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EDITED BY

Sarah Annalise Gignoux-Wolfsohn,
Smithsonian Environmental Research
Center (SI), United States

REVIEWED BY

David Anderson,
Washington University in St. Louis,
United States
Rachel Michelle Wright, Smith
College, United States

*CORRESPONDENCE

Nikki Traylor-Knowles
ngt14@miami.edu

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Advances in coral immunity 'omics in response to disease outbreaks

Nikki Traylor-Knowles^{1*}, Andrew C. Baker¹,

Kelsey M. Beavers², Neha Garg³, Jeffrey R. Guyon⁴,

Aine Hawthorn⁵, Nicholas J. MacKnight², Mo' nica Medina⁶, Laura D.
Mydlarz², Esther C. Peters⁷, Julia Marie Stewart⁶, Michael S. Studivan^{8,9}
and Joshua D. Voss¹⁰

¹Department of Marine Biology and Ecology, Rosenstiel School of Marine, Atmospheric, and Earth Science, University of Miami, Miami, FL, United States, ²Department of Biology, University of Texas Arlington, Arlington, TX, United States, ³School of Chemistry and Biochemistry, Center for Microbial Dynamics and Infection, Georgia Institute of Technology, Atlanta, GA, United States, ⁴Hollings Marine Laboratory, National Oceanic and Atmospheric Administration, National Ocean Service, National Centers for Coastal Ocean Sciences, Charleston, SC, United States, ⁵US Geological Survey (USGS) National Wildlife Health Center, Western Fisheries Research Center, Seattle, WA, United States, ⁶Department of Biology, Pennsylvania State University, University Park, PA, United States, ⁷Department of Environmental Science and Policy, George Mason University, Fairfax, VA, United States, ⁸University of Miami, Cooperative Institute for Marine and Atmospheric Studies, Miami, FL, United States, ⁹National Oceanic and Atmospheric Administration (NOAA) Atlantic Oceanographic and Meteorological Laboratory, Ocean Chemistry and Ecosystems Division, Miami, FL, United States, ¹⁰Harbor Branch Oceanographic Institute, Florida Atlantic University, Fort Pierce, FL, United States

Coral disease has progressively become one of the most pressing issues affecting coral reef survival. In the last 50 years, several reefs throughout the Caribbean have been severely impacted by increased frequency and intensity of disease outbreaks leading to coral death. A recent example of this is stony coral tissue loss disease which has quickly spread throughout the Caribbean, devastating coral reef ecosystems. Emerging from these disease outbreaks has been a coordinated research response that often integrates 'omics techniques to better understand the coral immune system. 'Omics techniques encompass a wide range of technologies used to identify large scale gene, DNA, metabolite, and protein expression. In this review, we discuss what is known about coral immunity and coral disease from an 'omics perspective. We reflect on the development of biomarkers and discuss ways in which coral disease experiments to test immunity can be improved. Lastly, we consider how existing data can be better leveraged to combat future coral disease outbreaks.

KEYWORDS: genomics, transcriptomics, coral disease, immunity, 'omics, coral immunity,

biomarker
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1 Overview

1.1 Coral disease and need for consensus in tools and interpretation

Since the 1970s, the rate, intensity, and recurrence of coral diseases have been well documented, particularly in the Caribbean, where coral cover has declined by at least 66–80% since the 1970s from absolute coral cover of ~50% to 10–17% (Gardner et al., 2003; Schutte et al., 2010; Jackson et al., 2014). While the causative agents and the primary mechanisms of these diseases are unknown, local stressors, such as increasing nutrients, pollution, and global stressors, such as increasing temperatures, have likely contributed to the increase in the frequency and severity of disease outbreaks (Harvell et al., 2002; Peters, 2015; Vega Thurber et al., 2020). These compounded stressors, many caused by human impacts, have created challenging and often inhospitable environments for corals to thrive. This has led to the need for more diagnostic tools to assess reef health to assist coral restoration practitioners and managers. The relatively recent development of ‘omics techniques such as transcriptomics (gene expression), proteomics (protein expression), and metabolomics (metabolite expression) hold promise for the development of such diagnostic tools. However, in practice, the development of useful biomarkers to assess coral health is challenging, and the speed with which new diseases are emerging and spreading has motivated

researchers to identify alternative approaches to assist in assessing coral health.

Stony coral tissue loss disease (SCTLD) is an example of a newly emerged disease whose severity and rapid spread have caused researchers to seek novel ‘omics approaches to understand, diagnose, and mitigate this deadly outbreak. First documented in 2014 on corals near the Port of Miami dredging project, it spread quickly throughout Florida’s Coral Reef (Precht et al., 2016; NOAA, 2018; Dobbelaere et al., 2020; Muller et al., 2020; Roth et al., 2020; Sharp et al., 2020) and subsequently to other parts of the northern Caribbean, including Mexico, the U.S. Virgin Islands, Puerto Rico, and Turks and Caicos (Alvarez-Filip et al., 2019; Estrada-Saldivar et al., 2020; Roth et al., 2020; Dahlgren et al., 2021; Heres et al., 2021; Meiling et al., 2021). SCTLD is known to affect more than 22 different coral species, and its rapid spread through the Caribbean is suspected to be linked in part to ballast-water releases and human activities (Rosenau et al., 2021). The ongoing spread of SCTLD, the impacts of which have yet to be incorporated into region-wide assessments of coral cover, illustrates the rapidly changing disease seascape to which coral reefs are exposed and the dire ecological consequences as new disease spreads across multiple species.

1.2 Overview of biomarkers

Biomarkers are critical tools used to assess and monitor health in a myriad of organisms. Typically used for early

detection and diagnosis, prognosis, and monitoring of disease treatments (Duan et al., 2005; Henry and Hayes, 2012; Kourou et al., 2015; Meyer et al., 2021), their use has been a cornerstone of most modern medical interventions. Within coral ‘omics research, the use of biomarkers is often proposed as one of the primary goals to understand coral disease, but their full utility is still evolving. Corals are holobionts that consist of coevolved relationships with the coral host, dinoflagellates, bacteria, viruses, fungi, archaea, and other macro-eukaryotes (Rohwer et al., 2002). The relationship between the coral hosts and the different holobiont components is considered complex because (1) there are many different partnerships-most of which are not well characterized, (2) there is variability in the types of microorganisms involved that varies depending on the coral species, the historical environmental conditions, and current environmental conditions, and (3) we do not know how these relationships are maintained, but the immune system is hypothesized to play a role in this. ‘Omics methods such as transcriptomics, proteomics, and metabolomics of the coral host have been developed into to assess the range of factors involved in coral disease, including current and past environmental conditions, the variable holobiont composition, and overall coral host health (Montilla et al., 2019; Vega Thurber et al., 2020) (Table 1), but experimental limitations remain a challenge in identifying the most appropriate and informative biomarkers of coral disease. This process is particularly impacted by the many pathways and molecular responses involved in coral immunity. Critical efforts to connect coral immune function with its response to disease have begun (Vega Thurber et al., 2020), but challenges identifying signatures of disease at a gene or protein level are still present.

