



Cnidaria: Anthozoans in the Hot Seat

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Introduction

Cnidaria is a diverse phylum, representing animals of dramatically different morphologies, life histories, and ecological functions but united by the presence of a specialized cell type—the cnidocyte. Cnidocytes secrete organelle-like capsules with eversible microtubules called cnidae (Daly et al. 2007). Anthozoa is the most speciose class of the phylum Cnidaria, with an estimated 7500 extant species (Daly et al. 2007), including the subclasses Hexacorallia and Octocorallia, which comprise stony corals and anemones, and soft corals and gorgonians, respectively (Won et al. 2001) (Fig. 1). Anthozoans are phylogenetically basal, both within the Metazoa as a whole and arguably within Cnidaria (Kayal et al. 2013), with Scleractinia (stony corals) appearing in the mid-Triassic (c. 250 million years ago [MYA]) (Romano and Palumbi 1996), possibly having evolved from anemones.

The first dinoflagellates, single-celled eukaryotes—“protists”—also purportedly appeared during the Triassic (Fensome 1993; Stanley 2006), and eventually, after a series of extinctions, formed an obligate endosymbiosis with a wide range of multicellular organisms, including anthozoans (Stanley 2006; Aranda et al. 2016). The majority of extant anthozoans live in this obligate endosymbiosis with members of the genus *Symbiodinium* (Aranda et al. 2016)—a relationship that underpins the ecological success of the class. In this intimate association, the *Symbiodinium* can provide over 90% of the energy requirements of the anthozoan (Muscatine and Porter 1977) and, in the case of hard coral, facilitate exoskeleton calcification, enabling the formation of tropical reef ecosystems (Fig. 2). In return, and in lieu of

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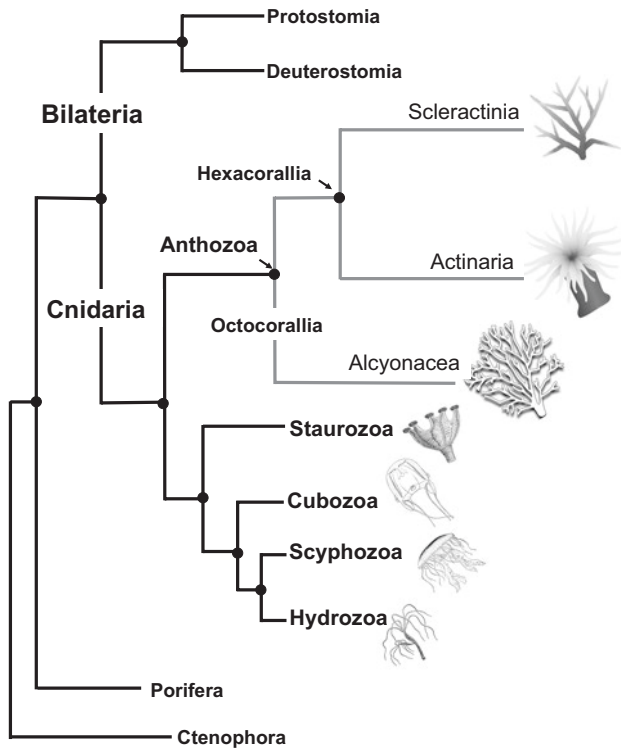


Fig. 1 Phylogenetic tree showing the position of Cnidaria

Fig. 2 A diverse and colorful Indo-Pacific coral reef. (Photo credit: Giles Winstanley)



living in typically nutrient-poor waters, the anthozoan host protects its algal partner and uses it to recycle waste carbon and nitrogen (Jeong et al. 2012). Under stress conditions, such as increased water temperature or infection, this obligate endosymbiosis can break down, turning the coral white as the cHL: Intelectin-1orophyll-pigmented *Symbiodinium* leave or die, revealing the coral skeleton through the translucent host tissue. The “bleached” anthozoan (Fig. 3) host is then susceptible to starvation, disease, and death (Fig. 4). This scleractinian coral–algal association is the best studied of the relationships anthozoans have with microbiota. It is

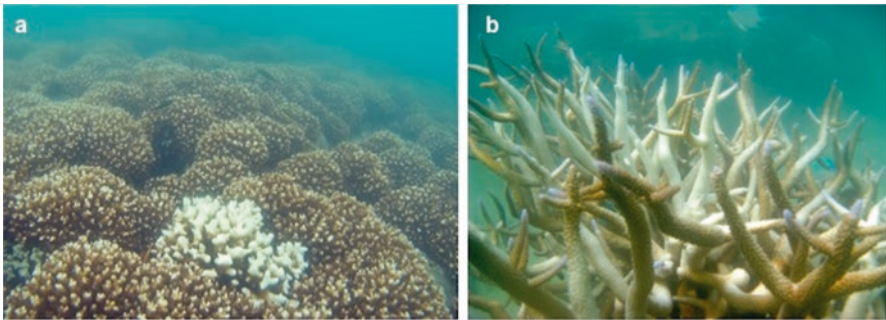


Fig. 3 Bleached scleractinian coral: (a) *Pocillopora* sp., Bahia Tomas, Costa Rica; and (b) *Acropora* sp., Orpheus Island, Great Barrier Reef, Australia. (Photo credit: C.V. Palmer)

Fig. 4 Bleached and diseased *Acropora millepora* (scleractinian coral), Orpheus Island, Great Barrier Reef, Australia. (Photo credit: C.V. Palmer)



becoming increasingly apparent that the specific, variable, and diverse microbiome associated with anthozoans is crucial to their health and likely modulated, in part, by coral immune mechanisms (Bourne et al. 2016). Deciphering the immunological intricacies of coral–microbe symbioses is an ecologically important field of research and will likely provide insight into the establishment and functioning of symbioses throughout the animal kingdom. This is particularly so as, despite their phylogenetic position (Fig. 1) and apparent morphological simplicity, anthozoans are immunologically complex (Miller et al. 2007; Shinzato et al. 2011b), with large genomes and gene families that are comparable with those of the Bilateria (Augustin and Bosch 2010). Unlike many bilaterians, however, anthozoans have evaded gene loss (Miller et al. 2007), making them an interesting group for studying the evolution of immunity as well as mutualisms.

The immune system is a highly integrated suite of mechanisms and processes that enable organisms to resist infection and maintain tissue integrity to promote survival (Medzhitov 2008; Cooper 2010). Like all organisms, anthozoans possess innate immune mechanisms (Palmer and Traylor-Knowles 2012), but as invertebrates they lack the more complex adaptive arm of immunity. Innate immunity provides a non-specific and immediate response to perceived endogenous and exogenous threats in a bid to re-establish homeostasis (Beutler 2004; Medzhitov 2008). Concomitantly, anthozoans use a diverse repertoire of immune receptors (Miller et al. 2007) (Table 1), signaling pathways (Wolenski et al. 2011), and effector and “stress” responses (Palmer et al. 2008), which eliminate pathogens, seal wounds, mitigate self-harm, and defend self by maintaining homeostasis (Palmer and Traylor-Knowles 2012; Mydlarz et al. 2016).

Shifts in environmental conditions, driven by climate change and local anthropogenic disturbances, are threatening the long-term survival of many species and systems, and coral reefs are among the most threatened (Hughes et al. 2017). Unfavorable environmental conditions are negatively affecting the health of coral reefs; the ancient, co-evolved symbiotic relationship that is so important to coral health is being pushed beyond its limit, resulting in mass bleaching and die-off events (Hughes et al. 2017). Longer-lived organisms, such as scleractinian corals, are particularly vulnerable to the anthropogenically increased rates of climate change, which exceed the time needed for a population to adapt through natural selection (van Oppen et al. 2017). To conserve coral reefs through this high rate of change, the potential of genetically engineered “super corals” that can withstand environmental change, is being explored (van Oppen et al. 2017). It is increasingly apparent that immunity, as the basis of the maintenance and reestablishment of health, needs to be at the forefront of coral reef health and disease research. Anthozoan immunology offers hope that we will better understand the drivers behind coral health in order to more effectively conserve and restore the reefs systems that are of high ecological and societal value.

Table 1 Summary of gene, protein, and signaling pathways involved in cnidarian immunity and stress response

Gene, protein, or pathway	Immune factor	Experiment	Organism	Citation
Toll-like receptor pathway	TLRs	Genome analysis	<i>Acropora digitifera</i>	Shinzato et al. (2011)
	TLRs	EST Database	<i>Acropora millepora</i>	Miller et al. (2007)
	TLR, TIR domain-only	Phylogenetic analysis	<i>Acropora digitifera</i> <i>Acropora millepora</i> <i>Fungia scutaria</i> <i>Montastrea cavemosa</i> <i>Pocillopora damicornis</i> <i>Seriatopora hystrix</i> <i>Exaiptasia pallida</i> <i>Anthopleura elegantissima</i>	Poole et al. (2014)
Toll-like receptor pathway	TLR2, TRAF3	White band disease transcriptome	<i>Acropora cervicornis</i>	Libro et al. (2013)
	TLRs	Bleaching and disease transcriptome	<i>Orbicella faveolata</i>	Anderson et al. (2016)
	TLRs	Stress transcriptome	<i>Pocillopora damicornis</i>	Traylor-Knowles et al. (2011)
	TLRs, TOLLIP	Larvae 454 transcriptome	<i>Acropora millepora</i>	Meyer et al. (2009)
	TLRs	Reciprocal transplant + heat stress transcriptome	<i>Acropora hyacinthus</i>	Seneca et al. (2015)
	TLR	Bacteria challenge transcriptome	<i>Pseudodiploria strigosa</i>	Ocampo et al. (2015)
	TLR2	EST Database	<i>Acropora millepora</i> <i>Acropora palmata</i>	Voolstra et al. (2011)
	TIR-1	qPCR, physical wounding with infection of bacteria	<i>Acropora aspera</i>	van De Water et al. (2015c)
	TLR	Injury-induced head regeneration transcriptome	<i>Hydra</i> sp.	Wenger et al. (2014)
	TLR	Transcriptome analysis	<i>Anthopleura buddemeieri</i> <i>Aulactinia veratra</i> <i>Calliactis polypus</i> <i>Telmatactis</i> sp. <i>Nemanthus annamensis</i>	Van der Burg et al. (2016)

