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The missing link: how the holobiont concept provides a genetic framework for rapid evolution and the inheritance of acquired characteristics

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The microbiome, encompassing the genetic material of all the microorganisms associated with a host organism, has an evolutionary potential that has been overlooked in the prevailing paradigm of the Modern Synthesis. Recognizing this untapped potential could shed light on various unresolved evolutionary phenomena that have remained elusive through the lens of genetic variants alone. Such phenomena include rapid evolution, inheritance of acquired characteristics, and the missing heritability problem. In this review, we explore the microbiome's potential role in these processes, considering the holistic holobiont perspective as a possible guiding framework for new insights. Drawing inspiration from the foundational contributions of Rosenberg, Zilber-Rosenberg, and their contemporaries, we emphasize the significance of the microbiome in driving evolutionary innovation. Building on our previous research, coupled with emerging studies highlighting the microbiome's relevance in addressing missing heritability, we advocate for its recognition as a wellspring of evolutionary innovation. Throughout, we collate and analyze recent evidence to bolster our position and delve into the broader implications of these findings.

KEYWORDS

holobiont, inheritance, coevolution, rapid evolution, microbiome

1 Introduction

The Modern Synthesis, an integrative framework that combines Mendelian genetics and Darwinian evolution, along with supplemental theories, has greatly expanded our comprehension of evolutionary biology. Its robustness is evident from its broad applicability across varied life science disciplines. Yet, as comprehensive as the Modern

Synthesis may seem, certain phenomena remain unsolved and unexplained. One such phenomenon is rapid evolution, where species exhibit adaptation in relatively short time span—often less than 100 generations (Buswell et al., 2011; Messer et al., 2016; Rudman et al., 2019), suggesting the existence of mechanisms beyond our current understanding. This fast adaptation implies an adaptive capability that exceeds what we might expect based on current genetic frameworks. An issue of equal importance is the apparent presence of Lamarckian inheritance—the inheritance of acquired traits. In this form of inheritance, traits acquired during a lifetime are passed onto future generations, seemingly without corresponding genetic modifications (Handel and Ramagopalan, 2010; Kováč, 2019). Further, we face the missing heritability problem, where the identified genetic variants cannot fully account for the phenotypic diversity within a population (Mahar, 2008; Manolio et al., 2009). These challenges signal a potential interplay of more intricate mechanisms shaping complex traits and driving population-level phenomena beyond the reach of traditional genetic underpinnings.

Recent findings suggest that epigenetic variation may contribute to rapid evolution and the inheritance of acquired characteristics (Ashe et al., 2021). This contribution is attributed to the capacity of epigenetic variation to enhance phenotypic plasticity and diversity, which in turn influence the effects of natural selection (Ashe et al., 2021). Moreover, specific epigenetic states can be inherited by offspring, thereby impacting their phenotypes (Chong and Whitelaw, 2004). Within a single generation, epigenetic variation can modify gene expression timing and levels, affecting individual fitness and their response to selective pressures. Nevertheless, due to their limited heritability and propensity to revert (Zeng and Chen, 2019), epigenetic mechanisms are secondary contributors to evolutionary change.

Given the questions these phenomena present, it becomes clear that our current understanding of evolution is perhaps not as complete as the Modern Synthesis would suggest. Some compelling explanations for rapid evolution, Lamarckian inheritance, and the missing heritability problem, might be found by shifting our gaze from the organism in isolation to the collective entity of host and microbiota. Which brings us to the role of the microbiome, comprising the genetic material of all microorganisms associated with a host organism, in the host physiology, development, and adaptation (Pflughoeft and Versalovic, 2012; Shreiner et al., 2015). In 2007, Eugene Rosenberg and Ilana Zilber-Rosenberg introduced the concept of the hologenome, offering a new perspective on the host-microbiome relationship (Rosenberg et al., 2007). This concept underscores the co-evolutionary nature of this relationship and the pivotal role of the microbiota in molding the host's phenotype and adaptive capacity. By considering the host and the microbiome as a unified entity termed the holobiont, this concept acknowledges the interdependence of these entities.

This perspective invites a more inclusive interpretation of inheritance, one that embraces not only genetic contributions but also influential non-genetic factors, such as parental care, social learning, and critically, the microbiome (Rosenberg et al., 2009; Danchin et al., 2011; Sandoval-Motta et al., 2017a). This view

acknowledges that a part of the microbiome is transferred across generations, thereby significantly influencing the host's physiological and developmental processes. In this context, our group previously performed simulations based on gene regulatory network models to show that host adaptation could be significantly enhanced when interacting with microbial symbionts (Huitzil et al., 2018). Our findings suggest that hosts with a more efficient exploitation of their microorganisms achieved higher reproductive success, passing on their genes and some microbiota to future generations. This co-evolutionary process promotes an increasing dependence between certain microorganisms and their host, favoring beneficial microbes through natural selection. Importantly, in our simulations we observed that the holobiont's adaptation to perform multiple functions improves when microbial networks are organized into specialized niches. This finding underscores the holobiont's structural and dynamical complexity, facilitating its evolution as an evolutionary unit (Rosenberg et al., 2010; Guerrero et al., 2013; Rosenberg and Zilber-Rosenberg, 2016; Foster et al., 2017).

