Immune System Components in Cnidarians

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Abstract

The phylum Cnidaria, the sister group to the Bilateria that branched off about 600 million years ago, is pivotal for understanding the early evolution of immunity. Unlike vertebrates, Cnidaria lack adaptive immunity. Despite this limitation and living in marine and aquatic habitats surrounded by microbes, Cnidaria are capable of mounting defense responses to pathogens and discriminating them from other microorganisms. The evolutionary relationships of cnidarian innate immune factors show remarkable homology to humans and in some cases striking diversification. The aim of this article is to review and categorize the components of innate immunity in Cnidaria and to give an overview of the interactions between the innate immune system of Cnidaria and the symbionts of these organisms.

Key Points

- Within their microbe-rich aquatic and marine habitats, cnidarians utilize their innate immune systems to both defend themselves against pathogens and structure their microbiome.
- Cnidaria is a diverse phylum spanning a variety of life history types and ecological niches, the components and complexity of cnidarian immune systems likely reflect this diversity.
- Bioinformatic studies reveal unexpected complexity in many innate immune gene families within the phylum.
- Cnidarian immune genes often have high levels of conservation with mammalian genes in sequence and function.
- Cnidarians form complex symbiotic interactions and thus can be used as models for understanding ancient mechanisms of host-microbe interactions.

Introduction

The phylum Cnidaria is comprised of remarkably diverse and ecologically significant taxa, such as the Hexacorallia (reef-building corals and sea anemones); Octocorallia (soft corals and gorgonians); Clade Endocnidozoa (parasites); swimming Scyphozoa (jellyfish); Cubozoa (box jellies); and Hydrozoa, a diverse group that includes all the freshwater cnidarians (such as the freshwater polyp Hydra) as well as many marine forms (Kayal *et al.*, 2018). Organisms within Cnidaria are diploblastic, with a collagenous matrix known as the mesoglea separating their two body layers. Cnidarians originated early in the history of metazoan evolution, as indicated by fossil evidence (Han *et al.*, 2010; Ou *et al.*, 2017; Park *et al.*, 2012) and molecular phylogenies (McFadden *et al.*, 2021; Park *et al.*, 2012) making them useful in the elucidation of evolutionarily ancient immune mechanisms. Like other invertebrates, cnidarians rely on innate immune mechanisms to detect and respond to microbes and distinguish self from non-self. The vast diversity in cnidarian life histories (solitary vs colonial, sessile vs planktonic, parasitic vs free living, hosting algal symbionts vs non-symbiotic) and habitats (marine vs freshwater, benthic vs pelagic) likely results in gradients of selective pressure for immune complexity within the phylum (Emery *et al.*, 2021).

Although some groups of cnidarians, including *Hydra* and *Nematostella vectensis* have a long history as model systems in comparative immunology (Darling *et al.*, 2005; Galliot, 2012), the development of genomic resources revealed unexpected complexity in immunity across the group and surprising homology with mammals. Unlike the reduced immune repertoire of *Caenorhabditis elegans* and more functionally derived immune repertoire of *Drosophila*, cnidarians possess most of the conserved ancestral gene families found in bilaterians and in some cases, represent the phylum in which these innate immune gene families likely first emerged (Brennan and Gilmore, 2018; Miller *et al.*, 2007; Quistad and Traylor-Knowles, 2016; Sackton *et al.*, 2007; Schulenburg *et al.*, 2004). Furthermore, development of new cnidarian model systems spanning a broader swath of the phylum has revealed variations in immune repertoires across the cnidarian phylogeny and across life history traits (**Fig. 1**) (Emery *et al.*, 2021). As such, cnidarians are excellent candidates for the study of the evolution of innate immune signaling pathways and the evolutionary malleability of immune systems.

The study of cnidarian immunity provides insights into the basic immunological 'tool kit' of early metazoans and the origins and evolution of immunity in mammals. Furthermore, because cnidarians form complex symbiotic interactions, investigation of cnidarian immunity can help inform ancient mechanisms of host–microbial interactions and the resulting evolutionary selection processes. The unique symbioses formed between cnidarians and both the photosymbiotic and commensal microbiota also provides an opportunity to understand the origins and dynamics of these symbiotic interactions, including how cnidarians recognize and sanction symbionts while defending against pathogens (Bosch, 2014; Mansfield and Gilmore, 2019). Finally, coral disease outbreaks present a current, increasing, and existential threat to coral reef ecosystems, necessitating the study of coral immunity to understand how reef-building corals respond to diseases and identify immune factors associated with resistance and tolerance of diseases and other environmental stressors (Burke *et al.*, 2023; Vega Thurber *et al.*, 2020). Characterization of the innate immune repertoire of cnidarians is, therefore, of fundamental, applied and ecological interest.

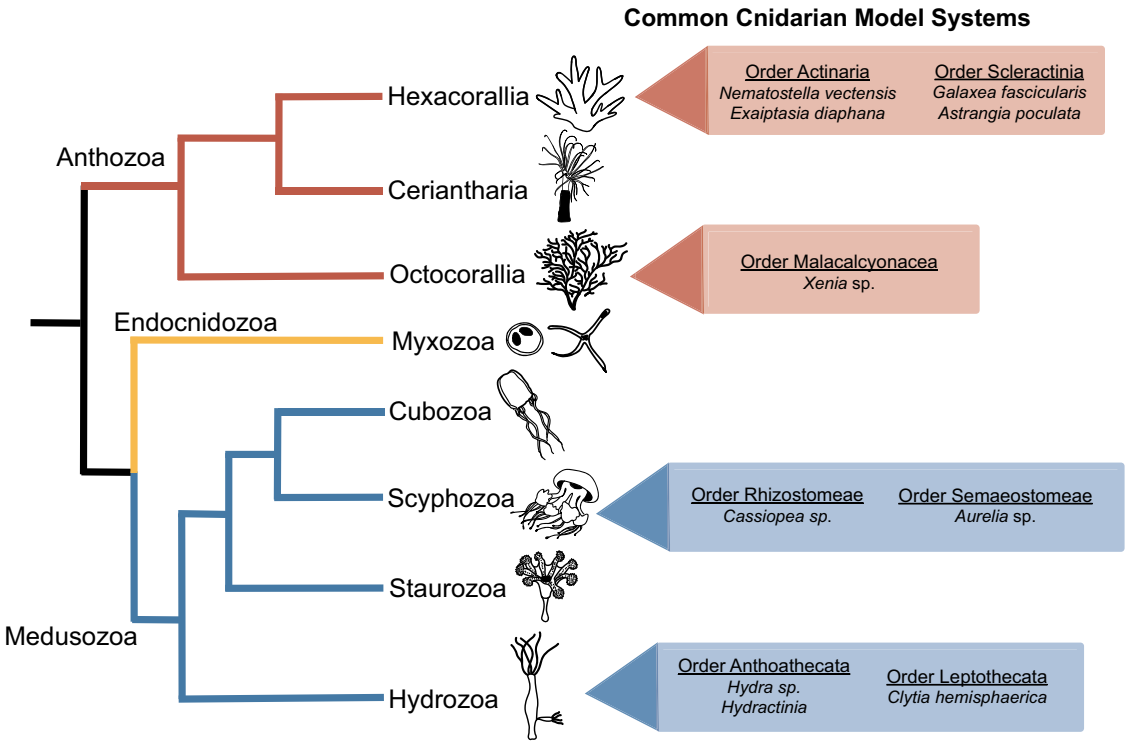

Fig. 1 Phylogenetic tree of Cnidaria, and the common model systems within some taxa.

Cnidarian Immune Responses

Cnidarians in freshwater or marine habitats are continuously exposed to a diverse array of microbes in addition to a variety of abiotic stressors such as temperature fluctuations and pollution. Like other invertebrates, cnidarians sense and respond to microbes and cellular dysfunction through pattern recognition receptors (PRRs) which detect microbe associated molecular patterns (MAMPs, broad term for conserved molecules found on both pathogenic and non-pathogenic microbes, and/or danger associated molecular patterns (DAMPs, host derived molecules indicative of cellular damage or stress) (Janeway and Medzhitov, 2002; Patel, 2018). Following ligand recognition, cnidarians utilize various pathways to orchestrate complex immune responses. The surprising complexity of cnidarian PRR repertoires and downstream immune signaling likely allows for microbe/stressor specific immune responses allowing cnidarians to both mediate interactions with symbiotic microbiota and defend themselves against pathogens (Bosch, 2014; Emery *et al.*, 2021; Li *et al.*, 2023).

Pattern Recognition and Immune Signaling

Toll-like receptors

Toll-like receptors (TLRs) are transmembrane PRRs that can be located on the cell surface or on intracellular membranes such as endosomes (Blasius and Beutler, 2010; Medzhitov, 2001). These PRRs can recognize a diverse array of ligands such as bacterial cell wall components, flagellin, foreign nucleic acids, and developmental cues (Akira and Takeda, 2004; Anthoney *et al.*, 2018; Medzhitov, 2001). Ligand recognition occurs through N-terminal leucine rich repeats which face outwards towards the extracellular space or the cytoplasm. On the opposite side of the membrane to which the TLR is bound is the C-terminal toll-IL receptor (TIR) domain, which initiates signal transduction through interactions with other TIR-domain containing proteins such as MyD88 (Akira and Takeda, 2004; Medzhitov, 2001; Vasselon and Detmers, 2002). This signal transduction can initiate various innate immune pathways such as MAPK, IFN, and NFκB signaling (Akira and Takeda, 2004; Vasselon and Detmers, 2002).