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Table 1 (continued)

Gene, protein, or pathway	Immune factor	Experiment	Organism	Citation
	TLR	Phylogenetic analysis	<i>Nematostella vectensis</i> <i>Hydra</i> sp. <i>Acropora millepora</i>	Hemmrich et al. (2007)
	TIR domain	Bioinformatic analysis	<i>Nematostella vectensis</i>	Reitzel et al. (2008)
	TIR domain only	Genome analysis	<i>Exaiptasia pallida</i>	Baumgarten et al. (2015)
Lectin pathway	Millectin	Bacteria exposure: phylogenetics analysis and binding assays	<i>Acropora millepora</i>	Kvennefors et al. (2008)
	Millectin	LPS and peptidoglycan immune challenge, measured with qPCR, immunohistochemistry	<i>Acropora millepora</i>	Kvennefors et al. (2010)
	Lectins	Algal-coral cell interactions, flow cytometry	<i>Fungia scutaria</i>	Wood-Charlson et al. (2006)
	Tachylectin	EST Database	<i>Acropora palmata</i> <i>Montastraea faveolata</i>	Schwarz et al. (2008)
	Tachylectin-2	Phylogenetic analysis	<i>Oculina patagonica</i> <i>Montastraea faveolata</i> <i>Acropora millepora</i>	Hayes et al. (2010)
	PdC: C-lectin	Suppression subtractive hybridization	<i>Pocillopora damicornis</i>	Vidal-Dupiol et al. (2009)
	Rhamnose-binding lectin	Gene expression measured with qPCR, bacteria, and symbiont binding assays	<i>Pocillopora damicornis</i>	Zhou et al. (2017)
	C-type mannose receptor 2, C-type lectin domain family 10 member A	White band disease stress transcriptome	<i>Acropora cervicornis</i>	Libro et al. (2013)
	C-type lectin	White plague disease transcriptome	<i>Orbicella faveolata</i>	Daniels et al. (2015)
	HL: Intelectin-1-1	Anthropogenic stress transcriptome	<i>Acropora millepora</i>	van de Water et al. (2015a, b, c)
	C-type lectin	Reciprocal transplant + heat stress transcriptome	<i>Acropora hyacinthus</i>	Seneca et al. (2015)

	CEL-III type lectins	qPCR, early larval settlement and development	<i>Acropora millepora</i>	Puill-Stephan et al. (2012)
	C-type lectins, fucolactins, D-galactoside/L rhamnose-binding lectins, galectins, tachylectins	Bacteria challenge transcriptome	<i>Pseudodiploria strigosa</i>	Ocampo et al. (2015)
	Tachylectin precursor	Thermal stress microarray	<i>Montastrea faveolata</i>	DeSalvo et al. (2008)
	PdC: Pocillopora damicornis C-lectin	qPCR, bacteria challenge	<i>Pocillopora damicornis</i>	Vidal-Dupiol et al. (2011a)
	Tachylectin-5A	Response to <i>Aplanochytrium</i> spp. parasite transcriptome	<i>Gorgonia ventalina</i>	Burge et al. (2013)
	C-type lectin	qPCR, bacterial challenge	<i>Acropora millepora</i>	Brown et al. (2013)
	Mannose phospholipase lectin receptor related, C-type lectin superfamily	Injury-induced head regeneration transcriptome	<i>Hydra</i> sp.	Wenger et al. (2014)
	Calreticulin, C-type lectin domain family 4 member F, Ficolin 1, Ficolin 2, Fucolactin 1, Fucolactin 4	EST Database	<i>Exaiptasia pallida</i>	Sunagawa et al. (2009)
	C-type lectin domain	Bioinformatic analysis	<i>Nematostella vectensis</i>	Reitzel et al. (2008)
	C-type lectin domains	Bioinformatic analysis	<i>Nematostella vectensis</i>	Wood-Charlson and Weis (2009)
	C-type lectin	Heat stress, larvae, microarray	<i>Acropora millepora</i>	Rodriguez-Lanetty et al. (2009)
NOD-like receptor pathway	nucleotide-binding domain and leucine-rich repeat containing gene family s	Genome analysis	<i>Acropora digitifera</i>	Shinzato et al. (2011a, b)
	nucleotide-binding domain and leucine-rich repeat containing gene family s	Phylogenetic analysis	<i>Acropora digitifera</i>	Hamada et al. (2013)
	NLCR: Nod-like receptor C5	White band disease transcriptome	<i>Acropora cervicornis</i>	Libro and Vollmer (2016)
	NACHT-domain containing	Bacterial challenge transcriptome	<i>Pseudodiploria strigosa</i>	Ocampo et al. (2015)
	nucleotide-binding domain and leucine-rich repeat containing gene family	Transcriptome analysis	<i>Anthopleura buddemeieri</i> <i>Atlactinia veratra</i> <i>Calliactis polybypus</i> <i>Telmactis</i> sp. <i>Nemanthus amannensis</i>	Van der Burg et al. (2016)
	nucleotide-binding domain and leucine-rich repeat containing gene family, TRIP-6	Genome analysis	<i>Exaiptasia pallida</i>	Baumgarten et al. (2015)

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Table 1 (continued)

Gene, protein, or pathway	Immune factor	Experiment	Organism	Citation
Complement pathway	C3	Genome analysis	<i>Acropora digitifera</i>	Shinzato et al. (2011a, b)
	C3	EST Database	<i>Acropora millepora</i>	Miller et al. (2007)
	Bf, C3	Anthropogenic stress transcriptome	<i>Nematostella vectensis</i>	van de Water et al. (2015a, b, c)
	MASPI	Bleaching and bleaching recovery transcriptome	<i>Acropora millepora</i>	Pinzon et al. (2015)
	MPEG-1	White band disease transcriptome	<i>Acropora cervicornis</i>	Libro et al. (2013)
	C3	qPCR, bacterial challenge	<i>Acropora millepora</i>	Kvennefors et al. (2010)
	lncRNA	Bleaching vs. healthy transcriptome	<i>Protopalychoa varibilis</i>	Huang et al. (2017)
	C3	qPCR, early larval settlement and development	<i>Palythoa caribaeorum</i>	Puill-Stephan et al. (2012)
	C3, Bf, MASP, A2M, CD109	Bacteria challenge transcriptome	<i>Pseudodiploria strigosa</i>	Ocampo et al. (2015)
	C3	Cloning of C3 using RT-PCR	<i>Swiftia exserta</i>	Dishaw et al. (2005)
Scavenger receptor pathway	C3, Bf	qPCR, physical wounding with infection of bacteria	<i>Acropora aspera</i>	van De Water et al. (2015a, b, c)
	Complement component-related sushi domain containing, C1q related, complement component 1, MASP	Injury-induced head regeneration transcriptome	<i>Hydra</i> sp.	Wenger et al. (2014)
	C2, C3, C5, C8	EST Database	<i>Exaipastia pallida</i>	Sumagawa et al. (2009)
	Bf, MASP, C3	Phylogenetics, qPCR, bacteria challenge	<i>Exaipastia pallida</i>	Poole et al. (2016)
	C3	Microarray analysis	<i>Fungia scutaria</i>	Schnitzler and Weis (2010)
	C3	Chronic heat stress study	<i>Porites astreoides</i>	Kenkel et al. (2013)
	SR-A, SR-E, SRCR only, SR-B	Phylogenetics and functional analysis	<i>Acropora digitifera</i>	Neubauer et al. (2016)
			<i>Acropora millepora</i>	
			<i>Fungia scutaria</i>	
			<i>Nematostella vectensis</i>	
		<i>Anthopleura elegantissima</i>		
		<i>Exaipastia pallida</i>		
SRCR	Bacteria challenge transcriptome	<i>Pseudodiploria strigosa</i>	Ocampo et al. (2015)	
SRCR	Longitudinal bisections transcriptome	<i>Calliactis polyopus</i>	Stewart et al. (2017)	

Interleukin receptor pathway	IL-R1-like	Phylogenetic study	<i>Acropora digitifera</i> <i>Acropora millepora</i> <i>Fungia scutaria</i> <i>Montastrea cavernosa</i> <i>Pocillopora damicornis</i> <i>Seriatopora hystrix</i> <i>Exaiptasia pallida</i> <i>Anthopleura elegantissima</i> <i>Acropora millepora</i> <i>Calliactis polypus</i>	Poole et al. (2014)
	IL-IR1, IL-IR2, IL-IR3	EST Database		Miller et al. (2007)
	IL-R1	Transcriptome of longitudinal bisections		Stewart et al. (2017)
	IL-IR-like	Transcriptome analysis	<i>Anthopleura buddemeieri</i> <i>Aulactinia veratra</i> <i>Calliactis polypus</i> <i>Telmatactis</i> sp. <i>Nemanthus annamensis</i> <i>Nematostella</i> <i>Hydra</i> <i>Acropora millepora</i>	Van der Burg et al. (2016)
	IL-IR	Phylogenetic analysis		Hemmrich et al. (2007)
	ILR1, ILR2, ILR3, ILR4	Genome analysis	<i>Exaiptasia pallida</i>	Baumgarten et al. (2015)
	TNFRSF: Tumor Necrosis Factor Receptor Super Family 1A	White band disease transcriptome	<i>Acropora cervicornis</i>	Libro et al. (2013)
	TRAF6	EST Database	<i>Acropora millepora</i>	Miller et al. (2007, b)
	TNFRSF: Tumor Necrosis Factor Receptor Super Family 16	White band disease transcriptome	<i>Acropora cervicornis</i>	Libro and Vollmer (2016)
	TRAF3	Reciprocal transplant + heat stress transcriptome	<i>Acropora hyacinthus</i>	Seneca et al. (2015)

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Table 1 (continued)

