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Host under epigenetic control: A novel perspective on the interaction between microorganisms and corals

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Abstract

Coral reefs have been challenged by the current rate and severity of environmental change that might outpace their ability to adapt and survive. Current research focuses on understanding how microbial communities and epigenetic changes separately affect phenotypes and gene expression of corals. Here, we provide the hypothesis that coral-associated microorganisms may directly or indirectly affect the coral's phenotypic response through the modulation of its epigenome. Homologs of ankyrin-repeat protein A and internalin B, which indirectly cause histone modifications in humans, as well as Rv1988 histone methyltransferase, and the DNA methyltransferases Rv2966c, Mhy1, Mhy2, and Mhy3 found in coral-associated bacteria indicate that there are potential host epigenome-modifying proteins in the coral microbiome. With the ideas presented here, we suggest that microbiome manipulation may be a means to alter a coral's epigenome, which could aid the current efforts to protect coral reefs.

KEYWORDS
beneficial bacteria, coral, epigenetics, global change, microbiome manipulation, resilience, probiotics

INTRODUCTION

Coral reefs are the most biodiverse and complex aquatic ecosystems on earth and provide food and shelter to support a diverse assortment of macro- and microorganisms.[1–3] These ecosystems are formed by holobionts composed of individual coral animals and their associated microorganisms. Coral-associated microorganisms encompass symbiotic dinoflagellates within the family *Symbiodiniaceae*, as well as bacteria, archaea, fungi, and viruses.[4] *Symbiodiniaceae* live within coral cells and perform photosynthesis, which provides most of the energy requirements for the majority of shallow water corals.[5,6] In turn, the coral provides shelter for the *Symbiodiniaceae*, leading to a long-term mutualistic relationship.

Global and local anthropogenic impacts have led to environmental changes that have caused an extreme decline in coral reef health in last decades.[7] Environmental changes affect many components of the coral holobiont and can lead to an imbalance between its members, which may result in coral bleaching, disease, and potentially death.[1,2,8,9] In a healthy coral holobiont, the coral works in concert with its associated microorganisms to metabolize and recycle essential nutrients and to inhibit potential pathogens through the production of anti-microbial peptides, anti-biofilm compounds, competition, or viral lysis [10–12]. Environmental change and stressors can interfere with these host-microbiota interactions, which can lead to dysbiosis and declines in coral health and performance [1,9]. Urgency is required to understand how corals acclimate to their environments in the context of deteriorating ocean conditions.

Differences in the ability of corals to acclimate to stress have, at least in part, also been attributed to differences in their symbiont assemblages.[13,14] For example, corals can acclimate to increasing

ocean temperatures by exchanging their resident *Symbiodiniaceae* populations with more heat-tolerant strains.[14] However, other research has found that despite maintaining the same *Symbiodiniaceae* population, heat-acclimated *Acropora millepora* coral colonies can become more resistant to temperature increases than colonies that were not previously heat-acclimated, possibly by upregulating stress response proteins like heat shock proteins.[15] Further research shows the coral host itself can directly and solely respond to environmental changes via phenotypic plasticity,[16–18] which can be maintained across generations.[1,18–21] Coral phenotypic plasticity may result from changes to its epigenome [17,22] through altering gene expression via chemical or structural modification of DNA and/or its associated proteins (e.g., histones).[23] Differences in epigenomes between genetically identical corals have been shown to correlate with phenotypes and bleaching responses.[24] These epigenetic changes can occur in corals within a single generation, providing another mechanism for short-term acclimation to environmental conditions[16–18,25] that can be passed on to offspring (i.e., transgenerational acclimatization).[26]

As microbial and epigenetic processes can both control coral health, we postulate here that these two aspects are directly or indirectly linked, providing a way for coral holobionts to adapt to environmental change. To explore this, we summarize the current knowledge on the roles that coral epigenetic changes have in environmental stress response, and, using previous knowledge on the specific roles that bacteria have on epigenetic state in other host systems, we identify homologs of epigenetic-modifying proteins in coral-associated bacteria. This survey provides support for a novel functional perspective for how coral-associated microorganisms may influence the host phenotype through modulation of the epigenome. This mechanism could be exploited in the future to increase coral holobiont resilience to environmental stressors or change.