Cnidaria is likely the phylum in which prototypical TLRs first arose in animals as more basal animal phyla like poriferans, ctenophores, and placozoans lack prototypical TLRs (Brennan and Gilmore, 2018). Within Cnidaria prototypical TLRs appear to only be present in Anthozoa (Brennan and Gilmore, 2018; Emery *et al.*, 2021). Anthozoan TLRs have been functionally characterized in the sea anemone *Nematostella vectensis* and the reef-building coral *Orbicella faveolata* (Brennan *et al.*, 2017; Williams *et al.*, 2018). The *N. vectensis* TLR plays a vital role in development and can recognize several MAMPs associated with gram-negative bacteria, bind human adaptor proteins MAL and MyD88, and activate NFκB (Brennan *et al.*, 2017). Similarly, the *O. faveolata* TLR can bind human MyD88 and the species upregulates members of the TLR-NFκB pathway in response to LPS (Williams *et al.*, 2018).

While Medusozoans lack prototypical TLRs, they have a multi protein system capable of performing the same function (Bosch *et al.*, 2009; Brennan and Gilmore, 2018). This system was first described in *Hydra*, where membrane bound proteins with extracellular leucine rich repeats recognize LPS and interact with a membrane bound protein containing an intracellular TIR domain (TLR-like protein) through an unknown mechanism to initiate activation of NFκB (Bosch *et al.*, 2009). While these TLR-like proteins have not been functionally characterized outside of *Hydra*, they are present in the genomes of species in Hydrozoa, Staurozoa, Scyphozoa, Octocorallia, and Hexacorallia (Emery *et al.*, 2021). Notably, many reef-building corals have expanded repertoires of these TLR-like proteins hypothesized to help mediate the composition of their complex microbiomes (Brennan and Gilmore, 2018; Dimos *et al.*, 2022; Emery *et al.*, 2021; Noel *et al.*, 2023; Poole and Weis, 2014; Thompson *et al.*, 2015).

NOD-Like Receptors

Nuclear oligomerization domain (NOD)-like receptors (NLRs) are intracellular PRRs responsible for sensing MAMPs such as bacterial cell wall components, foreign nucleic acids, and microbial toxins as well as DAMPs like reactive oxygen species (ROS) and calcium efflux (Chavarría-Smith and Vance, 2013; Fritz *et al.*, 2006; Kanneganti *et al.*, 2006; Lee *et al.*, 2012; Mariathasan *et al.*, 2006; Martinon *et al.*, 2009). Most human NLRs contain a N terminal effector domain, a central NACHT/nucleotide binding domain, and C terminal leucine rich repeats (Fritz *et al.*, 2006). Cnidarian NLRs can broadly be categorized into prototypical NLRs with LRRs and a NACHT domain, and NLR-like proteins that contain at a minimum a NACHT domain (Dimos *et al.*, 2019; Emery *et al.*, 2021). NLR-like proteins have been identified in the genomes of cnidarians in Hydrozoa (Emery *et al.*, 2021; Lange *et al.*, 2011), Scyphozoa (Emery *et al.*, 2021), Octocorallia (Emery *et al.*, 2021), and Hexacorallia (Dimos *et al.*, 2019; Emery *et al.*, 2021; Hamada *et al.*, 2013; Lange *et al.*, 2011) while prototypical NLRs are only present in Octocorallia and Hexacorallia (Dimos *et al.*, 2019; Emery *et al.*, 2021). Cnidarians typically have extensive NLR repertoires, though cubozoans and staurozoans seem to lack NLRs entirely (Dimos *et al.*, 2019; Emery *et al.*, 2021; Hamada *et al.*, 2013). Additionally, cnidarian NLRs contain many unique domain combinations that have not been reported in mammalian species, though have been identified in mollusks (Dimos *et al.*, 2019; Emery *et al.*, 2021; Hamada *et al.*, 2013; Lange *et al.*, 2011; Takeuchi *et al.*, 2022).

To date there are no functional studies of cnidarian NLRs, though their expression has been found to be differentially regulated in response to immune stressors and while hosting Symbiodiniaceae intracellularly (Dimos *et al.*, 2019; Emery *et al.*, 2024; Fuess *et al.*, 2017; Levy *et al.*, 2021; Roesel and Vollmer, 2019). Upon MAMP/DAMP recognition NLRs can initiate NFκB, MAPK, and IRF signaling (Elinav *et al.*, 2011; Fritz *et al.*, 2006; Martinon *et al.*, 2009). Additionally, ligand recognition can trigger the assembly of inflammasomes, which are multimeric protein complexes that play a key role in pyroptosis, a form of inflammatory cell death (Guo *et al.*, 2015). Though NLR activation of these pathways has not been experimentally tested in cnidarians, bioinformatic studies indicate that cnidarians possess the necessary upstream components to activate them (Dimos *et al.*, 2019; Emery *et al.*, 2021).

Retinoic Acid-Inducible Gene I-Like Receptors (RLRs)

Retinoic acid-inducible gene I-like receptors (RLRs) are a family of intracellular PRRs that recognize viral and abnormal host RNA (Rehwinkel and Gack, 2020). They are ATP binding proteins characterized by the presence of a DExD/H box helicase with the capacity of unwinding double stranded viral RNA (dsRNA) via ATP hydrolysis (Tanner and Linder, 2001; Yoneyama and Fujita, 2009). Three types of RLRs have been identified in this protein family: RIG-I, MDA5 and LGP2. In addition to the helicase, RIG-I and MDA5 contain tandem caspase activation recruitment domains (CARDs) that initiate downstream signaling that leads to effector responses via activation of transcription factors NFκB and interferon regulatory factors (IRFs) (Rehwinkel and Gack, 2020; Saito *et al.*, 2007; Yoneyama and Fujita, 2009). RIG-I and MDA5 differ by the length and conformation of RNA that they preferentially bind, whereas LGP2 acts as a regulator of antiviral responses (Im *et al.*, 2023; Rodriguez *et al.*, 2014; Saito *et al.*, 2007; Satoh *et al.*, 2010).

Cnidarian RLRs group phylogenetically with MDA5/LGP2 (Lewandowska *et al.*, 2021) and have been identified bioinformatically in anthozoans (Emery *et al.*, 2021; Lewandowska *et al.*, 2021; Mukherjee *et al.*, 2014; Zou *et al.*, 2009) but appear to be completely absent in medusozoans (Emery *et al.*, 2021; Lewandowska *et al.*, 2021). RLRs containing CARD domains (RIG-I/MDA5-like) are consistently present in anthozoans but this is not the case for LGP2, suggesting that, in anthozoans, this receptor is often secondarily lost (Emery *et al.*, 2021). A functional study of antiviral immunity in *N. vectensis* found that polyinosinic:polycytidylic acid (poly(I:C)), a long double stranded RNA mimic of the primary MDA5 ligand, initiated a highly complex anti-viral response including the upregulation of RNA interference (RNAi) machinery. This response is initiated by *N. vectensis* RLRb (NveRLRb), as it was the only *N. vectensis* RLR found to bind poly(I:C). Knockdown of NveRLRb resulted in downregulation of RNAi machinery and IRF1 (Lewandowska *et al.*, 2021). The link between NveRLRb and IRF1 is notable, as the key adaptor protein for activation of IRF/NFκB in RLR signal transduction, mitochondrial antiviral signaling protein (MAVS), is absent in cnidarians (Emery *et al.*, 2021). NveRLRb's involvment in upregulation of IRF suggests that other mechanisms are at play in cnidarians for the activation of immune transcription factors by RLRs (Lewandowska *et al.*, 2021).

Cyclic GMP-AMP Synthase (cGAS)-Like Receptors

Cyclic GMP-AMP synthase (cGAS)-like receptors (cGLRs) are a family of evolutionarily ancient cytosolic PRRs involved in innate immunity through the governance of nucleotide signaling (Jenson and Chen, 2024; Li *et al.*, 2023). Upon recognition of their nucleic acid ligands, cGLRs synthesize cyclic dinucleotide second messengers (CDNs), such as cyclic GMP-AMP, which in turn activates the stimulator of interferon genes (STING) (Jenson and Chen, 2024; Li *et al.*, 2023). Upon activation STING can induce autophagy or antiviral responses mediated by IRFs (Gui *et al.*, 2019; Jenson and Chen, 2024; Li *et al.*, 2023).