Coral biomarker development has largely focused on host gene or protein-level responses or identification of bacterial strains because they represent a single measurable unit suitable for deployment of disease diagnostics in a natural environment (Downs et al., 2000; Downs et al., 2005; Downs et al., 2009; Kenkel et al., 2014; Ushijima et al., 2014; Louis et al., 2017; Ushijima et al., 2020). However, there are many limitations to

Assay

Lab or Histology or this approach. For example, consistency in the statistical significance of these types of biomarkers has been elusive (Parkinson et al., 2020). The intrinsic complexity of coral species as holobionts has proven a limitation to underpin specific

mechanisms that either define a disease or are shared between different diseases. This is further compounded by the fact that corals span a wide range of evolutionary timescales and therefore may have very different strategies for dealing with different pathogens and subsequent diseases (Rowan, 2004; Bourne et al., 2009; Pinzón C. et al., 2014). In addition, within species, transcriptomic approaches have proven to be extremely variable, making biomarker development challenging (Traylor-Knowles and Palumbi, 2014; Louis et al., 2017; Parkinson et al., 2020). Lastly, technical hurdles, such as sample and library preparation, sequencing, and the type of bioinformatic

Summary of previous 'omics studies done on soft corals, octocorals, and stony corals.

	Species	Stress or Disease		Field Sampled	other tissue assays
Glynn et al., 1985	Pocillopora damicornis	Thermal stress	Lipidomics	Field	No
Latyshev et al., 1991	11 species of Scleractinia and 3 species of Milleporina corals	None	Lipidomics	Field	No
Harland et al., 1992	Porites porites, Montastrea annularis, Siderastrea siderea	None	Lipidomics	Field	No
Harriott, 1993	Acropora formosa, Pocillopora damicornis	None	Lipidomics	Lab	No
Harland et al., 1993	Pocillopora porites, Montastrea annularis, Goniastrea retiformis, Pocillopora verrucosa, Stylophora pistillata	None	Lipidomics	Field	No
Yamashiro et al., 2019	Pocillopora damicornis, Pocillopora verrucosa, Stylophora pistillata, Montipora aequituberculata, Acropora microphthalma, Porites lutea, Porites cylindrica, Fungia fungites, Galaxea fascicularis, Goniastrea aspera, Oulastrea crispata, Lobophytum crassum, Millepora murrayi, Tubastrea sp.	None	Lipidomics	Field	No
Carballeira et al., 2002	Sinularia macropodia, Capnella sp.	None	Lipidomics	Field	No
Oku et al., 2003	Goniastrea aspera	None	Lipidomics	Field	No
Ferrier-Pagès et al., 2005	Stylophora pistillata	None	Specific radioactivity (RAS)	Field and lab	No
Imbs et al., 2006	Gersemia rubiformis	None	Lipidomics	Field	No
Imbs et al., 2007	Acroporidae, Pocilloporidae, Poritidae, Faviidae, Pectiniidae,	None	Lipidomics	Field	No
Imbs et al., 2007	Fungiidae	None	Lipidomics	Field	No
Papina et al., 2007	Dendronephthya sp., Sarcophyton, Lobophytum, Cladiella, Lytophyton, Cespitularia, Clavularia, Caulastrea tumida	None	Lipidomics	Field	No
Imbs et al., 2009	Montipora digitata	Photosynthetically active radiation	Lipidomics	Field and lab	No
Imbs et al., 2009	Acanthogorgia, Acabaria, Chironephthya, Echinogorgia, Menella, Ellisella, Bebryce, Paralemnalia, Rumphella	None	Lipidomics	Field	No
Imbs et al., 2010a	Turbinaria reniformis	Variable light conditions	Lipidomics	Field and lab	No
Imbs et al., 2010b	93 species of reef-building and soft corals from Vietnam	None	Lipidomics	Field	No
Imbs et al., 2010b	Sinularia sp., Acropora sp.	None	Lipidomics	Field and lab	No
Imbs and Yakovleva, 2012	Sinularia capitalis, Montipora digitata, Acropora intermedia	Thermal stress	Lipidomics	Field and lab	No
Shinzato et al., 2011	Acropora digitifera	None	Genome sequencing	Lab	No
Imbs et al., 2012	Sinularia leptoclados, S. flexibilis, S. deformis, S. lochmodes, S. cf. muralis, S. densa, S. notanda S. cruciata	None	Lipidomics	Field	No
Pernice et al., 2012	Acropora aspera	None	Ion microprobe imaging	Field and lab	TEM, NanoSIMS
Weiss et al., 2013	Acropora millepora	Bacteria challenges	Transcriptomics	Lab	No
Wiedenmann et al., 2013	Montipora foliosa, Euphyllia paradisea, Acropora valida	Increased nutrients	Lipidomics	Lab	GFP fluorescence expression
Granados-Cifuentes et al., 2013	Acropora millepora	None	Transcriptomics	Field and lab	No
Ceh et al., 2013	Pocillopora damicornis	None	Ion mass spectrometry	Field and lab	NanoSIMS

Gordon et al., 2013	<i>Acropora aspera</i>	Physical aggitation	Metabolomics and HNMR metabolomics	Lab	No
Libro et al., 2013	<i>Acropora cervicornis</i>	White band disease	Transcriptomics	Feild	No
Sogin et al., 2014	<i>Porites compressa</i>	None	1H-NMR metabolomics	Field	No

(Continued)