Gene, protein, or pathway	Immune factor	Experiment	Organism	Citation	
RIG-like receptor	TRAF3, TNFRSF: Tumor Necrosis Factor Receptor Super Family 27, TNF, TNFRs, LITAF: Lipopolysaccharide-induced tumor necrosis factor-alpha factor TRAFs, TNFRs	Heat stress transcriptome	<i>Acropora hyacinthus</i>	Barshis et al. (2013)	
	Lymphotoxin-β receptor	Reciprocal transplant between different thermal regimens transcriptome LPS-exposed transcriptome	<i>Acropora hyacinthus</i>	Palumbi et al. (2014)	
RIG-like receptor	TRAF6	qPCR, physical wounding with infection of bacteria	<i>Orbicella faveolata</i> <i>Pseudodiploria strigosa</i> <i>Porites</i> <i>Porites astreoides</i>	Fuess et al. (2017)	
	TNF-related, TNF family member, TNFRSF: Tumor Necrosis Factor Receptor Super Family , TRAFs Caspase 3, Caspase 8, Caspase 10 TNF	Injury-induced head regeneration transcriptome	<i>Acropora aspera</i> <i>Hydra</i> sp.	van De Water et al. (2015a, b, c) Wenger et al. (2014)	
	Caspase 8, TRAF6	EST Library	<i>Exaipastia pallida</i>	Sunagawa et al. (2009)	
	DDX: DEAD-box helicases 60	Bioinformatic analysis	<i>Nematostella vectensis</i>	Reitzel et al. (2008)	
	Rig-like receptors	Genome analysis	<i>Exaipastia pallida</i>	Baumgarten et al. (2015)	
	Rig-1/JMDA: Melanoma Differentiation-Associated5 gene 1,	White plague disease transcriptome	<i>Orbicella faveolata</i>	Daniels et al. (2015)	
	Rig-1/JMDA: Melanoma Differentiation-Associated5 gene 2	Bleaching and Disease transcriptome	<i>Orbicella faveolata</i>	Anderson et al. (2016)	
		Bioinformatic analysis	<i>Nematostella vectensis</i>	Zou et al. (2009)	

NF-κB pathway	TAK: TGF-beta activated kinase-1, TRAF-6, NF-κB MyD88	EST Database	<i>Acropora millepora</i>	Miller et al. (2007, b)
		Phylogenetic study	<i>Acropora digitifera</i> <i>Acropora millepora</i> <i>Fungia scutaria</i> <i>Montastrea cavernosa</i> <i>Pocillopora damicornis</i> <i>Seriatopora hystrix</i> <i>Exaiptasia pallida</i> <i>Anthopleura elegantissima</i>	Poole et al. (2014)
	NF-κB NF-κB pathway	Larvae 454 transcriptome LPS exposed vs. control transcriptome	<i>Acropora millepora</i> <i>Orbicella faveolata</i> <i>Pseudodiploria strigosa</i> <i>Porites</i> <i>Porites astreoides</i>	Meyer et al. (2009) Fuess et al. (2017)
	NF-κB pathway NF-κB	Bacteria challenge transcriptome qPCR, physical wounding with infection of bacteria	<i>Pseudodiploria strigosa</i> <i>Acropora aspera</i>	Ocampo et al. (2015) van De Water et al. (2015a, b, c)
	MyD88 NFAT5, NF-κB, I-κB, NF-κB activating protein NF-κB	Knockdown of MyD88 Injury-induced head regeneration transcriptome Functional analysis of development	<i>Hydra magnipapillata</i> <i>Hydra</i> sp.	Franzenburg et al. (2012) Wenger et al. (2014)
	NF-κB, IκB, Bcl-3, and IκB kinase	Cloned cDNA and expressed in cell culture	<i>Nematostella vectensis</i> <i>Nematostella vectensis</i>	Wolenski et al. (2013) Wolenski et al. (2011)
	NF-κB	Characterization of Cys-Ser polymorphism	<i>Nematostella vectensis</i>	Sullivan et al. (2009)
	NF-κB, IκB, Bcl-3, NFAT: Nuclear factor of activated T-cells NF-κB inhibitor α	Phylogenetic study	<i>Nematostella vectensis</i>	Sullivan et al. (2007)
	MyD88, NF-κB	EST Library Transcriptome analysis	<i>Exaiptasia pallida</i> <i>Anthopleura buddemeieri</i> <i>Aulactinia veratra</i> <i>Calliactis polyopus</i> <i>Telmatactis</i> sp. <i>Nemanthus annamensis</i>	Sunagawa et al. (2009) Van der Burg et al. (2016)

(continued)

Table 1 (continued)

Gene, protein, or pathway	Immune factor	Experiment	Organism	Citation
Integrins	MyD88, IRAK: Interleukin-1 receptor-associated kinase, TRAF6, TAK: TGF-beta activated kinase1, IKK, NF- κ B	Phylogenetic analysis Genome analysis	<i>Nematostella</i> <i>Hydra</i> sp. <i>Acropora millepora</i> <i>Exaiptasia pallida</i>	Hemmrich et al. (2007) Baumgarten et al. (2015)
	NF- κ B, IKK α , TBK1, TRAF6, TRAF3	Proteomic and bioinformatics analysis of the skeletal organic matrix	<i>Stylophora pistillata</i> <i>Pocillopora damicornis</i> <i>Acropora digitifera</i> <i>Favia</i> sp.	Drake et al. (2013)
	Integrin- α	Expression analysis of coral fertilization	<i>Acropora millepora</i>	Iguchi et al. (2011)
	Integrin β cn1, AmIntegrin- α 1	Phylogenetics and expression analysis of coral gastrulation	<i>Acropora millepora</i>	Knack et al. (2008)
TGF- β signaling	Amltg α 1, Amltg β 2	cDNA isolation	<i>Acropora millepora</i>	Brower et al. (1997)
	Integrin β cn1	Bioinformatic analysis	<i>Nematostella vectensis</i>	Reitzel et al. (2008)
	Integrin β , Integrin- α 8, Integrin- α 4	Wound healing and regeneration	<i>Nematostella vectensis</i>	Dubuc et al. (2014)
	α -Integrin	microarray analysis	<i>Exaiptasia pallida</i>	Detournay et al. (2012)
	TGF- β	Bioinformatics, cellular analysis of TGF- β		
	TGF- β , TGF- β type I receptor	Bioinformatic analysis	<i>Nematostella vectensis</i>	Reitzel et al. (2008)
	HSP70	ELISA assay, lab experiment of tidal fluctuations	<i>Veretillum cymosorium</i>	Teixeira et al. (2013)
	HSP70	Lab temperature study	<i>Eunicella singularis</i>	Pey et al. (2011)
	HSP70	Lab heat shock study	<i>Corallium rubrum</i>	Haguenaer et al. (2013)
	HSP70, HSP90	Lab heat stress study	<i>Montastrea annularis</i>	Carpenter et al. (2010)
HSP70	Red soil exposure	<i>Pocillopora damicornis</i>	Hashimoto et al. (2004)	
HSP16, HSP60	Lab heat stress study	<i>Porites astroideus</i>	Olson et al. (2013)	
HSPs	Heat stress and embryogenesis, microarray	<i>Acropora palmata</i>	Portune et al. (2010)	
HSP70	Heat shock	<i>Goniopora djiboutiensis</i>	Sharp et al. (1997)	
HSP60	Heat stress and shock study	<i>Anemonia viridis</i>	Chotesh et al. (2001)	
HSP60	Salinity stress study	<i>Seriopora caltendrum</i>	Seveso et al. (2013)	

HSP60	Skeleton eroding band disease	<i>Acropora muricata</i>	Seveso et al. (2012)
HSP90	Heat stress study	<i>Dendronephthya klunzingeri</i>	Wiens et al. (2000)
HSPs	Heat and UV stress transcriptome	<i>Aniophleura elegantissima</i>	Richier et al. (2008)
HSP70, HSP90	Heavy metal and oil dispersant exposure study	<i>Montastraea franksi</i>	Venn et al. (2009)
HSP60, small HSPs	Cellular diagnostic for corals in their natural environment	<i>Montastraea annularis</i>	Downs et al. (2005)
HSP70	Characterized protein	<i>Sylophora pistillata</i>	Tom et al. (1999)
HSP70	Heat shock study	<i>Anemonia viridis</i>	Sharp et al. (1994)
HSP90	Heat stress and bleaching microarray	<i>Montastraea faveolata</i>	Desalvo et al. (2008)
HSP 93, HSP83, HSP70, HSP68, HSP45, HSP39	Heat stress study	<i>Aurelia</i> sp.	Black and Bloom (1984)
HSP70	Protein assay of corals from naturally hot environment	<i>Porites lobata</i>	Barshis et al. (2010)
HSP95, HSP90, HSP78, HSP74, HSP33, HSP28, HSP27, HSP82, HSP72, HSP68, HSP48	Heat stress study	<i>Montastraea faveolata</i> <i>Aiptasia pallida</i>	Black et al. (1995)
HSP70	Heat stress transcriptome	<i>Acropora hyacinthus</i>	Traylor-Knowles et al. (2017b)
HSP90, HSP97	Heat stress on embryos, microarray	<i>Montastraea faveolata</i>	Voolstra et al. (2009)
HSP90, HSP70	EST Library	<i>Exaiptasia pallida</i>	Sunagawa et al. (2009)
HSP70	Larvae transcriptome using 454 sequencing	<i>Acropora millepora</i>	Meyer et al. (2009)
HSPs	Reciprocal transplant between different thermal regimens	<i>Acropora hyacinthus</i>	Palumbi et al. (2014)
HSP60, HSP70, chIpsHSP: cHL: Intelectin-1otroplast small heat shock protein, sHSPs	Heat stress—no light and heat stress high UV	<i>Montastraea faveolata</i>	Downs et al. (2000)
HSP70, HSP60, HSP35	Heat shock study	<i>Acropora grandis</i>	Fang et al. (1997)
HSP60	Heat shock and light intensity shock	<i>Sylophora pistillata</i> <i>Turbinaria reniformis</i>	Chow et al. (2009)
HSP90, HSP70, HSP20	Bioinformatic survey	<i>Nematostella vectensis</i>	Goldstone et al. (2008)
HSP60	Field-sampled animals for different temperature regimens	<i>Anemonia viridis</i>	Choreash et al. (2001)