Investigations into the evolutionary conservation of the cGLR-STING pathway have found cGLRs and STING within Hydrozoa (Li *et al.*, 2023), Hexacorallia (Gui *et al.*, 2019; Kranzusch *et al.*, 2015; Li *et al.*, 2023), and Octocorallia (Li *et al.*, 2023). Unlike human cGAS, cnidarian cGLRs have not been found to recognize dsDNA, rather they recognize dsRNA and other unknown ligands (Li *et al.*, 2023). Notably, hexacorallians have large expansions of both cGLRs and STING, a trait that is uncommon within Metazoa. These expansions facilitate functional diversity within the cGLR-STING pathway, as three *Stylophora pistillata* cGLRs were found to all synthesize different CDNs. Further, *S. pistillata* STING proteins show specific affinities for subsets of these various CDNs, suggesting the ability to tailor downstream signaling responses to different CDNs (Li *et al.*, 2023). While the full range of STING mediated signaling responses is unknown within Cnidaria, in the anemone *N. vectensis* recognition of CDNs or their mimics by STING can induce autophagy (Gui *et al.*, 2019) and transcription of antiviral and antibacterial genes via the transcription factor NFκB (Margolis *et al.*, 2021).

Scavenger Receptors

Scavenger receptors (SRs) are a diverse group of transmembrane cell surface glycoproteins that play essential roles in immune defense, clearance of cellular debris, maintenance of tissue homeostasis and in phagocytosis of invading microbes (Areschoug and Gordon, 2009; Canton *et al.*, 2013). SRs recognize a wide range of ligands and can also interact with other PRRs, influencing their signaling (Amiel *et al.*, 2009; Canton *et al.*, 2013; Wei *et al.*, 2018). Though the domains within SRs responsible for ligand binding vary, they show similarity within their electrostatic profile likely resulting in their preference for polyanionic ligands (Canton *et al.*, 2013). SRs are highly heterogenous structurally. To account for this heterogeneity, SRs are divided into twelve classes, SR-A through SR-L (Taban *et al.*, 2022).

Bioinformatic analyses in Hydrozoa (Zárate-Potes *et al.*, 2019) and Hexacorallia (Neubauer *et al.*, 2016) have identified the presence SR-like genes. Hexacorallians display a large diversity of SR-like genes that resemble SR-As, SR-Bs, SR-Es and SR-Is. This same study found that in *Exaiptasia diaphana*, experimentally blocking SR ligand binding reduced colonization by Symbiodiniaceae and triggered an immune response (Neubauer *et al.*, 2016). As such, SRs may play a role in the establishment of the cnidarian-Symbiodiniaceae symbiosis (Mansfield and Gilmore, 2019; Neubauer *et al.*, 2016).

C-Type Lectins

C-type lectins (CTLs) are a diverse protein family of both soluble and transmembrane proteins characterized by the C-type lectin domain (CTLD) (Pees *et al.*, 2016). CTLs have been primarily associated with calcium dependent carbohydrate binding, however, they are also capable of binding to inorganic compounds, lipids, and proteins (Zelensky and Gready, 2005). In vertebrates, CTLs can recognize bacterial, fungal, protozoan, helminthic, and viral pathogens, and can induce phagocytic, antimicrobial, pro-inflammatory, or anti-inflammatory responses (Hoving *et al.*, 2014), as well as participate in development and the regulation of

homeostasis (Brown *et al.*, 2018). Although less studied, CTLs in invertebrate taxa could also have an important role in allorecognition (Zelensky and Gready, 2005) and potentially provide a mechanism for high immune specificity (Pees *et al.*, 2016).

Genomic and transcriptomic studies have found CTLs in Hexacorallia (Emery *et al.*, 2021; Kvennefors *et al.*, 2008; Wood-Charlson *et al.*, 2006; Zhao, *et al.*, 2018), Octocorallia (Emery *et al.*, 2021; Hu *et al.*, 2020), Hydrozoa (Emery *et al.*, 2021; Reidling *et al.*, 2000; Sahadevan *et al.*, 2014), Scyphozoa (Emery *et al.*, 2021), Cubozoa (Emery *et al.*, 2021), and Staurozoa (Emery *et al.*, 2021). The majority of species in these studies have large, diverse, and expanded repertoires of CTLs (Emery *et al.*, 2021; van de Water *et al.*, 2015; Wood-Charlson and Weis, 2009). The full functions of cnidarian CTLs are unknown, as few functional studies have been conducted. However, a homolog of mannose-binding lectin (a CTL) from *Acropora* was found to bind Symbiodinaceae, gram-negative, and gram-positive bacteria (Kvennefors *et al.*, 2008). Similarly, a CTL in *Xenia* sp was also found to bind Symbiodinaceae (Hu *et al.*, 2023) and a CTL isolated from *Pocillopora damicornis* was found to bind MAMPs (Zhou *et al.*, 2018). Further supporting the hypotheses that CTLs have a role in symbiosis and are immune receptors for a variety of compounds, cnidarian CTLs found in transcriptomic and proteomic studies were involved in wound healing (van de Water *et al.*, 2015), response to disease (Libro *et al.*, 2013), and mediating symbiosis with Symbiodiniaceae (Emery *et al.*, 2024; Hu *et al.*, 2023; Kvennefors *et al.*, 2008; Zhou *et al.*, 2018).

Complement System

The complement system is a host defense system that intersects both adaptive and innate immunity in vertebrates and consists of three activation pathways: the classical pathway, the alternative pathway, and the lectin-complement pathway (Sarma and Ward, 2011). Downstream of the activation pathway is the lytic pathway, which results in the formation of the membrane attack complex which functions to kill pathogens by disrupting their cell membranes (Fujita, 2002; Sarma and Ward, 2011). The emergence of the classical and lytic pathways likely coincided with the evolution of adaptive immunity, as these pathways are absent in invertebrates (Nonaka, 2014). In contrast the lectin-complement pathway seems to be evolutionarily ancient and is present in cnidarians (Emery *et al.*, 2021; Kimura *et al.*, 2009; Kvennefors *et al.*, 2010; Nonaka, 2014; Poole *et al.*, 2016).

Activation of this pathway occurs when lectins interact with MBL-associated serine proteases (MASPs) which then either directly activate C3 or cleave C2/C4 which then activates C3 (Fujita, 2002). Both anthozoan and medusozoan species have been found to have MASP, Bf/C2, and C3 in their genomes, though C3 is incomplete in scyphozoans (Emery *et al.*, 2021). In the absence of the lytic pathway and proteins necessary to form the membrane attack complex cnidarians likely utilize C3 for opsonization (Fujita, 2002; Kimura *et al.*, 2009). However, it has been suggested in other invertebrate species that bactericidal MACPF domain containing proteins, which are present in cnidarians (Emery *et al.*, 2021; Walters *et al.*, 2020), may replace the function of the membrane attack complex (Sun *et al.*, 2023). While we have no functional studies detailing the activity of Bf/C2 or C3 in cnidarians, the complement pathway has been implicated in mediating both algal symbiosis and pathogen responses (Kvennefors *et al.*, 2010; Poole *et al.*, 2016; Roesel and Vollmer, 2019).

Immune Transcription Factors

Cnidarians have several well conserved immune transcription factors. The best studied of these immune transcription factors is NFκB. In response to stressors NFκB mediates a pro-survival and pro-inflammatory immune response (Liu *et al.*, 2017; Tripathi and Aggarwal, 2006). NFκB proteins all contain the Rel homology domain that allows the transcription factors to dimerize, enter the nucleus, and bind DNA (Liu *et al.*, 2017; Williams and Gilmore, 2020). Ankyrin repeats are responsible for binding the Rel homology domain and restricting inactivated NFκB to the cytosol. This can occur through ankyrin repeats on the NFκB protein itself or more often through the NFκB inhibitor IκBα (Williams and Gilmore, 2020). Canonical activation of NFκB occurs following recognition of a stressor, DAMP, or cytokine via a multi-subunit IκB kinase (IKK) complex phosphorylating the IκBα. This phosphorylation results in the subsequent degradation of IκBα allowing for NFκB to be trafficked into the nucleus and induce transcription (Liu *et al.*, 2017).

NFκB, IκBα, and IKK sequences are present in both medusozoan and anthozoan species (Emery *et al.*, 2021). Often cnidarian NFκBs lack ankyrin repeat domains and look similar in their domain organization to c-Rel and RelA, as seen in *Nematostella vectensis*, octocorallians, scyphozoans, cubozoans, hydrozoans, and staurozoans (Emery *et al.*, 2021; Mansfield *et al.*, 2017; Williams and Gilmore, 2020; Wolenski *et al.*, 2011). However, the DNA binding profile of *N. vectensis* NFκB is most like *Homo sapiens* p50 and the *Exaiptasia* diaphana NFκB both of which contain ankyrin repeats (Mansfield *et al.*, 2017; Ryzhakov *et al.*, 2013). This may be the case for other cnidarian NFκBs lacking ankyrin repeats, however they are more distantly related to *E.* diaphana and *N. vectensis* and likely lost their ankyrin repeats through independent gene splitting events (Emery *et al.*, 2021; Williams and Gilmore, 2020). While the binding profiles of cnidarian NFκBs have not been compared outside of Hexacorallia, medusozoan and anthozoan NFκBs are responsive to pathogen exposure (Bosch *et al.*, 2009; Emery *et al.*, 2024; Fuess *et al.*, 2017; Roesel and Vollmer, 2019; Williams *et al.*, 2018) and may play a role in mediating symbiosis (Emery *et al.*, 2024; Mansfield *et al.*, 2017; Mohamed *et al.*, 2020).

