Help me, symbionts, you're my only hope: Approaches to accelerate our understanding of coral holobiont interactions

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Abstract: Tropical corals construct the three-dimensional framework for one of the most diverse ecosystems on the planet, providing habitat to a plethora of species across taxa. However, these ecosystem engineers are facing unprecedented challenges, such as increasing disease prevalence and marine heatwaves associated with anthropogenic global change. As a result, major declines in coral cover and health are being observed across the world's oceans, often due to the breakdown of coral-associated symbioses. Here, we review the interactions between the major symbiotic partners of the coral holobiont – the cnidarian host, algae in the family Symbiodiniaceae, and the microbiome – that influence trait variation, including the molecular mechanisms that underlie symbiosis and the resulting physiological benefits of different microbial partnerships. In doing so, we highlight the current framework for the formation and maintenance of cnidarian-Symbiodiniaceae symbiosis, and the role that immunity pathways play in this relationship. We emphasize that understanding these complex interactions is challenging when you consider the vast genetic variation of the cnidarian host and algal symbiont, as well as their highly diverse microbiome, which is also an important player in coral holobiont health. Given the complex interactions between and among symbiotic partners, we propose several research directions and approaches focused on symbiosis model systems and emerging technologies that will broaden our understanding of how these partner interactions may facilitate the prediction of coral holobiont phenotype, especially under rapid environmental change.

Keywords: Coral symbiosis; immunity; microbiome; global change; coral holobiont; Symbiodiniaceae

Introduction

Reef-building corals are the framework engineers for coral reef ecosystems that build one of the most biodiverse habitats in the world, (Reaka-Kudla et al. 1996) and are economically and ecologically critical (Moberg and Folke 1999; Costanza et al. 2014). Dramatic losses in coral cover are being documented globally as anthropogenic greenhouse gas emissions

increase and other direct human impacts drive environmental change (De'ath et al. 2012; Eddy et al. 2021). When seawater temperatures rise or chemistry changes, these shifts can lead to a loss of the coral's symbiotic relationship with its endosymbiotic algae in a process termed coral bleaching (Glynn 1991) and these episodes are increasing in frequency and severity (Sully et al. 2019). Predicting coral resilience to changing oceans has become a critical goal of coral reef research, yet, we are just beginning to disentangle the key mechanisms underlying symbiosis establishment, maintenance, and loss, which are crucial processes in understanding coral resilience.

Understanding symbiosis outcomes under changing oceans is challenging because corals are holobionts – assemblages of the coral host and many other living partners, including millions of single-celled dinoflagellates (family Symbiodiniaceae, (LaJeunesse et al. 2018)) living inside coral gastrodermal cells – that together form a discrete ecological unit (Rosenberg et al. 2007; Rosenberg and Zilber-Rosenberg 2018). In tropical, oligotrophic waters, these symbiotic algae provide essential organic byproducts to the host from photosynthesis (Muscatine and Cernichiari 1969). Algal symbiont diversity has become better appreciated thanks to molecular genetics approaches (reviewed in Quigley et al. 2018; Davies et al. 2022) and whole-genome datasets (Dougan et al. 2022), which have resulted in taxonomic revisions (LaJeunesse et al. 2018, 2021; Nitschke et al. 2020; Pochon and LaJeunesse 2021). However, how this genetic variation predicts functional variation remains an open question. Unique algal isolates can be functionally divergent (*e.g.,* Parkinson and Baums 2014; Beltrán et al. 2021), which is perhaps predictable given that reefs are highly variable and algae exhibit limited dispersal (Fitt et al. 1981), hypothetically leading to adaptive divergence in algal communities (Howells et al. 2011) or long-term acclimatization (Torda et al. 2017).

Although some coral species exhibit specificity for particular algae (Thornhill et al. 2014; Hume et al. 2020), others can associate with a diverse array of algae that can potentially shuffle under different environmental conditions (Baker and Romanski 2007). Hosts can associate with "homologous" (*i.e.,* symbiont strains hosted under ambient conditions) or "heterologous" (*i.e.,* opportunistic strains hosted following disturbance) algal strains (Davy, Lucas, and Turner 1997; Weis et al. 2001). A host may associate with multiple strains at any given time, the proportion of which can vary under changing environments (see Reich et al. 2017; Matthews et al. 2018). This potential flexibility is important because not all host-symbiont pairings are equally resilient under stress (Berkelmans and Van Oppen 2006; Hoadley et al. 2019). For example, whole-genome resequencing of over 250 corals during a bleaching event found that Symbiodiniaceae associations (*Cladocopium* vs. *Durusdinium*) were a stronger predictor of bleaching than host genetic variation (Fuller et al. 2020). Limited work also suggests that host symbiont preference could have a host genetic basis (Quigley et al. 2019; Reich et al. 2021), therefore symbiont-driven thermal tolerance may have higher heritability than expected. Thus, changes in symbiont associations (*i.e.,* symbiont shuffling (Baker 2003)) may enhance resilience to future stress events.

