Microbiome and Metabolome Contributions to Coral Health and Disease

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Abstract
Coral populations are declining worldwide as a result of increased environmental stressors, including disease. Coral health is greatly dependent on complex interactions between the host animal and its associated microbial symbionts. While relatively understudied, there is growing evidence that the coral microbiome contributes to the health and resilience of corals in a variety of ways, similar to more well-studied systems, such as the human microbiome. Many of these interactions are dependent upon the production and exchange of natural products, including antibacterial compounds, quorum-sensing molecules, internal signaling molecules, nutrients, and so on. While advances in sequencing, culturing, and metabolomic techniques have aided in moving forward the understanding of coral microbiome interactions, current sequence and metabolite databases are lacking, hindering detailed descriptions of the microbes and metabolites involved. This review focuses on the roles of coral microbiomes in health and disease processes of coral hosts, with special attention to the coral metabolome. We discuss what is currently known about the relationship between the coral microbiome and disease, of beneficial microbial products or services, and how the manipulation of the coral microbiome may chemically benefit the coral host against disease. Understanding coral microbiome-metabolome interactions is critical to assisting management, conservation, and restoration strategies.

Introduction
Disease threatens corals globally, impacting vast populations of corals and reef ecosystems (Bruckner, 2015). The incidence of coral disease has continued to increase over time, with this trend being especially prominent in the Caribbean (Tracy et al., 2019). In parts of Florida and the Caribbean, more than 80% of Acropora coral cover has been lost due to bleaching and disease outbreaks (Aronson and Precht, 2001; Patterson et al., 2002; Gardner et al., 2003). Along the Florida Reef Tract in particular, at least 24 of 45 scleractinian (stony coral) species have been affected by a recent outbreak of stony coral tissue loss disease (SCTLD), which has decimated upward of 30% of coral density (Precht et al., 2016; Alvarez-Filip et al., 2019; Meyer et al., 2019; Rosales et al., 2020). Coral disease is an issue not only limited to the Caribbean but also of significant concern in the Indo-Pacific (Sweatman et al., 2011; Ruiz-Moreno et al., 2012; Tracy et al., 2019). In the Great Barrier Reef (GBR), it is estimated that outbreaks of coral disease were responsible for 6% of all coral mortality from 1995 to 2009 (Osborne et al., 2011). However, the prevalence of disease varies and can be locally higher in some reef systems (Ruiz-Moreno et al., 2012).

There are many factors postulated to drive the global increase in coral disease outbreaks. Environmental phenomena, such as El Niño Southern Oscillation cycles and increased seawater temperatures, which are linked to more

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Abbreviations: BMC, beneficial microorganism for corals; DMSP, dimethylsulfoniopropionate; DMSO, dimethyl sulfoxide; GBR, Great Barrier Reef; ROS, reactive oxygen species; SCTLD, stony coral tissue loss disease; TDA, tropodithietic acid.

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frequent bleaching events, can contribute to disease frequency and intensity (Bruno et al., 2007; Sweatman et al., 2011; Ruiz-Moreno et al., 2012; Muller et al., 2018; Tracy et al., 2019). In the GBR, for example, regional data have shown a link between increased incidence of white syndromes (a collective term for tissue loss diseases) and warm temperature anomalies (Bruno et al., 2007). Similarly, along the Florida Reef Tract, elevated incidence of white band disease (WBD) and black band disease (BBD) has been recorded following bleaching events (Brandt and McManus, 2009; Muller et al., 2018). Additionally, nutrient enrichment from runoff has also been implicated in exacerbating the severity of diseases such as BBD, dark spot syndrome, and yellow band disease in Caribbean coral species (Bruno et al., 2003; Vega Thurber et al., 2014). Evidence suggests a link between sewage pollution exposure and an increased prevalence of tissue loss diseases in both Caribbean and Pacific waters (Kaczmarsky, 2009; Redding et al., 2013). Recently, infections by an endosymbiont, Candidatus Aquarickettsia rohweri, was discovered to correlate with nutrient stress; however, its role in disease is still unclear (Baker et al., 2022). Regardless of the drivers of disease outbreaks, the consequences of such events can be catastrophic both ecologically and economically.

