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Adapting with Microbial Help: Microbiome Flexibility Facilitates Rapid Responses to Environmental Change

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Animals and plants are metaorganisms and associate with microbes that affect their physiology, stress tolerance, and fitness. Here the hypothesis that alteration of the microbiome may constitute a fast-response mechanism to environmental change is examined. This is supported by recent reciprocal transplant experiments with reef corals, which have shown that their microbiome adapts to thermally variable habitats and changes over time when transplanted into different environments. Further, inoculation of corals with beneficial bacteria increases their stress tolerance. But corals differ in their ability to flexibly associate with different bacteria. How scales of microbiome flexibility may reflect different metaorganism adaptation mechanisms is discussed and future directions for research are pinpointed. It is posited that microbiome flexibility is a broad phenomenon that contributes to the ability of organisms to respond to environmental change. Importantly, adapting with microbial help may provide an alternate route to organismal adaptation that facilitates rapid responses.

1. Introduction

Over the course of recent years, the dramatic reduction in cost and increase of depth of DNA sequencing has led to widespread application of molecular approaches to describe the microbial diversity associated with all eukaryotic organisms and ecosystems.[1] It is now widely accepted that all multicellular organisms associate with a diversity of bacteria, protists, fungi, viruses, and other entities that contribute to the biology of their respective host and affect its physiology, development, and fitness.[1,2] Consequently, the host and its associated microbes, the so-called metaorganism, should be considered the functional biological unit[2–5] (**Figure 1**). In particular hermatypic corals (Cnidaria: Anthozoa), which are the foundation species of the ecologically and economically important coral reef ecosystems,[6,7] are "poster child" metaorganisms, given their general reliance on an obligate endosymbiotic relationship with photosynthetic microalgae in the family Symbiodiniaceae[8] (Figure 1). This partnership comprises the engine of the reef,[9] as it allows corals, fueled by microalgal photosynthates, to build their skeletons that give rise to the massive 3D calcium carbonate frameworks that serve as a habitat for millions of species.[7,10] Besides microalgae, corals associate with a suite of bacteria, fungi, and viruses (among others) collectively referred to as the coral holobiont.[2–5,11] Although the dedicated roles for many of these microbial partners are not completely understood, coral-associated bacteria have been shown to play a role in metabolic cycling,[12,13] pathogen defense,[14] and thermal tolerance.[15] The tight link between coral hosts and their associated microbiomes is further exemplified by the presence of co-evolutionary patterns,[16] commonly referred to as phylosymbiosis,[17] and was since then shown to occur in many taxa ranging from *Drosophila* flies to mice and hominids.[18]

Given the strong reliance of corals on their associated microbes, two compelling theories have been formulated that emphasize the importance of partner exchange under changing environmental conditions: the adaptive bleaching hypothesis (ABH),[19] which states that coral bleaching (i.e., the loss of microalgae from coral tissues triggered by stress) allows a host to associate with different partners; and the coral probiotic hypothesis (CPH)[20] that posits that a dynamic relationship between microbial partners and environmental conditions exists, which selects for the most advantageous coral holobiont composition. Thus, both hypotheses postulate that microbial community assembly can vary and that the specificity of host–microbial associations is rarely absolute, but changes as environmental conditions change. Further, change/exchange of microbial partners may happen on a timescale that far supersedes the pace of host acclimation or adaptation.[15,21] Despite the ABH and CPH theories being formulated more than a decade ago, there is no study available that presents unequivocal evidence either confirming or refuting the proposed hypotheses on microbial change (that is, microalgal and bacterial change) as a means of