Recently, the roles of other members of the microbiome (*e.g.,* bacteria, viruses, fungi, archaea, etc.) in maintaining holobiont health have become

more appreciated (Pollock et al. 2018; van Oppen and Blackall 2019). The majority of microbiome research has focused on bacteria, which, similar to the algae, provide hosts with essential nutrients (Robbins et al. 2019), nitrogen cycling (Rädecker et al. 2015) and carbon cycling (Kimes et al. 2010). The diversity and community composition of microorganisms within a coral interact to support a healthy holobiont through resource allocation (Bourne et al. 2016), particularly under stress (Webster and Reusch 2017). Indeed, corals exhibiting higher microbiome flexibility (*i.e.,* restructuring of microbial community) may possess a unique ecological advantage to better acclimate to environmental change (Voolstra and Ziegler 2020). These differences between 'microbiome regulators' (corals that maintain stable microbiomes; *e.g., Pocillopora verrucosa*) and 'microbiome conformers' (corals that modulate microbiomes in response to environment; *e.g., Acropora hemprichii*) may help to predict holobiont phenotypes under stress (Ziegler et al. 2019).

Clearly, each coral holobiont is a complex metaorganism, and understanding–and ultimately predicting–its response to future change depends on an integrated understanding of all partners and their interactions. Here, we present what is known about how diversity of corals and their different symbiotic partners interact to influence holobiont physiology and propose a set of research directions that leverage emerging cnidarian model systems to further disentangle how holobiont partner interactions might influence coral persistence under rapid change.

Host genetic diversity and its influence on holobiont phenotype

Coral host genetic diversity both within and between species is vast, and this diversity can lead to varied responses to environmental stressors. Sequencing technologies for non-model systems have improved our ability to detect this diversity and estimate genetic divergence between hosts across spatial scales, such as depth (Prada and Hellberg 2013; Serrano et al. 2016) and environmental gradients (Kenkel and Matz 2016). Similarly, genomic sequencing has facilitated further identification of sibling species (*i.e.,* cryptic species) within previously presumed coral species (Bickford et al. 2007). Cryptic speciation is a well-known phenomenon in corals (Knowlton 1993; Prada and Hellberg 2013; Forsman et al. 2020; Fifer et al. 2022); however, recent work suggests that these cryptic lineages may exhibit differential responses to global change (Gómez-Corrales and Prada 2020) and host unique algal communities (Rose et al. 2021). While coral genetic diversity may not always directly predict phenotypic diversity, phenotypic variation can be heritable (*i.e.,* narrow-sense heritability, h^2) across various coral traits (Bairos-Novak et al. 2021), including thermal tolerance (Dixon et al. 2015), settlement responsiveness (Meyer et al. 2011), calcification (Jury et al. 2019), and growth (Kenkel et al. 2015). This genetic variation highlights the need to include multiple genetic backgrounds in mechanistic studies, as each unique genotype may determine a phenotypic response.

As an additional layer of complexity, corals have a bipartite life cycle that involves planula larval dispersal, followed by recruitment to a substrate, and maturation into a benthic, sedentary adult (Baird et al. 2009). The selective pressures on planula larvae in the water column are likely very different from those experienced by the recruit or adult coral, which may lead to ontogenetic shifts in selection pressures, diverse symbiont acquisition

strategies (Hartmann et al. 2017; Ali et al. 2019; Epstein et al. 2019), and differences in adaptive potential across life stages (reviewed in (Putnam 2021)). For example, trait heritability has been shown to vary across coral life stages, with adult and larval stages exhibiting higher heritability of bleaching and growth when compared to the juvenile stage (Bairos-Novak et al. 2021). Such differences may constrain evolution through genetic trade-offs between traits and across life stages. These complex life cycles combined with differences in transmission strategies across hosts and partners make predicting coral performance under changing environments challenging.

The role of the microbiome in coral holobiont phenotype and resilience

Corals are composed of several microhabitats (*e.g.,* tissue, mucus, gastrovascular cavity, skeleton) hosting different microorganisms (Sweet et al. 2011; Pollock et al. 2018) that support functions within the holobiont. For example, anoxic conditions within coral gastric cavities at night likely support nitrogen fixation by anaerobic microorganisms (Bourne et al. 2016; Bove et al. 2020), which can in turn facilitate photosynthesis of Symbiodiniaceae (Rädecker et al. 2015). However, these compartments are often homogenized when sampling corals (Hughes et al. 2022), potentially concealing more specific microbiome signatures (Pollock et al. 2018; Armitage and Jones 2019; Biagi et al. 2020). Therefore, our understanding of how the spatial arrangement of the microbiome shapes holobiont function remains largely unknown (but see (Wooldridge 2010; Morris et al. 2019; Jiang et al. 2021)).

