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What are the physiological and immunological responses of coral to climate warming and disease?

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Summary

Coral mortality due to climate-associated stress is likely to increase as the oceans get warmer and more acidic. Coral bleaching and an increase in infectious disease are linked to above average sea surface temperatures. Despite the uncertain future for corals, recent studies have revealed physiological mechanisms that improve coral resilience to the effects of climate change. Some taxa of bleached corals can increase heterotrophic food intake and exchange symbionts for more thermally tolerant clades; this plasticity can increase the probability of surviving lethal thermal stress. Corals can fight invading pathogens with a suite of innate immune responses that slow and even arrest pathogen growth and reduce further tissue damage. Several of these responses, such as the melanin cascade, circulating amoebocytes and antioxidants, are induced in coral hosts during pathogen invasion or disease. Some components of immunity show thermal resilience and are enhanced during temperature stress and even in bleached corals. These examples suggest some plasticity and resilience to cope with environmental change and even the potential for evolution of resistance to disease. However, there is huge variability in responses among coral species, and the rate of climate change is projected to be so rapid that only extremely hardy taxa are likely to survive the projected changes in climate stressors.

Key words: bleaching, coral disease, innate immunity.

Introduction

With alterations in local environments associated with global climate change becoming increasingly evident, resolving the physiological responses of organisms to these changes is a priority. The capacity for a plant or animal to respond to new environments with physiological plasticity may enhance their survival (Peck, 2008). Corals are extremely sensitive to environmental factors and have the ability to integrate environmental signals (e.g. temperature, flow, sedimentation, nutrients) into organismal-level responses due to their clonal life history and colony-wide fluid conducting systems. This allows local signals to be transmitted throughout the entire colony, inducing whole organism level changes with relative unconstraint (Harvell, 1991; Hughes, 1983), as exemplified by their propensity for phenotypic plasticity (Blackstone, 2005; Bruno and Edmunds, 1998). While this plasticity provides an avenue for corals to respond to environmental change, the ability to acclimate seems to be overwhelmed by the rate and magnitude of climate change. Already, reefs are disappearing at an alarming rate, with 33% of coral species facing possible extinction (Carpenter et al., 2008). The loss of Indo-Pacific reefs is currently estimated at an average rate of 2% per year (Bruno and Selig, 2007), while meta-analyses from 25 years of survey data in the Caribbean show declines between 5.5% and 9.2% per year (Cote et al., 2005; Gardner et al., 2003). Therefore, it is not surprising that climate change, mainly temperature increases in the tropics, has driven coral decline in the last 20 years.

Complicating the effects of climate change on coral physiology is the unique symbioses corals have with both algae and surface bacteria. The algal symbionts, also known as zooxanthellae, live intracellularly in the gastrodermal layer (Fitt, 2000), and comprise a diverse group that is divided into eight genetically distinct clades and then further into subclades (Baker et al., 2004; LaJeunesse, 2001). Through their symbiotic relationship, zooxanthellae receive nitrogen and phosphorous from the waste of their host, utilize dissolved CO_2 from the water and create enough photosynthetic products to meet their own requirements and up to 95% of their hosts' (Muscatine, 1973). They play a key role in the production of the coral calcium carbonate skeleton, which ultimately creates the framework for every coral reef ecosystem (Muscatine, 1971). The algal photosynthate also contributes to the mucus layer, which covers the top of the coral (Brown and Bythell, 2005). Housed in this mucus layer are unique communities of bacteria, which differ from the surrounding seawater and are coral-species specific (Frias-Lopez et al., 2002; Ritchie and Smith, 2004). Bacteria are also known to reside in coral tissue and in the skeleton (Rosenberg et al., 2007). Both the algal and bacterial symbionts play important roles in the optimal maintenance of physiological function and coral health (Ritchie, 2006) and the entire association is known as the 'coral holobiont' (Rosenberg et al., 2007).

The effects of temperature stress are apparent in the two main physiological conditions that currently affect corals on a global scale: bleaching and disease. Coral bleaching is characterized by the loss of most of the coral's algal symbionts and/or their associated pigments (Brown, 1997). Bleaching can take place during periods of increased temperatures, which may be as little as 1–2°C above the daily average, and can be coupled with periods of increased solar exposure (Brown, 1997). This compromised state can lead to starvation, increased disease susceptibility and mortality. Coral epizootics have also increased in frequency and severity, with over 20 disease syndromes affecting over 60 hosts globally (Harvell et

al., 2007) (Fig. 1). Climate change and these emerging syndromes are linked through sea surface temperature compromising host immunity or increasing pathogen range and virulence (Harvell et al., 2009). Some corals do possess physiological mechanisms to overcome both bleaching and disease. Two prominent but controversial hypotheses, the adaptive bleaching hypothesis (Buddemeier and Fautin, 1993; Hoegh-Guldberg et al., 2002) and the coral probiotic hypothesis (Reshef et al., 2006), were proposed to explain the ability of coral to adapt to changing conditions. Both of these hypotheses generally state that the dynamic relationship between the coral animal and its symbionts selects for the most fit or advantageous coral holobiont in any given environmental condition (Reshef et al., 2006).

This paper is a contribution to *The Journal of Experimental Biology*'s Special Issue 'Survival in a Changing World', and therefore we assess the impacts of climate change on corals, highlighting the mechanisms of coral resilience to ocean warming. The crux of both coral susceptibility and resilience to warming lies in holobiont and symbiont physiological responses to temperature, UV stress and pathogens. Our focus is on coping mechanisms such as immunity to pathogens and resilience to warming that may contribute to the survival of some corals. The physiological responses to ocean acidification are not covered in this review, because we still know so little about how acidification will affect components of the coral holobiont other than calcification. Given the current high rate of coral decline and contributing global and local anthropogenic stressors, it is unlikely that even the compensatory factors outlined here will allow for the survival of intact coral reef ecosystems during upcoming rapid climate changes.

Coral responses to increased temperature and light

Coral reefs are currently in a state of flux resulting from the early stages of climate change. Increases in temperatures around the globe and changes in weather patterns, particularly El Niño Southern Oscillations, are dramatically influencing the health and composition of coral reefs through outbreaks of significant bleaching events (Harvell et al., 2001; Hoegh-Guldberg, 1999). In 1998, the most widespread bleaching event on record swept across the globe, and destroyed 16% of the world's coral reefs (Wilkinson, 2004). Bleaching events are predicted to become increasingly common, with conservative estimates predicting bi-annual occurrence by the year 2050 (Donner et al., 2005; Hoegh-Guldberg, 1999; Hoegh-Guldberg et al., 2007). The frequency of these events will result in massive alterations of coral reef ecosystems, the ramifications of which are the focus of many avenues of research.

