "Old Friends" hypothesis, dietary extinctions and the vanishing microbiome, antibiotic perturbations and alternative stable states, the emergence of pathobionts and inflammation-driven gene transfer, and the future of the holobiont: precision microbiome engineering.

Key words: Co-evolution; human host; commensal microbiota; holobiont; precision microbiome engineering.

1. The Evolutionary Foundations and Complexities of the Holobiont

The human body functions not as a solitary genetic entity but as a densely populated holobiont—an integrated ecological network comprising the host genome and the diverse, metabolically active genomes of trillions of symbiotic microorganisms. For millions of years, humans and their gastrointestinal microbiota have navigated a shared evolutionary trajectory. The depth of this co-evolutionary partnership is evidenced by recent large-scale metagenomic analyses spanning diverse global populations. Systematic comparisons of host and microbial phylogenies reveal that specific bacterial lineages, such as certain Bifidobacterium and Prevotella strains, have codiversified alongside human populations as they migrated out of Africa (1). As a testament to this profound evolutionary intimacy, species exhibiting the strongest signals of codiversification have independently evolved traits indicative of irreversible host dependency, including drastically reduced genomic architectures and extreme sensitivity to ambient oxygen and temperature (1).

However, the mechanisms drivingg this host-microbe co-evolution are highly complex and currently the subject of rigorous academic debate.

While strict vertical transmission and partner fidelity provide one explanation for parallel evolutionary histories, competing evolutionary models highlight the immense plasticity of the gut ecosystem. Recent high-resolution strain tracking indicates that geographic isolation and environmental filtering may play a more dominant role in microbial strain divergence than host genetics (2). Furthermore, the human gut is a hotspot for genetic exchange. Commensal genomes are highly dynamic, with in situ homologous recombination introducing variation at rates substantially higher than spontaneous mutation (3). This implies that while the taxonomic structure of the microbiome may track with human evolutionary history, the genetic composition of circulating microbial strains is continuously overwritten by environmental acquisition and horizontal gene flow. Regardless of the precise interplay between strict codiversification and environmental acquisition, the functional reliance of the human host on its ancestral microbial partners remains absolute. The overall framework linking host–microbe co-evolution, modern evolutionary mismatch, microbiota depletion, pathobiont expansion, and precision microbiome engineering is summarized in Figure 1.

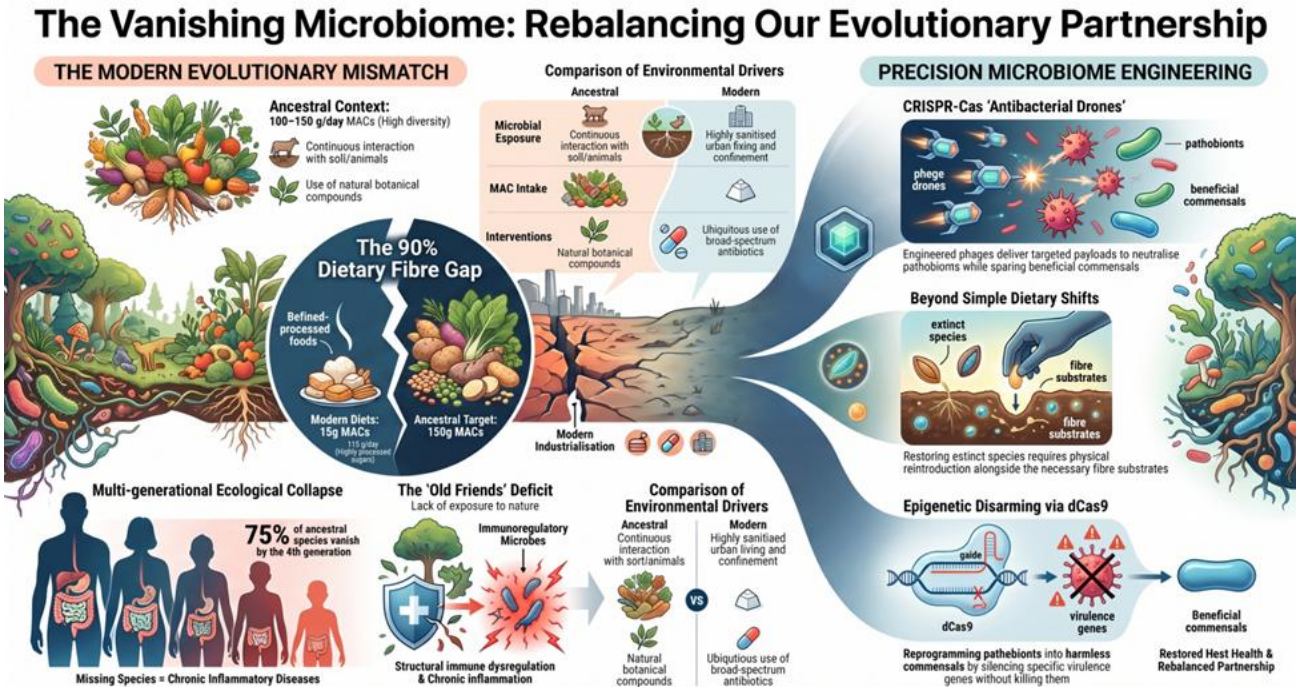


Figure 1. The Vanishing Microbiome: Rebalancing Our Evolutionary Partnership.