TABLE 1

Author, year Continued	Species	Stress or Disease	Assay	Lab or Field Sampled	Histology or other tissue assays
Vidal-Dupiol et al., 2014/	Pocillopora damicornis	Vibrio coralliilyticus	Transcriptomics		No
Closek et al., 2014	Orbicella faveolata	Yellow band disease	Transcriptomics	Field	No
Ocampo et al., 2015	Pseudodiploria strigosa	Bacteria challenges	Transcriptomics	Lab	No
Tang et al., 2015	Seriatopora caliendrum	None	Lipidomics	Field	No
Imbs et al., 2015	Xenia sp.	None	Lipidomics	Field	No
Imbs et al., 2015	Sinularia macropodia and Capnella sp.	None	Lipidomics	Field	No
Daniels et al., 2015	Orbicella faveolata	White plague	Transcriptomics	Field	No
Wright et al., 2015	Acropora hyacinthus	White syndrome	Transcriptomics	Field	No
Libro and Vollmer, 2015	Acropora cervicornis	White band disease	Transcriptomics	Field	No
Morgan et al., 2015	Orbicella faveolata	Yellow-band disease	Transcriptomics	Field	No
Quinn et al., 2016	Acorpora, Montipora, Pocillopora, Porites sp.	Algal/fungal contact	Liquid chromatography–mass spectrometry	Field	No
Sogin et al., 2016	Pocillopora damicornis	Elevated temperature and pCO ₂	Lipidomics & Metabolomics	Field and lab	No
Anderson et al., 2016	Orbicella faveolata	Yellow band disease, thermal stress	Transcriptomics	Field	No
Hillyer et al., 2017	Acropora aspera	Elevated temperatures	Metabolomics	Field and lab	No
Frazier et al., 2017	Montipora capitata	Growth anomaly	Transcriptomics	Field	No
Yuan et al., 2017	Pocillopora damicornis	Elevated ammonium	Transcriptomics	Lab	No
Hillyer et al., 2017	Acropora aspera	None	Metabolomics	Field and lab	No
Seveso et al., 2017	Goniopora columna	Black band disease	Transcriptomics	Field	No
Tang et al., 2017	Seriatopora caliendrum	ZnO nanoparticles	Lipidomics	Field and lab	No
Zhang et al., 2017	Platygyra carnosa	Growth anomaly	Transcriptomics	Field	No
Hartmann et al., 2017	Porites, Montipora, Acropora, Pocillopora	Algal/fungal contact	Metabolomics	Field	No
Bosh and Long, 2017	Mopsella spinosa, Menella flora, Menella praelonga, Acropora acuminate, A. cytherea, and Turbinaria peltata, Cladiella laciniosa, Sinularia brassica, Sinularia robusta	None	Lipidomics	Field	No
Imbs and Dang, 2017	Gersemia rubiformis	None	Lipidomics	Field	No
Petrou et al., 2018	Acropora millepora	Thermal stress	Synchrotron Infrared Microspectroscopy	Field and lab	No
Tang et al., 2018	Seriatopora caliendrum	Herbicide exposure	Lipidomics	Field and lab	No
Sikorskaya and Imbs, 2018	Sinularia siaesensis	None	Lipidomics	Field	No
Farang et al., 2018	Sarcophyton ehrenbergi, S. glaucum	Thermal stress	Metabolomics	Lab	No
Fuess et al., 2018	Eunicea	Unknown (black disease)	Transcriptomics	Field	Histology performed; disease tissue: increased melanin and decreased prophenoloxidase activity detected.

(Continued)

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Continued

	Species	Stress or Disease		Field Sampled	other tissue assays
Ochsenkühn et al., 2018	Acropora, Platygyra	White syndrome disease	Metatranscriptomics & metabolomics	Field	No
Lohr et al., 2019	Acropora cervicornis	None	Metabolomics	Field and lab	No
Andersson et al., 2019	Acropora cervicornis, Orbicella faveolata	None	NMR with MeOH vs Bligh & Dyer vs MBTE	Lab	No
Tang et al., 2019	Seriatopora caliendrum	Herbicide exposure	Lipidomics	Field and lab	No
Imbs et al., 2019	hydrocoral Allopore steinegeri, hydrocoral Millepora platyphylla, Millepora dichotoma	None	Lipidomics	Field	No
Vohsen, et al., 2019	Acropora palmata, Stichopathes sp., Leiopathes glaberrima, Lophelia pertusa Callogorgia delta	None	Metabolomics	Field	No
Lohr et al., 2019	Acropora muricata	None	Metabolomics	Field	No
Ricci et al., 2019	Eunicea	Unknown (black disease)		Field	Histology performed; granular amoebocyte (GA) mobilization, melanin in GAs, and fungal hyphae
Zhou et al., 2019	Pocillopora damicornis	Vibrio coralliilyticus	Transcriptomics	Lab	No
Matthews et al., 2020	Montipora capitata	None	Metabolomics	Field	No
Sikorskaya et al., 2020	Sinularia sp.	Thermal stress	Lipidomics	Lab	No
Roach et al., 2020	Diploria strigosa and Orbicella faveolata	Turf algae	Metabolomics	Field	Viral abundance and microbial size via SYBR and DAPI staining
Sikorskaya et al., 2020	Zoantharia Palythoa sp., Hexacorallia	None	Lipidomics	Field	No
Santacruz et al., 2020	Plexaura, Pseudopterogorgia, Eunicea, Plexaurella Pseudoplexaura	None	Metabolomics	Field	No
Abdelhafez et al., 2020	Nephthea sp.	None	Metabolomics	Field	No
Takagi et al., 2020	Pocillopora damicornis	Vibrio coralliilyticus and thermal stress	Transcriptomics	Lab	No
Kenkel et al., 2020	Porites lobata	White patch syndrome	Transcriptomics	Field and lab	No
Silva-Lima et al., 2020	Mussismilia braziliensis	White plague-like disease	Transcriptomics	Field	No
Young et al., 2020	Acropora palmata	White syndrome	Transcriptomics	Field	No
Mayfield et al., 2021	Orbicella faveolata	Thermal stress	Proteomics	Lab	No
Sweet et al., 2021	Acropora hyacinthus, Acropora millepora	Thermal stress	Metabolomics	Field and lab	No
Wong et al., 2021	Platygyra carnosa	Growth anomaly	Proteomics	Field	No
Roach et al., 2021	Montipora capitata	Thermal stress	Metabolomics	Field	No
Deutsch et al., 2021	Montastraea cavernosa	Stony coral tissue loss disease	Metabolomics	Field	No
Traylor-Knowles et al., 2021	Orbicella faveolata, Montastraea cavernosa	Stony coral tissue loss disease	Transcriptomics	Lab	No
Kelley et al., 2021	Montastraea cavernosa	Vibrio spp.	Transcriptomics	Field and lab	No
Mayfield, 2022	Orbicella faveolata	Thermal stress	Proteomics	Field and lab	No

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TABLE 1

Author, year

packages used in the analysis can yield variability within outcomes. However, despite these complications, a rapid biomarker would be beneficial to monitor coral health.

Assay Lab or Histology or
photosymbiont (Symbiodiniaceae), viruses, micro-
eukaryotes, archaea, and fungi. The most well characterized
of these

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1.3 Coral immune system function in disease

Given the rapid emergence of deadly diseases like SCTLD, understanding the immune response of corals to disease has become more important than ever. Innate immunity is a nonspecific immune process by which organisms combat foreign invaders (Palmer and Traylor-Knowles, 2012; Palmer and Traylor-Knowles, 2018). For corals, the first line of defense is the surface mucus layer, a critical boundary for trapping foreign particles and microbes (Palmer and Traylor-Knowles, 2012; Palmer and Traylor-Knowles, 2018). If this boundary is breached then an innate immune response can occur. This response is generally characterized in organisms as having the steps of (1) recognition of non-self and (2) activation of signaling pathways that lead to (3) an effector response. Like all invertebrates, corals possess pathogen recognition receptors (PRRs) that perceive microbe- or pathogen-associated molecular patterns (MAMPs, PAMPs) in different microbial communities. When compared to other metazoans, however, corals have a complex recognition system that possesses a highly redundant and abundant PRR network associated with many downstream signaling pathways (Emery et al., 2021). Much of what we understand of the coral innate immune response comes from measurements of different effector responses including phagocytosis (Palmer et al., 2011b; Snyder et al., 2021), the melanin response (Mydlarz et al., 2008; Palmer et al., 2011a; Pinzón C. et al., 2014), production of antimicrobial peptides (van de Water et al., 2018), reactive oxygen species (Mydlarz and Jacobs, 2006) and other antioxidants (Mydlarz and Harvell, 2007). Now with the use of 'omics, the recognition and signaling mechanisms that initiate these immune effector responses are being further discovered, characterized, and connected to phenotypic outcomes. However, with this progress comes more questions, due to the complicated holobiont interactions with coral hosts. These organisms are non-self, yet they bypass the coral immune system. Is the disease caused from an in hospite organism, or a foreign pathogen invading from the outside environment, a combination of both?