The current popular explanatory model for coral bleaching is the oxidative theory of coral bleaching, which posits that bleaching is the result of an overproduction of harmful reactive oxygen species (ROS), such as hydrogen peroxide or superoxide anions, by the zooxanthellae due to stressor-induced disruption of the photosystems and damage to photosystem II (PSII) (Downs et al., 2002; Jones et al., 1998; Lesser, 1997; Lesser, 2006; Smith et al., 2005; Warner et al., 1999). The resulting accumulation of ROS can then damage a wide range of cellular components, including membranes, proteins and DNA throughout the holobiont (Downs et al., 2002; Lesser, 2006). Ultimately, the symbiosis breaks down, leaving the host devoid of most symbionts and without the nutritional and other benefits they confer.

Once bleaching became a topic of regular study, irregularities in bleaching patterns were noted in field studies, including variation in the timing of onset, the degree and duration of bleaching, and the resistance and resilience of certain corals (Berkelmans and van Oppen, 2006; Marshall and Baird, 2000). Specific strategies appear to correlate with these observations, and it has become increasingly evident that the holobiont's response to stressors is dependent on a wide repertoire of mechanisms, and significant variation exists in the expression of these mechanisms. Some of these strategies may somehow be coupled with inherent characteristics such as life-history strategies and phenotypic plasticity (Fitt et al., 2009) whereas many are mediated through the production of various protective proteins (Baird et al., 2009). Because the coral holobiont is defined by its entire assemblage of organisms, including the algal and bacterial symbionts dispersed throughout the coral animal, these symbionts contribute significantly to the holobiont's behavior and functioning, including the response to stress (Buddemeier et al., 2004). As such, differences in stress tolerance are also attributed in part to differences in the symbionts identity and physiology (Baker et al., 2004; Mieog et al., 2009) and factors dependent on specific host-symbiont interactions (Abrego et al., 2008). As research continues to identify physiological differences in the various symbiont communities (Tchernov et al., 2004; Warner et al., 2006), it is becoming increasingly obvious that these symbionts can play a defining role in the survival of the entire holobiont during periods of stress. The source of this survival can be variable and is attributed to differences including antioxidant production (Lesser, 1996; Yakovleva et al., 2004), ROS production (Suggett et al., 2008), membrane stabilizing compounds (Mydlarz and Jacobs, 2004; Tchernov et al., 2004) and cellular repair mechanisms (Lesser, 1997; Lesser, 2006). Many of these are also utilized by the host, and are intrinsically linked to the host's survival strategies, including the production of specific protective compounds (Baird et al., 2009; Coles and Brown, 2003) and alterations in symbiont communities (Baker, 2001; Buddemeier and Fautin, 1993).

While the detrimental effects of bleaching such as decreased growth rates, lowered fecundity and diminished photosynthetic rates are undisputed, the variation in coral responses to the cumulative effects of bleaching is providing some evidence for possible survival. As ongoing studies document post-bleaching coral populations, researchers are finding indications of resistance and resilience, and in some instances, recovery, growth, acclimation and possible adaptation (Hughes et al., 2003; Hughes et al., 2007). The focus of this manuscript is to address mechanisms contributing to these small successes.

Holobiont responses to temperature and light

When coral survive the immediate bleaching event they must persist long enough to be repopulated by algal symbionts. Whether or not they meet their daily metabolic needs may depend on their energy reserves and their ability to feed heterotrophically, which is facilitated by their mucosal layer and resident bacterial community (Brown and Bythell, 2005). Heterotrophic feeding rates differ among three species: the branching *Montastrea capitata* and two *Porites* with different growth forms, the branching *Porites compressa* and the mounding *Porites lobata* (Grottoli et al., 2006). While bleached, *M. capitata* increased heterotrophic feeding rates to meet more than 100% of daily needs. By contrast neither of the *Porites* species fed at a higher rate, instead relying on energy reserves. Eight months post-bleaching *M. capitata* was twice as likely to recover and had lower mortality than the two *Porites* species (Rodrigues and Grottoli, 2007). Extrapolating from these findings, corals that can increase rates of heterotrophy may have higher survival rates and, without energy as a limiting resource, may have fewer detrimental side effects post-bleaching, such as lowered reproduction (Rodrigues and Grottoli, 2007).

In addition to the benefits derived by the host, feeding may also contribute to increased thermal tolerance and resilience of the zooxanthellae. In the thermally sensitive *Stylophora pistillata*, zooxanthellae in fed corals can more effectively dissipate excess excitation energy, retain higher concentrations of chlorophyll *a* and have less disruption to PSII than in unfed corals (Borell and Bischof, 2008; Shick et al., 2005). Maintaining healthier residual zooxanthellae populations may not only confer increased bleaching resistance but also aid in re-establishing the symbiotic community once stressors are removed from environmental conditions.

Trends have begun to emerge between specific life-history traits and survival after bleaching events, as evidenced by shifts in community compositions (Green et al., 2008; Loya et al., 2001; Marshall and Baird, 2000; McClanahan et al., 2004). Corals with branching or plating morphologies appear to have higher mortality rates after bleaching events (Adjeroud et al., 2009; Fitt et al., 2009; Loya et al., 2001; McClanahan, 2004; McClanahan et al., 2004). It has been suggested that these morphologies have thinner tissue that is less able to sequester protective proteins, and provide less shelter from stressors to the sensitive zooxanthellae harbored inside (Fitt et al., 2009; Loya et al., 2001; McClanahan, 2004). Many of the acroporids, such as *Acropora* and *Montipora* species, are branching or plating and are highly susceptible to bleaching in many areas of the world (Adjeroud et al., 2009; Loya et al., 2001; Marshall and Baird, 2000; McClanahan et al., 2004).