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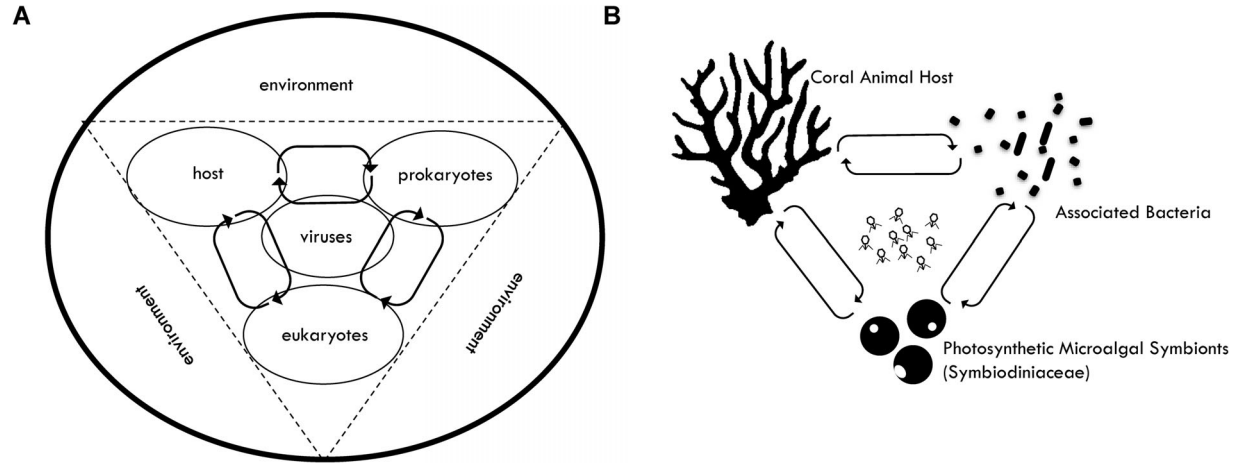

Figure 1. The metaorganism framework and coral holobionts. A) All multicellular organisms are metaorganisms composed of a eukaryotic host and associated microbial associates that form a functional biological unit (adapted with permission.[2] Copyright 2011, Elsevier). B) The coral holobiont denotes a prototypical metaorganism, given its obligate reliance on intracellular photosynthetic microalgal symbionts and its pervasive association with bacteria.[12]

coral holobiont adaptation. This is due to a variety of reasons. With regard to the microalgal symbionts (Symbiodiniaceae) neither the methodological (i.e., high-throughput sequencing), nor the taxonomic or the analytical framework were available to generate conclusive data that coral hosts can either "shuffle" their or engage with novel microalgal symbionts as a consequence of bleaching. For instance, only in 2018 the microalgal symbiont taxonomy was revised with erection of the family Symbiodiniaceae and corresponding genera to replace the complex and confusing system of clades and subclades.[8] Similarly, much confusion exists around use of the multicopy ITS2 gene array to denote microalgal species associations.[22] The advent of SymPortal (SymPortal.org) provides a novel analytical framework and approach to genetically resolve the microalgal symbionts of corals using next-generation sequencing data by making explicit use of the intragenomic ITS2 diversity and providing ITS2-type profiles representative of putative Symbiodiniaceae taxa.[23] A similar line of argument can be made for bacterial communities: before next-generation sequencing, the analysis of (complex) bacterial communities was confined to biochemical or molecular characterization of the microbiome at large and culture-dependent approaches. Conversely, with the advent of amplicon sequencing of the bacterial 16S rRNA gene, metagenomics/metatranscriptomics, and metagenome-assembled genomes alongside protocols to generate axenic/gnotobiotic corals, it should be possible to denote how differences in bacterial association affect the coral holobiont (phenotype).

Despite ample confirmation that corals do indeed switch their microalgal symbionts upon severe environmental changes,[24–26] questions remain as to the underlying ecological benefit and long-term stability of such changes.[27–29] Accordingly, fidelity rather than flexibility might constitute the norm in coral–microalgal associations,[30–32] in particular when employing highly resolving next-generation sequencing approaches and analytical pipelines that make explicit use of the sequenced intragenomic variation.[33–35] Apart from this, and despite the notion that the vast majority of corals seem to associate with one dominant microalgal symbiont, the presence and functional importance of rare background symbionts remains to be determined.[36–38]

Conversely to the overall stable and exclusive coral–microalgal associations, coral-associated bacteria are commonly much more diverse (on the order of 10^2–10^4 distinct bacterial taxa per coral host) and more evenly distributed.[40] Nevertheless, exceptions exist. For instance, corals abundantly associate with bacteria of the genus *Endozoicomonas* that can approach in extreme cases up to 90% of the relative bacterial abundance (based on 16S rRNA gene sequencing).[41–44] While a multitude of studies support the notion of a less rigid bacterial microbiome that may change over time/with age,[45,46] with environmental conditions,[47–49] or prevailing stress,[15,50] other work reports on rather consistent and coral-specific bacterial associations.[41,51–54] Thus, the presence and extent of a bacterial core microbiome and the propensity for change of coral-associated bacterial communities remain to be determined.