The coral microbiome is influenced by many factors, including host developmental stage (Sharp et al. 2012; Damjanovic et al. 2020), spatial scales (*e.g.,* across an individual (Rohwer et al. 2002) or geographic regions (Williams et al. 2022)), and environmental change (van Oppen and Blackall 2019; Voolstra and Ziegler 2020) – especially thermal stress (reviewed in Maire et al. 2022). However, interactions between microbes and other holobiont partners is particularly important for understanding coral resilience. For example, recent work identified relatively stable bacterial assemblages associated with *Durusdinium trenchii* even under thermal stress that may promote thermal resilience (Lawson et al. 2018; Camp et al. 2020). Similar to warming, the effects of ocean acidification on coral microbiomes is species-specific (Meron et al. 2012; Biagi et al. 2020), with changes mostly occurring in the mucus layer (Glasl et al. 2016; Biagi et al. 2020). Because environmental disturbances will continue to occur as global change persists, a deeper understanding of how multiple stressors interact with these microbial members of the coral holobiont is needed.

While significant advances in our understanding of Symbiodiniaceae-host (see Mieog et al. 2009; Morris et al. 2019) and bacteria-host (see Ainsworth et al. 2010; Webster and Reusch 2017) interactions have been made, the relationships between different members of the microbiome (*i.e.,* Symbiodineaceae and bacteria) remain less studied (but see Matthews et al. 2020). Recent characterization of bacterial communities associated with cultured Symbiodiniaceae have showcased high bacterial diversity across algal strains with three common bacterial groups serving as the core members of Symbiodiniaceae-bacterial assemblages (Lawson et al. 2018). The most abundant core member, Labrenzia, produces

dimethylsulfoniopropionate (DMSP), which may play a role in the coral stress response (Jones and King 2015). DMSP production has historically been attributed to Symbiodiniaceae; however, if Labrenzia are producing DMSP, then they may play a pivotal role in holobiont health. This group was also found to increase in abundance under thermal stress in cultures of *Cladocopium* spp. (Camp et al. 2020), suggesting it may function in the algal stress response as well. These critical Symbiodiniaceae-bacteria interactions are just beginning to be explored and require further elucidation.

Known molecular mechanisms underlying cnidarian-algal symbiosis

Symbiotic Cnidarians are faced with the challenge of establishment and maintenance of their algal symbionts while surrounded by a soup of microbes (Hernandez-Agreda et al. 2017). Cnidarians rely on innate immunity to differentiate between beneficial and pathogenic microbes (reviewed by (Nyholm and Graf 2012)). The primary mechanism for the host to detect friend versus foe is through Pattern Recognition Receptors (PRRs) that are either secreted by, presented on the surface of, or located entirely within animal cells (reviewed in Akira et al. 2006). Extracellular and transmembrane receptors may be important for symbiont recognition and establishment, while cytoplasmic PRRs may be involved in intracellular symbiont maintenance. PRRs recognize and bind specific patterns on microbial cells and initiate intracellular signaling cascades that modulate the host's immune system (reviewed in (Mansfield and Gilmore 2019)).

One PRR-microbe interaction implicated in the cnidarian-Symbiodiniaceae symbiosis occurs between host lectin receptors and symbiont glycans (Tortorelli, Rautengarten, et al. 2022). Symbiodiniaceae species have different cell-surface glycan assemblages, which may facilitate highly specific recognition and establishment (Logan et al. 2010). Phylogenetic analyses have implicated PRRs in symbiosis as demonstrated by an independent expansion of PRRs in symbiotic, but not non-symbiotic cnidarians (Baumgarten et al. 2015; Emery et al. 2021). Cnidarian ficolin-like proteins (CniFLs) are PRRs unique to symbiotic Cnidaria hypothesized to function in highly specific recognition and uptake of compatible symbiont types. In the sea anemone model for symbiosis *Exaiptasia pallida* (Aiptasia), CniFLs transition from upregulated in aposymbiotic individuals to downregulated following establishment of symbiosis with homologous symbionts (Baumgarten et al., 2015).

Symbiosis establishment with (homologous) algal symbionts induces anti-inflammatory immune pathways and reduces pro-inflammatory immune pathways, as measured through Reactive Oxidative Species (ROS) production (reviewed by Weis et al. 2008). Indeed, symbiosis between Aiptasia and homologous symbionts is associated with lower expression of pro-inflammatory gene pathways relative to aposymbiotic Aiptasia (Lehnert et al. 2014). The cytokine Transforming Growth Factor β (TGFβ) can suppress the inflammatory response (reviewed in Yoshimura et al. 2010) by downregulating certain cnidarian immune pathways (Fuess et al. 2020). Induction of TGFβ and repression of the immune response appear necessary for establishment of homologous symbionts in Aiptasia (Detournay et al., 2012). Nuclear Factor-κB (NF-κB) is an evolutionarily conserved transcription factor in the innate immune system activated by PRRs and

inhibited by TGFβ in Aiptasia (reviewed in Gilmore 2006; Mansfield and Gilmore 2019). NF-κB is downregulated following establishment of homologous symbionts in adult and larval Aiptasia compared to aposymbiotic larvae and adults (Wolfowicz et al. 2016; Mansfield et al. 2017). Aposymbiotic branches of the facultative coral *Oculina arbuscula* also exhibit enrichment of gene pathways involved in NF-κB immunity compared to symbiotic branches (Rivera and Davies 2021). Further, field-collected *Acropora palmata* exhibited upregulation of NF-κB transcription under short-term thermal stress (DeSalvo et al. 2010).