(continued)

Table 1 (continued)

Gene, protein, or pathway	Immune factor	Experiment	Organism	Citation
	HSP60, HSP70	Comparative study of HSP60 and HSP70	<i>Hydra vulgaris</i>	Bosch and Praetzel (1991)
	HSP70 sHSP	Petroleum contamination study	<i>Pocillopora damicornis</i>	Rougee et al. (2006)
	HSP90	Heat stress study	<i>Eumicea fusca</i>	Ross (2014)
	HSP70, HSP90, chaperone GP96: heat shock protein 90 kDa beta member 1	Heat stress, larvae, microarray	<i>Acropora millepora</i>	Rodriguez-Lanetty et al. (2009)
	HSPs	Heat stress transcriptome	<i>Acropora hyacinthus</i>	Barshis et al. (2013)
	HSP60	Heat stress treatment	<i>Hydra attenuate</i> <i>Hydra oligactis</i>	Bosch et al. (1988)
	HSP20, HSP70, HSP40	Acidification stress on larvae	<i>Acropora millepora</i>	Moya et al. (2015)
	HSP1, HSP70, HSP90	Acidification stress study	<i>Acropora digitifera</i>	Nakamura et al. (2012)
	HSP70	Heat and acidification on larvae	<i>Pocillopora damicornis</i>	Putnam et al. (2013)
	HSP112, HSP89, HSP74 HSP102, HSP98, HSP56, HSP25, HSP44, HSP38, HSP33	Heat and cold stress study	<i>Leptogorgia virgulata</i>	Kingsley et al. (2003)
	HSP90, HSP60, HSP16	Chronic heat stress study	<i>Porites astreoides</i>	Kenkel et al. (2013)
	HSP16	Heat light stress	<i>Porites</i>	Kenkel et al. (2011)
	HSP70	Bacteria challenge study, qPCR	<i>Acropora millepora</i>	Brown et al. (2013)
	HSP90, HSP70	Heat stress study, qPCR	<i>Acropora aspera</i>	Leggett et al. (2011)
	HSP90	Heat stress study, larvae, microarray	<i>Montastraea faveolata</i>	Polato et al. (2010)

Bcl, *B-cell lymphoma*, *Bf* Factor B, *cDNA* complementary DNA, *chIpsHSP* chloroplast small heat shock protein, *Cys-Ser* Cysteine-Serine, *DDX* DEAD-box helicases, *ELISA* enzyme-linked immunosorbent assay, *GP96* heat shock protein 90 kDa beta member 1, *HL* Intelectin-1, *HSP* heat shock protein, *IKK* IκB kinase, *IL-R* interleukin receptor, *IRAK* Interleukin-1 receptor-associated kinase, *LITAF* Lipopolysaccharide-induced tumor necrosis factor-alpha factor, *lncRNA* long non-coding RNA, *LPS* lipopolysaccharides, *MASP* mannose-binding lectin-associated serine protease, *MDA* Melanoma Differentiation-Associated, *MylD88* myeloid differentiation primary response gene 88, *NFAT* Nuclear factor of activated T-cells, *NF-κB* nuclear factor-κB, *NLCR* Nod-like receptor C, *MLR* nucleotide-binding domain and leucine-rich repeat containing gene family, *NOD* nucleotide-binding oligomerization domain, *PdC* *Pocillopora damicornis* C, *qPCR* quantitative polymerase chain reaction, *RT-PCR* reverse transcription polymerase chain reaction, *sHSP* small heat shock protein, *TAK* TGF-beta activated kinase, *TBK* NF-Kappa-B-Activating Kinase, *TGF* transforming growth factor, *TIR* terminal inverted repeat, *TOLLIP* Toll interacting protein, *TLR* Toll-like receptor, *TNFR* tumor necrosis factor receptor, *TRAF* tumor necrosis factor receptor-associated factor, *TRIP* Thyroid Receptor Interacting Protein

Anthozoan Innate Immunity

Cnidarians use a diverse suite of characteristic innate immune mechanisms to maintain and re-establish homeostasis (Palmer and Traylor-Knowles 2012). Unlike the majority of animals, which possess either a protective exoskeleton (e.g., Arthropoda) or a thick epidermal tissue layer (e.g., mammals), the protective physical and biochemical layers of an anthozoan include only a single-cell host epithelium and surface mucus layer (SML). Once these protective barriers have been breached, and in the presence of a threat, an innate immune response occurs in the three broad immunity phases described across phyla: *recognition* of a threat, *signaling pathways* to activate appropriate response, and *effector responses* that eliminate the threat and mitigate self-harm (Hoffmann et al. 1999).

Anthozoans, like all invertebrates and higher organisms, use a suite of pattern recognition receptors (PRRs) and soluble proteins to recognize a broad array of conserved microorganism-associated molecular patterns (MAMPs) e.g., lipopolysaccharides (Loker et al. 2004; O'Neill et al. 2013) and host-derived damage-associated molecular patterns (Medzhitov and Janeway 2000a; Beutler 2004; Palmer and Traylor-Knowles 2012). In insects and other arthropods, the binding of MAMPs and/or DAMPs to PRRs, such as the Toll-like receptor (TLR) (Medzhitov and Janeway 2000b), activates serine protease cascades (Cerenius et al. 2010) and rapid-acting transcription factors, such as nuclear factor (NF)- κ B. This leads to gene transcription and ultimately protein translation, which induces immune signaling pathways and appropriate effector responses (Medzhitov and Janeway 2000a). These receptors, signaling pathways, and downstream responses are being elucidated in anthozoans (see the summary in Table 1). Here we discuss progress in cnidarian immunology, with a focus on anthozoans, in relation to the broader field of invertebrate immunology.

The Mucosal Epithelia

SMLs evolved with the Cnidaria and are present in all multicellular phyla (Bythell and Wild 2011). Similar to the mucosal surfaces of the intestinal cell epithelia of the human gut (Artis 2008), the anthozoan SML overlays single-cell epithelia and is home to an array of commensal bacteria, distinct from the microbiota of the surrounding environment (Sweet et al. 2011). While the methods of many coral mucus studies may have led to variable accounts of the SML-associated microbiota (Sweet et al. 2011), it is evident that the SML represents a physical protective barrier and a niche for many members of the coral microbiome (Kaiko and Stappenbeck 2014).

The coral SML is composed of a mixture of secreted compounds, including large glycoproteins called mucins. Mucins are released from epithelial mucocytes and form gels of varying viscosity (Jatkar et al. 2010) that are ultimately responsible for providing epithelial protection (Bythell and Wild 2011). The coral SML is dynamic, enables the transfer of gases and storage of metabolites (Bythell and Wild 2011), is used to remove sediment (Fig. 5), and also varies with the environment and over

Fig. 5 Mucus sheet sloughing off of massive *Porites* sp., Orpheus Island, Great Barrier Reef, Australia. (Photo credit: C.V. Palmer)



time (Brown and Bythell 2005). Importantly, the SML offers a niche for commensal coral-associated microbes that fulfill important functions including nutrient provision and antimicrobial defense (Ritchie 2006; Krediet et al. 2013). While the ability of host immune systems to regulate populations of commensal bacteria is conserved across phyla, it is unclear how innate immune mechanisms distinguish beneficial and commensal microbes from potential pathogens (Rohwer et al. 2002; Artis 2008; Bourne et al. 2016). In the case of the coral SML, innate immunity of the host epithelium must be *hypo-responsive* to commensal microbes, while remaining *reactive* against pathogens (Rakoff-Nahoum et al. 2004; Artis 2008).

Effector Responses: Activation and Signaling

Effector responses eliminate a recognized threat that may be exogenously derived—like pathogens and toxins—or endogenously derived, such as signals from stressed or malfunctioning cells (Medzhitov 2008). The effector response resulting from endogenous activation of the immune system is sometimes referred to as a “cellular stress response”, and may be triggered by changes in environmental conditions (e.g., Kültz 2005). The immediate and typically non-specific nature of innate immunity means that many effector responses are often mediated without gene transcription, and are instead reliant on serine protease cascades and redox signaling (Cerenius et al. 2010). In the following sections we discuss anthozoan effector responses and provide information on the current information on related receptors and signaling pathways (Table 1).

Immune Cells, Phagocytosis, and Wound Healing

Mobile immune cells eliminate pathogens via phagocytosis, seal wounds, and release bioactive compounds at sites of infection. Cell–cell and cell–extracellular matrix communication is key for each of these effector responses, and often involves integrins (Johnson et al. 2009). Integrins are a group of transmembrane α – β heterodimer receptors that are involved in cell migration and differentiation, fibrillar matrix formation, and signal transduction (Takada et al. 2007). Integrins have been identified within many anthozoan genomes, and show a surprising amount of complexity (Table 1) (Knack et al. 2008). For example, there are three α - and four β -integrin subunits identified in *Nematostella vectensis*, the starlet sea anemone (Putnam et al. 2007; Reitzel et al. 2008), and two β -subunits in the hard coral *Acropora millepora* (Brower et al. 1997; Miller et al. 2007). In a study on *N. vectensis* wound healing and regeneration, one of the highest upregulated genes during wound healing was α -integrin (DuBuc et al. 2014). α -Integrin is part of the mitogen-activated protein kinase (MAPK) signaling pathway (Table 1), which is proposed to be one of the primary mechanisms involved in *N. vectensis* wound healing (DuBuc et al. 2014).