Only recently, Ziegler et al.[50] investigated the ability of corals to change their bacterial microbiome under changing environmental conditions as a proxy for their potential to assist coral holobiont acclimation/adaptation (**Box 1**). In order to consolidate disparate outcomes from coral studies that found either highly consistent or largely variable microbiomes (see above), Ziegler et al.[50] used corals from the genera *Acropora* (suspected to harbor rather variable bacterial associations) and *Pocillopora* (found to maintain largely invariant bacterial microbiomes) to conduct a large-scale environmental transplant study to systematically assess whether the degree of microbiome flexibility (i.e., the ability to harbor different bacterial communities; Box 1) differs between coral species. The work confirmed that the coral *Acropora hemprichii* indeed harbors a highly flexible microbiome that changes when exposed to various levels of anthropogenic impact to which coral fragments were transplanted. Conversely, the bacterial microbiome of the coral *Pocillopora verrucosa* remained remarkably stable, irrespective of the prevailing environment that coral fragments were transplanted to. In the following, we argue that this observed microbiome flexibility is a broad(er) phenomenon that supports metaorganism adaptation to rapid

Box 1.
Definition of Terms

Metaorganism	A metaorganism is the sum of a eukaryotic host and its associated (microbial) species with focus on those associates for which a function, that is, any form of contribution (beneficial or detrimental) to the metaorganism, is known or implied. The metaorganism framework posits that all (host) organisms associate with microbes that contribute to their physiology and fitness. Consequently, the metaorganism, that is, the unity of all member species, must be considered the functional biological unit.
Holobiont	A eukaryotic host with all external and internal associates. This multispecies consortium can include bacteria, archaea, protists, fungi, and viruses.
Microbiome	The sum of microbes in a particular environment, organism, or part of an organism (e.g., coral reef ecosystems, corals, mucus layer, etc.).
Microbiome flexibility[50]	The potential for dynamic restructuring of the host microbiome in the face of environmental change.
Microbiome conformer[50]	Those host species that show microbial adaptation to their surrounding environment.
Microbiome regulator[50]	Those host species that maintain a constant/consistent microbiome, that is, exhibit microbial regulation, irrespective of differences in the external environment.

Box 2.
The Microbiome Flexibility Hypothesis of Metaorganism Adaptation

The hypothesis	Microbiome flexibility is defined as the potential for dynamic restructuring of a host's microbial community in the face of environmental change.[50] The here-formulated hypothesis posits that microbiome flexibility is a broad phenomenon that contributes to the ability of organisms to respond and adapt to environmental change, which may take place on much shorter time scales than traditional organismal adaptation processes.
Support for the hypothesis	Recent transplantation experiments show that coral bacterial microbiome composition is linked to host thermal tolerance and that bacterial communities flexibly change upon transplantation into different environments.[15] However, this ability to flexibly associate with different microbes is coral species-specific.[50] These patterns are supported by other studies[55] and observable on a global scale.[56] A general contribution of the bacterial microbiome to development, physiology, and fitness of their respective host organisms is widely accepted.[1,2] Examples include, bioluminescent bacteria (*Aliivibrio fischeri*) providing disguising "counter-illumination" in the light organ of the bobtail squid,[57] *Buchnera* symbionts supplying essential amino acids to their aphid hosts[58], or wild-type *Drosophila* flies that live longer than their germ-free conspecifics.[59] Moreover, axenic animals show reduced metabolic functions,[60] may fail to mature past juvenile stages,[61] and are more prone to microbial disease/pathogens.[62] Importantly, controlled introduction of microbes into axenic organisms can restore the original function. Further to this, the success of probiotic applications, such as fecal transplants in humans[63] or the administering of certain microorganisms to corals to foster stress resilience,[64,65] demonstrates that microbial association is alterable and that changes affect the metaorganism phenotype.
Alternative explanations	First and foremost, changes in host-associated bacterial community compositions may simply denote parallel responses to changing environmental conditions and are of no functional significance to the metaorganism. Importantly, the mere presence of certain bacteria does not equate to functional importance or association. However, proof of a beneficial or fitness effect to the host (or metaorganism) through microbial change is challenging because of the inherent high degree of instability of many host-associated microbiota ("fluidic" nature of host-microbial interactions[5]). This is because host–microbe associations are not static and may differ with regard to host developmental stage[66], age,[46] over time,[45] or environmental conditions.[47] Further, even if a causative change in the microbiome community can be established, the effect may be "functionally neutral" (that is, replaced microbes are functionally redundant and/or new associates do not provide new functions), and thus, hard to measure.

environmental change. We discuss how differences in the ability to flexibly associate with bacteria may carry implications for metaorganism structure and functional adaptation (**Box 2**).