By expanding the traditional view of the Modern Synthesis to encompass the microbiome, we can highlight the crucial role it plays in shaping the host's phenotype, physiology, and adaptive potential. This perspective may offer novel insights into some of the unresolved questions in evolutionary biology, contributing to a more holistic and inclusive understanding (Collens et al., 2019; Veigl et al., 2019; Henry et al., 2021). Building upon this understanding, our group has further probed into the role of the microbiome in the context of the missing heritability problem (Sandoval-Motta et al., 2017a; Sandoval-Motta et al., 2017b; Huitzil et al., 2020). Our simulation-based studies have shown that the microbial genetic variants can have substantial influence on host phenotypes, and that the microbiome could significantly contribute to Genome Wide Association Studies (GWAS). Our findings indicate that the holobiont might generate significantly more variability than the host alone, potentially accounting for a large part of the missing heritability. These results illuminate that a comprehensive understanding of inheritance requires acknowledging the interdependence of the host-microbiome interactions.

Here we review the concept and preliminary evidence supporting the potential impact of the microbiome on rapid evolution and inheritance of acquired characteristics. We argue that the microbiome serves as a source of variation subject to natural selection, which can significantly influence these processes (Aldana and Robeva, 2021).

2 Rapid evolution

The concept of rapid evolution refers to the swift adaptation of an organism to a novel environment in fewer generations than standard evolutionary models would predict (Cox, 2004; Buswell et al., 2011). Although some mechanisms such as phenotypic plasticity and epigenetics have been proposed to explain this phenomena (Mounger et al., 2021; Pfennig, 2021), the underlying mechanisms remain elusive (Messer et al., 2016). In contrast,

holobionts, which comprise the combined genomes of hosts, their associated microorganisms, and their interactions, are theoretically capable of rapid evolution due to the high number of genes susceptible to mutations and the considerable genetic diversity within the microbiome (Moran, 2007; Jiggins and Hurst, 2011). Recent findings suggest that the microbiome may enhance phenotypic plasticity by introducing new genetic material to hosts (Kolodny and Schulenburg, 2020). Additionally, microorganisms can modify gene expression through epigenetic mechanisms (Miro-Blanch and Yanes, 2019; Rajeev et al., 2021). This capacity of the microbiome to generate phenotypic variation and modify gene expression has the potential to drive rapid evolution in holobionts.

In addition to phenotypic plasticity and epigenetic mechanisms, the microbiome can foster rapid evolution through the process of speciation (Brucker and Bordenstein, 2012; Douglas, 2014). This process occurs when microbial interactions with its host leads to the formation of reproductive barriers between populations with divergent microbial compositions. For instance, the microbiota of fruit flies can be altered through diet in just one generation, causing a remarkable difference in their mating preferences (Sharon et al., 2010). These preferences can persist for over 30 generations, however, if the flies are administered antibiotics, the mating preference vanishes, implying that gut bacteria are responsible for this behavior. Moreover, this trait can also be transferred to *Drosophila* populations by inoculating them with the associated bacteria (Sharon et al., 2010; Dittmer et al., 2016; Bell and Bordenstein, 2022).

Complementing these mechanisms, shifts in the composition of the microbiome have been recognized as a significant driver of rapid adaptation over short timescales. A compelling study conducted on *Drosophila melanogaster* demonstrated the powerful role microbiome composition can play as a selective force, inducing divergence in allele frequencies and influencing the host's genome (Rudman et al., 2019). The study further identified a substantial overlap between sites of differentiation in the experimental treatments and those that vary across seasons in wild populations. Such findings highlight the profound influence microbiomes exert on the fitness landscape and adaptation of natural populations, thus accentuating their critical role in guiding host evolution.

Highlighting an indirect yet impactful route to rapid evolution, alterations in the environment can induce swift adaptations in a member of the microbiome, setting off a domino effect that leads to significant changes in the host's fitness. Evidence of this mechanism comes from a recent study focused on *Pseudomonas fluorescens*, a constituent of the microbiome of the aquatic plant *Lemna minor*. The research identified that the microbiome's presence encourages accelerated evolution in this bacterium, resulting in the formation of biofilms. These biofilms in turn exert a substantial influence on the microbiome's species composition, precipitating changes that significantly impact the host plant's fitness across multiple generations (Tan et al., 2021). This scenario underscores the intricate eco-evolutionary dynamics within microbiomes, underlining their potential to shape host fitness through both direct and indirect pathways.