The lectin-activated complement pathway is also important for cellular immune responses. This pathway is highly conserved and promotes phagocytosis and pathogen killing by aggregating and opsonizing pathogens (Fujita et al. 2004). Lectins are a diverse family of PRRs that include ficolins and mannose-binding lectins (MBLs), which recognize specific bacterial MAMPs (Fujita et al. 2004). The primary complement pathway components include complement C3, Factor B (Bf), lectins, and MBL-associated serine protease (MASP) (Carroll 1998). A wide diversity of lectins have been found within cnidarians, and are activated, along with other complement pathway components, in response to various stimulants including pathogen challenge, initiation of symbiosis, thermal stress, and wound healing (see Table 1) (Ocampo et al. 2015). For example, in the scleractinian coral, *Pseudodiploria stri-gose*; the lectins C-type, fucolectins, D-galactoside/L rhamnose-binding lectins, galectins and tachylectins C3, Bf, and MASP; and pathway components A2M and CD109 are all activated in response to a pathogen challenge. (Ocampo et al. 2015). In *Hydra*, components of the lectin-activated complement pathway are upregulated during wound healing and regeneration of the head (Wenger et al. 2014). In particular, MASP is upregulated in bisected animals, and it is proposed that the lectin-activated complement pathway may promote opsonization of invading pathogens (Wenger et al. 2014). The presence and activation of the lectin-activated complement pathways in cnidarians demonstrates its key role in phagocytosis and cellular responses during an immune response to infection.

Congruent with the identification of immune cell receptors and complement pathway components within anthozoan genomes, multiple anthozoan immune cells have been identified (Palmer and Traylor-Knowles 2012). Mobile, phagocytic cells—amoebocytes—were first identified in the sea anemone *Actinia equina*, and were shown to have bioactive capabilities within the mesenterial filaments (Hutton and Smith 1996). Additionally, a population of cells showing phagocytic activity were identified in the sea anemone *Exaiptasia pallida* using fluorescent-activated cell

sorting (Rosental et al. 2017). Within gorgonians, immune cells have been identified in *Swiftia exserta* in response to injury (Olano and Bigger 2000) and unstimulated immune cells have been located using enzymatic histochemistry, suggesting a bioactive role in immunity (Menzel and Bigger 2015). Additional investigations in the gorgonian *Plexaurella fusifera* have provided insights into the processes and cells involved in anthozoan wound healing (Meszaros and Bigger 1999). Amoebocytes have also been observed in response to infection in *Gorgonia ventalina* (Mydlarz et al. 2008; Couch et al. 2013). In this response, melanin-producing amoebocytes of *G. ventalina* encapsulated infected tissue (Mydlarz et al. 2008). Similarly, encapsulation has been observed in a hybrid of *Sinularia maxima* (Slattery et al. 2013). Within scleractinian corals several types of immune cells have also been identified, including granular amoebocytes (Vargas-Angel et al. 2007; Renegar et al. 2008), melanin-containing cells (Palmer et al. 2010), chromophore cells (Domart-Coulon et al. 2006), agranular (hyaline) cells (Palmer et al. 2011b), and fibroblast-like cells in response to injury (Palmer et al. 2011b). Similar characteristics among many scleractinian coral immune cells suggest that they may originate from a common stem cell (Palmer et al. 2011b), consistent with observations of *Hydra* (Bosch et al. 2010).

Tissue damage requiring wound healing is a common occurrence for many organisms. Having an open lesion leaves an organism susceptible to infection, making it imperative that wounds are rapidly and effectively sealed. In scleractinian corals, wounding occurs naturally primarily via predation (fish bites; Fig. 6), boring invertebrates, algal abrasion, fragmentation, and storm damage, and is often associated with distinct changes in tissue coloration (Fig. 7). Wound healing across the Metazoa occurs in four sequential stages using specialized cells (Galko and Krasnow 2004; Martin and Leibovich 2005), and has been described in the scleractinian coral *Porites cylindrica*, based on histological analysis (Palmer et al. 2011b). The wound healing process is characterized by (1) insoluble clot (plug) formation to seal the lesion, prevent fluid loss, and minimize infection (Theopold et al. 2004), via the transglutaminase and melanin synthesis pathways in invertebrates (Palmer et al. 2012); (2) infiltration and phagocytosis of cellular debris and foreign organisms; (3)

Fig. 6 Very recent predation scars on a massive scleractinian coral of the genus *Porites*. (Photo credit: C.V. Palmer)

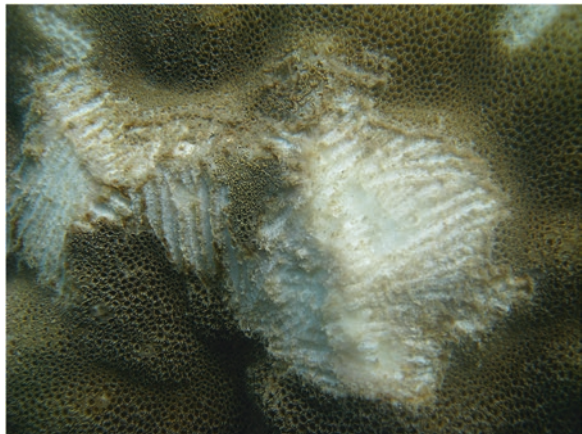


Fig. 7 Visibly distinct pigmentation on *Porites* spp (Photo credit: C. V. Palmer)



proliferation and formation of granulation tissue that consists of multiple cell types, collagen, and a basic extracellular matrix, providing a platform for re-epithelialization (Galko and Krasnow 2004; Biressi et al. 2010); and (4) re-epithelialization and wound maturation, often involving apoptosis (Martin and Leibovich 2005; Biressi et al. 2010; Palmer et al. 2011b). Immune cells involved in wound healing of the hard coral *P. cylindrica* include melanin-containing granular cells (Fig. 8), agranular amoebocytes, fibroblast-like cells, and granular amoebocytes (Palmer et al. 2011b).

The Melanin Synthesis Pathways

Melanin synthesis pathway by products (e.g., reactive species and quinones) and deposited melanin pigment are key constituents of the invertebrate immune repertoire (Söderhäll and Cerenius 1998). They are also the first classic invertebrate immune responses to be documented within anthozoans (Couch et al. 2008; Mydlarz et al. 2008; Palmer et al. 2008; Gimenez et al. 2014; Zaragoza et al. 2014). In arthropods, melanin synthesis is initiated by PRRs that trigger the activation of serine protease cascades, leading to the cleavage of the prophenoloxidase (PPO) zymogen and resulting in the formation of active phenoloxidase (PO) enzymes (Cerenius et al. 2010). The POs then initiate rapid proteolytic cascades involved the catalysis of monophenol hydroxylation, diphenol oxidation, and autocatalytic reactions that results in melanization (Cerenius et al. 2010). PPOs and POs exist in various isoforms that represent different components of several melanin synthesis pathway types. These pathway types include tyrosinase (Cerenius et al. 2008) and laccase

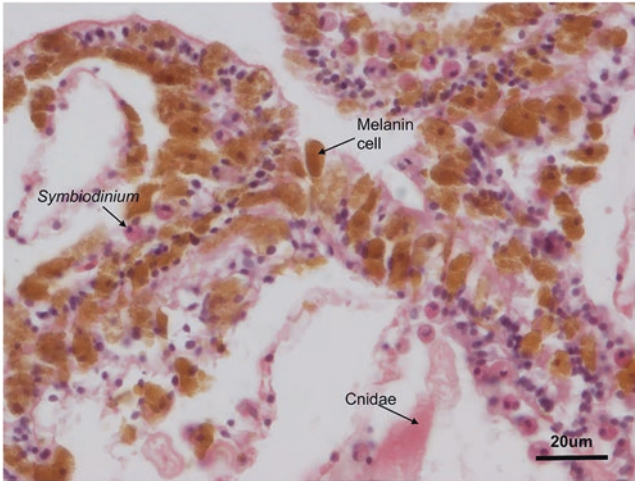


Fig. 8 Histological sections showing an epidermal tissue of scleractinian coral *Porites* sp. with a high concentration of melanin-containing granular cells as well as endosymbionts *Symbiodinium* and cnidae. (Photo credit: C.V. Palmer)

(Luna-Acosta et al. 2010), and likely have different functions (Sugumaran 2002; Cerenius et al. 2008; Palmer et al. 2012). For example, the tyrosinase-type melanin synthesis pathway is highly cytotoxic and therefore ideal for resisting infection (e.g., Bidla et al. 2008; Seppala and Jokela 2011), whereas the laccase-type pathway is less cytotoxic and likely has a role in cuticle formation within many invertebrates (Cerenius et al. 2008; Luna-Acosta et al. 2010).

The receptors and mechanisms involved in melanin synthesis pathway activation have not been elucidated for anthozoans, as for many other invertebrates (Takahashi et al. 2015). However, genes homologous to those associated with melanin synthesis pathways in some arthropods have been identified within the genomes or transcriptomes of several anthozoans, such as C-type lectins (Yu and Kanost 2004) (Table 1). In scleractinian corals many different types of lectins have been discovered, including C-type lectins, rhamnose-binding lectins, tachylectins, fucolectins, and galectins (Table 1). One well-studied example of the C-type lectin is “millectin”, discovered in *A. millepora*. Millectin can bind to both pathogens and algal symbionts (e.g., Kvennefors et al. 2008) (Table 1). However, another study found no increase in C-type lectin expression during bacterial challenge (Brown et al. 2013). The conflicting evidence for lectin reactivity suggests that the complete picture on the role of lectins in anthozoan immunity is still unknown (Palmer and Traylor-Knowles 2012).