CORAL EPIGENOMES RESPOND TO ENVIRONMENTAL CHANGES

Mechanisms of epigenetic modifications include DNA methylation, histone modifications, and non-coding RNAs. The former is most widely studied and involves the addition of a methyl group to a cytosine, usually restricted to CpG dinucleotides, resulting in changes to the gene expression,[23] likely by controlling access of transcriptional machinery.[27] Histone modifications can alter nucleosome structures via the phosphorylation, methylation, acetylation or ubiquitination of N-terminal amino acids; thus, changing the accessibility of the DNA and transcriptional regulation.[28]

In corals, changes in DNA methylation correlate with phenotypic changes in response to shifts in environmental conditions.[17] For example, the scleractinian corals *Pocillopora damicornis* and *Stylophora pistillata* show an increase in global DNA methylation when subjected to stressful low pH environments.[17,25] Specifically, *S. pistillata* reduces its expression of cell proliferation genes under low pH conditions as a compensatory mechanism to maintain colony growth rates despite decreased calcification rates, which results in significantly larger cell sizes.[17] This acclimatory phenotypic change is also correlated with increased methylation of genes controlling cell growth, which shows a positive correlation between DNA methylation and gene expression. Similarly, Dixon et al. [16] found that translocating *Acropora millepora* corals between environments with different temperature profiles leads to acclimatory changes in DNA methylation marks that more resemble the epigenome of non-translocated corals in the recipient habitat. This mirroring of DNA methylation marks by the translocated corals coincided with increased weight gain, lipid content, protein content, and carbohydrate content. Therefore, phenotypic plasticity may be driven by DNA methylation and changes to gene expression which help acclimate corals to different environments.

DNA methylation in corals is found to be mostly located in the gene body, rather than promoter regions, so methylation is hypothesized to have a more important role in transcriptional fidelity than in direct transcriptional regulation.[16,17,29] DNA methylation in corals is higher in highly expressed housekeeping genes and lower in dynamically expressed environmental response genes.[16,29,30] This pattern of bimodal distribution of DNA methylation with hypermethylation in housekeeping gene bodies is also observed in other invertebrates such as the pacific oyster [31] and honey bees.[32] Increased expression of genes increases the likelihood of creating partial proteins via spurious transcription mediated by cryptic promoters within gene bodies [33] To counter this phenomenon, DNA methylation can reduce spurious transcription of genes by disabling cryptic promoters within the gene body and thus increase transcriptional fidelity of genes under high expression.[17,33,34]

Histone modification in corals has been considerably less studied than DNA methylation. In mammals, H2A.X phosphorylation is triggered in regions that flank DNA damage and can be used as markers for DNA damage [35]. The only study available to date examining histone modifications in corals found that global histone H2A.X phosphorylation correlates with heat stress as well as with nitrogen or nitrogen and phosphorous enrichment.[36] Nitrogen enrichment is predicted to lead to growth of *Symbiodiniaceae*, which would drive phosphorous depletion in coral cells as well as increases in photosynthesis, leading to the production of reactive oxygen species (ROS), and hence oxidative DNA damage.[36] In corals supplemented with nitrogen and phosphorous, oxidative DNA damage could be repaired with the aid of H2A.X phosphorylation, which shows increased levels that last 35 days. Corals exposed to heat stress combined with only increased nitrogen, however, only show initial increases in H2A.X phosphorylation, but after 35 days, phosphorylation decreases, and DNA repair is impaired due to a lack of phosphorous. Here, increased coral symbiont proliferation may have indirectly affected histone modifications in the coral host through metabolic processes with detrimental effects for the host.[36] However, it remains to be seen whether histone modifications can have a role in coral acclimation to stressors and whether they are heritable.

