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(Article begins on next page)

# The disciplinary matrix of holobiont biology

Bordenstein, Seth R.; Gilbert, M. Thomas P.; Ginnan, Nichole; Malacrinò, Antonino; Martino, Maria Elena; Bahrndorff, Simon; Mundra, Sunil; Martin, Michael D.; Theis, Kevin R.; Hird, Sarah M.; Caro-Quintero, Alejandro; Sharpton, Thomas J.; Kohl, Kevin D.; Barnes, Christopher J.; Eisenhofer, Raphael; Aizpurua, Ostaizka; Andersen, Sandra B.; Brealey, Jaelle C.; Noer, Christina L.; Medina, Mónica; Limborg, Morten T.; Alberdi, Antton

The importance of microbiomes in host biology guides an intriguing convergence of micro- and macrobiological worlds. Consequently, the multidisciplinary framework of holobiont biology has emerged to integrate modes of genomic and functional variation that emphasize the centrality of microorganisms to the biosphere and the science of microbiome-based solutions for wide-ranging host activities, spanning agricultural production, conservation biology, and human diseases (1). The terms holobiont (the collection of host and associated microbial cells) and hologenome (all multispecies genetic material in the holobiont) are important to this conceptual change because they unify microbial symbiosis into the structure, function, and evolution of macroorganisms (2). Host organisms are thus defined to contain other organisms—viruses, bacteria, protozoa, and fungi—and their genomes. The functional relevance of these host-microbe associations will vary from inconsequential to harmful or essential, depending on the interactive milieu of members in the holobiont system (3).

Traditional views of host autonomy have in many cases led genome-wide association studies to explain a minority proportion of trait variance, especially for complex phenotypes such as behavior or chronic illness. This is referred to as the “missing heritability problem” and derives from the premise that host genotypes or vertically transmitted (parent-to-offspring) symbionts strictly encode most phenotypes. Yet in numerous systems, the hologenome explains more variation in traits than either the host or microbial genomes alone, including for human body mass index, high-density lipoprotein cholesterol, fasting glucose, hip circumference, and the likelihood of colon cancer (4). Not only do microbial genomes (and taxonomy) contribute to a fuller understanding of host phenotypic variation, they directly contribute to the composition of host genomic variation itself. For example, exposure of bunchgrass to different microbial members shapes the number of host quantitative trait loci underlying leaf area and root length (5). Moreover, experimental studies, artificial intelligence models, and biostatistics showcase how microbiomes underpin the physiological and genetic bases of diverse functions such as adaptive poison production by newt skin microbes that prevent predation (6), experimentally evolved insecticide resistance in wasps from metabolic activity by the gut microbiome (7), and dependency of hybrid plant vigor on microbiomes (8).

These varied observations highlight the importance of a hologenomic view of life that does not prescribe prominence to either host or microbial genomic contributions to a given trait. Fortunately, there are several opportunities to shift traditional studies of host biology toward this perspective. For example, long-read, cost-effective, and high-depth

DNA-sequencing technologies that produce the complete genomes of all members of a hologenome can help explain how single nucleotides, mobile genetic elements, and structural variations in hologenomes affect trait variation within and between holobionts. Additionally, studies of the spatiotemporal dynamics of microbiomes within different host anatomical compartments will clarify microbial contributions and their adaptive roles in the holobiont (6). Moreover, building analytical software with statistical methods that reform quantitative genetics to what we call “quantitative hologenomics” will optimize and fortify an understanding of microbial and host changes that cause phenotypic variation in holobionts (see the figure). Quantitative hologenomics at depth could be applied initially to simple model systems (such as *Drosophila melanogaster*), but as sequencing and assembly methods advance, it should tackle complex holobionts, such as polyploid plants that host thousands of distinct microbial lineages.

By taking a quantitative hologenomic approach, new methods could soon regularly process hologenomic information to determine the number and types of host and microbial genes, as well as microbial taxa, that combinatorically govern phenotypic variation. Such an all-in-one hologenomic approach will allow the identification of not only specific host and microbial effects in a hologenome but also the intergenomic and epistatic effects that cause trait variation.