In addition to the lectin pathway, many other pathways are linked to melanin synthesis. The TLR and Toll pathway are involved in melanin pathway activation in insects (Cerenius et al. 2010), and concomitantly TLR genes are present in anthozoans (Table 1). Similarly, tyrosinase genes, which are involved in melanin pathway activation, have been found within the genomes of the sea anemone *N. vectensis* and

the hydrozoan *Hydra magnipapillata* (Esposito et al. 2012). Expression of trypsin-like serine proteases has also been documented during immune challenge in the scleractinian coral *A. millepora* (Weiss et al. 2013), and a laccase-3 gene and shrimp PPO-activating enzyme (PPAE) homolog found in the scleractinian coral *Pocillopora damicornis* (Vidal-Dupiol et al. 2014). Also, a single contig predicted to encode a PO was found within the transcriptome of the Caribbean reef-building coral *P. stri-gosa* (Ocampo et al. 2015). Crucially, as rapid proteolytic cascades control melanin synthesis, gene expression studies will likely only loosely represent the immune activity of this effector response (Cerenius et al. 2010). As such, PO activity is frequently measured enzymatically in invertebrate immunology to determine presence and regulation of melanin synthesis pathways (e.g., Cerenius et al. 2008; Haine et al. 2008; Palmer et al. 2010).

Biochemical PO and PPO activities of the tyrosinase-type pathway were first reported in two reef-building coral species, *A. millepora* and *Porites* sp. (Palmer et al. 2008) and the gorgonian sea fan *G. ventalina* (Mydlarz et al. 2008). Tyrosinase-type PO and/or PPO activity has since been enzymatically demonstrated within numerous scleractinian corals from the Caribbean and Indo-Pacific (Palmer et al. 2012), soft corals (Alcyonacea), anemones (Actiniarian), and zoanthids (Zoantharia) (Palmer et al. 2010, 2011c, 2012a; Mydlarz and Palmer 2011; D'Angelo et al. 2012; Anithajothi et al. 2014; Gimenez et al. 2014; Sheridan et al. 2014; Zaragoza et al. 2014; van de Water et al. 2016). Laccase-type PO activity, which potentially has a role in coral photosensing and structural support (Palmer et al. 2012), has also been biochemically demonstrated in multiple scleractinian corals from the Indo-Pacific (Palmer et al. 2012) and Caribbean (Mydlarz and Palmer 2011), and in larvae and juveniles (Palmer et al. 2012). These reports demonstrate the ubiquity, and therefore likely significance, of melanin synthesis across anthozoans.

Melanin-associated encapsulation and structural support involves the degranulation of immune cells within which the melanin synthesis pathway is active (Galko and Krasnow 2004). Examples of these immune cells in other invertebrate organisms include crystal cells of insects (Bidla et al. 2008) and hemocytes of crustaceans (Söderhäll and Smith 1986). Melanization and associated amoebocytes have been shown to form a barrier against fungal infection, and were first documented within the anthozoan sea fan *G. ventalina* (Petes et al. 2003; Mullen et al. 2004; Mydlarz et al. 2008). Melanin-containing cells and/or melanin deposits have also been found within a suite of healthy Indo-Pacific corals (Scleractinia and Alcyonacea) (Palmer et al. 2010) and multiple Caribbean coral species (Mydlarz and Palmer 2011), suggesting such cells may be ubiquitous among anthozoans. The increase in melanin cell density in both compromised and infected coral tissue (Palmer et al. 2008, 2009a) and their degranulation at lesions (Palmer et al. 2011b) indicates their prominent role in coral immunity (Fig. 8).

Though the cytotoxicity of melanin synthesis hasn't been explicitly explored within corals, the upregulation of PO in injured (D'Angelo et al. 2012; Sheridan et al. 2014; van de Water et al. 2015c), pathogen challenged, and infected corals (Palmer et al. 2008, 2011a, c; Zaragoza et al. 2014) suggests pathway activities are

part of an effector response, as well as immune signaling (Mydlarz and Palmer 2011; Palmer et al. 2012). However, it has also been proposed that coral PO is used in growth, rather than immunity, due to the correlation between PO activity, fluorescence, and cell proliferation (D'Angelo et al. 2012). However, given the key role of PO in immunity throughout invertebrate phyla (Cerenius et al. 2010), upregulated PO in fast-growing coral tissue likely provides additional protection to the most at-risk parts of the coral colony. Growing tissues that demonstrate proliferation of melanin-containing granular cells and increased PO are also those most likely to come into contact with potentially harmful competitors, algae, and biofilm-associated microbes, as is the case during larval settlement (Palmer et al. 2012).

Coagulation

Coagulation is the process by which a liquid, such as invertebrate hemolymph, is converted into an insoluble clot—often in the form of a gel (Theopold et al. 2004). In invertebrates, coagulation ensures the rapid re-establishment of tissue integrity upon injury by preventing fluid loss and entrapping pathogens during infection (Cerenius et al. 2010). While there are likely multiple clotting mechanisms within invertebrates, one key pathway involves transglutaminases that form a gel upon interaction with plasma proteins (reviewed by Cerenius et al. 2010). Transglutaminases have previously been identified within several different invertebrates including molluscs (e.g., Nozawa et al. 2001) and many types of arthropods (see Cerenius et al. 2010), and is often followed by melanization for clot hardening (reviewed by Theopold et al. 2004). Transglutaminase activity has only been documented within one anthozoan: the reef-building coral *P. cylindrica* (Palmer et al. 2012). Within *P. cylindrica*, transglutaminase activity increased in response to injury (Palmer 2010), confirming its role within anthozoan wound sealing.

Antimicrobial Activity

Cnidarian antimicrobial peptides (AMPs) are cationic and hydrophobic, targeting the cell walls of microorganisms, and often providing broad-spectrum defense (Destoumieux-Garzón et al. 2016). Across the Metazoa, AMPs are typically located within granular immune cells and in association with epithelial tissue layers (Zasloff 2002). AMP transcription is initiated by the activation of the TLR pathway and subsequently the transcription factor NF- κ B complexes with other adaptor proteins (Anderson 2000). AMPs are then used to disrupt microbial cell membranes (Shai 2002) and inhibit bacterial metabolic processes (Brogden 2005; Vidal-Dupiol et al. 2011b). A wide variety of invertebrates have been shown to possess a diverse suite of AMPs (e.g., Lemaitre and Hoffmann 2007; Otero-Gonzalez et al. 2010; Destoumieux-Garzón et al. 2016). Within Cnidaria, AMPs have been identified within Scyphozoa jellyfish, *Aurelia aurita* (aurelin) (Ovchinnikova et al. 2006), the Hydrozoa *Hydra* (arminin) (Miller et al. 2007; Augustin and Bosch 2010; Franzenburg et al. 2013), and Anthozoa, as reviewed by Mydlarz et al. (2016). The AMP, Damicornin, has been isolated from the scleractinian coral *P. damicornis* and demonstrated activity in response to Gram-positive bacteria and fungi (Vidal-Dupiol et al. 2011b). Two other AMPs have been bioinformatically characterized from

P. damicornis—a mytimacin-like protein that binds to lipopolysaccharides and a bactericidal/permeability-increasing protein (LBP-BPI) (Vidal-Dupiol et al. 2014). The antimicrobial compound Homarine has previously been shown to demonstrate antifouling and predator deterrent functions in other invertebrates and was subsequently found to be a critical AMP for gorgonian *Leptogorgia virgulata* (Shapo et al. 2007). In several *Hydra* species the AMP, arminin, has been shown to have a distinct, species-specific function in dictating which bacterial communities can associate with specific polyps of *Hydra* (Franzenburg et al. 2013). This specificity is maintained even when different species of *Hydra* are co-cultured, suggesting that host immunity determines the composition of the bacterial community (Franzenburg et al. 2013). The diversity and the continual discovery of these bioactive compounds has promise for discovering novel AMPs that could have important medical applications.

As members of Cnidaria, anthozoans represent some of the most poisonous known organisms, producing toxic, bioactive compounds for defense and predation (Parisi et al. 2014). These bioactive chemicals are a key area of bioprospecting due to their potential for human medicine for their anti-inflammatory, cytotoxic and antinociception activities (reviewed by Cooper et al. 2014). Production of secondary metabolites enables this taxonomic group to be one of the most effective sessile benthic colonizers (Harvell et al. 1993; Changyun et al. 2008; Kelman et al. 2009). Between 2008 and 2014, 244 diterpenoids, a class of compounds with antimicrobial activity, were isolated from Gorgonian corals (Changyun et al. 2008), and while the biological function has not been assigned to each compound, this provides a glimpse of the potential complexity of immune, defense, and microbial interactions that are continually occurring on a coral reef. Compounds such as diterpenoids, sesquiterpenoids, and sterols are used for chemical defense and allelopathy, the use of chemicals to influence competitors' biology, by soft corals and gorgonians, providing protection against predation (Van Alstyne et al. 1994) (reviewed in Changyun et al. 2008). Similarly, the antimicrobial activity of scleractinian and gorgonian extracts has been widely reported (e.g., Harvell et al. 1993; Kim et al. 2000; Gochfeld and Aeby 2008; Palmer et al. 2011c), though the nature of the chemical compounds and mechanisms employed are not always clear. A homogenate of coral tissues is often used to measure antimicrobial activity, and this contributes to activities being highly variable. This is particularly notable in immune challenge experiments, where some experiments result in increased bacterial growth while others demonstrate effective antimicrobial activity (e.g., Gochfeld and Aeby 2008; Palmer et al. 2011c). However, there are cases where extracted compounds have clear antimicrobial activity, for example diterpenoids extracted from the soft coral *Sinularia flexibilis* (Aceret et al. 1998). Similarly, diterpenoids and sterols are also involved in *S. flexibilis* allelopathy (Fang et al. 2005) (reviewed in Changyun et al. 2008). Scleractinian corals are highly dependent on allelopathy (Koh 1997; Gochfeld and Aeby 2008; Kelman et al. 2009; Slattery and Gochfeld 2012), with high competition for space from other corals, algae and biofilms (Chadwick and Morrow 2011).

Apoptosis

Apoptosis is a tightly regulated form of cell death that occurs during normal development, stress, injury, and infection (Brentnall et al. 2013). It is linked to the endogenous activation of innate immunity in response to signals generated by damaged or malfunctioning cells, and typically occurs when stress and redox imbalance exceeds the tolerance limits of the cell (Medzhitov 2008). The intrinsic apoptosis pathway is activated and regulated by proteolytic enzymes called caspases (Brentnall et al. 2013). Extrinsic apoptosis is triggered by cell surface receptors in the presence of specific ligands, such as those on the membrane of cytotoxic cells, and is primarily mediated by the highly conserved tumor necrosis factor (TNF) receptor (TNFR) ligand superfamily (Quistad et al. 2014; Quistad and Traylor-Knowles 2016).