2. Evolutionary Mismatch and the "Old Friends" Hypothesis

The rapid environmental transformations catalyzed by the Neolithic Revolution, and subsequently accelerated by modern industrialization, occurred at a pace far exceeding the adaptive capacity of the human genome. This temporal discrepancy has resulted in an evolutionary mismatch, wherein traits and physiological dependencies that were highly advantageous in an ancestral setting become distinctly maladaptive in the modern world (4).

This mismatch is profoundly evident in the ontological development of the human immune system. According to the "Old Friends" hypothesis, which serves as a refined, evolutionary framework for the earlier hygiene hypothesis, the mammalian immune system evolved in continuous obligatory contact with specific commensal microbiota, environmental saprophytes, and macro-parasites like helminths (4). Because these organisms were ubiquitous in the ancestral Paleolithic environment, the immune system learned to tolerate them, eventually outsourcing essential regulatory functions to these microbial inputs (4). These "Old Friends" act as essential adjuvants, providing the continuous low-level stimulation required to induce regulatory T cells (Tregs). Tregs are critical for maintaining immunological tolerance, dampening background inflammation, and preventing the immune system from mounting destructive responses against harmless environmental allergens, native gut contents, or the host's own tissues (4).

The transition to industrialized, highly sanitized urban lifestyles—characterized by purified water, a lack of contact with diverse soil microbiomes, rising rates of cesarean deliveries, and modern architectural confinement—has fundamentally severed humanity's exposure to these immunoregulatory microbes (4). Deprived of the microbial data necessary to calibrate its inflammatory software, the modern immune system is left structurally dysregulated. This immunological mismatch is recognized as a primary driver of the sweeping epidemiological increases in chronic inflammatory disorders, ranging from asthma and allergic rhinitis to systemic autoimmune conditions and inflammatory bowel disease (IBD) (4). The principal drivers of evolutionary mismatch and their physiological consequences are summarized in Table 1.

3. Dietary Extinctions and the Vanishing Microbiome

Beyond the loss of environmental microbes, the industrialized diet constitutes a profound ecological shock to the native gut microbiome. The ancestral human diet, closely mirrored by contemporary traditional hunter-gatherer populations such as the Hadza of Tanzania, relies heavily on wild-foraged, fiber-rich plant materials. The Hadza consume upward of 100 to 150 grams of dietary fiber daily, and their gut microbiomes exhibit a remarkable degree of plasticity (5). Longitudinal profiling demonstrates that the Hadza microbiome undergoes robust seasonal cycling; specific microbial taxa and carbohydrate-active enzymes expand dramatically during the dry season, characterized by hunting and the consumption of fibrous tubers, and contract during the wet season, when the diet shifts toward berries and honey (5).

Table 1. Major drivers of evolutionary mismatch between ancestral and modern industrialized contexts.

Driver of Evolutionary Mismatch	Ancestral (Hunter-Gatherer) Context	Modern Industrialized Context	Physiological And Ecological Consequences
Environmental Microbial Exposure	Continuous interaction with soil, untreated water, and diverse animal vectors; high maternal transmission.	Highly sanitized urban living; indoor confinement; water filtration; increased cesarean birth rates.	Deficient regulatory T cell (Treg) induction; loss of immunological tolerance; exponential rise in autoimmune and allergic diseases.
Dietary Carbohydrate Intake	High consumption of diverse microbiota-accessible carbohydrates (MACs) (100–150 g/day); seasonal dietary cycling.	Low MAC intake (15 g/day); diets dominated by highly processed simple sugars and saturated fats.	Starvation of keystone fiber-degrading commensals; irreversible multi-generational loss of microbial diversity.
Antimicrobial Interventions	Exposure limited to naturally occurring botanical compounds; rare disruption of the gut ecosystem.	Ubiquitous use of broad-spectrum antibiotics, often beginning in early infancy.	Rapid depletion of microbial diversity; collapse of colonization resistance; expansion of opportunistic pathobionts.