1.4 Complexity of coral disease and holobiont

Corals are holobionts; they are host to many different microorganisms including bacteria, the dinoflagellate

symbiotic relationships is between the coral host and the dinoflagellates that live in its gastrodermis, an epithelium lining the interior of the polyps and coenenchyme (Brown et al., 1995; Brown, 1997; Weis, 2008). Dysbiosis between these two partners results in bleaching and is a hallmark of many coral diseases (Brown et al., 1995; Brown, 1997; Weis, 2008). Due to the complex symbiotic nature of the coral holobiont, the causative agent(s) of many coral diseases have been elusive to identify (Vega Thurber et al., 2020). Furthermore, the resulting organismal and cellular responses can be challenging to link to a specific pathogen(s). Coral health is tightly associated with the environment where dysbiosis, or the breakdown of microbial homeostasis often caused by environmental disturbances, can initiate disease pathologies including tissue lesions, bleaching, and tissue loss (Brandt and McManus, 2009; Vega Thurber et al., 2020). This has led to a focus in coral research to monitor the coral host and its immune response in response to disease outbreaks or environmental stressors (Mydlarz and Harvell, 2007; Pollock et al., 2014; Fuess et al., 2017; Vega Thurber et al., 2020). Changes in gene expression; protein, lipid, and carbohydrate synthesis; and alterations in metabolic cascades can be studied to understand the underlying disease processes. However, this approach is not without challenges. The complexity of the holobiont and the immune response has led to limitations in understanding large-scale patterns of change because results from different 'omics datasets can emphasize different findings that reflect the variation in the holobiomes of the affected corals. Lastly, immune outcomes can be varied depending on different abiotic stressors and the type of immune measurements being used. For example, *Montipora capitata* found in different pCO₂ environments had contrasting catalase and prophenoloxidase activity that correlated with environmental history and temperature stress, but melanin, another marker for immunity, only correlated with environmental history (Wall et al., 2018). This example highlights the complexity of the innate immune response within individual corals. The response is varied, and influenced by the type of stress exposure.

In this review, we examine the current use of 'omics approaches as a tool for understanding coral disease and in the development of biomarkers. We focus on diseases suspected to be biotic rather than abiotic (e.g. coral bleaching in response to thermal stress). We acknowledge that biotic and abiotic stressors are intricately linked but have chosen to focus on biotic diseases

because less is understood about these processes. We start by discussing the current state of coral disease 'omics in relation to coral immunity. We then highlight considerations for experimental design for doing large scale disease 'omics studies, and we consider how to move forward from disease 'omics studies to biomarker development. Lastly, we discuss the integration of 'omics into effective conservation and restoration strategies. This review can serve as a platform to push forward the development of

biomarkers and expand our understanding of coral disease outbreaks and coral immune function (Figure 1).

2 Role of the immune system in coral disease: what do 'omics approaches tell us?

Here, we summarize what is known about the 'omics immune response from each coral disease described to date, including what genes or proteins have been identified as critical to the response. We also provide, where possible, the histological context for each disease (Table 1). We start this section with gorgonians, which are not stony corals, but are critical for the background of coral disease because this is where the coral immunity field began, and thus gives context to the growth in this field.

2.1 Gorgonian diseases

One of the first models for coral disease was the sea fan (*Gorgonia ventalina*) aspergillois pathosystem. This model was tractable due to easy collection of specimens and clear identification of purple lesions that often revealed the site of pathogen infection and coral immune response driven by melanization and cell repair mechanisms (Petes et al., 2003; Mydlarz et al., 2008; Mydlarz et al., 2009). Based on this seminal research, it became evident that the visual signs of disease were not only caused by the aspergillois, but also by the host immune response. Histopathological examination of diseased sea fans helped to initially characterize cellular outcomes. For example, pleomorphic amoebocytes were found to function as the principal cells of the innate immune system in Cnidaria (Hyman, 1940; Meszaros and Bigger, 1999; Menzel et al., 2015). In gorgonians, these cells are relatively large and contain abundant acidophilic granules dispersed in the mesoglea of the coenenchyme (Figure 2; Bayer, 1954; Peters, 2015). The abundance of these acidophilic granular amoebocytes (AGrAs) varied with the condition of the colony, and focal aggregations of these cells have been seen in response to putative pathogenic microorganisms, such as *Aspergillus* and bacteria. AGrAs line up at the surface of the exposed mesoglea to form a barrier epithelium (Mydlarz et al., 2009; Tracy et al., 2020), and can produce a thick deposition of melanin-like material to prevent the fungi from infiltrating the gorgonian polyps and coenenchyme (Mullen et al., 2004).

Transcriptomic examination of diseased sea fans identified genes involved in pattern recognition, antimicrobial peptide production, and wound repair (Burge et al., 2013). These included immune-related genes such as tachylectin-5A, arenicin-2, and uromodulin (Burge et al., 2013). Likewise,

Tracy et al. (2021) identified increased expression from several candidate immune genes based on the results of Burge et al. (2013) when sea fans were exposed to copepods and *Aspergillus* in both field and laboratory experiments. They found higher densities of AGrAs in treatments with copepods only and copepods with *Aspergillus* co-infection indicating that copepods, based on histopathological examination.

The first proteomic study of diseased soft corals examined *Sinularia* tissue-loss disease (STLD) (Gochfeld et al., 2015). Examination of differentially abundant proteins revealed a significant increase in fluorescent protein expression in diseased tissue. Fluorescent proteins are known to act as antioxidants, and this finding indicates a stimulated antioxidant immune response of the coral host (Palmer et al., 2009; Gochfeld et al., 2015). Proteins associated with symbiont photosynthesis and stress responses (e.g., heat shock proteins) were also up regulated in diseased tissue. Histological examination of *Sinularia*-affected tissue samples revealed increased densities of AGrAs in response to unknown foreign cells and hyperplasia of gastrodermal cells, as well as necrosis (Slattery et al., 2013).