Within anthozoans, both caspases (Moya et al. 2016) and members of the TNF superfamily have been identified (Quistad et al. 2014; Quistad and Traylor-Knowles 2016) and they display more diversity than within other organisms (Quistad and Traylor-Knowles 2016), demonstrating the functional conservation of apoptotic pathways within the Metazoa. As for all animals (Jacobson et al. 1997), apoptosis plays a role in wound maturation in coral, by eliminating excess cells produced during the proliferation phase of wound healing (Palmer et al. 2011b) and disease mediation (e.g., Ainsworth et al. 2015; Lawrence et al. 2015). However, apoptosis in coral also occurs in response to changing environmental conditions, such as with reduced water pH (Kvitt et al. 2015) and has been most intensively studied in relation to thermal bleaching (e.g. Hawkins et al. 2013). Apoptosis is activated in the host through stimulation by the reactive species nitric oxide during the process of temperature-induced breakdown in anthozoan-algal mutualisms, known as bleaching (Hawkins et al. 2013). Apoptosis enables the release of *Symbiodinium* from the host endodermal cell and interacts with autophagy to expel the redundant symbiont (Dunn et al. 2007; Tchernov et al. 2011). Concomitantly, the TNFR signaling pathway, which can initiate either inflammation via NF- κ B or apoptosis (Aggarwal 2003), is activated in response to thermal stress (Barshis et al. 2013; Palumbi et al. 2014; Rose et al. 2015).

Reactive Species

Reactive species are essential molecules derived from oxygen or nitrogen, or other molecules, that are more reactive than the element from which they were derived, which in some cases, such as oxygen, is itself toxic (Halliwell and Gutteridge 2015). Reactive species are involved in cellular reduction–oxidation (redox) reactions that occur under normal processes of metabolism, cell signaling, development, and immunity (Bartosz 2009). Examples of reactive species include superoxide anion radical, hydrogen peroxide, hydroxyl radical, nitric oxide radical, peroxyxynitrite, and electronically excited states such as singlet molecular oxygen that vary reactivity (Halliwell and Gutteridge 2015; Sies 2015). These cytotoxic and abundant molecules are continually kept in check by suites of antioxidant compounds and enzymes, so as to prevent damage to biomolecules and cells (Halliwell and Gutteridge 2015). Changes in local abiotic conditions, such as chronic or acute changes in temperature, pH, or salinity, induce the production of cellular reactive species (Tomanek

2015), potentially leading to a state of oxidative stress in which antioxidants are no longer able to maintain redox homeostasis. Oxidative stress occurs when the production of toxic reactive species overwhelms a system's ability to eliminate them with antioxidant molecules and enzymes (Halliwell and Gutteridge 2015; Tomanek 2015). This situation can lead to extensive damage; due to their transmissibility across membranes, reactive species have the potential to adversely affect all parts of the cell—from DNA to lipids to membranes—leading to disease and potentially necrosis (Halliwell and Gutteridge 2015). Oxidative stress, as a result of increased reactive species produced by photosystem II of the algal endosymbiont of coral, is a key factor in coral bleaching—the breakdown of symbiosis with *Symbiodinium* spp. (Lesser 1997; Gardner et al. 2017). However, during bleaching the coral host also increases reactive species, creating an unfavorable environment for the symbionts, leading to their death and/or expulsion (Weis 2008). This is one example of how anthozoan stress and immune responses are inextricably linked with the cytotoxicity of reactive species.

Cytotoxic reactive species can also be used to a host's advantage by being produced deliberately during immune responses to kill pathogens. These may be as “by-products” of immune pathways, such as the melanin synthesis pathway (Cerenius and Söderhäll 2004), or by oxidase enzymes during phagocytosis, known as a respiratory burst (Berton et al. 2015). Respiratory bursts have been described within gorgonians (Mydlarz and Jacobs 2006) with the resultant reactive species released into the local environment (Shaked and Armoza-Zvuloni 2013). Additionally, in order to prevent self-harm, the increased production of reactive species and/or a measurable immune response is often coupled with an increase in antioxidants (Bartosz 2009), including within anthozoans (e.g., Mydlarz and Harvell 2007).

Antioxidants

The potential damage caused by oxidative stress means that the stakes are high when increasing reactive species production. In order to mitigate or minimize self-harm, a suite of antioxidants are always present and upregulated with increases in reactive species, such as during abiotic stress events or an immune response. Many compounds have antioxidant capacity, including pigments such as melanin (Meredith et al. 2006) and carotenoids (Cornet et al. 2007), but enzymatic antioxidants, such as superoxide dismutase, catalase and glutathione (peroxidases), and thioredoxin-dependent systems, are crucial in maintaining redox homeostasis (Williams et al. 2013).

Anthozoans possess many different types of enzymatic antioxidants, including peroxidases (Downs et al. 2002; Mydlarz and Harvell 2007), superoxide dismutase (Diaz et al. 2016), and catalase activity (hydrogen peroxide-scavenging) (Hawkridge et al. 2000; Mydlarz and Palmer 2011; Palmer et al. 2012). Consistent with a damage mitigation role during abiotic stress, coral antioxidant activity varies with shifts in environmental conditions and particularly during coral bleaching (e.g., Downs et al. 2002; Merle et al. 2007; Jin et al. 2016). Similarly, corals upregulate antioxidants in response to both injury and infection (Mydlarz et al. 2010; Mydlarz and

Palmer 2011; Palmer et al. 2011c; Palmer 2010), which indicates the necessity of redox stabilization during an immune response.

Heat Shock Proteins

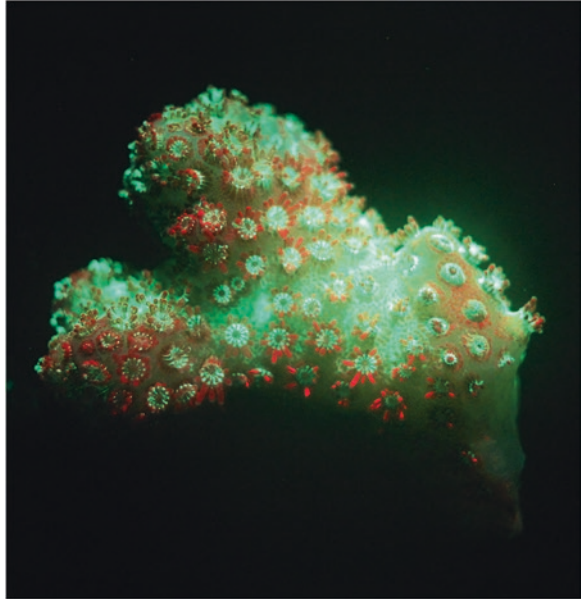
Heat shock proteins (HSPs) are ubiquitous soluble, constitutively expressed proteins responsible for a suite of cellular housekeeping functions that are essential to organism survival. HSPs fall into ten family categories, present in all metazoans. HSPs are molecular chaperones, assisting in protein folding and preventing denaturing and, though first identified in relation to heat shock in *Drosophila*, are not restricted to roles in thermal stress mitigation (Srivastava 2002). HSPs help ensure homeostasis, and are therefore involved in both abiotic stress and immune responses (Srivastava 2002; Tenor and Aballay 2007). HSPs can generate reactive species and activate melanin synthesis (Baruah et al. 2014), and, similar to many immune factors, transcription is related to the Toll family of immune receptors (Tenor and Aballay 2007). Anthozoans possess many types of HSPs (Table 1).

The first anthozoan HSPs were found within the scleractinian *Montastraea faveolata*, the sea anemone *E. pallida* (Black et al. 1995), and the scleractinian *Goniopora djiboutiensis* (Sharp et al. 1997). Subsequently, a HSP found in the scleractinian coral *Stylophora pistillata* (SP HSP70) was used to monitor coral stress responses (Tom et al. 1999). Congruently, coral HSPs are upregulated during environmental change events, including thermal stress and bleaching (Barshis et al. 2013; Ross 2014; Traylor-Knowles et al. 2017b), pH change (Moya et al. 2015), and in response to disease (Seveso et al. 2015). HSPs have also been proposed to confer resistance of corals to heat stress (Palumbi et al. 2014). Additionally, HSPs have also been shown to be involved in the stress response to laboratory bacteria challenge experiments (e.g., Brown and Rodriguez-Lanetty 2015). Specifically, HSP70 was discovered to be involved in promoting a primitive form of the defense response in the sea anemone *E. pallida* (Brown and Rodriguez-Lanetty 2015). Brown and Rodriguez-Lanetty further propose that this short-term priming could confer immune strength during seasonal times of pathogen exposure. While the traditional studies of HSPs have focused on their role in general stress response and thermal stress response, more evidence now suggests that they may have a broader role in the immune response in anthozoans.

Fluorescent Proteins

A striking feature of many anthozoans is their multiple fluorescent proteins (FPs) (Alieva et al. 2008) (Fig. 9). FPs consist of a chromophore that spontaneously forms in the presence of oxygen and which is housed within a hydrophobic core in a robust β -barrel structure (Sample et al. 2009). The barrel restrains the vibrations of the excited chromophore and prevents radiation-less loss of energy (Sample et al. 2009; Seward and Bagshaw 2009). FPs utilize their protein microenvironments to modulate and refine their photophysical characteristics, enabling them to absorb light at different wavelengths (Sample et al. 2009). FPs function by absorbing a photon of light at a low wavelength, for example within the blue or UV spectra, which then shifts the chromophore to an excited state through protonation (Sample et al. 2009).