In stark contrast, the modern Western diet is severely deficient in these microbiota-accessible carbohydrates (MACs), providing an average of only 15 grams per day (6). Because MACs serve as the primary carbon and energy source for the distal gut microbiota, their absence exerts an immense selective pressure that effectively starves the symbiotic ecosystem (6). When the primary energy substrate is removed, the gut microbiota is forced to shift its metabolism, sometimes turning to host-derived mucin glycoproteins, thereby degrading the protective colonic mucus barrier and heightening pathogen susceptibility (7).

More alarmingly, the loss of MACs drives systemic microbial extinctions that compound over time. Experimental models utilizing humanized mice demonstrate that transitioning to a low-MAC diet reduces the abundance of over 60% of commensal taxa within weeks (6). When this low-MAC diet is sustained across multiple generations—mimicking the multi-generational dietary shifts of industrialized human societies—the ecological damage becomes permanent (6). By the fourth generation of dietary fiber deprivation, nearly three-quarters of the ancestral bacterial species are entirely lost (6). Once these critical taxa are driven to extinction within an isolated host lineage, simply

reverting to a high-fiber diet is insufficient to restore the lost diversity (6). The physical reintroduction of the missing microbes, alongside the necessary MACs to sustain them, is required to recover the ancestral ecological state (6). This multi-generational attrition provides a compelling mechanistic explanation for the globally observed phenomenon of the "disappearing microbiome" in modernized nations (8).

4. Antibiotic Perturbations and Alternative Stable States

Compounding the effects of dietary starvation is the ubiquitous application of broad-spectrum antibiotics. While antibiotics are one of the most critical interventions in modern medicine, their ecological collateral damage on the gut holobiont is severe. The administration of common oral antibiotics, such as ciprofloxacin, induces a profound and rapid collapse of the commensal community, characterized by an immediate loss of taxonomic diversity and a dramatic shift in community composition within days of initial exposure (9).

While the gut ecosystem exhibits a certain degree of baseline resilience, high-resolution temporal tracking reveals that microbial recovery post-antibiotic treatment is frequently incomplete (9). Instead of returning to its precise ancestral equilibrium, the distal gut microbiota often stabilizes into a distinctly altered, alternative stable state (9). This regimen shift frequently involves the permanent loss of specific keystone species and a reduction in the community's overall functional redundancy. Repeated exposures, particularly those occurring during the critical developmental windows of early childhood, further ratcheting down diversity and have been epidemiologically linked to long-term metabolic and immunological sequelae, including childhood obesity, asthma, and altered systemic immune responses (8).

The most immediate danger of this antibiotic-induced perturbation is the collapse of colonization resistance. In a healthy state, the dense, diverse commensal microbiota outcompetes incoming pathogens for colonization niches and scarce nutrients, while simultaneously producing inhibitory compounds such as short-chain fatty acids (SCFAs) and bacteriocins (10). When broad-spectrum antibiotics obliterate this protective shield, the intestinal real estate becomes highly vulnerable to pathogenic invasion and the aggressive expansion of indigenous pathobionts (9).

5. The Emergence of Pathobionts and Inflammation-Driven Gene Transfer

Pathobionts are opportunistic members of the microbiota that reside harmlessly as minority constituents under homeostatic conditions, but which exploit ecological disturbances to trigger profound local and systemic pathology (11). Classical examples include toxin-producing Clostridioides difficile and adherent-invasive Escherichia coli (AIEC) (11). Unlike obligate pathogens acquired from external sources, pathobionts are native components of the holobiont that have evolved to capitalize on evolutionary mismatches, thriving when the competitive pressures of the commensal network are removed (11).

The unchecked expansion of pathobionts initiates a catastrophic feedback loop centered on intestinal inflammation. Inflammatory responses—whether induced by a primary infection, immune dysregulation (such as in IBD), or an aberrant reaction to a Western diet—radically alter the luminal environment. Inflammation generates reactive oxygen and nitrogen species, effectively disrupting the strict anaerobiosis of the distal colon and selectively favoring the growth of facultative anaerobes, particularly those within the Enterobacteriaceae family (12).

This inflammation-driven bloom transforms the gut from a stable commensal bioreactor into a highly volatile evolutionary crucible. Under normal conditions, the high density of obligate anaerobes and the presence of inhibitory metabolites suppress bacterial conjugation, making horizontal gene transfer (HGT) a relatively restricted event (12). However, when inflammation triggers parallel blooms of pathogenic and commensal Enterobacteriaceae, these species are brought into intimate physical contact at unprecedented densities (12).