IRFs are another type of immune transcription factor present in cnidarians. Considerably less is known about the function of IRFs in cnidarians, as no functional studies have been conducted. IRFs are named for their induction of an antiviral response characterized by proinflammatory cytokines known as interferons. However, interferons are absent in invertebrates so likely cnidarian IRFs mediate the expression of other genes related to innate immunity (Secombes and Zou, 2017). They may act as a cofactor with NFκB, induce other proinflammatory cytokines, or play a role in cell cycle regulation through promoting apoptosis

(Feng *et al.*, 2021; Tamura *et al.*, 1995). Cnidarian IRF expression has been found to be upregulated in response to regeneration (Wenger *et al.*, 2014), bacterial pathogen exposure (Emery *et al.*, 2024; Wright *et al.*, 2017), and poly(I:C) exposure (Lewandowska *et al.*, 2021). In addition to NFκB and IRF signaling, cnidarians have a suite of more generalized stress response transcription factors that can play a role in immune stress responses including activator protien-1 (AP-1), forkhead box O (FOXO), and activating transcription factor 5 (ATF5) (Agron *et al.*, 2017; Bridge *et al.*, 2010; Dimos *et al.*, 2019).

Cytokines

Cytokines are secreted signaling proteins that regulate processes including immunity, inflammation, tissue homeostasis, and apoptosis. Cytokines in the transforming growth factor β (TGFβ), interleukin (IL), and tumor necrosis factor (TNF) families have been identified in cnidarians. TGFβ cytokines have been found to regulate development in Anthozoa and Medusozoa (Holstein, 2022; Krishnapati and Ghaskadbi, 2024) and immunity in Anthozoa (Berthelier *et al.*, 2017; Detournay *et al.*, 2012; Fuess *et al.*, 2020). In the context of cnidarian immune stress responses, TGFβ likely is anti-inflammatory as pharmacological enhancement of the TGFβ pathway resulted in the dampening of hexacorallian immune responses to LPS (Detournay *et al.*, 2012; Fuess *et al.*, 2020). Interleukin cytokines and IL-receptors have been identified in anthozoan genomes (Poole and Weis, 2014; Saco *et al.*, 2021). These cytokines have not been functionally characterized in cnidarians, though they may be proinflammatory as they were identified by their homology to IL-17 family cytokines (Saco *et al.*, 2021), which often induce inflammation (McGeachy *et al.*, 2019).

Members of the TNF ligand/receptor (TNF/TNFR) superfamily are present in both medusozoan and anthozoan species (Quistad and Traylor-Knowles, 2016; Quistad *et al.*, 2014; Steichele *et al.*, 2021). The TNF/TNFR superfamily has been found to induce apoptosis and inflammation as well as mediate cell differentiation and proliferation (Quistad and Traylor-Knowles, 2016). There is evidence for Hydra TNF/TNFR signaling having functions in cell differentiation (Steichele *et al.*, 2021) and wound healing (Wenger *et al.*, 2014). The induction of apoptosis via TNFR signaling is highly conserved from cnidarians to humans. Reef-building coral TNF was found to induce apoptosis in human cells and reciprocally, human TNF-α induces caspase activity and cell death in corals (Quistad *et al.*, 2014). Reef building corals have diverse repertoires of the TNF/TNFR superfamily proteins that are responsive to thermal stress (Barshis *et al.*, 2013; Palumbi *et al.*, 2014) and disease exposure (Traylor-Knowles *et al.*, 2021). Given the diversity of this superfamily within hexacorallian species, cnidarian TNF/TNFRs likely have more roles that have yet to be described (Quistad and Traylor-Knowles, 2016).

Effector Responses

Antimicrobial peptides

Following microbe recognition and invasion, there is an activation of an inducible defense system marked by an increased expression of highly active antimicrobial peptides (AMPs). AMPs are known as prominent effector molecules of the innate immune system in vertebrates and invertebrates, where they act by disrupting the structure or function of microbial cell membranes (Bosch, 2014; Zhang *et al.*, 2021).They are gene-encoded small peptides, most consisting of 10–100 amino acids, are amphipathic, typically carry an overall positive charge, and show a broad spectrum of antimicrobial activity (Zhang *et al.*, 2021). Some cnidarian AMPs are taxa specific with distinct expression patterns, as seen in *Hydra* (Augustin *et al.*, 2017; Bosch *et al.*, 2009; Fraune *et al.*, 2010; Klimovich and Bosch, 2024), while others are shared across taxa (Leal *et al.*, 2022).

Many of the identified cnidarian AMPs that are not species specific are small cysteine rich proteins that have characteristics of defensins, a large well conserved AMP family (Leal *et al.*, 2022). The first of these cysteine rich AMPs to be identified was Aurelin, an AMP with the common structural features of invertebrate defensins that was isolated from the moon jellyfish *Aurelia aurita* (Ovchinnikova *et al.*, 2006). Aurelin has been found to have antimicrobial activity against Gram-negative and Gram-positive bacteria (Ovchinnikova *et al.*, 2006). In silico analysis found homologs of Aurelin in eleven different cnidarian species spanning Hexacorallia and Scyphozoa and homologs of *Mus musculus* β-defensin in nine species spanning Cubozoa, Hydrozoa, and Hexacorallia (Leal *et al.*, 2022). Aurelin also has structural similarities to Stichodactyla toxin and (ShK)-like toxins, though it lacks the complete residues needed for interacting with K+ channels (Ovchinnikova *et al.*, 2006; Shenkarev *et al.*, 2012). Structural similarities to ShK toxins have also been identified in the stony coral AMPs Damicornin and amAMP1, indicating a common molecular ancestor between these AMPs and ShK toxins (Mason *et al.*, 2021; Vidal-Dupiol *et al.*, 2011). Additionally, other known cnidarian toxins have antimicrobial properties and thus likely have dual functions (Logashina *et al.*, 2017; Trapani *et al.*, 2014).

Antimicrobial Enzymes

The immune systems of cnidarians employ other antimicrobial proteins that target specific components or pathogen virulence factors through enzymatic activity. Proteases are often secreted by pathogens to degrade host tissues, allowing the pathogen to colonize, feed on the host, and evade host immune responses (Travis *et al.*, 1995). By inhibiting these virulent compounds, protease inhibitors protect the host's tissues and reduce microbial pathogenesis (Kanost, 1999). Kunitz-type serine protease inhibitors from *Actinia tenebrosa* have potent activity against bovine trypsin, chymostrypsin, and some human sequence-related peptidases (Chen *et al.*, 2019). This type of protease inhibitor is common in anemones (García-Fernández *et al.*, 2016; Kvetkina *et al.*, 2020; Shiomi *et al.*, 1989) but may also be present in Schyphozoa (Choudhary *et al.*, 2019; Liu *et al.*, 2015). Kazal-type serine protease inhibitors are also present in Cnidaria. These protease inhibitors have been found to inhibit bacterial growth in

the hydrozoan *Hydra magnipapillata* (Augustin *et al.*, 2009) and the scyphozoan *Cyanea capillata* (Zhou, Liu, *et al.*, 2018). The kazal-type serine protease inhibitors of *Hydra magnipapillata* also have direct bactericidal activity (Augustin *et al.*, 2009), while *Cyanea capillata*'s kazal-type serine protease inhibitors likely also have anti-fungal abilities (Zhou *et al.*, 2018).

Cell walls are another target of cnidarian antimicrobial enzymes. Lysozyme breaks down peptidoglycan in bacteria cell walls and chitinase degrades the chitin in cell walls of fungus and arthropod exoskeletons. Lysozyme-like activity has been found in Hexacorallia (Bisanti *et al.*, 2024; Mydlarz *et al.*, 2009; Stabili *et al.*, 2015), Octocorallia (Couch *et al.*, 2008), and Schyphozoa (Stabili *et al.*, 2019, 2021). Chitinase has multiple potential functions in cnidarians, including a putative role in allorecognition (Mali *et al.*, 2004), growth in chitinous cnidarians (Mali *et al.*, 2004), digestion of arthropod zooplankton (Yoshioka *et al.*, 2017), and anti-fungal defense (Douglas *et al.*, 2007). A study in *Gorgonia ventalina* found that the octocorallian released chitinase with antifungal activity into the surrounding water upon injury and exposure to the fungus *Aspergillus sydowii*, suggesting a potential role in constitutive immune defense (Douglas *et al.*, 2007).

Interestingly, activity of all three of these antimicrobial enzymes have been found in the sea fan coral, *Gorgonia ventalina*, the host of an outbreak of Aspergillosis caused by *Aspergillus sydowii* in the Caribbean. Both protease inhibitors (Mann *et al.*, 2014) and chitinases (Douglas *et al.*, 2007) were active against the fungal pathogen both *in vivo* and *in vitro*, and lysozyme-like activity was shown to vary with environmental conditions such as eutrophication which may increase disease threats to those corals (Couch *et al.*, 2008). The sea fan model presents a good example of how these enzymes work together to provide a comprehensive defense strategy for cnidarians against a variety of microbial threats.