Epigenetic inheritance in coral was originally inferred due to observations that offspring are more resistant to stress conditions if their parents were previously exposed to and acclimatized to the same stressor.[37] For example, offspring from *P. damicornis* colonies that experienced high temperature and pCO_2 (partial pressure of

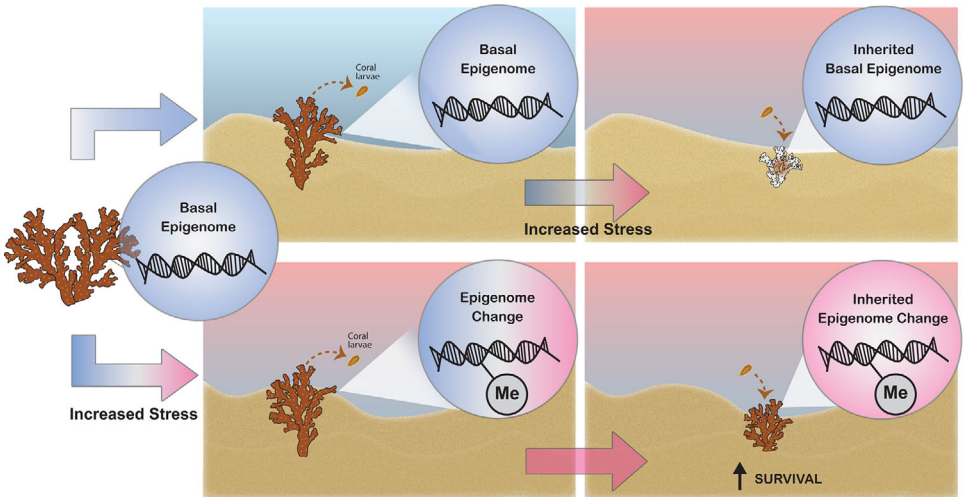

FIGURE 1 Epigenomes can be vertically transmitted across generations. Coral epigenomes can change within a generation as a response to environmental stress. These epigenomes are vertically transmitted to their offspring, which might increase the survivability of offspring that are exposed to the same stress (right column). Me, methylation

carbon dioxide) have higher survival rates to those stressors than offspring from colonies that had not experienced these conditions.[37] Correlated epigenome and genome differences from the same coral species located in different environments also imply that there is a heritable relationship between them.[38] Furthermore, hypermethylation patterns in stress response genes also can be transmitted from high temperature acclimated adult corals to their offspring, which correlates with higher survival in the coral offspring [26] (Figure 1). While still a lot of further research needs to be undertaken in the field of coral epigenetics, these nascent studies illustrate how changes in the epigenome could facilitate both short-term response and trans-generational changes to environmental conditions.

BACTERIA CAN MODIFY HOST GENE EXPRESSION

Host gene expression can also be modulated by epigenetic changes in response to microbe-associated molecular patterns (MAMPs), such as lipopolysaccharides (LPS) and glycans, which are detected by pattern recognition receptors (PRRs).[39] The detection of commensal bacteria by mouse intestinal epithelial cells leads to decrease in the expression of toll-like receptor genes due to increased methylation in the 5′ region of the *TLR4* gene.[39] This relationship is necessary to prevent the overactivation of immune pathways in response to nonpathogenic bacteria and maintain homeostasis in the mouse gut.[39]

The expression of PRRs in the coral *P. damicornis* has been shown to decrease in response to temperature stress,[40] potentially altering the recognition of pathogenic MAMPs and thus potential downstream epigenetic activation. This was demonstrated when pairing temperature stress with the coral pathogen *Vibrio coralliilyticus*, as coral immune response pathways related to pattern recognition and microbial killing were downregulated.[40] Notably, the presence of the coral pathogen without temperature stress causes an upregulation of pattern recognition genes as well as other immune response pathways, suggesting an activation of the coral immune system that is diminished during temperature stress.[40]