1.1. Degrees of Microbiome Flexibility Reflect Different Adaptation Strategies

Following the notion, that changes in the microbial community may represent a mechanism for rapid adaptation to environmental changes, different degrees of microbiome flexibility may thus be a reflection of distinct holobiont ecological adaptation strategies (**Figure 2**). High microbiome flexibility (i.e., restructuring of the microbial community through gain and/or loss of taxa) presumably promotes rapid metaorganism adaptation to environmental changes, but at the risk of losing putatively essential associates. Depending on the functional redundancy of the original community composition, the functions provided by replaced or excluded taxa may also be lost. In addition,

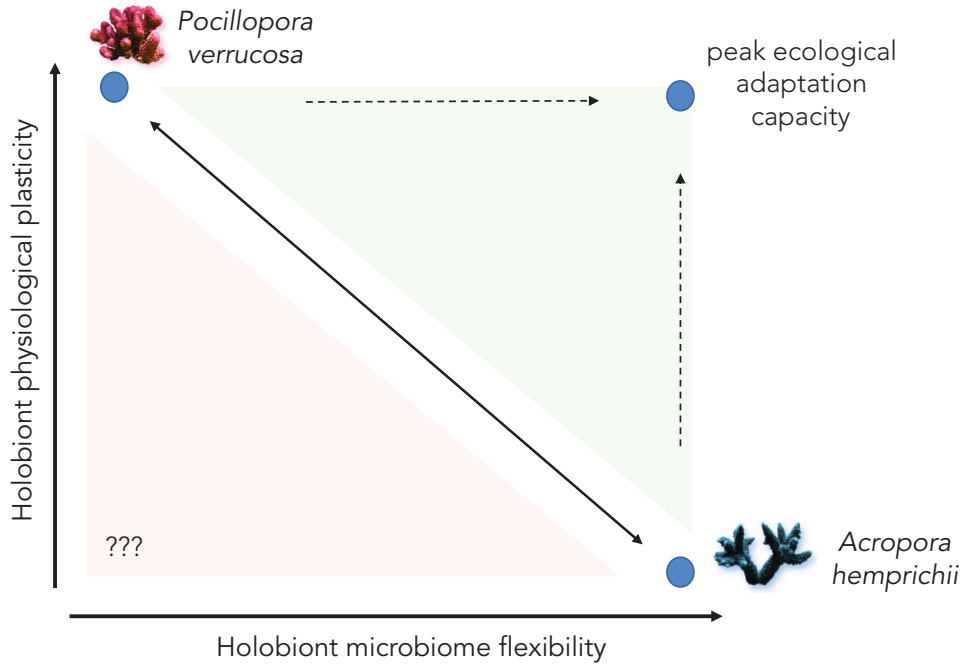

Figure 2. Degrees of microbiome flexibility as distinct strategies to support ecological adaptation. Microbiome flexibility, that is, the potential for dynamic restructuring of a host's microbial community in the face of environmental change, differs between host species.[50] We posit that different degrees of microbiome flexibility may thus be a reflection of distinct metaorganism ecological adaptation strategies. Corals with low microbiome flexibility presumably harbor high physiological plasticity, whereas species with high microbiome flexibility harbor low physiological plasticity. Accordingly, peak ecological adaptation capacity, relevant for organisms threatened by climate change, may be reached if physiological plasticity and microbiome flexibility are maximized. It is currently unknown through which mechanisms this may be achieved, but recent studies have shown the promise of probiotics,[65,70] environmental priming,[15,50,71,72] or even genetic engineering.[73] It is also unknown if species exist that exhibit low physiological plasticity and low microbiome flexibility, which may represent valuable study systems for our understanding of environmental resilience.

reorganization of flexible microbiomes may supposedly open the door to pathogen invasion during unstable phases of microbiome transition and render the host species more susceptible to disease. This hypothesis is supported by high disease incidence[67] and susceptibility[68,69] in Acroporid corals with high microbiome flexibility and the general dearth of coral disease in Pocilloporid corals with low microbiome flexibility.[67] Low microbiome flexibility presumably supports stable relationships with essential microbial associates and their inherent functions, but at the cost of low capacity for rapid microbiome adaptation and potential functional collapse in the absence of functional redundancy.