Interestingly, NF-κB is not downregulated in adult and larval Aiptasia nor adult *Pocillopora damicornis* harboring heterologous symbionts, indicating that the host fails to detect heterologous symbionts through the same mechanism as homologous symbionts (Mansfield et al. 2019). Additionally, Aiptasia populated by heterologous symbionts induce multiple oxidative response pathways and accumulate more ROS and Reactive Nitrogen Species compared to Aiptasia hosting homologous symbionts (Lehnert et al. 2014; Matthews et al. 2017). These data suggest that hosts associated with heterologous symbionts are chronically responding to oxidative stress even under ambient conditions, but it may also suggest conferred tolerance through antioxidant priming (Matthews et al. 2017). Though hosting heterologous symbiont strains appears to confer maintained immunity, nutritional benefits have been associated with hosting homologous strains (Starzak et al. 2014; Rädecker et al. 2018). Homologous-hosting Aiptasia assimilate more symbiont metabolites than those hosting heterologous symbionts (Matthews et al. 2017, 2018). Symbiosis maintenance involves host control over Symbiodiniaceae cell density through regulation of the symbiont's cell cycle and nitrogen cycling in both *O. arbuscula* and Aiptasia (Rivera and Davies 2021; Gorman et al. 2022). It is also noteworthy that heterologous symbiont density is lower (at least in Aiptasia) than homologous symbionts (Matthews et al. 2018; Tsang Min Ching et al. 2022), implicating greater host control over cell proliferation in heterologous partnerships. Further research is required to understand the conference of metabolic benefits by different strains under stress conditions.

In general, this work supports the emerging hypotheses for the molecular mechanisms that might differ between cnidarians harboring homologous and heterologous algal strains, as summarized in **Figure 1**. Cnidarians harboring heterologous symbionts are frequently classified as more stress-tolerant than those harboring homologous symbionts because of two hypotheses, which are not mutually exclusive: 1) hosts are able to maintain constitutively higher innate immunity, which allows for immune priming to better quench increased ROS under stress and 2) lower algal symbiont densities in hosts associated with heterologous symbionts leads to less ROS produced. The role of the molecular pathways explored in this section may be further clarified through targeted knock-out, knock-down, and overexpression experiments. Additionally, the roles of specific localized tissues and cell-types in symbiosis control and nutrient exchange will be resolved with further implementation of emerging technologies (*e.g.*, single-cell RNA-seq) across many species, lineages, and treatment conditions as discussed below (see *Leveraging Novel Technologies)*.
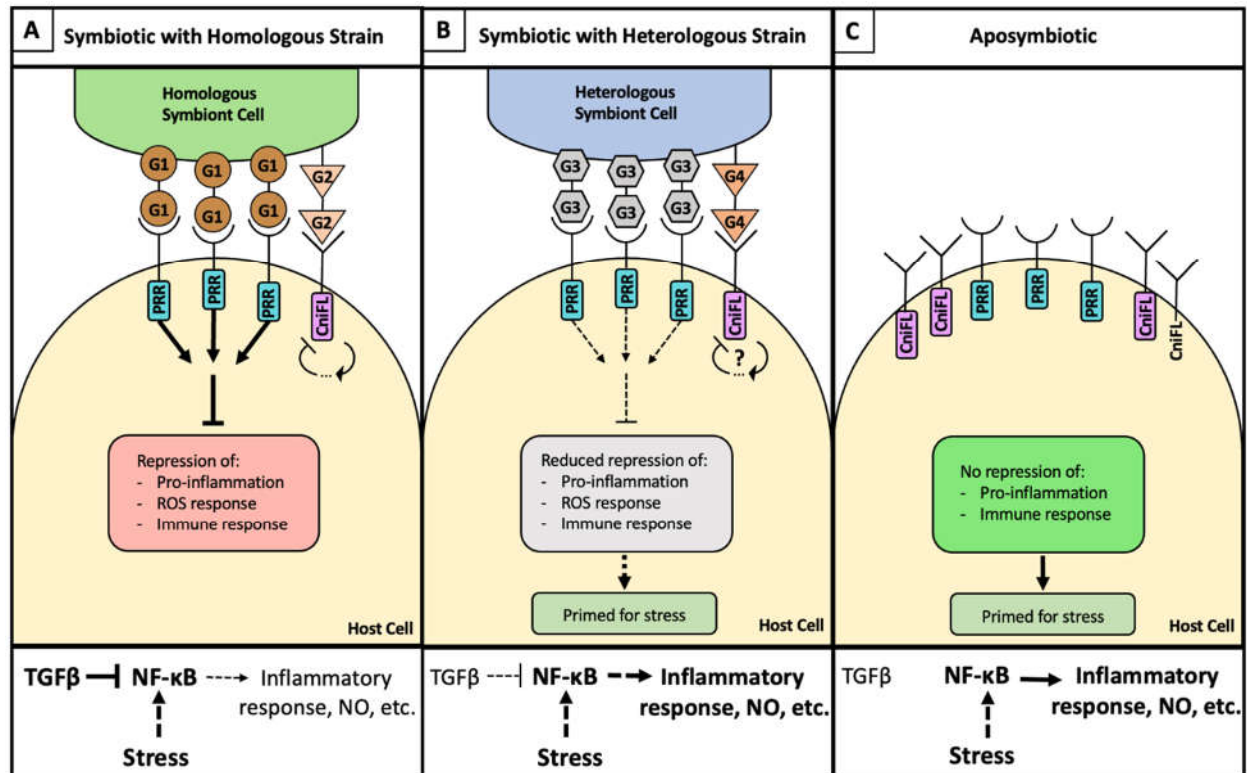
Figure 1. Proposed mechanism of immunity regulation in three scenarios of cnidarian-algal symbiosis. A) When a homologous symbiont strain is detected by a host cell, Pattern Recognition Receptors (PRRs) on the host cell surface recognize and bind glycans (G1) presented on the symbiont cell. This high affinity binding induces an intracellular signaling cascade that downregulates pathways responsible for inflammation, the reactive oxygen species (ROS) response, and the immune response. This repression may be via the inhibition of NF-κB – and therefore the inflammatory response and nitric oxide (NO) production – by TGFβ. Other glycans (G2) bind CniFLs on host cells, which participate in a negative feedback loop. **B)** When a heterologous symbiont strain is detected by a host cell, PRRs on the host cell surface have lower binding affinity for symbiont glycans (G3). Therefore, the intracellular signaling cascade is either induced to a lower degree or fails to be induced (depending on the binding affinity between G3 and PRRs). The reduced signaling cascade (and lower TGFβ) means that pro-inflammation, the ROS response, and the immune response (characterized by NF-κB immunity) are not inhibited. This reduced repression may prime host cells for future stress. It remains unclear whether CniFLs can recognize and bind heterologous symbiont glycans (G4). **C)** In aposymbiotic hosts, the intracellular signaling cascade involving TGFβ repression of NF-κB is not induced, so inflammation and the NF-κB immune response remain high. Additionally, there is a high density of CniFLs presented on the host cell to detect symbionts in the environment. Bolded arrows and text indicate stronger induction/repression of a pathway or response. Dashed arrows indicate transient (e.g., stress) or partial (e.g., inflammatory response) pathway induction/ repression, whereas solid arrows indicate continuous induction/repression.