Disparities in resistance and resilience to stress between taxa are becoming increasingly evident across geographical ranges, and while many species are being negatively affected, others seem to be increasing in relative abundance. Corals that form massive boulder-like colonies appear to be, in general, less susceptible to bleaching and mortality (Marshall and Baird, 2000; McClanahan, 2004; McClanahan et al., 2004). Reports of population cover from reefs around the world document resistance and recovery of the massive *Porites* species (Adjeroud et al., 2009; Green et al., 2008; Loya et al., 2001). Corals with 'weedy' characteristics (small, with short life spans and quick colonization) may also have an advantage (Green et al., 2008). In the Caribbean, the increase in abundance of *Porites astreoides* in field surveys supports this trend; its ability to inhabit marginal habitats and self-fertilize may contribute to the persistence of this species when many others are declining steadily (Green et al., 2008). The putatively invasive *Tubastrea coccinea*, believed to have been introduced to the Caribbean from the Indo-Pacific approximately 60 years ago and now found from Brazil to the Florida Keys, has similar weedy characteristics and is effective at colonizing due to a novel growth strategy to outmaneuver competitive algae (Fenner and Banks, 2004; Vermeij, 2005).

One of the factors that may be contributing to survival in species with thicker tissue is the presence of protective proteins and compounds, which act in a variety of ways to mitigate damage induced by both light and temperature. The production of these proteins clearly demonstrates the delicate interplay between host and symbionts. One of the first of these mutually protective proteins produced in response to thermal stress are heat shock proteins (Hsps), and are produced by both the host and symbiont to stabilize proteins and assist cellular functioning (Coles and Brown, 2003; Smith-Keune and Dove, 2008). In some studies, increases in Hsps in response to both high irradiances and elevated temperatures are correlated with increased resistance to bleaching (Brown et al., 2002; Chow et al., 2009; Downs et al., 2000; Fitt et al., 2009).

Fluorescent proteins (FPs) are a group of pigments produced by the coral animal that accumulate throughout the tissue (Brown et al., 2002; Palmer et al., 2009b) (Fig. 1C), and are proposed to be photoprotective through their abilities to dissipate and reflect excess light that may otherwise damage the host and symbionts (Salih et al., 2006; Salih et al., 2000) as well as their antioxidant potential (Bou-Abdallah et al., 2006; Palmer et al., 2009a). The types and concentrations of FPs vary greatly between species, contributing to differences in observed tolerance levels (Coles and Brown, 2003; Field et al., 2006; Matz et al., 1999; Palmer et al., 2009a; Salih et al., 2006). Their effectiveness during periods of elevated temperatures has been questioned, as these pigments may be sensitive to temperatures over 32°C, reducing their role in potential acclimation to climate change (Dove, 2004; Smith-Keune and Dove, 2008).

Mycosporine-like amino acids (MAAs) are extensively found in marine organisms acting as natural sunscreens by absorbing UV radiation (Banaszak et al., 2006). Photosynthetic organisms produce several basic forms of MAAs to mitigate photoinhibition (Ferrier-Pages et al., 2007), including the zooxanthellae, which upregulate their production of MAAs after elevated UV exposure (Banaszak et al., 2006; Ferrier-Pages et al., 2007; Lesser, 1996). Although unable to produce the MAAs directly, the coral host and bacterial symbionts can modify the basic MAAs acquired from algal symbionts and heterotrophic feeding into a number of additional MAAs, which are then sequestered in host tissues and mucosal layers (Brown and Bythell, 2005; Dunlap and Shick, 1998; Ferrier-Pages et al., 2007; Shick et al., 2005). Some differences in the tolerance of hosts and symbionts may be attributable to different kinds and concentrations of MAAs produced by specific zooxanthellae, and differences in what MAAs are found in host tissues (Banaszak et al., 2000; Banaszak et al., 2006; Dunlap and Shick, 1998; Ferrier-Pages et al., 2007; Shick et al., 2005). During starvation MAAs are preferentially retained over other proteins, demonstrating their important role (Shick et al., 2005).

MAAs are also likely to function in a variety of secondary roles, which may contribute to holobiont thermotolerance. Mycosporine-glycine, one of the most ubiquitous of the MAAs, has shown properties that suggest it can act as an antioxidant prior to the initiation of holobiont antioxidant production (Banaszak et al., 2006; Dunlap and Shick, 1998; Oren and Gunde-Cimerman, 2007; Yakovleva et al., 2004). Antioxidants scavenge free-radicals, making them the primary defense against ROS, and are produced by both the host and zooxanthellae. Each antioxidant targets specific ROS and together convert ROS into harmless by-products, such as water, so an array are simultaneously produced, including superoxide dismutase (SOD), catalase and ascorbate peroxidase (Coles and Brown, 2003; Lesser, 2006). Some of the differences in thermal tolerances of coral can be attributed to differences in antioxidant production from both the host and the zooxanthellae in response to stress (Brown et al., 2002; Fitt et al., 2009; Yakovleva et al., 2004).

Symbiont responses to temperature and light

Stress tolerance can also be attributed to physiological characteristics associated directly with zooxanthellae. When the holobiont experiences bleaching conditions, the zooxanthellae begin to rely more heavily on their non-photochemical quenching systems to compensate for the decreased efficiency of their photosystems and prevent the accumulation of ROS (Coles and Brown, 2003; Hill et al., 2005), and zooxanthellae that can increase rates of non-photochemical quenching after exposure to increased temperature have been associated with bleaching tolerance (Warner et al., 1996). The integrity of cellular membranes also varies, and can factor into stress tolerance. Some zooxanthellae produce more lipids in their thylakoid membranes whereas others may contain low molecular weight lipophilic compounds, both of which enhance membrane

stability during temperature stress and decrease the production and passage of ROS (Mydlarz and Jacobs, 2004; Tchernov et al., 2004).

Zooxanthellae community composition can be influenced by various environmental factors experienced by the holobiont, such as sea surface temperature, currents, depth, UV radiation and sedimentation (Rowan, 1998; Warner et al., 2006). Changes in these communities results in a genetic change of the entire holobiont over a short period of time, allowing for a rapid and yet flexible source of adaptation (Buddemeier et al., 2004; Buddemeier and Fautin, 1993). This potential is articulated by the controversial adaptive bleaching hypothesis (Buddemeier and Fautin, 1993; Buddemeier et al., 2004), which provides a mechanism allowing for instantaneous genetic change in the holobiont that otherwise may not have the capacity to evolve swiftly. During periods of stress, zooxanthellae can inadvertently inflict damage on the host, culminating in the bleaching event. The bleached host can be repopulated by a symbiont with a higher threshold for stress, thereby enhancing the entire holobiont's chances of survival. If this occurs while the stressors are still present, these new symbionts have some advantage during times of stress stemming from an increase in their thermal tolerance through the strategies discussed above. Increases in the rates of coral hosting thermally tolerant strains on reefs after bleaching events appears to provide support for this hypothesis (Baker, 2001; Buddemeier et al., 2004; Jones et al., 2008; Mieog et al., 2007; Thornhill et al., 2006; Ulstrup and van Oppen, 2003).