1.2. What are the Mechanisms that Underlie Microbiome Flexibility?

Several mechanisms may act in shaping different degrees of microbiome flexibility of metaorganisms. The flexible microbiome of *Acropora* corals consists of several equally abundant bacterial taxa. Experimental manipulation of microbial mesocosms indicates that initial community evenness promotes retention of system functionality under environmental stress.[74] High functional redundancy of the bacterial community thus represents one potential factor promoting high microbiome flexibility, whereby environmental stress leads to selective pressure between functionally redundant taxa.[75] In this scenario, shifts in microbiome composition may occur without risking to lose important functions and enable rapid metaorganism adaptation. In contrast, the stable microbiome of *P. verrucosa* corals is dominated by a single bacterial taxon (*Endozoicomonas*). Of note, Ziegler et al.[50] also found that the remaining bacterial community of *Pocillopora* corals after exclusion of the Endozoicomonadaceae bacterial family was even more stable than that of *Acropora* corals, indicating a potential stabilizing effect of the dominant taxon on the community beyond its own presence. Other studies have shown that under certain conditions, the dominance of one taxon may have a stabilizing effect on the entire bacterial community through effects on host immunity (reviewed in[76,77]) or regulation of quorum sensing and quenching (reviewed in[78]). However, in the case of the said *Pocillopora–Endozoicomonas* relationship, this is entirely unknown. Interestingly, the microbiome of *Acropora* corals was also associated with Endozoicomonadaceae, but the association was less stable. This suggests that the same bacterial taxon can exhibit different relationship characteristics in different coral species.

Notably, flexibility in terms of changing community composition as alluded above is not the only mechanism for microbiomes to functionally adapt.[4,21] For instance, deep-sea mussels harbor multiple strains of the same bacterial taxon with different functional profiles, suggesting potential for shuffling at the strain or population level (inaccessible through means of 16S metabarcoding approaches).[79] Further, bacteria, such as those in the human gut microbiome, may take up new genes via horizontal gene transfer, as a source of genic/genetic

Box 3.
Testing the Hypothesis

Testing the role of microbiome flexibility in metaorganism environmental adaptation can be distilled into two important questions:

1) Can the phenotype and fitness of an organism be changed through modification of associated microbes?
Such modifications would encompass different organizational levels that need to be investigated, including relative abundance changes of certain bacterial associates[50] at the species or strains level,[79] as well as genetic/genomic modifications of associated bacteria at the molecular level, such as acquisition of new genes (e.g., through horizontal gene transfer) or modification of genes through point mutations.[82] Descriptions of these mechanisms come from different animal systems and comprehensive efforts focusing on one host species are a prerequisite to quantitative insights into the pervasiveness of any of these mechanisms.

2) Can the phenotype and fitness of an organism be changed by association with different (that is, novel/foreign) microbes?
An obvious starting point here is the use of model organisms with available axenic, that is, germ-free, lines. Through addition of controlled microbial consortia (native or non-native) to axenic lines, mono- or poly-associated gnotobiotic animal models[62,85] can be obtained to test microbially-mediated functions and effects on metaorganism fitness. The field of probiotics represents an alternative approach that does not rely on axenic animals and that has been successfully applied to non-model organisms such as stony corals.[65] When combined with experiments that assess the fitness of manipulated metaorganism compositions, such approaches will help to test the hypothesis of microbiome flexibility in metaorganism adaptation.

novelty.[80,81] In addition, microbial diversification via point mutations may produce microbes with distinct and selectable properties, as evidenced in a study by Moran et al.[82] in which a highly specific bacterial symbiont (*Buchnera*) increased thermal tolerance of its associated aphid hosts. Moreover, epigenetic regulation of bacterial gene activity[83] and/or bacteria-mediated epigenetic regulation of host gene activity[84] are putative mechanisms that underlie microbiome flexibility and support ecological adaptation of metaorganisms. The herenamed mechanisms are probably not mutually exclusive and may lead to complex patterns of metaorganism adaptation, which are currently not well understood (**Box 3**).