Proposed paths forward to disentangle the functional consequences of partner interactions.

To better understand and predict coral symbiotic partnerships under environmental change, we propose several paths forward that would

broaden our understanding of holobiont interactions and resulting phenotypes.

Increasing the number of host-algal pairings in cnidarian studies

Certain cnidarian model systems have been developed to facilitate the study of the biochemical processes that modulate associations and dissociations of cnidarian hosts with microbial partners. The sea anemone Aiptasia has provided a platform for many advances in our molecular understanding of these symbioses because it participates in a facultative symbiosis with certain strains of Symbiodiniaceae, is simple to maintain in laboratories of all scales, can produce larvae naive to symbionts under inducible conditions, and is easily biochemically manipulatable (Grawunder et al. 2015; Weis et al. 2008).

While the work conducted with Aiptasia has significantly shaped our understanding of host-Symbiodiniaceae pairings, it has predominantly been conducted on a single, or very few, Aiptasia strains. CC7, the most commonly used Aiptasia strain, is male and may have different energetic priorities than female conspecifics. Additionally, significant genetic variation in many traits and different host-symbiont interactions can drive responses to the environment. Therefore, we encourage researchers to expand their work to include additional strains at various developmental stages, to build out strain libraries by pulling genotypes from diverse regions that experience unique environmental conditions, and to make these anemones broadly available to the community (**Figure 2**). Many other models for symbiosis are emerging including *Cassiopea xamachana*, which represents a promising model system for some symbiosis questions and demonstrates certain benefits over Aiptasia, including the ability to induce settlement and metamorphosis, which has failed in Aiptasia (reviewed in Ohdera et al. 2018). The necessary expansion of calcifying coral models will be explored in the subsection *Further develop calcifying coral models*. We recognize that this work involves challenges related to feasibility; however, experiments could be conducted sequentially and collaboration between laboratories is encouraged. We also stress careful documentation of genetic background in husbandry and experiments, and support open-source protocol sharing of animal rearing, spawning, and experimentation, as has been implemented by the Aiptasia Symbiosis Resource group (https://aiptasia-resource.org/).