In another gorgonian species, *Eunicea calyculata*, histological studies of tissue affected by *Eunicea* black disease also revealed increased densities of AGrAs, most containing melanin granules, and fungal hyphae penetrating the coral tissue (Ricci et al., 2019). Proteomic analysis of diseased *E. calyculata* identified differentially abundant proteins associated with immunity, reproduction, inflammation, and antimicrobial responses (Ricci et al., 2019). There were four up-regulated proteins in diseased samples that correlated to significantly differentially abundant transcripts quantified using transcriptomics in an earlier study (Fuess et al., 2018): a C-type lectin, a histone, a heat shock cognate 70, and a carbonic anhydrase. One of the highest upregulated proteins in diseased corals was arachidonate 5-lipoxygenase, an enzyme involved in the inflammatory response and possible recruitment of amoebocytes or melanocytes to sites of tissue damage in coral (Fuess et al., 2018; Ricci et al., 2019).

In contrast to gorgonians, histopathological examinations of scleractinian corals have shown they lack large AGrAs in the mesoglea, which is relatively thin compared to that in the octocorals, although the microscopic anatomy of only a few species has been studied (Peters, 2015). Scleractinian corals have external and internal contiguous layers of cuboidal to columnar cells that contain ciliated supporting cells and mucocytes forming a protective surface mucopolysaccharide layer. Some species have small amoebocytes with small or larger acidophilic granules between epithelial cells in the epidermis (external) and gastrodermis (internal), whereas others are found only between mucocytes in mesenteries (Figure 2). Amoebocytes may also produce melanin granules in some species. It is therefore crucial to compare the 'omics of octocorals with hexacorals along with their histology to give context to the 'omics outcomes that are measured.

2.2 White band, white syndrome, and white plague

One of the first studies to use transcriptomics to investigate the immune response of diseased stony corals was done in *Acropora cervicornis* affected by white-band disease (WBD) on Panama reefs (Libro et al., 2013). The main differentially expressed pathways

species (ROS), antioxidants, and general stress response genes. However, no differential expression of toll-like (TLR) receptor signaling, complement, and prophenoloxidase (PPO) innate immune pathways were identified. The authors concluded that WBD-induced apoptosis of coral host cells, which subsequently mounted a powerful immune response driven by phagocytic engulfment and degradation of apoptotic cells. No WBD-affected

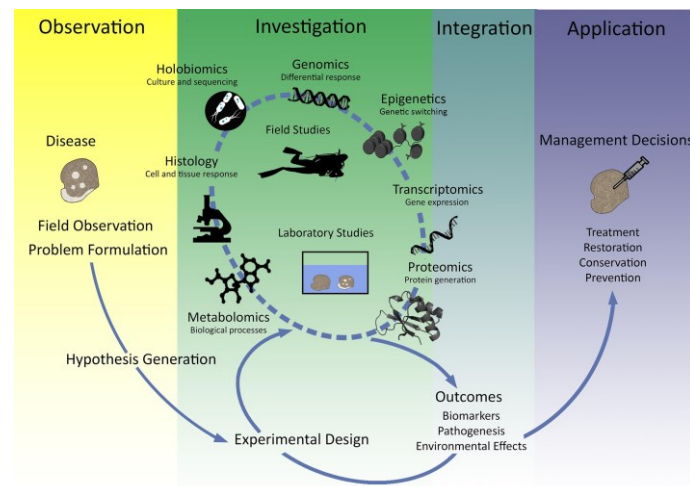


FIGURE 1

Integrative summary of the use of 'omics technologies for coral disease outbreaks. Summary figure of how hypothesis driven experimentation to investigate immune function as measured by 'omics technology is critical for application of marine management and conservation outcomes.

identified in the response to WBD were immunity, apoptosis, arachidonic acid metabolism, calcification and calcium homeostasis, cell growth and remodeling, and lipid and fatty acid metabolism. Libro et al. (2013) found 69 immunerelated differentially expressed transcripts, including pattern recognition receptors (namely C-type lectins), mediators of phagocytosis, producers of reactive oxygen

or apparently healthy samples were collected at the same time for histology; however, samples were processed and examined for other *A. cervicornis* samples from Bocas del Toro, Panama, presenting WBD (Casas et al., 2004), later confirming the infection of mucocytes by a novel Rickettsiales bacterium, *Candidatus Aquarickettsia rohweri* (Miller et al., 2014; Klimes

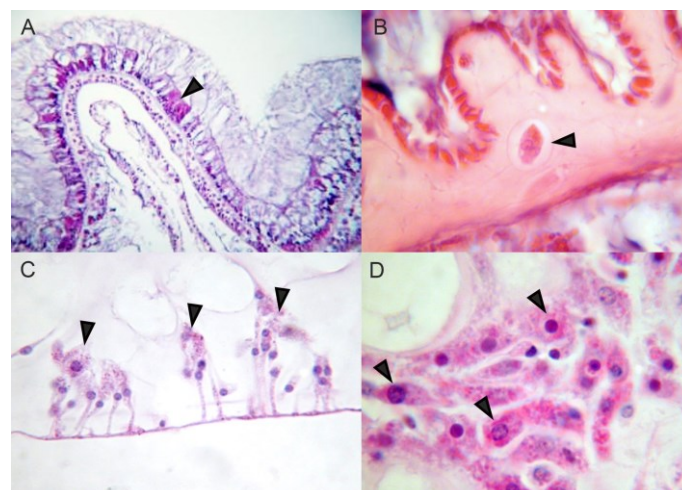


FIGURE 2

Amoebocytes in Hexacorals and Octacorals (A) Scleractinian hexacoral *Orbicella faveolata*, arrowhead indicates eosinophilic granular amoebocytes in surface epithelium. (B) Scleractinian hexacoral *Pseudodiploria strigosa*, arrowhead indicates amoebocyte transiting through mesoglea. (C) Octocoral *Plexaurella fusifera*, arrowheads indicate eosinophilic granular cells on surface. (D) Octocoral sea fan *Gorgonia ventalina*, arrowheads indicate eosinophilic granular amoebocytes in mesoglea.

et al., 2019). Cell degradation was evident; however, “phagocytic engulfment” of apoptotic cells was not observed. In a study several years later on *Acropora palmata* and *A. cervicornis*, histological evidence discovered two different etiologies for what was presumed to be WBD. One was described as true WBD and the other was described as rapid tissue loss (RTL) (Miller et al., 2019). RTL is characterized by acute patchy sloughing off of tissue from the skeleton with increased mucus production. At a cellular level, changes to the calicodermis, along with necrosis and/or apoptosis within the basal and surface body walls, were observed. For WBD, the histopathology varied, but similar changes were also observed in other WBD-affected acroporid (Miller et al., 2019). Subsequent studies of these same *A. palmata* samples found that a strong immune response was initiated in affected corals, but that the Symbiodiniaceae gene expression was not modulated, indicating that this disease may be one of the coral host rather than the algal symbionts (Young et al., 2020).