1.3. Is Microbiome Flexibility a Universal Phenomenon?

Based on the above, we posit that "scales" of microbiome flexibility exist, either 1) at the level of the relative increase/decrease of certain bacterial associates (*sensu*[50]) including association with novel bacteria (from the environment), 2) at the level of strains within species (*sensu*[79]), or even 3) at the level of horizontal gene transfer (HGT) where certain genes are exchanged between microbial taxa as a source of genic/genetic novelty to assist microbial-assisted metaorganism ecological adaptation. These conceits imply that high "taxon-based" microbiome flexibility is not better or worse than low "taxon-based" microbiome flexibility (*sensu*[50]), but that other mechanisms are available that do not manifest in microbial community change per se. In other words, different solutions to the "same problem" may exist, and it will be exciting to map the different mechanisms of microbial-assisted metaorganism adaptation. Common among all such putative mechanisms is that they are presumably fast for several reasons, as outlined in the following (**Figure 3**). First, mechanisms of microbial adaptation do not rely on mutation/recombination and subsequent selection (see above). Second, mechanisms of ecological adaptation do not rely on the population size of the host, but on that of the associated bacteria, which is presumably orders of magnitude larger for single-celled microbes. Nevertheless, the precise time it takes for microbial associations to change or "adapt" is not known and may differ depending on environmental pressure and host species. Presumably, it can be very fast, in the course of hours, as experiments with short-term acute heat stress assays may suggest.[15] However, it remains to be determined whether the process is dynamic. For instance, one could imagine a process of winnowing as a process of microbial community change, that is, the (sub)selection of specific bacteria from an initial broader community, as observed during early ontogeny and establishment of host-microbial symbioses.[86–89]

2. Future Directions for Research

Notably, it is currently not at all clear how far microbiome flexibility is "selected" (respectively, at what level) or just "coincidence". For instance, it may be entirely reasonable to assume that changes in host-associated bacterial communities denote a parallel response to changes in the external environment (initially), entirely decoupled from the host or remaining metaorganism (Box 2). The newly associated taxa would still need to be retained at one point, otherwise microbial taxa would seemingly fluctuate with the surrounding environment, in contrast to the fairly stable associations one can observe.[56] However, if bacteria "work well" in a given environment, they might also be successful in that same environment, and specificity does not need to be absolute. Evidence for this may come from coral probiotics experiments,[65,70] where so called Beneficial Microorganisms for Corals (BMCs),[64] that is, "cocktails" of bacterial strains with putative beneficial functions to the host, are applied to a coral, which subsequently becomes more stress resilient. Unfortunately, at present, the longevity of this phenomenon is unknown, although