This same expansion of genetic backgrounds needs to also be applied to Symbiodiniaceae strains (**Figure 2**). Given the diversity of Symbiodiniaceae within and between genera (LaJeunesse et al. 2018; Beltrán et al. 2021), and that each strain can have a unique interaction with a host genotype (Parkinson and Baums 2014), expansion of strains is critical. Further, it remains important to assess how crossing different host and algal symbiont genetic backgrounds may alter holobiont physiology under both ambient and stressful conditions. Lastly, we recommend consistent and regular genomic screenings of all symbiont libraries and stringent oversight of symbiont culturing to avoid contamination.
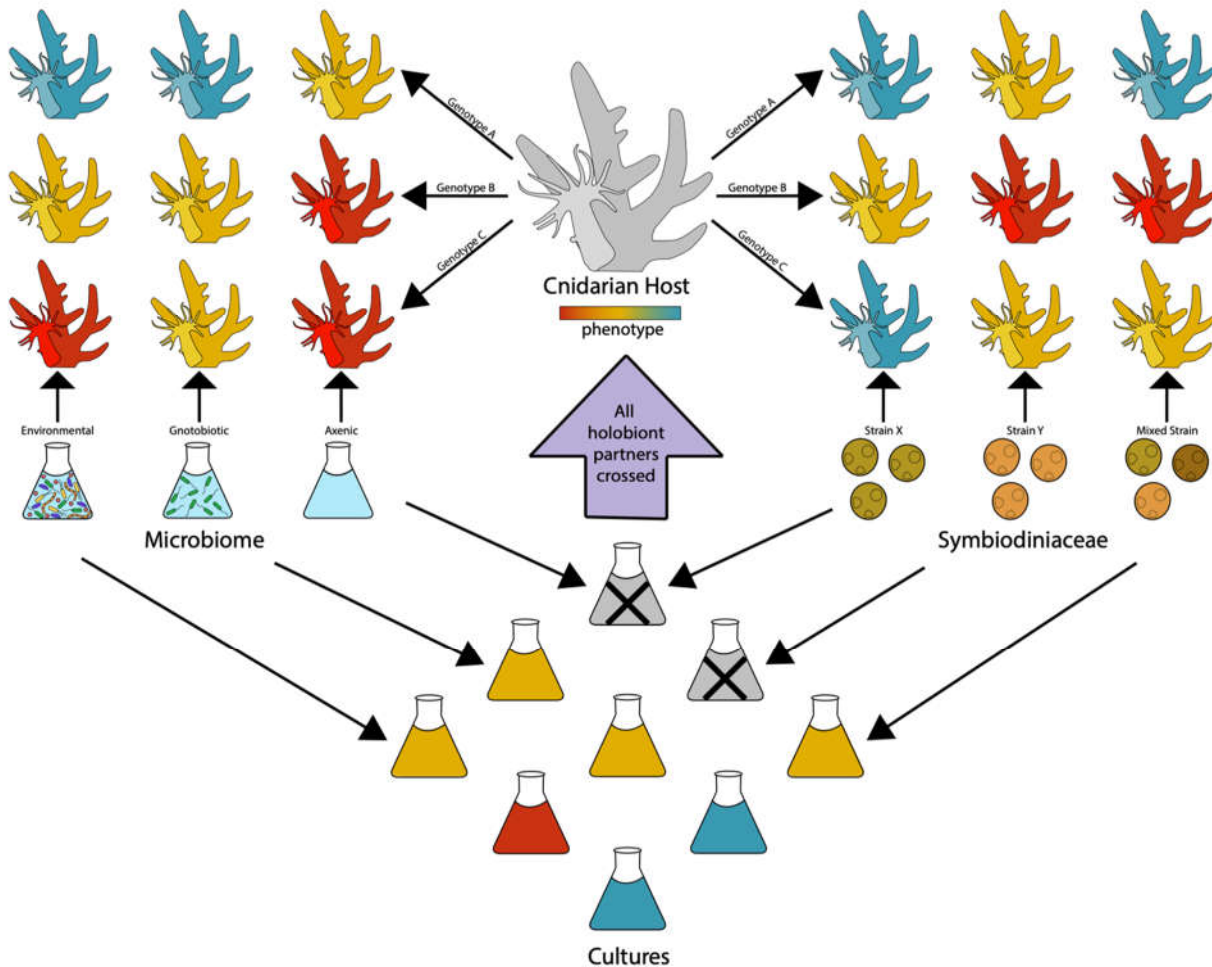
Figure 2. Experimental approaches for future studies on cnidarian holobiont interactions. Focus on increasing host genetic diversity, different monoculture and/or known mixed Symbiodiniaceae strains and microbial communities of varying complexity. We expect that an individual may exhibit multiple phenotypes (depicted by color of host, represented as a coral and anemone, or culture flask; grey flasks represent failed cultures) depending on associated partners that may result in differing levels of resilience or resistance to stress. Crossing these different pairings under both ambient and stressful conditions may elucidate roles of partners in holobiont responses that help predict holobiont health. The purple arrow depicts future directions once baseline interactions are known across different partner pairings.