Holobiont biology is thus poised to increase the explanatory depth of what Darwin famously referred to as the mystery of mysteries in *On the Origin of Species*: namely, how one genetic lineage or organism evolves to become two. Hosts and their microbiomes often assemble with varying degrees of specificity whose interactions may shape lineage splitting and the origin of new holobiont diversity. For example, animal and plant holobionts in terrestrial or aquatic habitats frequently harbor diverse microbial communities that assemble in concordance with host phylogenetic relationships, a pattern called “phylosymbiosis,” in which closely related hosts have more similar microbiomes than do divergent hosts (9). Phylosymbiosis may in part arise from natural selection, neutral forces, and environmental conditions that shape holobiont diversification over evolutionary timescales. Moreover, microbiome variation across related hosts can cause reproductive isolation between lineages by enabling holobiont genotypes to use new ecological resources or by directly contributing to hybrid sterility and inviability that reduce interbreeding.

Consequently, new hologenomic databases are emerging in which microbial and host sequences are cataloged together to accurately reflect the hologenomic variation that drives form and function. Examples include the Earth Hologenome Initiative (<https://www.earthhologenome.org>) to standardize wildlife hologenomic data worldwide and *Drosophila* Evolution over Space and Time (<https://dest.bio>), which is the largest repository of *D. melanogaster* hologenomic data and incorporates hundreds of population samples collected across 20 countries and four continents (10). The Tara Oceans expeditions sequenced numerous pelagic marine holobionts and multicellular (coral reef) holobionts in its second iteration (11). Such databases are useful for quantitative studies that resolve questions such as how population bottlenecks reduce hologenomic diversity and holobiont fitness, as seen in a recent survey of 50 *D. melanogaster* genetically distinct populations (12), or how coral holobionts will fare in

the Anthropocene under the effects of strong selection because of climate warming (11). Cultivation, cataloging, and sequencing human microbiome diversity parallel these efforts, including the Microbiome Conservancy (<https://microbiomeconservancy.org>) and Microbiota Vault (<https://www.microbiotavault.org>).

The holobiont concept is increasingly more evident in the scientific literature; research centers; popular media; sci-art creations; and classroom lectures on evolution, medicine, and philosophy. International holobiont and hologenome meetings and workshops, covering both basic and applied aspects, are also burgeoning with support from private foundations and government agencies. Still to change, however, are precollege and college courses that conventionally decouple the concepts of development, anatomy, cell biology, and evolution from microbiology. Desiloing this approach and establishing a relevant, holobiont view will be transformational for education, outreach, and student research. Curriculum could emphasize the depths of microbial diversity in the tree of life, the essentiality of endosymbiosis to organelle evolution, and the relevance of microbiomes to holobiont biology.

Cataloging and manipulating these incontrovertible entities of nature is not solely academic; rather, it is crucial to the urgent management of 21st-century challenges, including conservation biology, anthropogenic disturbances, sustainable food and feed production, development of new therapeutics, and restoration of microbial environments (13). With the realization that microbiomes enhance host functions, new approaches are improving animal and plant fitness by selecting and engineering microbiomes with specific effects on host fitness, such as enabling the use of minerals and nutrients previously inaccessible to plants—promoting sustainable food and feed production.

To embrace the complexity of a symbiotic world across terrestrial and aquatic environments (14), holobionts and hologenomes contribute an added dimension in biology's hierarchical organizational among the “endless forms most beautiful” that Darwin elegantly portrayed in *On the Origin of Species*. Just as the host body is recognized as a dynamic assemblage of its own interacting cells that forge anatomical structures with specialized functions, holobiont biology recognizes dynamic assemblages of interacting and/or interdependent host and microbial cells. This lexicon and concept are not simply semantic upgrades; they precipitate critical thinking and new questions at traditional boundaries of biological organization and mechanistic processes. Recognizing the symbiotic nature of life and the interconnectedness of micro- and macrobiology echoes a forward-looking statement by evolutionary microbiologist Carl Woese, who in 2004 stated the value of diverse views in science (15): “Science is an endless search for truth. Any representation of reality we develop can be only partial. There is no finality, sometimes no single best representation. There is only deeper understanding, more revealing and enveloping representations.”

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