Despite these encouraging studies, debate surrounds their ultimate interpretation. One of the factors confounding the confirmation of this hypothesis is the ability of some hosts to contain more than one zooxanthellae clade at a time. Whether the host is being populated by a new symbiont, referred to as symbiont switching, or is being repopulated by an already existing symbiont, known as shuffling, that has a competitive advantage in the new conditions has yet to be decisively determined (Baker, 2003; Berkelmans and van Oppen, 2006; Jones et al., 2008). Also, while researchers have seen changes in populations immediately following bleaching events (Baker, 2001; Berkelmans and van Oppen, 2006; Jones et al., 2008; Thornhill et al., 2006), reefs may return to the same pre-bleaching algal composition after a sustained period of average temperatures, resulting in a loss of the acquired stress tolerance (Thornhill et al., 2006). This may be explained by advantages the thermally sensitive symbionts have during periods lacking stress; just as zooxanthellae can vary in thermotolerance, they also exhibit differences in other physiological characteristics that may have trade-offs under normal conditions. Growth rates clearly demonstrate this trade-off, where corals hosting symbionts thought to be thermally sensitive have faster growth compared with those hosting tolerant strains (Cantin et al., 2009; Little et al., 2004). These advantages last only as long as the environment remains stable, and the frequency of environmental perturbations is predicted to play a role in the permanence of new symbiont combinations (Ware et al., 1996).

The microbial community inhabiting the surface of the coral is found in a mucopolysaccaride layer and is sensitive to environmental factors such as temperature. Community changes were observed in naturally bleached *Oculina patagonica* (Koren and Rosenberg, 2008) and *Acropora millepora* (Bourne et al., 2008b), with community shifts favoring pathogenic bacteria. Experimental manipulations with temperature also induced changes in the microbial symbionts of several corals. Increases in bacterial and fungal symbionts as well as virulence factors were observed in *P. compressa* using metagenome analysis (Thurber et al., 2009), and within tissue bacteria shifts were seen in *Acropora aspera* and *S. pistillata* following experimental bleaching (Ainsworth and Hoegh-Guldberg, 2009). The potential functional changes associated with these community shifts were explored by Ritchie (Ritchie, 2006), and found that the protective antibacterial activity associated with coral mucus in *Acropora palmata* was lost during bleaching. Therefore, some bacteria that inhabit the coral mucus and the mucus itself may be protective and act as a first line of defense against opportunistic invading bacteria (Nissimov et al., 2009; Ritchie, 2006; Shnit-Orland and Kushmaro, 2009), and when temperature stress and bleaching occur, the probiotic effect is disrupted and may result in disease outbreaks.

The ultimate question is whether the increases in thermotolerance, no matter what the source, are enough to deal with impending climate change. With the prediction that corals will have to increase their thermotolerance at a rate no less than 0.2°C per decade, but possibly as much as 1°C, it seems unlikely that current ranges of thermotolerance are enough to cope with any of the predicted climate scenarios (Donner et al., 2005).

Coral responses to disease

Climate change has exacerbated the severity of coral diseases, and the links between temperature and disease outbreaks are accumulating (Bruno et al., 2007; Harvell et al., 2002; Harvell et al., 2007; McClanahan et al., 2009; Miller et al., 2006). Coral diseases affect reef-building scleractinian corals as well as gorgonian corals, such as the sea fan. The study of coral diseases is particularly confounding due to the polymicrobial nature of most diseases, and fulfilling Koch's postulates has been difficult for many coral diseases and not without much controversy (Lesser et al., 2007; Work et al., 2008). Further, fulfilling Koch's postulates for one microbe–coral combination does not ensure that this interaction will be true for all other corals harboring the suspect microbe (Harvell et al., 2007). The pathogens that cause diseases and syndromes span most phyla; bacterial pathogens cause diseases such as Yellow Band Disease (Cervino et al., 2008) (Weil et al., in press) and white plagues and syndromes (Denner et al., 2003; Rosenberg and Ben-Haim, 2002; Sussman et al., 2009); fungal pathogens cause sea fan Aspergillosis (Kim and Harvell, 2004); cyanobacteria trigger Black and Red Band Diseases (Page and Willis, 2006; Richardson, 1992; Richardson and Kuta, 2003); protists such as ciliates cause Skeletal Eroding Band (Croquer, 2006; Page and Willis, 2008) and Brown Band (Bourne et al., 2008a); virus-like particles may cause Skeletal Growth Abnormalities (Thurber et al., 2008). However, corals do possess effective immune defenses to fight these pathogens, and some elements of physiological plasticity and resilience have been documented. In this section we examine the effects of environmental factors associated with climate change on diseased corals, the effectiveness of the immune response and the contributions of the symbiotic relationships.

Holobiont responses to pathogens

Corals, like other invertebrates, have an immune system based on self/non-self recognition and cellular and humoral processes. To date, no true adaptive components have been identified in these innate systems (Soderhall and Cerenius, 1998), although elements suggesting memory and specificity are found in invertebrates as basal as sponges and coral (Bigger et al., 1982; Hildemann et al., 1977). Recognition receptors such as Toll-like receptor domain genes (Miller et al., 2007; Schwarz et al., 2008) complement C-3 like proteins (Dishaw et al., 2005), and lectins (Kvennefors et al., 2008) have been characterized in corals [see Dunn (Dunn, 2009), for a comprehensive review on immunorecognition in the Cnidaria]. Being clonal invertebrates, coral must rely on physiochemical