Further develop calcifying coral models

While the use of Aiptasia (and other emerging models) provides valuable insights into the molecular underpinnings of symbiosis, it remains a solitary polyp that does not calcify like reef-building corals. Given this limitation, other models are emerging to study coral symbiosis, including the facultatively symbiotic species *Astrangia poculata*, which is found along the western Atlantic coastline of the USA (Neff 2020). The use of *A. poculata* may offer a more realistic model for understanding the role of each symbiotic partner (Holcomb et al. 2012; Burmester et al. 2018) given the importance of

symbiosis in coral skeletal growth rate (Chalker and Taylor 1975). *Astrangia poculata* has provided valuable insight into algal symbiosis regulation (Dimond and Carrington 2008), the impact of algal symbionts on microbial community composition (Sharp et al. 2017), how symbiosis may mediate stress in calcifying corals (Burmester et al. 2017; Wuitchik et al. 2021), and differences in skeletal structure based on symbiotic state (Dellaert et al. 2022). This ability to modulate symbiont state is valuable; however, to date, no studies have reported successfully inoculating *A. poculata* with different (*i.e.,* heterologous) symbiont strains. While other studies have reported acquisition of novel algal symbionts in adult corals (Puntin et al. 2022; Scharfenstein et al. 2022), inoculation of *A. poculata* with heterologous algal strains should remain a priority.

Several other reef building species are emerging as potential models, including *Oculina arbuscula* (Rivera and Davies 2021) and *Galaxea fascicularis* (Puntin et al. 2022), which can also have their symbiotic states experimentally manipulated. In fact, *G. fascicularis* has been successfully bleached and then reinoculated with presumed heterologous strains of Symbiodiniaceae (Puntin et al. 2022), providing a promising system to cross different host genotypes with algal strains as proposed above (Figure 2). This ability to control and modify symbiosis in combination with previous mechanistic (*e.g.,* ion transport for calcification (Al-Horani et al. 2003, 2005)) and microbiome (Tang et al. 2020; Wepfer et al. 2020) research make it an ideal candidate to explore partner interactions.

Lastly, a wealth of resources have been created for the model tropical reef-building coral *Acropora millepora,* which was the first to have its transcriptome sequenced (Meyer et al. 2009) and a linkage map developed (Wang et al. 2009). It also has one of the most robust genome assemblies to date (Fuller et al. 2020) and has been used in a plethora of spawning studies. It remains one of the more tractable model systems for genome editing (see *Leveraging novel technologies subsection*; (Cleves et al. 2018)), and robust methods for spawning (both *in situ* and *ex situ*), settlement, and algal symbiosis establishment exist (Craggs et al. 2017, 2020; Pollock et al. 2017).

Conduct research with and without microbiome members

To study specific interactions between the host, algal symbiont, and microbial partners, we suggest employing the use of axenic (*i.e.,* germ-free) and gnotobiotic (*i.e.,* known microbial state) cnidarian host and symbiont models (Figure 2). The use of axenic and gnotobiotic models is common practice in many systems (especially mammalian models) to assess the functional role that specific host-microbe interactions have on phenotype (Basic and Bleich 2019) and presents a promising avenue to study partner interactions in symbiotic cnidarians. While gnotobiotic cnidarian models have yet to be successfully produced (Hartman et al. 2022), several strains of axenic Symbiodiniaceae have been developed and have been successfully infected into Aiptasia models (Xiang et al. 2013; Matthews et al. 2020). However, additional strains from diverse algal genera would be beneficial along with their associations with specific microbial communities. A protocol for the generation of microbe depleted Aiptasia has already been developed (Costa et al. 2021), showcasing progress towards the generation of completely axenic and eventually gnotobiotic Aiptasia strains.

While generating axenic and gnotobiotic corals may be in the future, researchers can currently inoculate corals with known beneficial microorganisms for corals (BMC) and evaluate phenotypic outcomes to better understand the microbiome's role in holobiont health (Peixoto et al. 2017; Santoro et al. 2021; Zhang et al. 2021; Li et al. 2022). Inoculating hosts with different microbial communities is widely used across disciplines (Ma et al. 2011; Hansen et al. 2012) to assess a variety of phenotypic and immune responses, and these techniques represent a promising frontier for corals as well. Studying host responses to targeted microorganisms or microbial communities will uncover the role of these associations and how they might be linked with holobiont stress, vulnerability, resistance, and resilience.

Developing high throughput screening approaches

Development of additional technologies to rapidly assess phenotypic traits is needed and remains a major bottleneck to the types of experiments required to understand complex interactions between multiple symbiotic partners. Recent high-throughput approaches for assessing thermal tolerance at the whole coral level (*e.g.,* coral bleaching automated stress systems (CBASS; (Voolstra et al. 2020)) and single cell levels (Behrendt et al. 2020) have incorporated short-term thermal challenges followed by stress characterization through measurement of a couple physiological variables such as maximum PSII photochemical efficiency (F_v/F_m) and cell density. However, these approaches remain focused on the algal symbiont and development of additional traits is needed. Further developing trait databases, such as the coral trait database (Madin et al. 2016) are urgently needed. While this database hosts data for 56 traits–some of which overlap with the algal symbiont (*i.e.,* gross photosynthesis, mitotic index, symbiont density, algae hosted, algal transmission mode, chlorophyll A)–this resource could be complemented by the development of algal and microbiome versions.