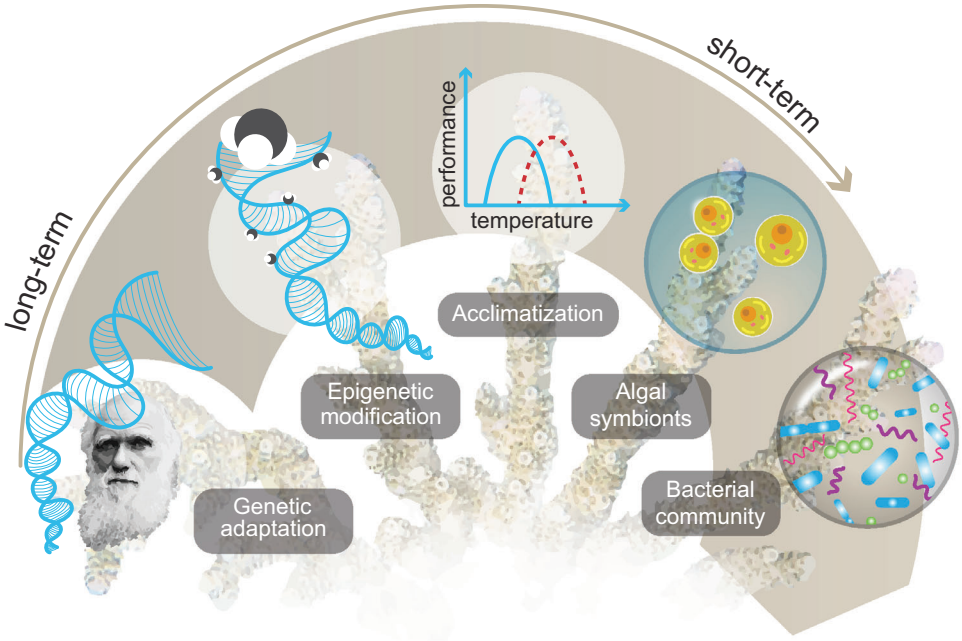

Figure 3. Overview of (coral) metaorganism (ecological) adaptation mechanisms. Putative mechanisms are ordered by time scales on which they may occur (from left to right): from long-term processes such as (host) genetic adaptation on the left that manifest over the course of generations, to epigenetic modifications that presumably happen over the course of one generation to the next, to physiological acclimation that happens within the lifetime of an individual, to microbial community changes that may happen within the course of months, weeks, or hours. Given the latter, flexible microbial association may constitute a fast-response mechanism to rapid environmental change.

preliminary data support that association is stable as long as the external stressor ("selective agent") is in effect.

Another point of clarification lies in the role of "founder effects" of colonization, that is, if bacteria which are already present determine what other bacteria may associate.[90] In the case of corals, several research groups now work with antibiotics to deplete the native microbiome.[91,92] The idea here is that, using antibiotics (or cocktails thereof), corals or coral larvae can be largely freed from bacteria; this then allows to reinoculate such gnotobiotic or ideally axenic corals with bacterial isolates to determine if the nature or order of isolates determine the bacteria that associate thereafter.[66,93] For instance, using *P. verrucosa* the conjecture would be that association with the highly dominant and stable *Endozoicomonas* would affect the type of bacteria that associate thereafter. More broadly, this avenue of research would allow to study how access to selected bacteria initially may determine the shape of the microbiome then-after (Box 3).

It may also be of relevance to determine the precise location in or on the host where microbial flexibility "plays out". This is best accomplished using microscopic approaches, although sequencing approaches, or combinations thereof may complement each other.[56,94–97] For instance, plant hosts have cell walls with an interstitial space adjacent to it, where bacteria can reside in a controlled "playpen", which assumingly facilitates the association with "foreign" bacteria.[94] Conversely, animal cells only have membranes as a barrier to the outside world, although many animal surfaces feature a mucus/mucoid layer. The mammal gut,[95,96] the surface of the freshwater polyp Hydra,[97] or coral tissue[91] are all covered by mucus sheets or layers and this is where a lot of microbes reside. In line with this, coral studies that differentiated between the microbial communities associated with the host tissue and mucus found prevalent differences between the two,[98,99] whereby tissue-associated bacteria more strongly reflect host traits in comparison to mucus-associated communities, which align better with the prevailing environment and ecology of a coral host.[16] Surprisingly, skeletal-associated communities harbored the largest diversity,[16] emphasizing that although coral mucus is the compartment exposed to the "outside world", microbial communities are not a mere reflection of the prevailing environment (see above). Nevertheless, coral mucus is supposedly a good place to start to understand patterns of microbiome flexibility.[100] For instance, a recent study showed significant differences in the prokaryotic communities associated with coral recruits pending exposure to the mucus-associated microbes of four different coral species.[101] As such, transplantation of the mucus from one host to another seems to change specificity of bacterial association, although it remains to be determined if microbiome flexibility can be changed through such a procedure as well. This in turn would have consequences for our mechanistic understanding of microbiome flexibility.

Interactions between members of the metaorganism that potentially do not involve the coral host, as for example between microalgae and bacteria,[102–104] add another layer of complexity. Based on the first description of bacterial microbiome flexibility in corals of the genera *Acropora* and *Pocillopora*,[50] the corresponding microalgal communities of these hosts seem to follow similar patterns of flexibility, and exhibit higher flexibility of *Acropora*'s microalgae communities than those of *Pocillopora*.[105] Studies that investigated microalgal and bacterial communities in natural coral populations provide first insight into putative

cross-kingdom microbiome flexibility: both seem to associate with host population structure and habitat characteristics in more or less congruent patterns.[106,107] Notably, global co-occurrences of microalgal and bacterial taxa in coral hosts[108] indeed suggest that similarity in microbiome flexibility may be directly linked to the co-occurrence of certain taxa, also during early ontogeny,[109] and may not be determined by the host or just coincidental. This notion is further supported by the putative presence of Symbiodiniaceae-associated microbiomes,[110] distinct bacterial communities in sea anemones with and without microalgae,[93] and co-localization of bacterial aggregates with microalgal cells in coral tissues.[56] Symbiotic interactions between microbes of a metaorganism have potentially profound implications for cross-compartment microbiome flexibility and metaorganism adaptation, and deserve extra attention.