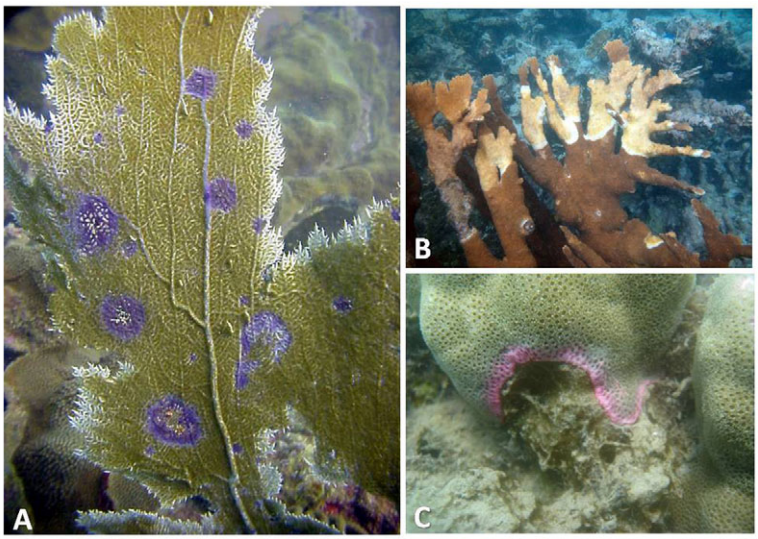

Fig. 1. Coral syndromes and diseases. (A) The sea fan, *Gorgonia ventalina* with purple pigmented aspergillotic lesions (photo by E. Weil), (B) *Acropora palmata* infected with White Band Disease (photo by E. Weil), and (C) massive *Porites* sp. with pink non-normal pigmentation (photo by C. Palmer).

barriers and cellular processes as a first line of defense against invading pathogens.

Prophenoloxidase (PPO) is an integral part of innate immune effector processes in invertebrates and is involved in wound healing, encapsulation, parasite and disease resistance, and the general coordination of immune responses (Mydlarz et al., 2008; Nappi and Christensen, 2005). PPO is the precursor to the active protein, phenoloxidase (PO), which is activated by the release of proteases during the initial pathogen invasion. Corals have PPO activity as well as melanin, the end-point of the PPO cascade and a potent physiochemical barrier (Mydlarz et al., 2008; Palmer et al., 2008). The mucus layer overlaying coral tissue is produced by coral mucocytes and can also act as a protective barrier to incoming pathogens (Teplitski and Ritchie, 2009). Amoebocytes are the putative coral immune cells, which wander throughout the mesoglea (Mydlarz et al., 2008). Ameobocytes have been identified in *Montastraea cavernosa* in response to sedimentation (Vargas-Angel et al., 2007), as well as in *Porites* spp. aggregated near skeletal anomalies (Domart-Coulon et al., 2006) and in hyperpigmented areas (Palmer et al., 2008). Another important aspect of innate immunity includes proteins and compounds with direct antibacterial activity. Corals have been shown to produce such bactericidal compounds, which inhibit both Gram (–) and Gram (+) bacterial growth *in vitro* (Geffen and Rosenberg, 2005; Geffen et al., 2009; Gochfeld and Aeby, 2008; Kim, 1994; Koh, 1997).

Some of these immune responses have been shown to be inducible with pathogen exposure or in naturally diseased corals. Melanin is induced in sea fans infected with the fungus *Aspergillus sydowii* (Petes et al., 2003) along with an increase in PPO activity (Mydlarz et al., 2008). In *A. millepora*, PPO activity is also induced in infected or hyperpigmented tissue while in *Porites* spp. it is not induced in non-normal pigmented tissue (Palmer et al., 2008), indicating some variability in this response across different coral taxa. Amoebocytes are also inducible and aggregate near diseased tissue in sea fans (Mydlarz et al., 2008), skeletal anomalies potentially caused by viruses in *P. compressa* (Domart-Coulon et al., 2006) and foreign particles in gorgonians (Meszaros and Bigger, 1999; Olano and Bigger, 2000). FPs are locally induced on *P. compressa* with trematode infections and injured *A. millepora* (Palmer et al., 2008; Palmer et al., 2009b). Their direct function is still unknown but may be involved in mitigating immune-related oxidative stress potential (Palmer et al., 2009b). In some instances, FPs and other hyperpigmentations are associated with inflammatory responses, such as amoebocyte aggregation and PPO upregulation (Mydlarz et al., 2008; Palmer et al., 2008). It is important to note, however, that not all host pigmentation responses are attributed to immune and inflammatory-like reactions. Antimicrobial activity is also increased in diseased corals. In sea fans an increase in antifungal activity in *Aspergillus*-infected tissue was found (Kim et al., 2000), *Montipora* tissue infected with White Syndrome had higher levels of antibacterial activity against marine bacterial strains (Gochfeld and Aeby, 2008), as did *Montastraea favoelata* tissue infected with Yellow Band Disease (Mydlarz et al., 2009).

Understanding the effects of temperature on immune defenses is crucial to predict the consequences of climate change on emerging coral diseases. It is expected that corals with immune plasticity will be more resilient to the combined effects of increased temperature and pathogen pressures. While such studies are still scarce, several initial studies suggest a certain level of immune plasticity exists. In sea fans exposed to increased temperatures both antifungal activity (Ward et al., 2007) and wandering amoebocytes increased (Mydlarz et al., 2008). In *M. faveolata* collected during the 2005 bleaching event, levels of PPO were significantly higher than in following years, although in the same corals antibacterial defenses were suppressed (Mydlarz et al., 2009). It is still unclear how induction of immune defenses with infection or temperature will affect the survivorship of coral especially given the overwhelming evidence of coral disease outbreaks that occur post-bleaching or contemporaneously with temperature stress (Bruno et al., 2007; Harvell et al., 2001; Harvell et al., 2009; Jones et al., 2004; McClanahan et al., 2009). The constitutive immune defenses and capacity to induce immune responses are expected to vary among coral species leaving some corals more resistant to diseases than others.

Coral diseases are highly variable spatially and temporally (Croquer and Weil, 2009; Page and Willis, 2008; Willis et al., 2004). Disease prevalence is typically correlated to coral cover and high host abundance (Bruno et al., 2007; Willis et al., 2004) but diseases do not always affect the most abundant species on the reef (Croquer and Weil, 2009; Ward et al., 2006). Overall, the prevalence and frequency of different syndromes varies among families, suggesting some coral taxa are more susceptible than others. Branching and plating corals, such as Acroporidae and Pocilloporidae, are highly