Immune parameters, such as phenoloxidase activity, which activate the immune-related melanization cascade, and/or bactericidal activity, also change in corals due to the presence of bacterial LPS and/or high temperature conditions.[41] The combination of LPS treatment and heat stress leads to a decrease in the bactericidal activity in the Caribbean corals *Montastraea faveolata* and *Stephanocoenia intersepta*.[41] However, LPS treatment and heat stress together cause an increase in the phenoloxidase activity in *Stephanocoenia intersepta*, when compared to ambient conditions, and *Porites astreoides*, when compared to LPS treatment without heat stress.[41] This modulation of gene expression profiles related to immune response pathways, and more specifically the increase of phenoloxidase activity as a result of LPS exposure during heat stress, provides a promising avenue for further discovery into the bacterially mediated epigenetic control of coral gene expression.

BACTERIA INFLUENCE HOST EPIGENOMES

While many studies suggest that environmental stress can correlate with changes to a coral's microbiome [42–44] or epigenome (see above), evidence that coral-associated microorganisms cause epigenetic modification in their hosts is currently lacking. Such a mechanism would have very impactful ramifications, as microorganisms can be vertically transferred between generations [45] and thus could change the coral epigenome over multiple generations.

The interaction between bacteria and host epigenomes has, however, been extensively studied in other systems.[46] Commensal bacteria in humans indirectly control epigenomes in early life stages via bacterially produced nutrients that prime the host epigenome

to help develop proper responses to diseases that may occur later in life.[47] Similarly, probiotic *Lactobacillus* species are able to prevent increases in histone acetylation levels, and thus control inflammation, caused by pathogenic *Escherichia coli* in human intestinal epithelia.[48]

Most research, however, relates to bacterial pathogens and their modulation of the host epigenome.[46,49] The bacterial pathogen *Helicobacter pylori* triggers histone modifications [50] and hypermethylation of promoter regions of tumor suppressor genes, which leads to tumorigenesis in the stomach.[51] Likewise, pathogen stress in plant species causes changes to DNA methylation levels of defense genes which alters the plant's phenotype.[52] In the human gut, the detection of intracellular MAMPs from the pathogen *Listeria monocytogenes* leads to the acetylation and phosphorylation of H4 and H3 histone proteins, which activates expression of pro-inflammatory genes.[46] The *L. monocytogenes* effector proteins internalin B (InlB) and listeriolysin O (LLO) then indirectly modify the host immune response by changing the host's epigenome. InlB binds to a tyrosine kinase receptor on the cell surface, triggering a cascade that represses transcription regulation genes via histone deacetylases,[46] and LLO leads to the global deacetylation and dephosphorylation of histones and downregulation of several immune genes.[46] As a consequence, the human cells' epigenetic control of pro-inflammatory response to infection is dampened by specific bacterial effectors.

In another example, the human pathogen *Mycobacterium tuberculosis* secretes three enzymes that directly modulate the epigenetic state within the host cell: Rv1988, a methyltransferase that methylates histones associated with genes promoting defense against pathogens, including the production of reactive oxygen species; Rv3423, a histone acetyltransferase; and Rv2966c, a DNA methyltransferase.[46] Similarly, the intracellular opportunistic pathogen *Mycoplasma hyorhinis* encodes three DNA methyltransferases, Mhy1, Mhy2, and Mhy3, that also directly change the epigenetic state within the host cell.[53]

Recently, metagenome assembled genomes (MAGs) associated with the coral *Porites lutea* were found to have an abundance of ankyrin-repeat proteins (ARPs), which help mediate protein-protein interactions in eukaryotic cells.[54] The ankyrin-repeat containing protein AnkA has been studied in the tick-derived human pathogenic bacteria *Anaplasma phagocytophilum*, where it disrupts the host's antimicrobial response.[55] AnkA translocates into the host nucleus and binds onto regulatory regions of the host chromatin, silencing defense genes responsible for producing ROS and decreasing H3 histone acetylation,[55] possibly by increasing histone deacetylase activity.[56] Some gammaproteobacteria symbionts of sponges also contain ARPs that prevent proper phagosome functioning in amoeba cells.[57] Therefore, ARPs may be utilized by pathogenic or mutualistic intracellular bacteria to epigenetically suppress the host's immune response and establish a niche within the host cell.