Fig. 9 Reef coral fluorescence. (Photo credit: G. Ampie)



Energy is emitted as light of a longer, red-shifted wavelength as the chromophore returns to its ground state. In the excited state, FPs produce reactive species, which, if not moderated, can lead to photobleaching of FPs and impact the local microenvironment through oxidative stress (Halliwell and Gutteridge 2015). The protein scaffold of the FP is a molecular sink for reactive species, which thus protects the chromophore and surrounding microenvironment (Sample et al. 2009). Across different FPs there are multiple types of chromophore, which contribute to the spectral diversity found in FPs across taxa (Bogdanov et al. 2009). Cnidarian FP diversity is used commercially as markers of gene and protein expression, and has revolutionized modern biomedicine (Sample et al. 2009).

All organisms, from microbes to large mammals, use pigments for signaling, crypsis, or mitigation of oxidative stress. In the animal kingdom, the type and intensity of coloration is often indicative of immune competence (e.g., Nolan et al. 2006). However, while color production in the ocean is common (Widder 2010), the biological roles of the highly conserved scleractinian FPs remains debated (Takashashi-Kariyazono et al. 2016). The function of FPs in scleractinians is postulated to be primarily for the maintenance of the endosymbiotic relationship with *Symbiodinium* (Gittins et al. 2015). *Symbiodinium* is of great importance to the overall health of scleractinian coral, so it is beneficial for the scleractinian coral host to protect them. FPs alter the local light environment of the scleractinian host, and therefore may facilitate photosynthesis (Smith et al. 2017), provide protection during high light conditions (Salih et al. 1998), and act as a photo-attractant (Hollingsworth et al. 2005). However, the presence of FPs in anthozoans that lack *Symbiodinium* (azooxanthellate) (Wiedenmann et al. 2004) suggests that they have additional or alternative roles within cnidarian biology.

The visible increase of fluorescence in scleractinians with compromised tissue (Fig. 7) (Palmer et al. 2008; Palmer et al. 2009a) and its coincidence with elevated PO activity (Palmer et al. 2008; D'Angelo et al. 2012; Palmer et al. 2012; Palmer 2010) suggests that FPs may have a role in immunity. Concomitantly, and consistent with the general description of the biochemistry of FPs (Sample et al. 2009), scleractinian FPs scavenge hydrogen peroxide (Palmer et al. 2009b), indicating that FPs are potentially very useful for managing oxidative stress potential during immune responses and periods of environmental stress (Seneca et al. 2010; Roth and Deheyn 2013; van de Water et al. 2016).

Ecological Immunity: Focus on Scleractinian Corals

Ecological immunology theory postulates that variations among and within constituent immunity and immune responses are due to energetic trade-offs among costly life history traits like reproduction, growth, and maintenance/immunity (Sheldon and Verhulst 1996; Sadd and Schmid-Hempel 2009). Scleractinian corals, from both the Indo-Pacific (Palmer et al. 2010, 2012) and Caribbean (Mydlarz and Palmer 2011; Palmer et al. 2011c), demonstrate high intra-taxon variation in baseline levels of immunity, which for the Indo-Pacific scleractinians predicts susceptibility to both disease and bleaching at the family level (Palmer et al. 2010). These family-level differences in immunity corresponded to life history strategies; for example, fast-growing scleractinians with high reproductive output (e.g., Acroporiidae) are among those with the lowest constituent immunity (Palmer et al. 2010). Similarly, a short-term temporal study of three Indo-Pacific scleractinians found that constituent PO activity varied among species and with water temperature fluctuations (van de Water et al. 2016), indicating that immune function is influenced by the environment and life history of the scleractinian.

One of the first signs of coral distress is the increased production of mucus (Brown and Bythell 2005) (Fig. 5). The increased production of mucus requires large energetic investments, which leads to the depletion of metabolic reserves, resulting in an immune-compromised state (Sheridan et al. 2014). Similarly, following a thermal bleaching event, involving the loss of energy-providing *Symbiodinium*, disease is often the cause of scleractinian death (Fig. 4) (Brandt and McManus 2009). The breakdown of this mutualism results in a starvation state and an energy deficit, leaving the scleractinian host ill-equipped to resist infection, as for other invertebrates (e.g., Siva-Jothy and Thompson 2002). Similarly, infection is energetically costly as resources are invested in resisting, or tolerating, the disease (Mayack and Naug 2009).

The effects of paying the high energetic costs to promote health have been observed in scleractinian corals when comparing thermally bleached and diseased colonies to healthy ones (Palmer et al. 2011a). Both the thermally bleached and diseased colonies of the scleractinian *A. hyacinthus* had lower levels of PO and peroxidase activity than healthy controls (Palmer et al. 2011a). The exception being at the disease lesion edge, where immune response was equivalent to constituent

levels of immunity in healthy controls (Palmer et al. 2011a). As with other invertebrates, the ability of a coral host to deliver an optimal immune response and maintain healthy constituent immune levels depends on the availability of energy (Sheridan et al. 2014). Energy availability and trade-offs therefore likely contribute to the intra-species variation in immunity observed within scleractinians (Wright et al. 2017; Palmer 2010). It is increasingly apparent that the environmental context needs to be considered with measurements of immunity (van de Water et al. 2015a; Wright et al. 2017). It is also evident that innate immune responses and responses to environmental change (“stress responses”) are intertwined. Immunity therefore has the potential to be used as an effective indicator of coral health (Palmer et al. 2010; Traylor-Knowles and Palumbi 2014; Jin et al. 2016). Thus, the expansion of coral ecological immunology is important for analyzing the influence of more frequent climate extremes on scleractinian corals as well as the ecosystems that they support.

Immunity, Climate Change, and Conservation of Scleractinian Corals

In this Anthropocene era, humans have placed themselves in an arms race against an aggravated natural world. Scientists and conservationists are racing to understand complex systems, develop technologies and conserve organisms and ecosystems before human-induced climate change shifts them beyond repair in this sixth mass extinction event. Coral reefs have declined globally and at an accelerating rate since the 1980’s e.g. (Bruno and Selig 2007; Hughes et al. 2017). Now, even with dramatic reductions in global carbon production, the persistence of coral reefs as biodiverse, economically significant systems (Graham et al. 2014) rests largely on our ability to conserve and effectively restore them through increasingly severe conditions. Cnidarian immunity will be critical in determining the long-term success of scleractinian species and coral reef communities (Palmer and Traylor-Knowles 2012; Mydlarz et al. 2016).

Anthozoans demonstrate a “stress response” to environmental perturbations, which is often investigated as distinct from immunity. With warming waters, increased hurricane activity, increased pathogen load, and ocean acidification, climate change stands to significantly undermine cnidarian immunity and therefore coral reef health. Scleractinian immune mechanisms have the potential to mitigate many of these assaults; however, studies investigating how these factors influence constituent immunity and immune responses are somewhat limited (e.g., Palmer et al. 2011c; van de Water et al. 2015c; Traylor-Knowles et al. 2017a). As such, cnidarian immunology has not yet been incorporated into the fields of coral conservation and restoration, though they stand to be highly informative.

In the face of climate change, our inefficacy in conserving and protecting wild coral reef systems is concerning. For example, the Great Barrier Reef, one of the world’s best-protected marine systems, has undergone catastrophic coral loss in the past 2 years (Hughes et al. 2017). While the term “restoration” refers to the act of

returning something to its original condition, in the context of climate change it is well-acknowledged that reefs of the future will look quite different to the reefs of the past (Graham et al. 2014). With this in mind, starting in the 1990s, coral restoration projects using coral out-planting (coral gardening) have been undertaken to promote biodiversity conservation and ecosystem function of scleractinians (Rinkevich 1995). Coral gardens are now abundant globally (Rinkevich 2014) and are a main method for restoring reef habitats. Coral gardening involves propagating small fragments of specific scleractinian genotypes on tree-like structures in mid-water nurseries, monitoring them to understand their disease and stress tolerances, and then out-planting them to prepared reef areas (Rinkevich 2014). Rapid coral colony growth through micro-fragmentation methods are promising; however, the physiological consequences of high fragmentation are as yet unknown (Forsman et al. 2015) and, as growth is high in terms of energetic cost, may come at the cost of impaired immunity (van der Most et al. 2011). However, numerous coral gardening restoration projects have been deemed successful, and arguably offer a viable mechanism for mediating the effects of climate change through ecological engineering (Schopmeyer 2012; Rinkevich 2014).

An alternative method to coral gardening restoration is larval seeding, where scleractinian coral larvae are reared *ex situ* and introduced in high densities to denuded reefs. However, the long-term benefits are still not well-understood (Edwards et al. 2015). Additionally, assisted evolution, via the use of selective breeding, epigenetics and microbiome manipulation, has recently begun to be used to create corals that are able to tolerate more extreme climate conditions (van Oppen et al. 2017). Assisted evolution has the potential to be integrated into ongoing coral gardening restoration efforts, and it is argued that the rate of coral loss means this is essential. van Oppen et al. (2017) have proposed targeting genes that underpin the “ubiquitous minimal cellular stress response” (Kültz 2005) and highlight coral stress and thermal resilience studies (e.g., Barshis et al. 2013). It is increasingly clear that cellular stress responses cannot be decoupled from immunity (Baruah et al. 2014; Pinsino and Matranga 2015), and therefore including specific immune-related genes as targets for assisted evolution and restoration will likely be of benefit.

Conclusion

In this chapter we have summarized the rapidly expanding field of cnidarian immunology, touching on the identified immune mechanisms, their roles in immune responses, and the relevance of cnidarian immunology to understanding ecological patterns in health and disease, and in improving restoration efforts. There are many gaps in our knowledge, including understanding the gene versus proteolytic regulation of responses to immune challenge and adverse conditions, as well as the identification of additional anthozoan-specific immune mechanisms. Many mechanisms still remain to be more extensively explored within anthozoans, including endocrine-like signaling (Song et al. 2015; Tarrant 2015) as well as locating sites of immune

compound production, storage, and use. Lastly, cnidarian immunology will greatly benefit from more understanding of how the immune pathways fit together and influence each other. Cnidarian immunology is a burgeoning field that stands to inform conservation efforts, and biomedicine, as well as the field of comparative immunology.

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