susceptible to diseases such as Skeletal Eroding Band and White Syndrome (Page and Willis, 2008; Willis et al., 2004). Corals in the Poritidae seem to persist after other more susceptible corals decline in the Caribbean (Croquer and Weil, 2009; Ward et al., 2006) and Great Barrier Reef (Page and Willis, 2008; Willis et al., 2004). However, in the Philippines Poritidae are main hosts to Porites Ulcerative White Spot Disease and tumors (Raymundo et al., 2005) and are also susceptible to trematode infections in Hawaii (Palmer et al., 2009b; Ravindran and Raghukumar, 2006). Similarly, while Faviidae are host to many diseases on the Great Barrier Reef, prevalence is typically low (Page and Willis, 2008; Willis et al., 2004). In the Caribbean, favid species are not only host to some of the most virulent diseases such as Yellow Band Disease and White Plague but disease is typically very prevalent in this taxonomic group (Croquer and Weil, 2009; Ward et al., 2006). Although there is intra-family variation in disease susceptibility in different geographical areas, some trends do emerge. Faster growing, thinner-tissued corals such as acroporids and pocilloporids seem most susceptible, possibly due to low investment in immunity (Palmer et al., 2008; Willis et al., 2004) whereas slower growing Poritidae have thicker tissue and are typically quite resilient to multiple stressors (Green et al., 2008). The inter-family and inter-specific differences in immunity combined with local stressors will probably inform these global patterns of disease resistance.

Symbiont responses to pathogens

The responses of both the algal and bacterial symbionts to diseases have been investigated due to the proposed importance of both of these symbioses to holobiont immunity (Harvell et al., 2007; Ritchie, 2006; Teplitski and Ritchie, 2009). The effect of disease on the populations of algal symbionts in the coral is quite different from the effects of temperature alone. Bleaching, as described above, causes a change in the community structure of algal symbionts; diseases however do not seem to impart the same effect. In sea fans infected with the fungal pathogen *Aspergillus sydowii*, the zooxanthellae clades did not change between healthy and infected sea fan tissue, even though zooxanthellae numbers were greatly reduced in infected tissue (Kirk et al., 2005). In a study of many scleractinian coral diseases including Dark Spot, Black Band and Yellow Band Diseases, zooxanthellae clades were also genetically stable between infected tissue and healthy adjacent tissue (Correa et al., 2009). However, Toller et al. found differences in zooxanthellae clades between Yellow Band infected tissue and healthy tissue on the same colony (Toller et al., 2001). Yellow Band Disease is a particularly interesting disease to examine zooxanthellae populations because it is believed the disease affects the algal symbionts (Cervino et al., 2004). Metalloproteases isolated from pathogens associated with White Syndromes on the Great Barrier Reef differentially affected *Symbiodinium* clades (Sussman et al., 2009). Therefore, zooxanthellae clade composition may contribute to disease susceptibility especially in diseases where symbionts are believed to be the target.

Even though algal symbiont populations are relatively stable in diseased corals, bacterial communities are very dynamic. Both temperature and disease have the potential to change the structure of the bacterial communities in the mucus layer. Diseases such as Aspergillosis (Gil-Agudelo et al., 2006), Black Band and White Plague (Sekar et al., 2006; Sunagawa et al., 2009) all induce bacterial community changes in infected tissue compared with healthy tissue. It is thus far unknown if these changes arise as a cause or an effect of infection. Variations in community structure, whether caused by temperature or disease, are concurrent with functional changes. The mucus layer and its bacterial inhabitants can protect the coral host, either as a barrier to incoming pathogens or by exuding antibacterial compounds that inhibit non-resident bacteria (Nissimov et al., 2009; Shnit-Orland and Kushmaro, 2009) or even pathogenic bacteria known to cause disease (Ritchie, 2006). Under normal conditions these bacterial communities appear to have a protective effect, although under temperature stress, potentially pathogenic bacteria like *Vibrio* species increase, possibly facilitating infection and disease (Ritchie, 2006; Teplitski and Ritchie, 2009). Proximity to fish farms also caused a shift in microbial communities, with more human and known coral pathogens present on corals near fish farm effluent than in control sites (Garren et al., 2009). In this short-term experiment, the corals near fish farm effluent did not develop disease and the microbial communities shifted back to their original composition after 22 days, showing unexpected resilience to eutrophication and bacterial invasion.

The effect on coral immunity of hosting diverse algal and bacterial symbionts is unknown, although it is likely that the same pattern recognition receptors (PRR) are utilized in the recognition of symbionts and pathogens, as is the case in other host–microbe interactions (Weis et al., 2008). Because many of these receptors rely on recognition of pathogen-associated molecular patterns, such as glycans and lipolysaccarides, it very likely they can recognize potential pathogens as well as potential symbionts. Upon initial infection, the zooxanthellae enter the host cell by phagocytosis and there is evidence that its presence prevents further phagosome maturation, which possibly prevents degradation by the lysozome (Chen et al., 2005; Hong et al., 2009; Schwarz et al., 2008). This has led to the development of hypotheses that posit that algal symbionts potentially elicit an immune reaction and that the persistence of the symbiosis depends on the coral host suppressing some components of immunity (Weis and Allemand, 2009; Weis et al., 2008). During the onset of symbiosis several genes typically involved in immunity were upregulated, such as receptors with lectin and PRR domains and signaling gene homologs known for host–microbe responses such as MAPK cell signaling pathway (Schwarz et al., 2008; Voolstra et al., 2009).

Several immune-related pathways are also upregulated during the breakdown of symbiosis. Intracellular signaling molecules, such as nitric oxide (Perez and Weis, 2006) and ROS, are induced during bleaching in the symbiont and coral host (Bouchard and Yamasaki, 2008; Lesser, 1997; Mydlarz and Jacobs, 2006). Both of these radicals play important roles in the inflammatory response and are typically induced during pathogen invasion for their toxicity and signaling properties (Mydlarz et al., 2006; Weis, 2008). The PPO pathway was also induced in naturally bleached coral, with a significant negative correlation between zooxanthellae numbers and PPO levels. The cause of this pathway elevation is still unknown but may involve calcium regulation and other factors that affect zooxanthellae and immunity independently (Mydlarz et al., 2009). Although preliminary, these data potentially support the symbiosis-mediated immune suppression hypothesis since during bleaching, damaged zooxanthellae signal their presence with free radicals and initiate host immune responses (Perez and Weis, 2006; Weis et al., 2008) and it remains to be seen how these intracellular events affect overall immunocompetence. Because disease outbreaks typically follow bleaching events (Miller et al., 2006; Muller et al., 2008), immune pathway upregulation due to bleaching in addition to detrimental physiological changes such as depletion of energy reserves and changes in protective mucus functions, all probably contribute to temperature-related disease dynamics.