Many coral-associated bacteria also harbor ARPs,[54] which may help bacteria avoid phagocytosis and maintain stable endosymbiotic relationships within coral cells. Coral gastrodermal cells and endosymbiotic *Symbiodiniaceae* live in close association with endosymbiotic bacteria [58,59] These bacteria contribute nutrients to and extend the metabolic capabilities of the coral holobiont,[58] which further strengthens the commensal relationships between the coral, *Symbiodiniaceae*, and endosymbiotic bacteria, and provides an opportunity for molecular crosstalk between bacteria and host that may alter coral epigenomes.

Changes in coral epigenomes could also be driven by metabolites produced by coral-associated bacteria.[25] For example, folate, riboflavin, and other B vitamins are involved in the synthesis of S-adenosylmethionine, which is a methyl group donor in DNA methylation.[60] Interestingly, folate synthesis and riboflavin synthesis were identified in *Endozoicomonas* [61], which are symbionts in many different coral species.[62] These endosymbiotic bacteria also possess several transport and secretion mechanisms, which may be used for transferring molecules between the bacteria and *Symbiodiniaceae* or coral host.[61]

CORAL-ASSOCIATED BACTERIA MAY CONTAIN EPIGENOME-EFFECTOR PROTEINS

Many bacteria, such as extracellular pathogens *Helicobacter pylori*, *Agrobacterium tumefaciens* or *Vibrio cholerae*, have the capacity to deliver effector proteins into human, plant or invertebrate cells, respectively, using type IV or VI secretion system.[63] Secretion systems, such as the Type III secretion systems, have also been highlighted as potential drivers in the evolution of symbiotic relationships.[64] Several secretion systems, including those of type IV, have also been found in the microbiomes of several coral species [65] and could similarly be used to deliver effector proteins from the bacterial symbiont to the host.

To further explore the presence of epigenetic-modifying proteins in bacteria associated with corals, we searched for potential homologs of known epigenome-modifying proteins from other host systems (see above) in the predicted proteins of seven genomes of bacterial isolates from *P. damicornis* (average genome size 4.8 Mb), [Sweet et al., 2021 - https://journals.asm.org/doi/10.1128/mSystems.01249-20] 52 *P. lutea*-associated MAGs (average genome size 3.5 Mb) [54], and 11 bacterial genomes from the octocoral *Eunicella labiata* (average genome size 4.4 Mb).[67] The genomes were chosen to detect the possible existence of epigenome-modifying proteins in bacteria from three distinct coral hosts. The list of bacterial genomes is not exhaustive. Using BLASTP (minimum e-value of 1e-5, minimum identity of 35% [68] and minimum alignment length of 40), we found potential homologs to the AnkA protein from *A. phagocytophilum*; the LLO and InlB proteins from *L. monocytogenes*; Rv1988, Rv2966c, and Rv3423 from *M. tuberculosis*; and Mhy1, Mhy2, and Mhy3 from *M. hyorhinis* (Table 1 and Supporting Information).