Melanin Synthesis

Melanin is an important component of cnidarian invertebrate immunity involved in pathogen encapsulation (Mydlarz *et al.*, 2008), wound healing (Palmer *et al.*, 2011), and pigmentation (Mydlarz and Palmer, 2011; Palmer *et al.*, 2008). Enzymatic melanin synthesis and deposits of melanin have been detected biochemically and/or histologically in many cnidarians spanning Octocorallia and Hexacorallia (Changsut *et al.*, 2022; Mydlarz *et al.*, 2016; Palmer *et al.*, 2011; Ricci *et al.*, 2019). Melanin synthesis occurs within these taxa in response to disease (Fuess *et al.*, 2018; Ricci *et al.*, 2019), MAMP exposure (Palmer *et al.*, 2011), and injury (Palmer *et al.*, 2011). Melanin concentrations and synthesis have also been shown to vary with bleaching (Mydlarz *et al.*, 2009) and with symbiotic state (Changsut *et al.*, 2022; Harman *et al.*, 2022). Interestingly, high constitutive concentrations of melanin in tissues and high enzymatic synthesis activity seems to be correlated to disease resistance (Pinzón *et al.*, 2014; Van Buren *et al.*, 2024) and stress tolerance (Palmer *et al.*, 2008, 2010).

The melanin synthesis cascade is initiated by signaling pathways such as Wnt and MAPK and the presence of tyrosine which subsequently trigger several enzymatic and non-enzymatic reactions that result in the synthesis of melanin (D'Mello *et al.*, 2016). The main enzymes that perform the rate-limiting step of melanin synthesis are type-3 copper proteins including prophenoloxidase, catechol oxidases, and tyrosinases which can broadly be described as phenoloxidase candidates (PO-candidates) (Hoeger and Harris, 2020). However, the presence of the genes responsible for these proteins haven't been found in all cnidarians. In a concomitant transcriptomic and proteomic study of a gorgonian coral with a highly melanized phenotype, the putative melanin synthesis gene, prophenoloxidase was not present (Fuess *et al.*, 2018), although in the proteome laccase, a multicopper oxidase that can also perform the rate limiting step of melanin synthesis (Janusz *et al.*, 2020), was found to be significantly upregulated in highly melanized tissue (Ricci *et al.*, 2019). A comparative study of cnidarian PO candidates spanning Hexacorallia, Schyphozoa, Cubozoa, and Hydrozoa found the majority of cnidarian tyrosinase-like sequences had the conserved histidine residues necessary for PO function (Bailey *et al.*, 2019). It appears that cnidarian PO candidates most closely resemble tyrosinase, as they lack the hemocyanin domains seen in insect prophoenoloxidases and phylogenetic analysis found they group most closely with tyrosinases (Van Buren *et al.*, 2024). Gene expression studies indicate tyrosinase as the primary PO-candidate for disease resistance (MacKnight *et al.*, 2022; Van Buren *et al.*, 2024) and for melanin synthesis in immune cells (Levy *et al.*, 2021) within Anthozoa. Overall, melanin synthesis and the PO-candidate enzymes that perform it are integral to the innate immune responses of anthozoans.

Reactive Oxygen Species and Nitric Oxide

Reactive oxygen species (ROS) are highly reactive molecules containing oxygen including but not limited to hydrogen peroxide (H_2O_2), superoxide ($O_2^{\cdot-}$), hydroxyl radicals ($OH^{\cdot}$), and singlet oxygen ($^1O_2$) (de Almeida *et al.*, 2022; Li *et al.*, 2021). These reactive molecules can be used by cells to kill invading pathogens as they cause damage to DNA, lipids, and proteins (Li *et al.*, 2021). ROS can also facilitate pathogen clearance through promoting antibacterial autophagy or the release of extracellular traps (Li *et al.*, 2021; Thiam *et al.*, 2020). Often in response to various stressors large amounts of ROS will be rapidly generated via NADPH oxidase (NOX2) and released in a process known as an oxidative or respiratory burst (Rada and Leto, 2008; Segal, 2008). In human macrophages mitochondrial ROS (mitoROS) also contributes to the increase in ROS production upon pathogen recognition via reverse electron transport (Hatinguais *et al.*, 2021; Shekhova, 2020). Respiratory bursts can kill bacteria, activate negative chemotaxis in bacteria, and activate other stress response signaling pathways (Benov and Fridovich, 1996; Li *et al.*, 2021; Schmitt *et al.*, 2014; Shekhova, 2020). Respiratory bursts have been documented in cnidarians in association with bacterial exposure (Armoza-Zvuloni, Schneider, and Shaked, 2016), injury (Mydlarz and Jacobs, 2006), heat stress (Doering *et al.*, 2023; Mydlarz and Jacobs, 2006), feeding, and physical stimulus (Armoza-Zvuloni *et al.*, 2016).

Reactive oxygen species are widely considered a double-edged sword, as they are powerful signaling and antimicrobial molecules but can also cause damage to the host (Li *et al.*, 2021; Silwal *et al.*, 2020). In addition to respiratory bursts, stressors can

also elicit ROS production by causing dysfunction in organelles such as the endoplasmic reticulum (ER) and mitochondria (de Almeida *et al.*, 2022). Thus, mitigating oxidative stress during stress responses is incredibly important for survival. Cnidarians have several known mechanisms for mitigating oxidative stress. They employ enzymatic antioxidants such as superoxide dismutase (SOD) and catalase (CAT) to detoxify ROS (Cotinat *et al.*, 2022; Couch *et al.*, 2008; Fuess *et al.*, 2016; Merle *et al.*, 2007; Tarrant *et al.*, 2014). Additionally, cnidarians can employ both ER and mitochondrial unfolded protein responses to attempt to recover from disruptions to the protein environment within their cells that can be caused by oxidative stress (Dimos, Mahmud, *et al.*, 2019; Maor-Landaw *et al.*, 2014; Oakley *et al.*, 2017; Ruiz-Jones and Palumbi, 2017).

Nitric oxide (NO) is a small molecule with a variety of functions in immunity in addition to its signaling role in nervous systems (Blaise *et al.*, 2005; Bogdan, 2001). Nitric oxide is produced via nitric oxide synthase (NOS), a protein found in a wide variety of cnidarians (Doering *et al.*, 2023; Malafoglia *et al.*, 2016; Morrall *et al.*, 2000; Wang *et al.*, 2017; Zhou *et al.*, 2019). As they are more likely to encounter microbes, NO production as part of the innate immune response often occurs in epithelial cells or in immune cells, though various other cell types are capable of synthesizing NO (Bogdan, 2001). In response to pathogens, NO or its derivative reactive nitrogen species (RNS) can be used to kill bacteria or viruses through disrupting DNA structure, damaging proteins, and disrupting membrane lipids (Bogdan, 2001; Fang, 1997). In mammalian immune cells NO can react with ROS in phagosomes to create highly reactive molecules more effective at killing pathogens (Carreras *et al.*, 1994). Additionally, in other animals NO can modulate inflammatory immune signaling (Bogdan, 2001; Shreshtha *et al.*, 2018). Within Cnidaria, the production of NO in response to a bacterial pathogen has been directly shown in stony corals (Zhou *et al.*, 2019). Additionally, the jellyfish *Cassiopea xamachana* upregulates NOS as part of its pathogen response (Emery *et al.*, 2024) and *Hydra* upregulates NOS in response to heat shock (Malafoglia *et al.*, 2016). Similarly, NO has been indicated to play a role in the thermal stress response and subsequent bleaching of symbiotic anthozoans (Hawkins *et al.*, 2013; Jury *et al.*, 2022; Perez and Weis, 2006).

Programmed Cell Death

Programmed cell death can have several functions in the context of immune responses, including the clearance of dysfunctional cells, killing intracellular pathogens, and inflammatory signaling (Nagata and Tanaka, 2017). The molecular mechanisms of programmed cell death, caspases, BCL-2 proteins, adaptor proteins, death receptors, and inhibitors of apoptotic proteases are present in the majority of cnidarian species and form a more complex network for cell death regulation than what is seen in the model organisms *C. elegans* and *D. melanogaster* (Lasi *et al.*, 2010a, 2010b; Shrestha *et al.*, 2020). Though caspases, BCL-2 proteins, and apoptotic protease activating factor (APAF-1) are not present in myxozoan species likely as an adaptation for their parasitic lifestyles (Neverov *et al.*, 2023). Cnidarian caspases likely can be activated via extrinsic and intrinsic pathways (Lasi *et al.*, 2010a, 2010b; Shrestha *et al.*, 2020).

Apoptosis has often been found to be involved in cnidarian immune stress responses. *N. vectensis* have been found to induce apoptosis upon exposure to the viral MAMP poly I:C (Kozlovski *et al.*, 2024). Additionally, several gene expression studies indicate that various cnidarians induce apoptotic signaling following pathogen or MAMP exposure (Beavers *et al.*, 2023; Fuess *et al.*, 2017; MacKnight *et al.*, 2022). Apoptosis can be protective in the context of innate immune responses, as it can kill intracellular pathogens limiting their spread and remove dysfunctional cells without inducing further inflammation (Rothlin *et al.*, 2020). However, coral species with stronger upregulation of apoptosis during immune responses often have greater susceptibility to diseases (Fuess *et al.*, 2017; MacKnight *et al.*, 2022). A propensity to switch from pro-survival signaling to apoptotic signaling sooner than other species could be the mechanism resulting in this greater disease susceptibility (Fuess *et al.*, 2017). Alternatively, higher levels of apoptotic signaling in disease susceptible coral species may reflect faster disease progression and greater disruptions to cellular homeostasis in these more susceptible cnidarians.