The role of a healthy microbiome and metabolome is not as well described in corals compared to other systems, such as the human gut microbiome. Therefore, understanding the dynamics and functions of these commensal and mutualistic communities can provide a helpful and important baseline that aids in disease diagnostics and pathogen identification (Pollock et al., 2011; Meyer et al., 2019). The enhancement of current microbial and metabolomic databases and/or development of new, more comprehensive databases would allow for comparative analysis between healthy and diseased corals and facilitate the discovery of biomarkers, allowing for a faster and more comprehensive response to disease outbreaks (Downs et al., 2000; Ochsenkühn et al., 2018; Voolstra et al., 2021; Deutsch et al., 2021). To obtain such a database, one must characterize and define the coral holobiont and metabolome, identify beneficial microbes and their role, and understand how manipulation of the microbiome and metabolome influences coral health.

This review focuses on the coral microbiome and the coral host’s potential to utilize microbial symbionts for disease resistance, with an emphasis on reef-building, scleractinian coral species. We review the importance of metabolomic approaches in addressing coral host-microbe interactions and highlight the putative role of beneficial microbial symbionts in disease resistance. We advocate for approaches that elucidate the functional role of the coral microbiome by incorporating multidisciplinary studies that characterize the interactions between the host, beneficial microbes, and potential pathogens. Such studies would increase our understanding of coral microbial communities and host health, allowing for better assessment and potential management options for coral reef restoration and conservation.

Disease Elicits Host Chemical and Microbial Response

Metabolomic approaches address biological issues through the assessment of metabolic pathways, chemical structures, and metabolite sources, expanding on the function of cellular interactions (Bundy et al., 2009). Metabolomics relies on the use of gas chromatography (GC) and liquid chromatography (LC), mass spectrometry (MS), and proton nuclear magnetic resonance (1H NMR) spectra to analyze the entire metabolic profile of an organism at a given time (Bundy et al., 2009). In the case of corals, metabolomic studies allow for the examination of the metabolic response of the entire holobiont to a set of conditions. This allows the detection of metabolites derived from microbes that are not easily culturable, therefore providing a more holistic view of the chemical defense response of the coral holobiont to disease and other stressors. Metabolomics data can provide important information about the dynamics of disease and other stress responses and can be used to identify bioindicators of disease and other stressors prior to the emergence of visual symptoms (Pomfret et al., 2019; Deutsch et al., 2021).

Visual signs of disease or bleaching are the primary indicators for assessing coral health (Boilard et al., 2020). However, this method does not address non-visible indicators for stress and is therefore primarily efficient in the detection of late-stage or large-scale disturbances. Early detection in changes to coral physiology is imperative to managing reef stressors and host health. Thus, utilizing a holistic approach to coral disease that examines microbial community compositions and metabolomic profiles is necessary in characterizing coral and microbial responses to stress. High-throughput 16S rRNA sequencing has traditionally been used to characterize microbial communities in diseased corals. Clark et al. (2021) compared microbial diversity compositions of coral disease lesions for five separate coral species (Colpophyllia natans, Pseudodiploria strigosa, Montastraea cavernosa, Orbicella faveolata, and Siderastrea siderea) experiencing SCTLD and found that all except one, S. siderea, had higher relative abundances of the bacterial order Rhodobacterales. Additionally, three of the five species had higher relative abundance of Clostridiales compared to healthy and unaffected tissues of the same species (Clark et al., 2021). Another study by Meyer et al. (2019) characterized SCTLD coral lesions from the species M. cavernosa, Diploria labrinthiformis, and Dichocoenia stokesii and showed a higher relative abundance of the bacterial orders Flavobacteriales, Clostridiales, Rhodobacterales, Alteromonadales, and Vibrionales. Such changes in the coral holobiont could lead to microbial dysbiosis and ultimately influence metabolic processes occurring within the host.

During coral stress, healthy or beneficial microbial groups that regulate the coral metabolome may become compromised,
changing the concentration and output of metabolites within the coral holobiont. For example, heat stress can result in the accumulation of dimethylsulfoniopropionate (DMSP) in coral cells (Raina et al., 2013). This buildup of DMSP in heat-stressed corals has been shown to attract the coral pathogen *Vibrio coralliilyticus* to the coral *Porites* damicornis (Garren et al., 2014; Frade et al., 2016). Higher concentrations of DMSP may be acting as a chemoattractant here, triggering chemotaxis in *V. coralliilyticus*, causing it to aggregate to the potentially susceptible coral host (Garren et al., 2014; Frade et al., 2016). In the case of *V. coralliilyticus*, chemotaxis and motility appear to play a large role in pathogenesis (Ushijima and Hase, 2018). Higher temperatures may trigger higher concentrations of DMSP, which correlates with increased motility and chemotaxis by this bacterium (Garren et al., 2015) as well as coincides with conditions that increase the precension of virulence-regulating gene products (Ushijima et al., 2016). Further, chemotaxis is common among marine bacteria and is thought to play a large role in shaping ocean microbiomes (Raina et al., 2022); therefore, studying the chemical signals associated with corals may provide insight into the bacterial-host relationships occurring in these environments.