Although many of the proteins in our database have pathogenic functions, their roles as epigenetic effectors provide insight into how homologous proteins may interact in other systems. Homologs to InlB indicate the potential for coral-associated bacteria to have proteins that may indirectly alter histone acetylation when identified by receptors on the surface of coral cells (Figure 2). InlB interacts with the

TABLE 1 Coral-associated bacteria with potential homologous proteins to bacterial epigenetic effectors from humans

		# of homologous proteins (e ≤ 1e-5, ≥35%, ≥40 aa)								
Coral source	# of bacteria	AnkA	InlB	LLO	Rv1988	Rv2966c	Rv3423	Mhy1	Mhy2	Mhy3
Pocillopora damicornis	7	0	0	0	1	1	0	0	0	0
Porites lutea	52	19	12	0	4	21	0	1	5	1
Eunicella labiata	11	3	0	0	2	9	0	0	0	0

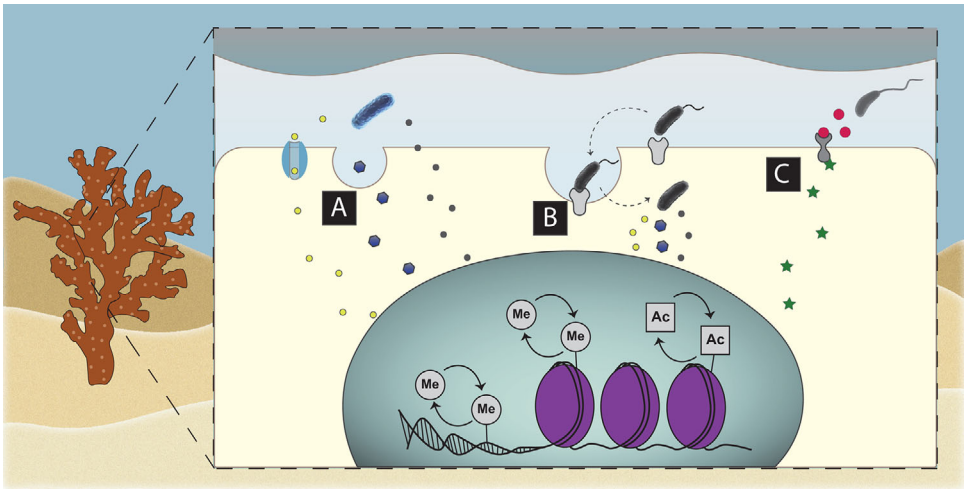

FIGURE 2 Coral-associated bacteria produce compounds that potentially alter the DNA methylation or histone post-translational modifications via direct or indirect mechanisms. Direct modifications to coral epigenetic state may occur by compounds produced by (A) extracellular bacteria (e.g., homologs to Rv1988, Rv 2966c, Mhy 1, Mhy 2, Mhy 3) or (B) intracellular bacteria (e.g., homologs to AnkA). Extracellular bacteria may also produce compounds that are recognized by coral receptors (C), indirectly causing a cascade within the coral cell that results in changes to the epigenome (e.g., homologs to InlB). Ac, acetylation; Me, methylation

receptor tyrosine kinase c-Met, which triggers the nuclear translocation of the histone deacetylase Sirt2 that downregulates several genes related to transcriptional regulation.[69] Interestingly, Sirt2 deacetylates forkhead box O transcription factors, which lowers intracellular ROS.[70] ROS can be produced by invertebrates as defense against pathogens [71] but has also been recognized in corals to damage host cells during bleaching.[72] This implies a potentially beneficial outcome of InlB homolog interactions with coral cell receptors. Protein homologs to Rv1988, Rv2966c, Mhy1, Mhy2, and Mhy3 suggest direct interactions with the coral's epigenome.

Of the 70 investigated coral-associated bacterial genomes and MAGs, 53 contained homologs for at least one of the known epigenome-modifying proteins (Table S1). The most prevalent epigenetic effector protein was Rv2966c (31 bacteria), followed by Rv1988 (7 bacteria). Rv1988 may be of particular interest due to its role in methylating histones controlling genes involved in producing ROS.[46] Because of the role of ROS in cell damage during bleaching,[72] bacteria-controlled downregulation of genes involved in the production of ROS might reduce coral cell damage when exposed to stressors. Further work is necessary to understand the specific role and importance of this and other epigenome-modifying proteins in coral health or disease.