Gene expression patterns of each member of the holobiont can also be considered a trait and represents a high throughput approach; however, linking gene expression to coral phenotypes remains difficult. In the plant community, researchers have better linked gene expression patterns to their trait database (Kattge et al. 2011) by creating a plant gene annotation platform that provides common standards for semantic integration in the form of ontologies (Planteome: Cooper et al. 2018). The development of such a resource for cnidarians would transcend our understanding of gene function. In lieu of developing a novel database, which represents a mammoth task that requires continuous funding to maintain, one approach to link gene expression with cnidarian responses is through meta analysis. For example, Dixon et al. (2020) re-analyzed 600 coral gene expression profiles (genus *Acropora*) and established two general coral environmental stress responses with contextual annotations for unannotated genes based on their consistent response to stress across independent projects. These sorts of approaches that can better link research globally and will help build our understanding of coral diversity in order to better predict responses.

Leveraging novel technologies

Advances in biomedicine have been facilitated by the development of immortal cell lines for molecular manipulation and microscopy analysis. The generation of cnidarian cell lines has been met with limited success (see Rosental et al. 2017; Fricano et al. 2020; Kawamura, Nishitsuji, et al. 2021; Nowotny et al. 2021), although achievements have been made with respect to *in vivo* symbiosis (Kawamura, Sekida, et al. 2021). Functional cell lines of cnidarian models will allow researchers to apply exogenous biochemical stimuli, such as TGFβ and nitric oxide, which would expand our knowledge of gene function. Current studies using mammalian cell lines expressing cnidarian proteins (*i.e.*, Williams et al. 2018) may be missing key post-translational modifications and/or protein-protein interactions that only occur in native host cells, highlighting the need for further technology development in this area.

Single-cell RNA-seq (scRNAseq) is a developing technology that has been successful in several Cnidaria taxa (Sebé-Pedrós et al. 2018; Hu et al. 2020; Chari et al. 2021; Levy et al. 2021); however most studies to date have been conducted under baseline conditions to establish cell-type signatures of gene expression (*i.e.,* cell atlases) through developmental stages. The use of scRNAseq to characterize cell-type gene expression patterns under different stimuli will further unveil the cell types responsible for organismal responses to various stressors. Additionally, scRNAseq manipulation experiments can help determine the benefit-to-burden balance that hosts must weigh when in symbiosis with homologous versus heterologous symbiont strains. The development of spatial scRNAseq (reviewed in Longo et al. 2021) or multiplexed error-robust fluorescence *in situ* hybridization (Chen et al. 2015) technologies for other systems can be leveraged in cnidarian research to deepen our understanding of the spatial organization of cell types relative to the organismal body plan. Additionally, proteomic (Oakley et al. 2016; Jaimes-Becerra et al. 2019; Sproles et al. 2019; Tortorelli, Oakley, et al. 2022) and metabolomic studies (Hillyer et al. 2017; Matthews et al. 2017, 2018; Williams et al. 2020) are essential for determining functional patterns of intra- and inter-cellular regulation under different conditions and holobiont partnerships.

Lastly, the development and implementation of gene knockdown (via RNA-interference (Dunn et al. 2007); reviewed in Rentzsch et al. 2019; Quiroga-Artigas et al. 2020) and genome editing (via the CRISPR-Cas9 system (Cleves et al. 2018)) in Cnidaria has allowed researchers to resolve the functional role of specific genes involved in immunity, development, and more. Indeed, NF-κB has been previously knocked down in the non-symbiotic sea anemone *Nematostella vectensis* via morpholinos, clarifying the protein's role in cnidocyte cell development (Wolenski et al. 2013). We propose that NF-κB, and cnidarian-specific PRRs be knocked down via RNA-interference or knocked out via CRISPR-Cas9 in a symbiotic cnidarian model that can be reared from larvae to adulthood - such as *Cassiopea xamachana* - with the acknowledgement that mosaic phenotypes and inviable phenotypes may be likely outcomes. Additional advances in tractable mutagenesis models in mammal systems have allowed researchers to study the direct link between microbial member networks to host phenotypes (Goodman et al. 2009); we suggest the exploration of implementing similar models in cnidarian systems. Finally, we recommend that transgenic lines be infected

with different strains of symbiont and/or microbiome combinations and placed under various challenges to clarify the role of these mechanistic pathways in symbiosis, dysbiosis, and environmental stressors. Combining these data-rich methods in a multi omic context will improve informed diagnostic approaches to coral work *in situ.*

Conclusions

Coral bleaching is perhaps one of the most intriguing processes in nature because it represents the outcome of cellular dysfunction between symbiotic partners that is easily observed by eye, but its influence spans ecosystem scales. A major goal of coral reef science is to understand and predict these symbiosis outcomes under increasingly changing environments, but this work remains a serious challenge due to the complex interactions between holobiont members, each of which possess immense genetic diversity. While an impressive amount of work has uncovered basic mechanisms involved in cnidarian-algal symbiosis and descriptive studies of microbiome associations are hypothesis generating tools, we propose that mechanistic research would benefit from expanding to use a broader repertoire of genetic diversity and leveraging emerging technologies. We are optimistic that the many ways in which these partners interact will offer hope to the coral reef crisis as we are just scratching the surface of understanding how these partners can mix and match, which may offer fuel to the coral holobiont to adapt and acclimate to their rapidly changing environments.

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