Some pathogenic bacterial groups or disturbance events are capable of even further disrupting the coral holobiont through the production of antimicrobial compounds or activating the host immune response. An example of this is in heat-stressed *Mussismilia hispida* corals, which showed an increase in DMSP and dimethyl sulfoxide (DMSO) as well as a decrease in lipids and photosynthetic efficiency (Santoro et al., 2021). These changes have the potential to increase coral mortality through the increase of toxic sulfur metabolites, the potential breakdown of the cell membrane, and the reduction of energy produced through photosynthesis. Similarly, another study used metagenome analysis to show the potential metabolic pathways in bacteria, expressing that there was a higher number of metabolic functional genes within samples taken from SCTLD lesions, including from bacterial orders Rhodobacterales and Flavobacteriales (Rosa et al., 2022). This may be related to the bacteria’s proliferation or antibiotic resistance. However, future studies that pair metagenomic with functional metabolomics are needed to further elucidate which genes and metabolites are utilized by bacteria during the onset of disease.

**Coral Natural Defenses**

Though metabolomics can be an informative approach to understanding *in situ* responses within the coral holobiont, its application in coral microbial studies is lacking, and the field requires a more robust database for the identification and function of metabolites. This includes utilizing metabolome analysis to identify and quantify metabolites that play key roles in host fitness. Although specific metabolites are not always identified, identifying beneficial microbial groups and understanding their potential contributions to the coral host can also aid in our understanding of coral health. It is theorized that corals select microbes from the environment to allow them to adapt to their surroundings (Shnit-Orland and Kushmaro, 2009; Peixoto et al., 2017; Rosado et al., 2019). This may be an evolutionary adaptation in response to the apparent lack of an adaptive immune system (Reshef et al., 2006). The manipulation of microbial communities or symbionts for host benefit has been described by the coral probiotic hypothesis (Reshef et al., 2006) and further expanded upon to include the caveat that microbiome flexibility and maintenance tend to be host specific (Reshef et al., 2006; Peixoto et al., 2021; Santoro et al., 2021). Several studies to date have demonstrated antibiotic activity of coral-associated bacteria against pathogenic and ecologically relevant bacteria. Interestingly, a portion of these coral-derived isolates demonstrate inhibitory activity against putative coral pathogens during laboratory assays. In a large screening of 776 strains isolated from *Acropora palmata*, 8% inhibited the growth of *Serratia marcescens*, a known coral and mammal pathogen; and 20% demonstrated inhibitory activity against one or more of a suite of indicator strains (Ritchie, 2006). When isolates from *A. palmata* were selectively grown on mucus from the coral, the percentage that inhibited *S. marcescens* growth increased to 35% (*n* = 17) (Ritchie, 2006). Another study by Pereira et al. (2017) isolated 900 strains from 4 Brazilian coral species (*Madracis decactis, Mussismilia hispida, Tubastrea sp.*, and *Polythoa caribacorum*), the surrounding water, and sediment to evaluate their diversity. Of these, a subset of 144 isolates were tested for antibacterial activity against a suite of terrestrial and marine pathogens (Pereira et al., 2017). From those isolates, 38% demonstrated antimicrobial activity against at least one pathogen, and 94% (*n* = 55) of the active strains inhibited the growth of *S. marcescens* (Pereira et al., 2017). Additionally, the authors identified that coral mucus samples contained relatively higher abundances of α-proteobacteria and γ-proteobacteria, with bacteria belonging to the genus *Bacillus* constituting a large proportion of the isolates demonstrating antimicrobial activity. These studies demonstrate that beneficial microorganisms for corals (BMCs) have the ability to contribute antimicrobial activity against potential pathogens and that corals likely contain a plethora of these microbial groups that may contribute to host immunity and other essential functions.