On this note, it should be pointed out that an understanding of the role of phages (viruses) in all this is at best in its infancy.[111] Viruses infect all cellular life, including bacteria and eukaryotes, and are assumed to interact dynamically with the coral holobiont, that is, they influence microbiome community structure, coral physiology, and likely play a role in coral bleaching and disease.[111–116] A seminal study by Barr et al.[117] showed that throughout the animal kingdom, the surface mucus layer of cells enriches phage-to-bacteria ratios (phages or bacteriophages are viruses that infect and replicate within bacteria and archaea). This is explained by the bacteriophage adherence to mucus (BAM) model,[117] which suggests that metazoan mucosal surfaces and phages coevolve to maintain phage adherence. For the host, this provides a mechanism to limit or control bacterial adhesion, whereas the phage benefits through more frequent interactions with potential bacterial hosts. This implies that virus/bacteriophage communities might be a direct component structuring microbial community assemblage. In line with the above study, coral mucus seems to represent a hot spot for viruses and phages,[118] and it would be compelling to show whether microbiome flexibility can be affected by phage manipulation. That phage therapy (i.e., inoculation of bacteriophages which target specific bacteria) can change microbial community structure in an effort to target pathogenic bacteria has been shown to work in principle by Efrony et al.[116] However, it remains to be shown whether microbiome regulators can be converted into microbiome conformers (Box 1) and *vice versa* via viral manipulation, which would impact our understanding of the mechanism(s) underlying microbiome flexibility.

All of the above holds implications for the putative presence of a "core microbiome". The core microbiome in its essence posits that host-associated microbial communities are specific, and therefore, certain bacterial taxa are consistently associated with certain multicellular hosts. The concept of microbiome flexibility challenges this notion to a certain degree, although of course it does not posit that all microbial taxa are subject to change. Further, microbes may change but that does not translate into functional differences. Even at the most basic level, we are far from understanding whether a diverse host microbiome is good or bad, respectively suggests loss of host control, or whether an increase in bacterial diversity is any indication of whether a given environment is good or bad.[119,120] These are all exciting questions to pursue in the future and may be answered through experimental manipulation of bacterial association in a holistic framework combining reductionist and integrative approaches as outlined by Jaspers et al. (Box 3).[5] Future research should focus on exploring more broadly how patterns of microbial association translate into metaorganism health states through embedding microbial community patterns in a conceptual (mechanistic) framework.

3. Conclusions

All multicellular organisms are submersed in a microbial world and associate with bacteria that contribute to their biology. A number of studies now support the notion that the microbiome may contribute to ecological adaptation. This can manifest through various processes, for example, association with novel bacterial taxa, functional differences between associated microbial strains, or through the acquisition of novel genes from the environment via mechanisms of horizontal gene transfer. We denote the potential for restructuring of the host microbial community as microbiome flexibility, and different host species exhibit varying degrees of microbiome flexibility. At present, many questions remain to be answered in order to obtain a comprehensive picture of this phenomenon. For instance, it is unknown whether microbiome flexibility at large differs between organisms across the tree of life, the prevalent underlying mechanisms, the pace at which microbiomes adjust and how stable those changes are, or the role of the host or other entities in orchestrating such changes. Nevertheless, technical advances to deplete host-associated bacteria and exposure to selected bacteria may provide a research perspective to answer many of these questions. In this realm, first results from coral probiotics, that is, the targeted exposure of beneficial bacteria to the host, seem promising in their ability to modify the biology of the host and presumably change the microbial community of the outer surface mucus layer. Given the pervasiveness of mucoid layers on epithelial surfaces, the basic principle may be widespread. Accordingly, and although we are far away from a detailed understanding of the patterns and processes at play, the underlying concept of a flexible microbiome holds promise as a fast-track mechanism to climate change adaptation.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

adaptation, climate change, holobiont, metaorganism, microbiome flexibility

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