Extending the focus to humans, rapid evolution appears to play a significant role here as well. Recent studies bring to light that the

infant gut microbiome experiences swift evolutionary shifts in the early days following birth, exhibiting markedly increased rates of evolutionary modification and replacement of dominant resident strains compared to adults (Chen and Garud, 2022). This phenomenon of rapid evolution within the infant gut could affect the persistence of lineages and the holistic development of the gut microbiome. In a broader context, human microbiomes have deviated from ancestral states at an expedited pace, undergone a stark decrease in microbial diversity, and adapted to animal-based diets (Moeller et al., 2014). These findings suggest that the microbiome may be an important factor in the rapid evolution of humans. However, more research is needed to fully clarify the extent of its influence.

A substantial body of correlational evidence is emerging to underscore the proactive role of microbial communities in facilitating rapid host evolution. Corals, for instance, show increased adaptive capabilities, potentially facilitated by their symbiotic relationships (Howells et al., 2012; Hume et al., 2016; Torda et al., 2017; Ziegler et al., 2017). Likewise, both cichlid fish and guppies have rapidly adapted, possibly due to the incorporation of specific bacteria from their environment (Baldo et al., 2017). In a similar vein, the rapid evolution of a mildly pathogenic bacteria living in worms can protect its host from infection by a more virulent pathogen, highlighting the importance of considering microbiome evolution as a driver of infection outcomes (King et al., 2016). These studies collectively highlight the potential for microbial communities to be active contributors rather than merely passive participants in host adaptation. While much of this evidence is correlational, there are also studies that delve into more definitive relationships. For example (Moran and Yun, 2015) offer significant insights by directly illustrating how variations in the genotype of symbionts can have a substantial impact on host phenotype and ecology.

The microbiome's role in driving rapid evolution within host organisms has gained significant attention. Previous examples have highlighted the potential of the microbiome in promoting rapid evolution, yet a comprehensive framework that fully elucidates its role in this process is still lacking. In previous studies, we've proposed an integrative approach that combines mathematical models with the holobiont concept to unravel the underlying mechanisms of microbial interactions and their contribution to adaptation in holobionts. Drawing upon our own research and incorporating insights from other research groups, we have already made strides in exploring the evolutionary consequences of the holobiont concept, emphasizing the significant influence of microbial interactions. However, to achieve a comprehensive understanding, a unified model that integrates various mechanisms is essential.

3 Lamarckian-like adaptations in holobionts

Jean-Baptiste Lamarck's theory of inheritance of acquired characteristics, which proposed that traits acquired by an organism during its lifetime could be passed on to its offspring,

bears striking parallels to the phenomena we observe in host-microbiome co-evolution. While Lamarck's theory was largely discredited with the advent of Mendelian genetics and the Modern Synthesis (Kováč, 2019), recent studies have illuminated intriguing avenues through which similar principles may apply, particularly in the context of persistent multi-generational effects resulting from host-microbiome co-evolution (Elgart and Soen, 2018; Rafaluk-Mohr et al., 2018; Zare et al., 2018; Rudman et al., 2019). As such, the relevance of Lamarck's postulates has seen a potential resurgence, not as a comprehensive model of evolution, but rather as a contributing factor in the complex co-evolutionary mechanisms that drive the development of increasingly interdependent associations between hosts and their microbiota.

Recent evidence, challenging traditional views on genetics and disease susceptibility, suggests that certain acquired traits may indeed be inherited across generations (Handel and Ramagopalan, 2010; Dias and Ressler, 2014; van Steenwyk et al., 2018; Bozler et al., 2020). For instance, descendants of individuals who experienced significant hardships such as famine or trauma may also exhibit a health impact of those events (Painter et al., 2008; Callaway, 2013). This transgenerational effect has been observed in studies involving descendants of those who experienced the Dutch famine of 1944–45. Women who were subjected to maternal undernutrition *in utero* exhibited distinct health alterations in their offspring. These changes were not manifest in birth weight, but in a reduced birth length, increased neonatal adiposity, and a higher propensity for poor health in later life (Painter et al., 2008). Interestingly, these health complications were not limited to the directly exposed generation. Chronic disease rates escalated, persisting in the second generation and reinforcing the idea of transgenerational effects of *in utero* famine exposure. Emerging research further underscores the influential role of the gut microbiome in metabolic, inflammatory and cardiovascular diseases (among others) with nutritional factors significantly altering it (Tang et al., 2019; Nova et al., 2022). Severe nutritional restrictions, as observed in conditions like anorexia nervosa, can drastically modify the gut microbiome, thereby potentially impacting health across generations (Seitz et al., 2019). These findings underscore the need for further investigations into the gut microbiome's role as a potential vector for transgenerational health effects.