In addition to apoptosis, cnidarians are also capable of pyroptosis (Jiang *et al.*, 2020) and forming extracellular phagocyte traps (ETosis) (Robb *et al.*, 2014). Pyroptosis is a type of inflammatory cell death mediated by gasdermin. When cleaved by caspases the N terminal domain of gasdermin oligomerizes and forms pores in the cell membrane causing the cell to swell and eventual membrane rupture (Yu *et al.*, 2021). Reef-building coral gasdermin has the ability to induce pyroptosis following cleavage by caspase 3. Additionally, this same study found that pyroptosis was induced by *Vibrio coralliilyticus* infection (Jiang *et al.*, 2020). The final type of programmed cell death that cnidarians are capable of is specific to phagocytes (Robb *et al.*, 2014). This type of cell death, known as ETosis (also known as NETosis) involves the expulsion of chromatin from the cell to form mesh-like extracellular traps that can capture and kill a wide variety of pathogens (Thiam *et al.*, 2020). To date, ETosis has only been described in *Actinia equina*, where a portion of mesogleal cells are capable of forming extracellular traps similar in structure to other invertebrates (Robb *et al.*, 2014). It is unknown if any Medosozoans are also capable of ETosis.

Cellular immunity

Barrier defenses

An important feature of cnidarian immunity is the protection provided by the surface mucus layer at the cell-environment interface (Bakshani *et al.*, 2018; Savoca *et al.*, 2022). Within cnidaria the surface mucus layer is thought to have evolved to facilitate ciliary feeding (Brown and Bythell, 2005). The development of the mucus layer is hypothesized to represent a pivotal event in evolutionary history leading to the development of mucus-lined organs in higher metazoans. The separation and exclusion of bacteria from body tissues by the newly evolved surface mucus layer likely allowed for the curation and

establishment of a core microbiome (Bakshani *et al.*, 2018). In addition to being the site of interactions between cnidarians and their associated commensal microbial communities, the surface mucus layer is also the site of complex interactions between microbes (Bakshani *et al.*, 2018; Schröder and Bosch, 2016; Silveira and Rohwer, 2016).

The role of the surface mucus layer and its associated microbiome in immunity is two-fold. The presence of mucin glycoproteins lends mucus its highly viscous gel structure and presents a physical barrier for pathogen penetration (Bakshani *et al.*, 2018; McShane *et al.*, 2021). Some cnidarian epithelia also have an additional layer of defense that separates their apical epithelial cell surfaces from microbes in the form of a glycocalyx (Böttger *et al.*, 2012; Tucker *et al.*, 2012). This structure intersects with the surface mucus layer, is comprised of transmembrane glycoproteins, glycolipids, and glycans, and limits access to the cell surface via steric hindrance (Böttger *et al.*, 2012; Kuo and Paszek, 2021; Schröder and Bosch, 2016). In addition to the barriers of the mucus layer and glycocalyx, further protection is provided by the mucus layers continually being sloughed off and regenerated, removing trapped potential invaders (Bakshani *et al.*, 2018).

Cnidarian mucus also provides chemical protection, as it contains host and/or microbial-derived AMPs and antimicrobial enzymes (Bakshani *et al.*, 2018; Schröder and Bosch, 2016; Stabili *et al.*, 2015). The antimicrobial properties of cnidarian mucus are sensitive to abiotic and biotic stress (Ritchie, 2006; Rivera-Ortega and Thomé, 2018). Ultraviolet irradiated mucus in thermally stressed *C. xamachana* (Rivera-Ortega and Thomé, 2018), thermally stressed *Acropora palmata* (Ritchie, 2006), and diseased *Pseudodiplora strigosa* (Rivera-Ortega and Thomé, 2018) showed decreased antimicrobial properties. However, in some cases bacteria within the surface mucus layer can compensate for these changes in host derived antimicrobial activity (Rivera-Ortega and Thomé, 2018). Gene expression studies also link putative changes in mucosal properties to disease, as the mucin-like glycoprotein deleted in malignant brain tumors 1 (DMBT1) which has significant roles mucosal innate immunity and microbial homeostasis is downregulated in coral diseases (Beavers *et al.*, 2023; Wright *et al.*, 2017).

Immune Cells

Putative cnidarian immune cells were first described in histological preparations where they appear amoeboid, and often are also granular and acidic (Chapman, 1978; Palmer, 2011). Due to their gross morphology, they are often referred to as amoebocytes in the literature. The presence of amoebocytes has been reported in Hexacorallia (Palmer *et al.*, 2011; Parisi *et al.*, 2014; Patterson and Landolt, 1979; Snyder *et al.*, 2021), Octocorallia (Meszaros and Bigger, 1999; Mydlarz *et al.*, 2008; Olano and Bigger, 2000), Schyphozoa (Hofmann and Honegger, 1990; LaDouceur *et al.*, 2013; Lyndby *et al.*, 2020; Toullec *et al.*, 2024), Cubozoa (Chapman, 1978), and Endocnidozoa (Napara and Raĭkova, 2003; Raikova, 2008). Importantly, the presence of amoebocytes in a cnidarian is insufficient evidence for their role as specialized immune cells in that organism, as likely not all amoebocytes are homologous and some populations of cnidarian amoebocytes do not function as specialized immune cells (Gold and Jacobs, 2013; Lyndby *et al.*, 2020). However, there is substantial evidence for amoebocytes playing important immune functions within Cnidaria. Cnidarian amoebocytes have been found to aggregate near wounds in Hexacorallia (Palmer *et al.*, 2011; Patterson and Landolt, 1979), Octocorallia (Meszaros and Bigger, 1999; Olano and Bigger, 2000), and Scyphozoa (LaDouceur *et al.*, 2013). Additionally, Octocorallian amoebocytes have been found to aggregate to the sites of fungal infection (Mydlarz *et al.*, 2008) and to unknown disease lesions (Slattery *et al.*, 2013; Williams *et al.*, 2011).

Putative cnidarian immune cells have been best functionally characterized in Hexacorallia, where phagocytosis of bacteria by amoebocytes has been reported in anemones (Babonis *et al.*, 2016; Hutton and Smith, 1996; Snyder *et al.*, 2021) and reef building corals (Snyder *et al.*, 2021). The development of fluorescent activated cell sorting (FACS) protocols has allowed for isolation of hexacorallian phagocytes (Snyder *et al.*, 2021). This method found populations of phagocytic cells capable of engulfing bacteria, fungal antigens, and damaged cells in *N. vectensis* and *Pocillopora damicornis*. Target engulfment in these phagocytic cells is associated with high levels of ROS and low pH in lysosomal vesicles, both of which are mammalian phagocyte markers indicative of phagolysosome maturation. Further, two distinct morphologies were identified in phagocytic cells in both species: granular spheroid and amoeboid (Snyder *et al.*, 2021).

The recent use of single cell RNA sequencing in studies across diverse cnidarian taxa (Chari *et al.*, 2021; Cole *et al.*, 2024; Dong *et al.*, 2024; Hu *et al.*, 2020; Levy *et al.*, 2021; Li *et al.*, 2024; Sebé-Pedrós *et al.*, 2018; Siebert *et al.*, 2019) has advanced our understanding of cnidarian immune cells. The creation of cnidarian transcriptomic cell atlases has resulted in the identification of specialized immune cells and their associated markers in Hydrozoa (Dong *et al.*, 2024), Scyphozoa (Dong *et al.*, 2024; Li *et al.*, 2024), and Hexacorallia (Cole *et al.*, 2024; Levy *et al.*, 2021). Interestingly, these single cell atlases indicate that medusozoan species either have no specialized immune cells (Chari *et al.*, 2021; Siebert *et al.*, 2019) or a single putative immune cell type (Dong *et al.*, 2024; Li *et al.*, 2024). In contrast, two distinct immune cell types have been identified in anthozoan cell atlases (Cole *et al.*, 2024; Levy *et al.*, 2021) in line with the findings of Snyder *et al.* (2021). In the scyphozoan *Aurelia coerulea*, specialized immune cells were identified through their expression of immune genes including intelectin-1, intelectin-2, and IRF2 (Li *et al.*, 2024). IRFs, specifically IRF1/2, may be key immune cell markers shared across Cnidaria, as they are also molecular signatures in both the putative immune cell types in the hexacorallians *N. vectensis* (Cole *et al.*, 2024) and *Stylophora pistillata* (Levy *et al.*, 2021). In *N. vectensis*, two distinct immune cell populations are partitioned between the ectoderm and gastroderm. These populations display very little overlap in transcriptional profiles outside of the expression of IRF1 paralogs and NFκB (Cole *et al.*, 2024). The two immune cell types identified in *S. pistillata* showed more overlap in their markers and both express NFAT, IRF 1/2, STING, and NLRs. *S. pistillata* immune cell type 1 is defined by its expression of IRF3/9, interleukin-1 receptors, and various secreted proteins including Perforin/MACPF. In contrast, *S. pistillata* immune cell type 2 is defined through its overexpression of tyrosinase, antimicrobial proteins, apoptotic signaling, protein turnover genes, and genes involved in inflammatory responses (Levy *et al.*, 2021).