In the Indo-Pacific, white syndromes (WS) affect a variety of acroporid coral species. In the field, WS is characterized by variable and rapid tissue-loss lesions that leave the coral skeleton bare and exposed (Sussman et al., 2008). In the coral *Acropora hyacinthus*, the main signaling pathways identified in the response to WS using transcriptomics were those involved in the immune response, lipid and carbohydrate metabolism, oxidative stress, tissue regeneration, and calcification (Wright et al., 2015). The immune response to WS was also found to be similar to WBD with up-regulation of C-type lectins, complement factors, and transcripts potentially involved in lysosomal degradation via ROS production and proteolytic enzymes (Libro et al., 2013; Young et al., 2020). Pairwise comparisons between three distinct health states (disease lesion, apparently healthy tissues of diseased tissues, and healthy tissues) found no significant differences between apparently healthy tissues of diseased tissues and healthy tissues, indicating that the response to WS is limited to the immediate area affected by the advancing tissue loss (Wright et al., 2015). Although no transcriptomic signatures of the algal symbionts were reported in this study, the authors noted that the upregulation of lipid-based metabolism in diseased tissues may indicate a decline in carbohydrate exchange by Symbiodiniaceae, possibly due to stress-induced symbiont loss (Wright et al.,

tissue that surrounds the tissue-loss margin along an exposed, denuded skeleton in *Orbicella faveolata* (Reeves, 1994; Bruckner and Bruckner, 2006). Using a multiomics approach to examine coral host immune responses, CYBD affected tissue was found to have significant upregulation of various inflammation-related genes, suppression of mitochondrial associated genes, and a reduction in antimicrobial peptide expression (Closek et al., 2014). Overall gene expression patterns supported distinct changes between apparently healthy and diseased conditions; however, the visually healthy tissues of diseased corals included some differentially expressed genes that responded similarly compared to diseased samples, whereas some were more similar to trends seen in healthy samples. These patterns indicate the challenges in using differential gene expression (DGE) analysis to determine biomarkers in corals that appear healthy (Closek et al., 2014).

In another transcriptomic study of CYBD, authors focused on identifying immune pathways in diseased tissue as well as the coral immune repertoire (Anderson et al., 2016). The authors found evidence of novel homologues of the wnt and notch protein family, nod-like receptors, and dicer-like proteins within the disease transcriptome. Taken together these studies show that *O. faveolata* is having an immune response, but that there are nuances and challenges to using DGE as a tool for biomarker identification. This is exemplified by the fact that corals that looked visually healthy had a lot of variation in their DGE. DGE in corals is very sensitive and rapid (Traylor-Knowles, et al. 2017).

2.4 Growth anomalies

Growth anomalies (GA) affect more than 40 different species of coral, and are described as abnormal skeletal growths characterized by hyperplasia of the basal body wall, reduced oocyte development, and reduced symbiont densities (Sutherland et al., 2004; Domart-Coulon et al., 2006; Burns et al., 2011; Work et al., 2015; Zhang et al., 2017). Off the coast of Hawai'i, high prevalence of GA has been documented on colonies of *Montipora capitata* in areas of dense human populations; however the precise cause of the disease is still not understood (Takabayashi et al., 2010; Aeby et al., 2011). To

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2015). While histological outcomes of the samples sequenced by Wright et al. (2015) are not known, a previous study on WS affected tissue in *A. hyacinthus* found apoptosis present, as measured by TUNEL assay (Ainsworth et al., 2007).

2.3 Yellow band disease

Caribbean yellow band disease/yellow blotch disease (CYBD) is a tissue-loss disease characterized by a pale, yellow-colored band of

further understand the molecular drivers of this disease, [Spies and Takabayashi \(2013\)](#) used quantitative real-time-polymerase chain reaction (qRT-PCR) methods to quantify the DGE of several previously identified immune and onco-genes including galaxin, murine double minute 2 (MDM2), tumor necrosis factor (TNF), tyrosine protein kinase (TPK), and bg-crystallin (BGC). TNF was unchanged in GA compared with healthy and non-GA areas, whereas galaxin, a coral calcification gene, was upregulated in non-GA areas ([Spies and Takabayashi, 2013](#)). Later, a transcriptomic analysis of *M. capitata* affected by GA was performed and several genes involved in collagen, osteogenesis, and skeletal matrix production were significantly upregulated in GA-affected tissues ([Frazier et al., 2017](#)). An ortholog for the human bone morphogenetic protein 1 (HBMP1) was upregulated, as well as tumor necrosis receptor-associated factors (TRAFs), both of which are involved in the immune response. While these two studies have some contradictions in gene expression patterns, it does appear that both immune and calcification genes play an important role in GA ([Andersson et al., 2020; Andersson et al., 2021](#)).

Like *M. capitata*, transcriptomic and proteomic studies of GA on *Platygyra carnosa* both showed differential expression of genes related to immune responses, including several TRAFs ([Zhang et al., 2017](#)). Both *P. carnosa* and *M. capitata* GA also showed similar patterns in reduced expression of genes involved in calcification, and increased expression of fluorescent proteins in GA tissues. The proteomic analysis also found a suite of proteins associated with amino acid synthesis and lysosomes downregulated in the GA-affected sample that may indicate malnutrition and disruption of protein catabolism. Additionally, an increased abundance of ribosomal proteins and heat shock proteins in GA were identified. Reduced abundances of putative pattern recognition molecules and lysosomal proteins were also identified leading to the hypothesis that the stress response in GA was not triggered by microbial invasion. While the cause of these GA is still not well understood, it does seem to elicit an immune response that is primarily driven by interactions with TRAF signaling and changes in calcification.

2.5 Stony coral tissue loss disease

The pathology of stony coral tissue loss disease (SCTLD) is characterized by the presence of multifocal lytic necrosis that starts within the gastrodermis and progresses to the outer epithelial layer ([Aeby et al., 2019; Landsberg et al., 2020](#)). First reported in 2014, this disease affects at least 24 different Caribbean coral species, is waterborne, and the causative agent is suspected to be microbial in origin ([NOAA, 2018; Dobbelaere et al., 2020; Landsberg et al., 2020; Muller et al., 2020; Work et al., 2021](#)). While the causative agent of the disease is still

unknown, there is growing evidence that algal symbionts are tightly implicated in the etiology of this disease based on (1) histological studies showing rapid deterioration of gastrodermal cells ([Aeby et al., 2019; Landsberg et al., 2020](#)), (2) differential susceptibility of corals manipulated to host different Symbiodiniaceae ([Dennison et al., 2021](#)), (3) reduced incidence in bleached corals with reduced symbiont loads ([Neely et al., 2020](#)), and (4) correlations between SCTLD disease signs and the presence of viruses in associated Symbiodiniaceae ([Work et al., 2021; Veglia et al., 2022](#)). Metabolomic approaches have tended to support these conclusions, with different Symbiodiniaceae-related lipid classes (including betaine lipids, glycolipids, and tocopherols) being differentially expressed between apparently healthy and diseased corals ([Deutsch et al., 2021](#)). This is very similar to what was previously found during coral bleaching where changes in lipids and glycolipids within specific genera of Symbiodiniaceae are associated with thermotolerant or thermosensitive corals ([Tchernov et al., 2004; Rosset et al., 2019; Sikorskaya et al., 2020; Sikorskaya et al., 2021; Deutsch et al., 2021; Roach et al., 2021](#)). At a transcriptomic level, SCTLD is associated with the expression of many different stress genes, immunity, and apoptosis genes including peroxidases, bax-like, fibrinogen-like, protein tyrosine kinase, and transforming growth factor beta ([Traylor-Knowles et al., 2021](#)). Both the metabolomic and transcriptomic study of SCTLD reveal changes in lipid production and a concomitant immune response in the coral host, reaffirming the tight interaction between the holobiont members ([Deutsch et al., 2021; Traylor-Knowles et al., 2021](#)). As this disease is one of the newest described coral diseases, 'omics studies are currently limited in number, but are increasing rapidly due to reduced costs of sequencing approaches and improved annotation of 'omics references (e.g., genomes, transcriptomes, proteomes). Previous studies of other coral diseases described above laid the foundation for examination of coral immunity, and specifically emphasized the need for consistency among approaches and implementation of multiomics pipelines to better characterize immune responses and pathways.