Raina et al. (2016) isolated bacteria from various corals from the GBR and tested those isolates for activity against two species associated with coral tissue loss diseases, *Vibrio coralliilyticus* and *Vibrio owensii*. The authors used 1H NMR and mass spectrometry approaches and found that the coral isolate *Pseudovibrio* sp. P12 was capable of metabolizing DMSP to produce the sulfur-containing antibiotic tropo-dithietic acid (TDA) (Raina et al., 2016). Additionally, genome analysis of Pseudovibrio sp. P12 identified DMSP catabolism-associated genes likely used for TDA synthesis (Raina et al., 2016). Like *Pseudovibrio*, *Roseobacter* spp. has
been documented to be involved in DMSP catabolism and the production of antimicrobial products, such as thioto-
pocin and TDA (Bruhn et al., 2005; Raina et al., 2009; Luo and Moran, 2014). A number of coral-associated microor-
ganisms are able to metabolize DMSP, which likely plays an important role in the structuring of coral microbiomes; 
this has implications for coral health (Raina et al., 2009). Another compound capable of providing antagonistic in-
teractions with pathogens is labrenzibactin. This compound 
was recently discovered from a Montipora sp.-associated 
bacterium in the genus Labrenzia (Raj Sharma et al., 2019). 
The compound inhibited the growth of the gram-negative 
plant pathogen Ralstonia solanacearum and the gram-
positive human-associated bacterium Micrococcus luteus 
(Raj Sharma et al., 2019). While this compound has not yet 
been investigated for its activity against ecologically relevant 
microbes, its ability to inhibit the growth of gram-negative 
and gram-positive bacteria suggests that it may serve as a 
broad-spectrum antimicrobial that protects the coral host. 
Beneficial microorganisms for corals can also impact corals 
directly by microbial succession, niche occupation, or 
the prevention of dysbiosis through pathogen deterrence 
(Santoro et al., 2021). Some BMCs may not be detected us-
ing metagenomic analyses or through culturing; therefore, 
it is important to also use metabolomic analysis to iden-
tify biomarkers that vary in the presence of BMCs (Sweet 
et al., 2021). More detailed work is needed to examine 
metabolomic changes over time and along various stress 
gradients.

**Coral Probiotics and Microbiome Manipulation**

Beneficial microbes support numerous processes within the 
coral host and its surroundings, including nitrogen fixa-
tion, sulfur cycling, production of antimicrobials, and scav-
enging reactive oxygen species (Reshef et al., 2006; Peixoto 
et al., 2017; Santoro et al., 2021). These microbial groups 
can alter the metabolic structure among corals, leaving be-
hind biomarkers that may ultimately affect the coral’s abil-
ity to respond to environmental stress. Beneficial microor-
ganisms for corals have recently been proposed as a tool for 
coral restoration and improvement of coral health because 
the frequency of bleaching events and emergence of coral 
diseases continue to rise, creating opportunities for inter-
ventions in the coral microbiome.

Due to the complexity and elusive nature of the coral micro-
bioiome, the development of BMC inoculates or probiotic 
treatments proves to be challenging. However, recent stud-
ies have outlined four important functions that microbial 
groups may demonstrate in order to be considered a BMC. 
To be considered a BMC, microbial groups may demonstrate 
antagonistic or antimicrobial activity against potential path-
ogens and/or degradation of DMSP, as discussed earlier in 
this review (Rosado et al., 2019; Peixoto et al., 2021). Bac-
terial strains in the genera Endozoicomonas and Roseobacter 
are both common examples of bacteria found in healthy 
corals that are known to assimilate DMSP and synthesize 
antimicrobial compounds such as TDA (Raina et al., 2016; 
Damjanovic et al., 2020). As noted previously, BMCs can 
decrease compounds such as DMSP and DMSO and increase 
lipogenesis, aiding in the metabolic restructuring of the coral 
holobiont. Another category of BMCs include those that 
mitigate stress or toxic compounds (Peixoto et al., 2017, 
2021; Santoro et al., 2021). Reactive oxygen species (ROSs) 
are produced by corals and the endosymbiotic algae under 
elevated temperatures (Nielsen et al., 2018). Reactive oxy-
gen species seep into coral cells, where ROSs induct the 
antioxidant system; this results in host tissue damage and 
Symbiodinium expulsion (Nielsen et al., 2018). During a trial 
of elevated salinity, an increase in the compound floridoside 
emitted by Symbiodinium effectively lowered ROSs and de-
creased bleaching susceptibility. Photoprotective compounds 
produced by photosynthetic organisms can also reduce ROS 
damage (Dunlap and Shick, 1998; Nielsen et al., 2018). Cy-
nobacteria, heterotrophic bacteria, and microalgae produce 
mycosporine-like amino acids that act as a natural photo-
protective compound by absorbing UV radiation (Ravindran 
et al., 2013). Finally, involvement in early life stages is the 
fourth category that microbial taxa may meet to be consid-
ered a BMC. To date, there are various microbial inter-
actions that aid in the settlement of corals and have been 
associated with spawning, indicating a role in juvenile sur-
vival. Alteromonas and Roseobacter bacteria increase in the 
water column during a broadcast spawning event, likely due 
to their persistence in healthy coral microbiomes and their 
involvement in DMSP degradation and antimicrobial prop-
erties (Ceh et al., 2012). The bacterial genus Endozoicomonas 
is inherited by the brooding coral Pocillopora acuta, likely 
because it has similar antimicrobial functions and DMSP 
regulation (Damjanovic et al., 2020). Several Pseudseudo-
alteromonas spp. produce the compound tetrabromopyrrole, which 
induces settlement and/or metamorphosis in a large range of 
Caribbean and Pacific corals (Sneath et al., 2014; Tebben 
et al., 2011).