Holobiont Immunity

Introduction

The concept of the cnidarian "holobiont" was first described by Rohwer *et al.* in 2002 as a unit consisting of the coral animal, algal endosymbiont, and associated prokaryotes (Knowlton and Rohwer, 2003; Rohwer *et al.*, 2002). The concept has since been expanded to include all microbiota in association with a host to reflect the dynamism of cnidarian assemblages (Blackall *et al.*, 2015; Thompson *et al.*, 2015; Vega Thurber *et al.*, 2020; Voolstra *et al.*, 2024). Cnidarian-associated microbial communities, including photosymbionts, protists, bacteria, archaea, fungi, and viruses, are important components of the holobiont which influence the health of cnidarian hosts and the ecosystems in which they serve as ecosystem engineers (Bosch and McFall-Ngai, 2011; Glasl *et al.*, 2016; Voolstra *et al.*, 2024). Increasing evidence suggests that the innate immune system in cnidarians is not only used to destroy harmful microorganisms but also has a role in structuring the beneficial microbial assemblages which comprise the holobiont (Bosch, 2014; Stabili *et al.*, 2018). Consequently, exploring the structure and function of coral-associated symbioses, and the roles of host immunity in regulating diverse microbial symbioses, is a major objective of current research in Cnidaria.

Immune Regulation of Symbiodiniaceae

Photosymbiosis is common within Cnidaria, with the majority of taxa forming an endosymbiotic relationship with dinoflagellates in the family Symbiodiniaceae (Mansfield and Gilmore, 2019; Nitschke *et al.*, 2022). The ability to host Symbiodiniaceae intracellularly has independently evolved in Hydrozoa, Scyphozoa, Octocorallia, and Hexacorallia (Kayal *et al.*, 2018; Nitschke *et al.*, 2022; Rodríguez *et al.*, 2019). This symbiosis provides the host with essential nutrients, including photosynthetically fixed carbon (Davy *et al.*, 2012) and inorganic nutrients (Ferrier-Pagès *et al.*, 2016; Rädecker *et al.*, 2015). In exchange, symbionts receive nitrogenous waste products, inorganic nutrients, and carbon dioxide (Davy *et al.*, 2012; Ferrier-Pagès *et al.*, 2018). The cnidarian host's reliance on their algal symbionts for nutrition can be facultative, as seen in *E. diaphana*, or obligate, as seen in tropical reef building corals.

Due to the intracellular nature of this relationship, establishment, maintenance, and breakdown of cnidarian-algal symbiosis is heavily regulated by multiple host immune pathways (Mansfield and Gilmore, 2019; Weis, 2019). In many cases, the association between cnidarians and Symbiodiniaceae is quite specific, as many species only establish stable endosymbiosis with a single or limited number of symbiont genera (Gabay *et al.*, 2019; Sharp *et al.*, 2024; Tran *et al.*, 2024; Weis *et al.*, 2001). This specificity is likely reliant upon interactions between Symbiodiniaceae specific MAMPs and host PRRs (Davy *et al.*, 2012; Mansfield and Gilmore, 2019). The discernment between preferred and non-preferred symbionts likely occurs both extracellularly and intracellularly (Jacobovitz *et al.*, 2021; Tran *et al.*, 2024) and the mechanisms of recognition may vary across independent evolutions of the symbiosis. As such, multiple types of PRRs have been implicated in the establishment of endosymbiotic Symbiodiniaceae (Hu *et al.*, 2023; Jacobovitz *et al.*, 2021; Kvennefors *et al.*, 2008; Mansfield and Gilmore, 2019; Neubauer *et al.*, 2016). Of these, perhaps the most well-described are glycan-lectin interactions between photosymbionts and hosts respectively, which appear to be essential for symbiont recognition in both Hexacorallia and Octocorallia (Hu *et al.*, 2023; Kvennefors *et al.*, 2008; Weis, 2019).

Following recognition, algal symbionts must circumvent host immunity to establish stable endosymbiosis. Across Cnidaria, the presence of endosymbiotic Symbiodiniaceae induces significant changes in expression of diverse immune genes (Emery *et al.*, 2024; Lehnert *et al.*, 2014); many of these changes result in host immunosuppression (**fig. 2**) (Levy *et al.*, 2021; Mansfield *et al.*, 2017; Rivera and Davies, 2021; Wolfowicz *et al.*, 2016). For example, upon recognition compatible photosymbionts are able to escape vomocytosis (live expulsion) through immunosuppression and the establishment of an intracellular niche marked by lysosomal-associated membrane protein 1 (LAMP1) (Jacobovitz *et al.*, 2021). Studies implicate changes in NFκB signaling as mediating photosymbiosis-induced immunosuppression during symbiosis onset (Mansfield *et al.*, 2017; Wolfowicz *et al.*, 2016).

Following establishment, photosymbiosis enters the maintenance stage, which relies on consistent cross-talk with host immunity (Davy *et al.*, 2012). Specifically, the maintenance of stable symbiosis in some cnidarians, namely tropical reef-building corals, seems to require continued host immunosuppression (Mansfield and Gilmore, 2019; Weis, 2019). Studies in facultatively symbiotic cnidarians in Scyphozoa (Emery *et al.*, 2024) and Hexacorallia (Mansfield *et al.*, 2017; Rivera and Davies, 2021; Valadez-Ingersoll *et al.*, 2023) report downregulation of NFκB in symbiotic animals relative to aposymbiotic animals under favorable conditions. The mechanisms of this immunosuppression are currently unclear, though recent studies point to TGFβ signaling (Berthelier *et al.*, 2017; Detournay *et al.*, 2012; Fuess *et al.*, 2020). Evidence of trade-offs between photosymbiosis and immunity have been observed in obligately symbiotic coral *O. faveolata* (Fuess *et al.*, 2020), facultatively symbiotic coral *Oculina arbuscula* (Rivera and Davies, 2021), facultatively symbiotic anemone *E. diaphana* (Valadez-Ingersoll *et al.*, 2024) and facultatively symbiotic jellyfish *C. xamachana* (Emery *et al.*, 2024). These trade-offs are likely complex, as starvation has been found to increase immunocompetence in symbiotic *E. diaphana* (Valadez-Ingersoll *et al.*, 2024). Additionally, symbiotic immunosuppression does not appear to be universal across cnidarians; multiple studies of the facultatively symbiotic coral *Astrangia poculata* have documented positive associations between symbiont density and immunity (Changsut *et al.*, 2022; Harman *et al.*, 2022; Villafranca *et al.*, 2023). These contradictions demonstrate a clear need for further investigation of the associations between stable photosymbiosis and immunity across diverse cnidarian species.

Finally, numerous host immune processes have been implicated in the breakdown of cnidarian-algal symbioses (i.e. "bleaching"). Bleaching can occur as a result of several different environmental triggers, most prominently temperature stress (Lesser, 2011), though disease can also result in dysbiosis (Cervino *et al.*, 2004; Landsberg *et al.*, 2020). While the mechanisms of bleaching remain unresolved, a preponderance of evidence points towards a role of host immune cascades and effector responses. Corals experiencing heat stress produce high concentrations of nitric oxide, p53, and caspases which trigger various immune cascades (Helgoe *et al.*, 2024). Furthermore, an increase in immune effector responses (apoptosis and autophagy) has been recorded during bleaching, indicating a potential role of these effectors in symbiont elimination (Weis and Allemand, 2009). Symbiophagy, or the digestion of symbionts via phagolysosome maturation (Perez and Weis, 2006) has been observed in several obligately symbiotic corals (Downs *et al.*, 2009) and the obligately symbiotic medusa of *Cassiopea* (Toullec *et al.*, 2024). This method of symbiont clearance during dysbiosis is thought to be advantageous in the context of thermal bleaching (Toullec *et al.*, 2024) but is likely associated with negative outcomes in Stony Coral Tissue Loss Disease (SCTLD) (Beavers *et al.*, 2023). Further, symbiont identity can influence outcomes of thermal stress exposure (Newkirk *et al.*, 2020; Tivey *et al.*, 2022) and disease (Beavers *et al.*, 2023), indicating additional complex interactions between host immunity and symbiosis in the context of stress responses.