2.6 Common themes

The use of 'omics approaches to study the immune system reaction to coral diseases has generated several converging themes. From a broad perspective, overwhelmingly we can see that the coral immune system is reacting to disease. Genes and proteins from many different immune signaling pathways are differentially regulated in disease-exposed versus unexposed (i.e., apparently healthy) tissues. An often-discussed hypothesis that corals are immunocompromised does not appear to be supported by these previous studies, in fact one could

hypothesize that the opposite could be true; an overactive immune state may be present in corals. While comparative studies between coral species could shed some light on this (Fuess et al., 2017), other cnidarian models show evidence of immune memory, supporting the hypothesis that immune activity in anthozoans can be modulated based on prior disease exposure (Brown and Rodríguez-Lanetty, 2015). Future studies on coral disease could benefit from focusing on the possible hyper-activity and hyper-responsivity of the coral immune system, and the possible etiologies of disease or resistance that could result from each state (Wright et al., 2017).

While each of the 'omics studies discussed above present their data in different ways, there does appear to be convergence on several immune-related processes including extracellular matrix stability, mucus production, and markers of inflammation, and apoptosis. Many of these processes and resulting biomarker candidates are likely indicative of latestage tissue degradation as a direct result of disease presence. Early time sampling before visual signs of disease could elucidate more about genetic mechanisms of these different diseases, and would be beneficial to take into consideration during experimental design. Lastly, few of these 'omics studies incorporated histopathological examinations into their analysis thus our understanding of the cellular pathologies is still not connected with the gene expression outcomes. This missing link between the gene expression and the cellular outcomes needs to be further developed so that a better understanding of the disease mechanisms can be achieved.

3 Considerations for experimental design for disease 'omics studies

In this section, we discuss aspects of experimental design and sampling approaches for both field and lab experiments relative to coral immunity and disease. We focus on how to maximize the chance of success in downstream 'omics analyses, by identifying consistent sampling approaches to enable quantification of molecular processes and to facilitate cross-comparisons across datasets.

3.1 Recommendations for enhancing cross-dataset comparisons

The ability to identify and characterize modulation of immune pathways and functions related to disease susceptibility and resistance relies on (1) a focus on hypothesis-driven research in field and lab settings, (2) robust experimental design and consistency in experimental approaches among studies, and (3) communication and collaboration of research efforts to

maximize the impacts of individual studies. Oftentimes, we are limited in the ability to sample coral populations affected by disease, particularly when focusing on threatened or endangered species. Sourcing both diseased corals and apparently healthy corals for lab-based experiments can also pose challenges depending on the spatial scale of the endemic zone and potential seasonal variability in disease prevalence. To limit impacts on remaining coral populations affected by disease while still maximizing growth in our understanding of coral immune responses, research efforts could also be directed toward better understanding 'normal' metabolic and immune functions through analysis of apparently healthy individuals. Given the variability of diseased corals in the wild, generating additional information about baseline function may provide context to case study observations and experiments, better replicating how we approach rare human diseases by identifying deviations from normality. Additionally, emphasis needs to be placed on consistency of experimental approaches among species, regions, and potentially even diseases, to allow for cross-study comparisons and meta-analyses. Methods used for experimental design and sampling needs to be transparent and well documented. Here, we outline recommendations to improve statistical robustness and enhance comparisons across datasets, in the context of lab- and field-based experiments. These efforts will broadly contribute to the ability to collect robust 'omics data in both settings and will improve our ability to characterize common immune responses to disease challenges, and subsequently, to identify and validate suitable biomarkers of disease susceptibility/ resilience for screening across coral populations. This information can be used for operationalization of 'omics-based predictions of resilient genotypes to increase success of conservation and restoration initiatives. We acknowledge that this will not be an easy task, as fitness trade-offs exist, however, with the abundance of 'omics data now available cross-analyzation of different types of stressors and diseases are feasible and may help to disentangle potential trade-offs.

3.2 Field sampling

There is an inherent difficulty in conducting field sampling efforts and lab-based experiments consistently, in that coral diseases tend to change in terms of prevalence and perhaps even etiology among regions and through time (Aeby et al., 2019; Shore and Caldwell, 2019; Meiling et al., 2021). Few species are readily available in sufficient density for field and lab experiments, and within Florida where the disease was first observed, it is not feasible to source disease-naïve corals from the wild. Furthermore, of the species remaining in sufficient numbers to support sampling and experiments it may be

impossible to identify colonies that have not been exposed to prior intervention efforts including antibiotic and probiotic treatments (Paul et al., 2019; Ushijima and Aeby, 2019; Meyer, 2020; Peixoto et al., 2021).

Furthermore, analysis of 'omics samples from field experiments pose challenges to robustness of statistical designs. For example, environmental variability across microhabitats where coral colonies are sampled, or variation in microbial symbiont communities among coral colonies can introduce unexplained variance into statistical models examining treatment responses (i.e., following antibiotic or probiotic intervention). Most field-based designs also do not allow for replication of coral genotypes across treatments, except in cases such as reciprocal transplant experiments. As a result, the high levels of environmental stochasticity associated with sample collections, in conjunction with relatively low control over genotypic/symbiont variability, can result in data noise that overwhelms any treatment effects. There are several potential ways to mitigate these issues, foremost, increased replication within treatments for better resolution of genotypic and habitat variability. The former may also be improved through data collection of additional environmental parameters, as some 'omics analysis pipelines (e.g., weighted gene co-expression network analysis, or WGCNA; (Langfelder and Horvath, 2008)) can examine links in molecular responses to quantitative traits and parameters. For improved genotypic replication, experimental designs may consider a repeated-measures approach, where colonies are revisited and sampled over time for fate-tracking purposes. This would also facilitate examination of colony survival through time related to disease progression, and responses to intervention treatments. Such designs require extra considerations, however, to minimize overall impacts on colonies related to multiple sampling events, or potential compounding effects on treatments. Repeated-measures approaches should therefore attempt to minimize sample volumes, such as shifting from skeletal fragments taken from a colony margin with hammer/chisel or extraction of 2.2-cm diameter core biopsies, to shallow tissue scrapes or syringe samples of polyps. There are tradeoffs to smaller samples, namely the prevention of conducting other analyses on collected samples (i.e., histology), but the sampling approach can be modified accordingly based on the research questions of the study. More than one sample may be needed from the same colony, for example, core biopsy preserved for histology and core biopsy frozen or preserved for DNA/RNA analyses; these should be taken as close together as possible from each sampling location on a colony with the same visual tissue response. Additionally, efforts to sample from consistent areas on different coral colonies can be prioritized and well documented (e.g. Drake et al., 2021). Finally, field experiments often have unexplained variance due to sampling times, as the amount of