Taking the discussion of transgenerational health effects a step further, we can extend the paradigm to consider Lamarckian-like adaptations. A case in point is the sea anemone *Nematostella vectensis*. Its microbiome changes according to temperature and salinity fluctuations, facilitating the host's adaptation (Mortzfeld et al., 2016; Baldassarre et al., 2022). These changes, which manifest as both adjustments in the bacterial community and host gene expression, have been found to be transmissible to the offspring (Baldassarre et al., 2022). Specifically, the bacterial community adjusts by maintaining a "core microbiota" while a "dynamic microbiota" changes its composition, either increasing or decreasing the abundance of certain species. The results suggest this transmission of fitness could be due to the vertical transmission of specific beneficial bacteria, epigenetic modifications, or a combination of both. This highlights the important role

microbiota-mediated transgenerational acclimatization can play in enabling species to adapt more rapidly to climate change than anticipated (Webster and Reusch, 2017).

Advancing the understanding of transgenerational effects in health and the potential Lamarckian-like adaptations, recent studies on animals including rats and wasps have highlighted the significant role of environmental factors such as diet and pollutant exposure. Both have been shown to cause alterations in an organism's gut microbiota, which are transmissible to subsequent generations. For instance, the influence of a high-fat diet in one generation of rats was profound enough to induce an increased fat deposition in their offspring, remarkably even when the same dietary exposure was absent in the next generation (Buckley et al., 2005; Astbury et al., 2018). Similarly, wasps (*Nasonia vitripennis*) exposed to the pesticide atrazine showcased an adapted microbiome, fostering the growth of gut bacteria capable of metabolizing the pesticide and thereby perpetuating inherited resistance across generations (Wang et al., 2020). These examples, featuring both diet and environmental pollutant-induced modifications, underscore the considerable role of microbiota in mediating transgenerational adaptations and health effects.

In view of recent advancements in understanding transgenerational health impacts, it becomes clear that an expanded paradigm, incorporating aspects of Lamarckian-like adaptations, can offer fresh perspectives. An expanded framework can pave the way for novel interpretations of genetic inheritance and environmental adaptation, especially concerning the transfer of certain acquired traits across generations. However, further research is necessary to understand the mechanisms governing these adaptations not only in terms of the host's physiology and its remarkable symbiosis with the microbiome, but also in their joint evolutionary trajectory (Sandoval-Motta et al., 2017a; Sandoval-Motta et al., 2017b; Huitzil et al., 2018; Huitzil et al., 2020; Aldana and Robeva, 2021), and how they interact with environmental factors to shape the evolution of holobionts.

4 Discussion

The innovative work of Rosenberg and Zilber-Rosenberg has heralded a paradigm shift, highlighting the role of holobionts in rapid evolution and Lamarckian-like adaptations. However, the full implications of these discoveries in evolutionary theory and genetics are yet to be fully comprehended and explored.

This new approach is redefining how organisms might adapt to rapidly changing environments and warrants potential practical applications, such as microbiome engineering to fortify species vulnerable to climate change (Epstein et al., 2019; Rodriguez and Durán, 2020; Patel et al., 2022; Allsup et al., 2023). As global warming becomes increasingly pressing, the idea of microbiome engineering surfaces as a potent adaptive strategy (Rodriguez and Durán, 2020). This pursuit could benefit from an in-depth examination of the microbiome's role in rapid evolution. While the intricate metabolic pathways involved are yet to be thoroughly elucidated, recent investigations into host-microbe interactions at the metabolome level are indicative of the plausibility of swift

symbiotic responses to environmental flux (Contreras et al., 2016; Diener et al., 2020; Martínez-López et al., 2022).

Simultaneously, the holobiont framework breathes new life into Lamarckian principles. Contemporary evidence reinforces this perspective, demonstrating that microbial interactions can significantly affect the host germline, thereby influencing transgenerational effects (Rosenberg et al., 2009; Elgart et al., 2016; Moeller and Sanders, 2020). Consequently, the interaction between the microbiome and the host germline might foster emergent phenotypes, portions of which could be inherited.

With burgeoning evidence substantiating the heritability of microbial influences, our awareness of the ubiquitous presence and profound influence of the microbiome signifies a paradigm shift in our self-perception. We must recast ourselves, not as isolated entities, but as complex ecological systems intertwined within a vast network of interacting external and internal ecologies.

Author contributions

SH: Conceptualization, Writing – original draft, Writing – review & editing. CH: Conceptualization, Writing – review & editing. MA: Conceptualization, Writing – review & editing. AF: Conceptualization, Writing – original draft, Writing – review & editing.

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