Microbiome-Immune Cross-Talk

In addition to maintaining relationships with algal photosymbionts, cnidarians are host to incredibly diverse microbiomes comprised of viruses (Bosch *et al.*, 2015; Thurber and Correa, 2011), archaea (McCauley *et al.*, 2023), bacteria (McCauley *et al.*, 2023), fungi (Paulino *et al.*, 2020; Yue *et al.*, 2015) and other microeukaryotes (Bonacolta *et al.*, 2023). Cnidarian microbiomes are distinct from their surrounding environment, diverse, and complex, with the greatest complexity found within Hexacorallia (McCauley *et al.*, 2023). There is extensive spatial heterogeneity in the diversity of microbes housed by the cnidarian host; unique communities of microbes inhabit the surface mucosal layer and the different body parts of cnidarians (Bonacolta *et al.*, 2021; Kramar *et al.*, 2019; Ricci *et al.*, 2022). Maintenance of these complex, specific microbial communities requires extensive input from the host immune system (Bosch, 2014). While much is unknown about the mechanisms through which the majority of cnidarians tailor their microbiomes, there is evidence that *Hydra* utilize their AMPs for this task via the transcription factor FOXO (Augustin *et al.*, 2017; Bosch, 2014; Mortzfeld *et al.*, 2018). Proteins interfering with bacterial quorum sensing are used by the jellyfish *A. aurita* (Weiland-Bräuer *et al.*, 2019) and the reef-building coral *Acropora millepora* (Mason *et al.*, 2024) to manipulate

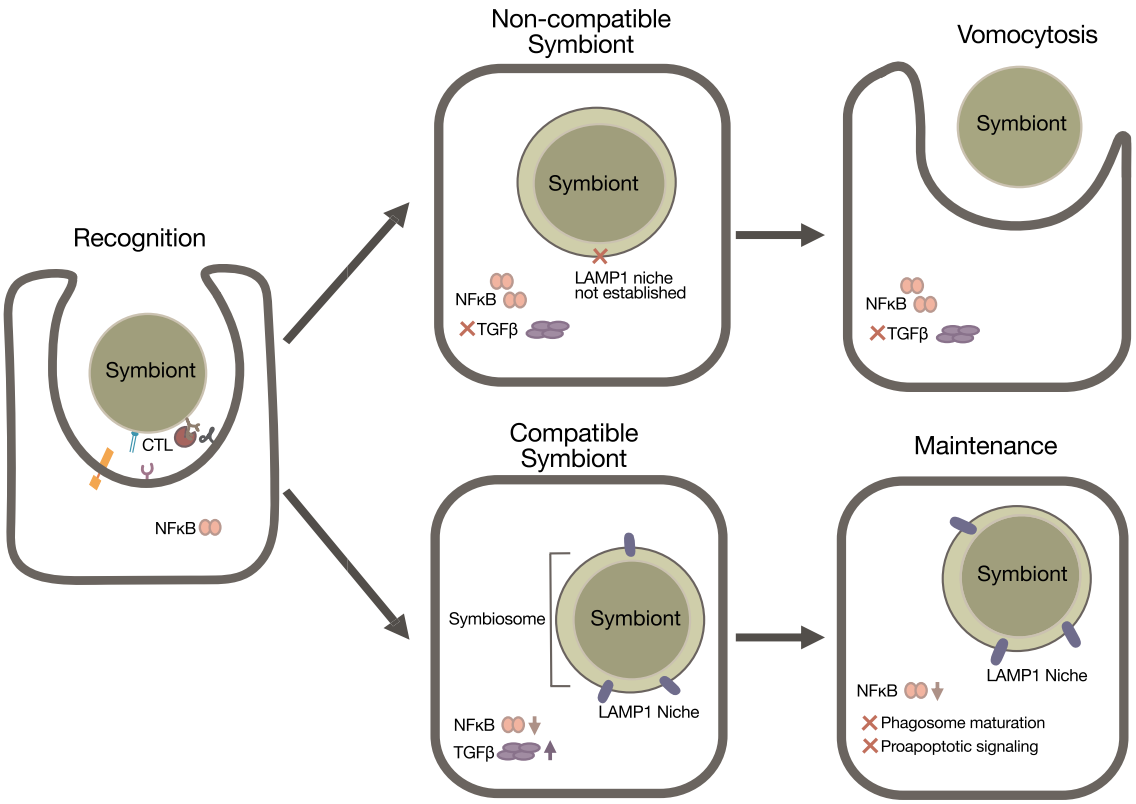

Fig. 2 Hypothesis of the ways in which cnidarian immunity recognizes compatible symbionts, expels non-compatible symbionts, and how cnidarian immunity changes while hosting Symbiodiniaceae intracellularly. Based on studies in Anthozoa, primarily Mansfield *et al.* (2017) and Jacobovitz *et al.* (2021).

the microbiome. Additionally, phages within the surface mucus layer may also play a role in the control and selection of the bacterial microbiome (Barr *et al.*, 2013; Silveira and Rohwer, 2016).

The microbiomes of cnidarians have significant impacts on host fitness, as they can influence nutrient acquisition (Peixoto *et al.*, 2021; Röthig *et al.*, 2021), toxic compound mitigation (Fragoso ados Santos *et al.*, 2015; Peixoto *et al.*, 2017), pathogen control via antimicrobial compounds (Peixoto *et al.*, 2021; Rivera-Ortega and Thomé, 2018; Shnit-Orland and Kushmaro, 2009) and pathogen control via consumption (Ravindran *et al.*, 2023). Additionally, in the case of reef building corals, pathology of diseases can involve dysbiosis within the bacterial microbiome (MacKnight *et al.*, 2021; Vega Thurber *et al.*, 2020; Voolstra *et al.*, 2024). Certain microbes have profound positive impacts on host coral health as they are associated with resistance to thermal stress (Bonacolta *et al.*, 2024; Rosado *et al.*, 2019) and disease (Ushijima *et al.*, 2023). The acknowledgment of the beneficial roles of microbiota in overall host fitness has led to expansive new exploration of potential probiotic treatments for corals (Li, Yang, *et al.*, 2023; Peixoto *et al.*, 2021).

In conclusion, research in recent years has greatly advanced understanding of the cnidarian holobiont, including the bi-directional relationship between symbiotic partners (photosymbionts and commensal microbiota) and host immunity. Still many questions remain regarding the mechanisms controlling establishment, maintenance, and breakdown of these diverse relationships, and the consequences of each process for overall host fitness.

Concluding Remarks and Future Directions

The Cnidaria, as a diverse group of early diverging metazoans, provide a unique opportunity to address many pressing questions in the emergent fields of evolutionary immunology and ecological immunity. First, as understanding of the cnidarian immune system has deepened over the past decade, increasing evidence supports their position as a true representation of ancestral innate immunity. This contrasts with other commonly used models such as *D. melanogaster* and *C. elegans*, both of which have been demonstrated to have unique, taxon specific, modifications of their immune systems which make them poor models for understanding overarching evolution of immune responses. Indeed, as suggested in this chapter, cnidarians' innate immunity is similar to the systems described in mammals, albeit likely representative of ancestral states. Nevertheless, based on their similarity to mammals, cnidarians are arguably ideal models for both investigating questions related to basic innate immune function, and interrogating the evolutionary origins of key immune functions.

Beyond their functionality as a model system, cnidarians also comprise immense diversity in form and function, spanning diverse life history styles and ecological niches. Preliminary analyses suggest that cnidarian immune systems reflect this diversity, though further investigation across the breadth of this taxa is necessary to fully disentangle these patterns (Emery *et al.*, 2021). Indeed, broad scale comparative analysis of immune system structure and function across the breadth of cnidarian taxa provides a unique opportunity to both investigate the evolutionary malleability of immune systems (a key question in evolutionary immunology) and resolve hypotheses regarding the evolutionary origins of vital immune pathways. Additionally, many diverse cnidarian groups leverage their innate immune system to regulate microbial symbiosis (Bosch, 2014; Mansfield and Gilmore, 2019). Thus, the use of cnidarian models provides an excellent opportunity to elucidate ancient immunological mechanisms that regulate high microbial specificity.

Finally, an urgency exists to understand cnidarian immunity as the environmental and ecological conditions in which they live deteriorate. In the face of existential threats to coral reef ecosystems via anthropogenic forces understanding interactions between host coral immunity and symbiotic microbes in stressful conditions is essential for the development of effective conservation strategies. Due to its accessibility to researchers, the use of 'omics approaches to answer these questions has far outpaced functional studies of coral immune signaling. This focus on 'omics has generated a wealth of resources and knowledge towards understanding the role of coral immunity during stress (Traylor-Knowles *et al.*, 2022). However, due to the scarcity of studies characterizing gene functions in reef building corals or their proposed model systems, the interpretations of 'Omic studies heavily rely upon the annotations of genes of interest to infer their function, a practice that is not ideal given it excludes taxa specific genes and the evolutionary distance between cnidarians and the organisms in which the annotations originated. To this end, investment into tractable lab models and the development of protocols for cell type specific studies, cell culture, CRISPR, and RNA silencing have the potential to greatly advance the field of coral research and our holistic understanding of cnidarian immunity. Recently several promising advances towards these goals have been made, with the closing of the *E. diaphana* life cycle in laboratories (Maegele *et al.*, 2023), FACS protocols (Rosental *et al.*, 2017; Snyder *et al.*, 2021), and successful gene knockouts (Cleves *et al.*, 2020) and knock-ins (Warner *et al.*, 2023) in reef-building corals. However, long-term sustainable cnidarian cell culture remains elusive. These advances along with the ability to isolate specific tissues/cell types prior to transcriptomic profiling (Cui *et al.*, 2023; Rosental *et al.*, 2017) are key innovations in the field of cnidarian research and powerful tools to advance our understanding of immunity within the phylum.

Investment into the development of emerging model systems and functional genomic tools within those systems across the breadth of cnidarian species is an essential next step towards establishing this group as a powerful model of innate immune evolution and eco-immunity. Cross-collaboration across the field of cnidarian immunity has great potential for reaching these goals by uniting 'Omics research and functional experimentation in order to advance the use of Cnidaria as innate immune models.

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