MICROBIAL MODIFICATION OF CORAL EPIGENOMES MAY PROMOTE HEALTH

Differing host responses to environmental changes can lead to a lack of predictability for epigenome modifications.[73] Dysbiosis caused by stressors can further complicate how bacteria control host epigenomes and the stability of epigenetic changes caused by this control.[74] However, some bacteria that are administered on corals when exposed to environmental stress can be detected via amplicon sequencing,[66] which suggests that they can establish themselves as part of the microbiome. Therefore, epigenome responses to bacteria-host interactions, and their stability during stress conditions, may inform how bacterial manipulations can be implemented to cause modifications in coral phenotypes.

One way the coral epigenome may also be altered is through the action of its microbial members, which has been proven in other eukaryotic hosts [75], but has yet to be explored in corals. Symbiotic microbes can contribute to the maintenance and propagation of corals, while possibly aiding in coral resistance to detrimental environmental changes.[8,76] By manipulating the microbiome of *P. damicornis* through the addition of beneficial microorganisms for corals (BMCs), Rosado et al. [66] showed that coral bleaching

could be reduced in the presence of the pathogen *Vibrio coralliilyticus* at normal and high temperatures. Although BMCs have been shown to aid in coral resistance [66,77–79], [Santoro et al., 2021 - https://advances.sciencemag.org/content/7/33/eabg3088] through the regulation of genes involved in the coral immune response and protection against heat stress (Santoro et al., 2021 - https://advances.sciencemag.org/content/7/33/eabg3088), or even increase energy reserves and calcification rates,[80] the exact mechanisms producing the improved phenotype are not fully known. BMCs are chosen for their roles in coral holobiont nutrition and growth (via dimethylsulfoniopropionate degradation or increased cycling and provision of nutrients), removal of toxic compounds or stress mitigation (including decreasing intracellular ROS), early life development, and/or pathogen control.[76] One explanation would be that BMCs cause epigenetic changes in immune or environmental response genes resulting from one or more of these BMC functions which affects the coral's ability to defend itself against environmental stress or pathogens. Therefore, microbiome manipulation could present an exciting opportunity for harnessing epigenome modifications to promote long-term health of corals.

CONCLUSION

Several coral rehabilitation techniques have been proposed as ways to facilitate adaptation of coral to rapid global changes.[1,36], [Peixoto et al., 2019 - https://www.frontiersin.org/articles/10.3389/fmars.2019.00686/full] For example, "assisted evolution", aims to, along with other proposed approaches, selectively breed stress-resistant corals.[1] Likewise, facilitating phenotypic changes via deliberate induction of epigenetic modifications in corals has the potential to quickly acclimate coral to stressors and vertically transmit such resistances. It remains to be seen how bacteria can contribute to the epigenetic control of gene expression in corals. As in other host-associated systems, there is the possibility that coral pathogens such as *V. coralliilyticus* can negatively affect the host's epigenetic control of the immune response and diminish coral resistance or resilience to environmental stress. On the other hand, commensal or mutualistic bacteria may also directly or indirectly (e.g., through the biological control of putative epigenomic-modulating pathogens) interact with host epigenomes to improve phenotypic responses to environmental change, which may explain the resistant and resilient phenotypes observed in previous microbiome manipulation experiments. As coral reef conditions continue to worsen, research into the interaction between coral epigenomes and the associated bacteria has the potential to impact coral adaptation experiments.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Adam R. Barno wrote the primary manuscript with significant contribution from Helena D. M. Villela, Manuel Aranda, Torsten Thomas, and Raquel S. Peixoto. Helena D. M. Villela designed and prepared the figures. All authors were involved in critical revision.

DATA AVAILABILITY STATEMENT

Data sharing not applicable – no new data generated.

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