Evolution of resistance

One source of resilience in natural populations is the sufficient variability in traits to allow rapid evolution. The process of evolution of disease resistance is ubiquitous but poorly studied in natural populations. Although rare to detect in ecological time in nature (Altizer et al., 2003), there are increasing examples of enhanced host resistance following an epizootic (Duncan and Little, 2007; Ibrahim and Barret, 1991). Invertebrates such as the copepods, *Daphnia*, are excellent models for evolution for host resistance. Duffy and Sivars-Becker detected increased resistance in experimentally infected populations of *Daphnia dentifera* populations from lakes that experienced epizootics but not in control populations (Duffy and Sivars-Becker, 2007). An epidemiological model confirmed the plausibility of host evolution as an explanation for increased *Daphnia* population resistance. Another recent study of evolution of resistance in field populations involves *Daphnia magna* populations artificially infected with the microsporidean *Octosporea bayeri*. Populations exposed to *O. bayeri* in ponds developed resistance over 15 generations and became less impacted than unexposed populations to new infections (Zbinden et al., 2008).

In coral, few examples of increased host resistance following an epizootic have been described. Vollmer and Kline (Vollmer and Kline, 2008) detected a small fraction of *Acropora cervicornis* genotypes resistant to White Band Disease in Panama following a massive epizootic, but there are no pre-epizootic estimates, so it is not possible to know what pattern of evolution occurred. Seasonal bleaching of *O. patagonica* in the Mediterranean occurred regularly between 1994 and 2002 and was attributed to the pathogen *Vibrio shiloi* (Kushmaro et al., 2001; Rosenberg and Falkovitz, 2004). The pathogen was repeatedly isolated from bleached corals, caused bleaching in experiments and was known to produce temperature-sensitive virulence factors (Banin et al., 2000; Banin et al., 2003). Since 2005, however, *V. shiloi* can no longer be isolated from summer bleached corals and no longer causes bleaching in experimental infections (Ainsworth et al., 2008; Rosenberg et al., 2007), leading to extensive dialogue and controversy over the tenets of bacterial bleaching and the associated probiotic hypothesis (Ainsworth et al., 2008; Leggat et al., 2007; Lesser et al., 2007). Current summer bleaching of *Oculina* continues to occur and is not attributed to bacterial pathogens (Ainsworth et al., 2008), and most mass-bleaching events occur independently of bacterial pathogens (Leggat et al., 2007). *In vitro* experiments do demonstrate that upon exposure to *V. shiloi*, *Oculina* can now lyse the bacteria as it penetrates the tissue and prevent an infection from establishing, perhaps resulting in a resistant host (Reshef et al., 2006). Although the hypothesis that *Oculina* has evolved resistance to *V. shiloi* is an appealing explanation, further evidence is required for confirmation.

In the Florida Keys during 1995, *Dichocoenia stokesii* was the most susceptible species of corals infected by White Plague Type II Disease caused by *Aurantimonas coralicida* (Denner et al., 2003). Since then, new colonies of this coral have repopulated the area and are no longer susceptible to the pathogen and are able to arrest lesions shortly after they begin (Richardson and Aronson, 2002), leading the authors to suggest that the host has evolved some resistance mechanisms. Interestingly, this disease has not recurred in large numbers in the years following the initial 1995 outbreak. Another similar example is the evolution of resistance in the sea fan – Aspergillosis pathosystem.

The prevalence of sea fan Aspergillosis was detected at peak levels between 1994 and 1997 and then declined (Kim and Harvell, 2004). This is one of the few cases of a coral epizootic where the host survived despite intense mortality, and the pathogen has now waned to low endemic levels, making it an instructive case to consider for understanding evolution of coral resistance. Possible explanations for the decline include: (1) changes in environmental conditions (e.g. temperature or pollutants), (2) reduced pathogen input or virulence, and (3) increased host resistance (Kim and Harvell, 2004). As there is no indication that the environment has changed in a way to disfavor Aspergillosis or that the input has decreased, the focus has been on the host resistance hypothesis. This hypothesis is supported by an earlier study finding reduced variance in antifungal resistance of sea fans at reefs with more severe disease outbreaks, suggesting a residue of local selection for resistance (Dube et al., 2002). Ten years of studying marked fans on permanent transects in the Florida Keys and Mexico revealed large mortality from the epizootic, a marked change in sea fan size structure and a large bottleneck in reproduction following peak epizootic years (J. F. Bruno, S. P. Ellner, I. Vu, K. Kim and C.D.H., unpublished data). The plausibility of the host resistance hypothesis was tested with a population model by evaluating whether host evolution could proceed quickly enough to explain the observed decrease in overall prevalence from ~30% in 1997 to <10% by 2003. As long as resistant individuals exist in the initial population, the kind of selection imposed by the sea fan epizootic would be expected to increase resistance. The model simulated the findings that large, susceptible, very fecund colonies were culled from the population during the epizootic, and the remaining smaller colonies were more resistant to infection.

The model is conservative in that the simulated rise and fall in disease prevalence is smaller and slower than the observed trend in nature. These simulations confirm that rapid evolution in host resistance due to differential mortality could play a role in the decline of the epizootic (J. F. Bruno, S. P. Ellner, I. Vu, K. Kim and C.D.H., unpublished data). Thus, host evolution by natural selection could also explain both how resistant sea fans accumulate and slow the epizootic and how the degree of the size-dependence in infection risk changed as the epizootic progressed. Ultimately, the ability of coral populations to evolve resistance is the final frontier of resilience. Little is known about successful evolution in nature but it is most likely to occur in corals with very large, sexually reproducing populations and relatively rapid generation times, such as gorgonian sea fans, a relatively 'weedy' taxon. Evolution of host resistance can often be countered by pathogen evolution, obscuring the response of host populations to selection (Zbinden et al., 2008). In the sea fan Aspergillosis case, the evolution of resistance is particularly likely to be successful because (1) the levels of host mortality were well documented and extremely high (J. F. Bruno, S. P. Ellner, I. Vu, K. Kim and C.D.H., unpublished data) (Dube et al., 2002; Kim and Harvell, 2004; Nagelkerken et al., 1997), (2) fungi in general are not known for extremely rapid evolution, so would likely not counter host evolution, and (3) *Aspergillus* populations in sea fans are largely believed to be clonal and not sexually reproducing.