Probiotic application can be used to manipulate antag-
onistic interactions between corals and coral stressors, which 
could potentially change microbial diversity and coral me-
tabolomic profiles. Santoro et al. (2021) inoculated Mussi-
similia hispida corals with a BMC consortium and a saline 
solution placebo to examine how BMC addition would aid 
survival and resilience of the coral subjected to heat stress. 
The BMC treated corals showed significantly different bac-
terial community structure than placebo treated corals dur-
ing heat stress. However, microbial communities were more 
similar between treatment times during the recovery period 
from heat stress. Additionally, BMC treated corals showed 
signs of DMSP degradation, lipid maintenance, and ROS 
mitigation, contributing to an overall higher survival rate 
compared to placebo treated corals. This study emphasizes 
that BMC consortium is more readily taken by the coral 
host as it experiences stress and attempts to restructure the
microbiome to a pre-stress state. This leads to questions about probiotic application time frames, because it is unclear how long BMC communities will remain in the coral host. Morgans et al. (2020) inoculated Acropora millepora corals with Symbiodiniaceae probiotics after experimentally exposing corals to heat stress. Corals that contained the inoculant showed higher resistance to heat stress and bleached compared to corals that did not receive the inoculant (Morgans et al., 2020). However, unlike the study by Santoro et al., the species of Symbiodiniaceae applied were not detected during microbial analysis of the coral tissues. This is because the inoculant may instead be indirectly supplementing heterotrophic nutrition to the coral, thus providing the coral with nutrients needed to mitigate thermal stress.

Using BMCs as a tool for coral restoration and survival is promising because probiotic applications show mitigation against coral stressors and a significant increase in host survival and fitness. However, taking visual surveys and understanding the microbial composition alone will not inform researchers or reef managers of the chemical interactions happening within the coral holobiont. Metabolomic measurements are needed to provide in situ analysis of interactions in the holobiont, providing researchers a better understanding of the needs of the coral and characterization of the coral condition. Perhaps this method of sampling will inform individuals more about which BMC consortium is best and provide a better selection of microbial symbionts to the host to increase its chances of survival.

Limitations and Conclusions

Much of the current understanding of microbial roles in coral health relies on manipulative experiments that use culturable bacterial strains. Such experiments allow for confirmation of direct cause-and-effect relationships between members of the coral holobiont and their environment, including the chemically mediated interactions that occur. However, research into new culturing techniques has not kept up with the research described here, significantly limiting culture-based approaches (Joint et al., 2010). Multi-omic approaches, including metagenomics, metatranscriptomics, and metabolomics, can enhance our understanding of microbial roles in coral health by giving a culture-independent view of the microbial and molecular diversity present.

Establishing parameters of coral health is a gradual process that incorporates the analysis of coral-microbe relationships and how biochemical products improve host fitness. However, incorporating metabolomic research in the context of coral disease and coral health has proven to be difficult due to limited resources within metabolite databases and inconsistencies across sampling methods (Bundy et al., 2009; Joint et al., 2010). The identification of metabolites within a sample may be conditional, because changes in metabolites are temporary and because some metabolites have a rapid turnover (Dorrestein et al., 2014; Low et al., 2017).

Because the metabolome is diverse and sensitive to minor changes in stimuli, studies examining the metabolome require consistency, enhanced information recovery, and reduced variability between test subjects for data reproducibility (Dorrestein et al., 2014; Low et al., 2017). Standardization could help metabolomic approaches to elucidate the mechanisms for which microbial constituents influence the coral host and provide key insights into how corals manage their microbial communities under environmental stress.

Current technologies can aid in elucidating host-metabolome-microbiome connections by saturating metabolite reference databases with known findings and allowing for the interpretation of new metabolites. Furthermore, interdisciplinary approaches that examine the microbiome, the metabolome, and immunological responses simultaneously in the same specimens can create a model system that helps explain current observations and discoveries. This information would pave the road for future research, predictive modeling, and the potential development of treatments or management strategies for disease.

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