Experimental models using Salmonella enterica serovar Typhimurium perfectly illustrate this dynamic. Salmonella utilizes its Type Three Secretion System-1 (TTSS-1) to actively trigger host inflammation, which suppresses competing commensals and fuels its own growth alongside native E. coli (13). Within this inflamed environment, the conjugative horizontal transfer of plasmids—such as the colicin plasmid p2—surges dramatically, reaching transconjugation efficiencies of nearly 100% in vivo (13). Consequently, the inflamed human gut serves as an unparalleled engine for the rapid reassortment of virulence factors, fitness determinants, and antimicrobial resistance

(AMR) genes (12). Commensal bacteria readily acquire multi-drug resistance plasmids, serving as hidden reservoirs that ensure the persistence and systemic dissemination of resistance long after the initial pathogen has been cleared (12). The differences between homeostatic and inflamed gut environments, including their effects on horizontal gene transfer, are summarized in Table 2.

6. The Future of the Holobiont: Precision Microbiome Engineering

The modern trajectory of the human-microbiome holobiont suggests a future defined by biological vulnerability. The compounding loss of microbial biodiversity, the pervasive absence of immunoregulatory "Old Friends," and the recurrent induction of dysbiosis via modern diets and antibiotics threaten to establish a permanent state of host susceptibility. As pathobionts exploit these disrupted ecosystems, driving inflammation and accelerating the horizontal transfer of drug resistance, conventional broad-spectrum antibiotics are rapidly losing their efficacy (12).

To secure the biological future of human beings, the medical paradigm must shift from blunt, ecologically destructive interventions toward precision microbiome engineering. Because opportunistic pathobionts and resistant organisms often share close phylogenetic ties with beneficial commensals, traditional antibiotics cause unacceptable collateral damage (14). The next frontier in managing the host-microbe relationship lies in targeted, sequence-specific therapeutics, utilizing the very mechanisms bacteria use for viral defense: the CRISPR-Cas system.

Table 2. Gut environmental states and horizontal gene transfer dynamics.

Microbial State	Gut Environment Characteristics	Dominant Bacterial Taxa	Horizontal Gene Transfer (HGT) Dynamics
Homeostatic (Commensal)	Strict anaerobiosis; high concentrations of SCFAs; intact colonic mucus barrier.	Obligate anaerobes (Firmicutes, Bacteroidetes); diverse, stable community.	Suppressed; low density of facultative anaerobes and high competitive exclusion restrict plasmid conjugation.
Dysbiotic (Inflamed)	Elevated reactive oxygen/nitrogen species; degraded mucus barrier; altered bile acid profiles.	Facultative anaerobes (e.g., Enterobacteriaceae); expansion of pathobionts (C. difficile, AIEC).	Highly amplified; transient enterobacterial blooms drive near 100% transfer efficiencies of AMR and virulence plasmids.

Pioneering research demonstrates that CRISPR-Cas systems can be reprogrammed to function as sequence-specific antimicrobials (15). By utilizing engineered bacteriophages to deliver these targeted payloads, clinicians can selectively hunt and neutralize specific pathobionts without disrupting the broader, protective microbiota (15). When the delivered CRISPR-Cas machinery recognizes a specific genetic signature—such as a unique pathobiont virulence factor or a specific carbapenem-resistance plasmid—it induces fatal double-strand DNA breaks exclusively in the target organism (15).

In highly complex in vivo and in situ models, engineered phages delivering CRISPR-Cas3 or Cas9 have demonstrated the ability to selectively reduce the burden of targeted E. coli strains within biofilms and the mammalian intestinal tract, effectively curbing the pathogen while leaving the commensal network intact (16). Furthermore, non-lethal variations utilizing catalytically dead Cas9 (dCas9) allow for the epigenetic silencing of targeted virulence genes, effectively disarming a pathobiont and reprogramming it to function as a harmless commensal (15). This level of precision, combined with the strategic reintroduction of missing ancestral strains and the restoration of dietary MACs, provides a comprehensive technological roadmap for rebuilding colonization resistance and reversing the evolutionary mismatch of the modern era (6).

Our co-evolutionary history clearly dictates that human biology cannot be optimally sustained in isolation from its microbial partners. The future of human health will fundamentally depend not on the eradication of microbes, but on our sophisticated capacity to act as stewards of the microscopic ecosystems upon which our physiology relies.

Declarations

1. ***Consent to publication***
   We declare that all authors agreed to publish the manuscript in this journal based on the signed

Copyright Transfer Agreement and followed publication ethics.

2. ***Ethical approval and consent of participants***
None.

3. ***Disclosure of conflict of interests***
We declare that no conflict of interest exists in this work.

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5. ***Availability of data and material***
We declare that the data supporting the results reported in the article are available in the published article and from the corresponding author upon reasonable request.

6. ***Authors' Contributions***
QW contributed to the conception and design. ZC and LZ collected and analyzed the data. ZC, LZ, and QW wrote the first draft of this manuscript. ZC, LZ, and QW revised and edited the manuscript. All authors reviewed and approved the final version of the manuscript.

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