Conclusions

In this review we outline physiological mechanisms that underlie coral resistance to temperature stress and disease. The mechanisms of the coral host include heterotrophy, cellular immunity, Hsps and FPs, and those of the coral symbionts include their own cascade of heat- and pathogen-resistant proteins in algal symbionts as well as probiotic functions in coral mucus bacteria and the mucus itself (Fig. 2). Collectively, these processes produce a resistant, remarkably resilient coral holobiont. Even though we review coral responses to temperature

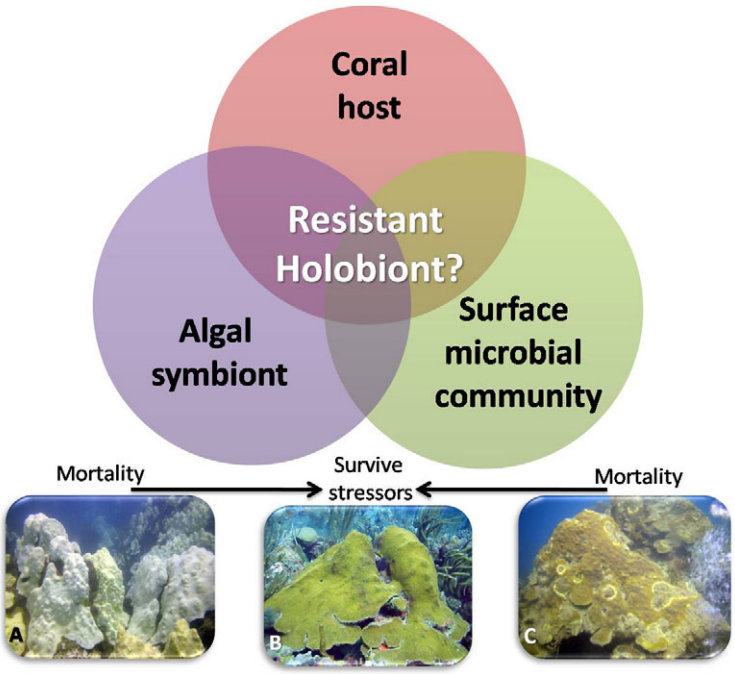

Fig. 2. Interactions between the different components of the coral holobiont to resist the effects of climate change. Factors that influence physiological resilience in corals may include life-history characteristics as well as cellular and molecular level responses. Algal and microbial symbionts may undergo community changes as well as functional changes that influence holobiont thermotolerance and defensive properties. Plasticity in these responses may mitigate mortality from bleaching and diseases. Images: (A) bleached *Montastraea* spp. colonies, (B) healthy *Montastraea faveolata* colony, and (C) Yellow Band diseased *M. faveolata* colony (all photos taken in La Parguera, Puerto Rico by E. Weil).

stress and pathogen pressure separately, there are many shared characteristics. For example, faster growing corals with thinner tissue are more susceptible to both bleaching and diseases and suffer higher mortality than massive, boulder corals (Loya et al., 2001; Willis et al., 2004). The antioxidant capabilities of a coral may determine how successfully it survives a bleaching event, as well as how effectively it resists pathogenic bacteria, as many immune pathways have cytotoxic side-effects. From the symbiont perspective, both bleaching and disease cause significant changes in the surface microbial communities that lead to changes in functional antibiotic properties. The importance of thermotolerant zooxanthellae clades in enhancing survival at elevated sea surface temperatures raises the question of the potential role of endosymbiont identity and function in disease resistance. This may be particularly important in the syndromes like Yellow Band Disease and some White Syndromes that seem to affect the symbionts directly.

The coral species with the greatest resilience, ability to acclimate and potential to evolve resistance to temperature stress and disease will probably dominate reefs in coming years. Evolutionary potential should depend on rapid generation times, large sexually reproducing populations, and the pace and tempo of selection. Examples of what is already being seen on reefs include the dominance of *P. astreoides* and various gorgonians in the Caribbean and *Porites lutea* in the Indo-Pacific and the loss of acroporid corals on reefs in both locales (Green et al., 2008; Loya et al., 2001). Another possibility for the introduction of novel genotypes that may possess increased stress tolerance lies with species that participate in mass spawning events, where gametes are released in synchronization and may hybridize (Kawecki, 2008; Willis et al., 2006). The few hybrids that have been identified in the wild populate and thrive in marginal habitats the parental species cannot colonize (Richards et al., 2008; Vollmer and Palumbi, 2002). As marginal habitats are typically characterized as being higher stress environments, these hybrids may provide the potential for evolution of resistant genotypes.

While the capacity for human intervention to bolster the survival of coral reefs may seem impossible, strategies are still being explored. Some strategies for mitigating effects of coral disease have shown promise. Physical removal of Black Band Disease from infected corals (Teplitski and Ritchie, 2009) and shading of corals infected with White Plague (Muller and van Woesik, 2009) in the Caribbean were both successful in halting the progression of these diseases. Biological treatments such as phage therapy (Efrony et al., 2009) and the use of probiotic bacteria as biocontrol agents are interesting possibilities [see Teplitski and Ritchie (Teplitski and Ritchie, 2009) for a comprehensive review]. An additional theoretical approach is to try and stimulate coral immune system using a probiotic bacteria, comparable with immune priming in other systems (Teplitski and Ritchie, 2009). The continued study of coral constitutive and inducible immune defenses will reveal the longer-term sustainability of this approach. We have summarized studies showing components of the coral immune repertoire that are indeed induced by infection or abiotic factors.

As research identifies resilient reefs that persist despite multiple disturbances, such as parts of the South Pacific and East African regions (Adjeroud et al., 2009; McClanahan et al., 2007), these areas may be targeted for future investigation, management and conservation (Hughes et al., 2003; West and Salm, 2003). Research concerning the environmental and genetic factors that contribute to the persistence of these reefs can contribute to the establishment of new and possibly interconnected marine protected areas, with the ultimate goal of conserving the genetic diversity of corals that show a heightened survivorship (Hughes et al., 2003; McClanahan et al., 2007; West and Salm, 2003). Management must also be expanded beyond the scope of marine ecosystems to include the many land-based anthropogenic stressors such as pollution and increased sediment run-off, as controlling these sources of stress at local levels will provide greater reef resilience and resistance (Hughes et al., 2003; Nystrom et al., 2008; West and Salm, 2003). Given the global importance of coral reefs, understanding the mechanisms involved in enhancing coral thermotolerance and immunity is crucial to developing and implementing successful management and conservation programs to combat the stress of climate change and insure the presence of coral reefs, in one form or another, for the future.

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