time needed to sample a coral underwater and, for example, preserve it on a moving boat, is generally greater than for a lab experiment. Considerations to field operations and personnel should be made to minimize both the time between sampling underwater and topside preservation, as well as the time delay between individual samples collected (such as across sites). Lastly, the environment in which the coral is collected needs to be taken into consideration. Corals are extremely sensitive to their local environment, and measurements such as depth, light, and water flow may have effects on 'omics outcomes.

3.3 Lab based studies

While lab-based experiments have some limitations in that they do not often replicate ecologically relevant environmental stochasticity or genotypic variability found in the wild, they are useful for 'omics analyses that require a consistent treatment effect and controlled genotypic variability to maximize inferential power. For examining disease exposure in particular, ex situ designs allow for greater control over potential co-infections among replicates or environmental effects on disease transmission and progression. As a result, lab experiments could prioritize statistical independence of replicates within treatments using individual micro-aquaria rather than communal tank systems. This eliminates pseudo-replication and minimizes the chance of coinfections occurring from one experimental coral fragment to another. These types of designs often require more coral biomass, especially considering that multiple disease donor fragments are required versus a single fragment in a communal design, but independence of transmission replicates will allow for more robust downstream statistical analysis. Such designs also lend themselves to examination of disease susceptibility/resistance across multiple genotypes, as clonal fragments can be allocated across treatments (Miller et al., 2014; Muller et al., 2018; Young et al., 2020). Additionally, it has become more apparent from a growing number of studies addressing molecular mechanisms related to disease exposure that there may be a sizable impact of genotype and/or symbiont communities on coral responses to disease challenges. Therefore, lab-based experiments accounting for genotypic effects would be beneficial, specifically those that incorporate multiple replicates of genotypes within treatments to allow for statistical comparison of variation in response variables (e.g., gene expression, microbial communities, algal symbiont communities).

Finally, as lab experiments often involve prior fragmentation to achieve a suitable number of coral fragments, future studies could consider a recovery period to allow fragments to heal prior

to disease exposure. Recently cut margins may provide a means of entry for pathogens and could artificially inflate transmission rates and time to onset of visible disease signs. Studies have suggested that there is variation in wound healing times among coral species (Work and Aeby, 2010; Rodriguez-Villalobos et al., 2016; Traylor-Knowles, 2016; Edmunds and Yarid, 2017; Counsell et al., 2019), but a period of 2–3 weeks is likely to be sufficient to repair fragmentation damage at cellular levels, provided that water quality, light levels, and food supplementation are optimal. Additionally, fragments should be quarantined and observed for mortality prior to experiments, especially those that are collected from the wild. Conversely, with extended time (months) in laboratory aquaria, there may be changes in holobiont composition, such as microbiomes and/or endosymbiont communities, that can impact the health status or representability of lab-reared corals relative to wild samples (Galand et al. 2018). Such changes through time may influence molecular responses to experimental treatments and may therefore affect downstream ‘omics analyses. To aid in our understanding of the ‘omics outcomes, histological examination of subsets of (1) apparently healthy coral samples collected in the field, (2) samples taken at the end of the acclimation period prior to application of experimental treatments, and (3) control coral samples maintained separately but under the same environmental conditions as experimental corals should be preserved. This would be useful to evaluate health status or rule out other causes of mortality observed in experimental fragments (e.g., husbandry-related, or pathogens other than the disease of interest). Histological markers that indicate stress or disease include areas of necrosis, tissue fragmentation not associated with the sample collection, algal symbiont loss, degeneration, and atrophy of tissue, excessive calicodermal proliferation, granular cell accumulation that can include identifiable etiologies such as algal, fungal, or filamentous bacterial overgrowth, ciliate invasion, or metazoan parasites in a sample (Galloway et al., 2007; Work et al., 2016). These may be found in field sampled corals and are not always associated with visible gross lesions on the coral colony. If this is found in the initially apparently healthy coral samples collected from the field, then it is an indication that the coral is not healthy and the downstream disease and ‘omics analysis may be confounded by a pre-existing disease condition.

Perhaps the second greatest challenge in conducting robust disease exposure experiments comes in the timing of visible disease signs and sampling. There is likely temporal variability at the transcriptomic and holobiont levels related to disease infection and progression, but these processes have not been well-studied in corals. Time series studies would ideally be performed to identify variation in multiomic responses related to pathogen exposure through time, to better understand the mechanistic processes related to disease infection and

progression, and to inform future studies of the ideal time to sample to best capture molecular responses. In the case of SCTLD, several studies have been conducted to examine microbial communities in wild diseased corals and in laboratory transmission experiments (Aeby et al., 2019; Rosales et al., 2020; Meiling et al., 2021; Studivan et al., 2022). It is hypothesized that many of the bacterial taxa found in disease samples represent opportunistic growth of heterotrophs and do not necessarily capture the primary pathogens (Ushijima et al., 2020). It has also been suggested that the white denuded skeleton lesions typically used to characterize SCTLD in the field may represent a late-stage sign of the disease (Aeby et al., 2019). Samples collected earlier in the disease process may facilitate the identification of pathogenic microbes as primary invaders, as well as the ability to quantify the molecular response of the coral to disease, biotic, or abiotic pathogens (Rosales et al., 2020; Traylor-Knowles et al., 2021).

3.4 Considerations in analysis of ‘omics data

At the analysis stage, increased replication in experimental designs has downstream benefits because outliers are more easily removed from a dataset without sacrificing statistical robustness. Initial data visualization tools can be used to identify potential outliers. These include principal component analysis, and the programs: arrayQualityMetrics (Kauffmann et al., 2008) and ANGSD (Korneliusson et al., 2014). Outputs from these programs can then be compared to metrics captured during library preparation and sequencing (e.g., FASTX-Toolkit (Gordon and Hannon, 2010) or Trimmomatic (Bolger et al., 2014)). These metadata can help to remove aberrant samples that may be driving or masking treatment effects in statistical models. Complicated experimental designs, such as those with multiple species or treatments, may also impact robustness through the reduction of replication within groups. An iterative approach may be more useful, where experimental designs are first tested and optimized within a few species, and following success, can be expanded to incorporate other species or treatments. This is especially true for cross-comparisons and meta-analysis of datasets across regions within the Caribbean, where previous experiments have demonstrated substantial variation in disease etiology and susceptibility to SCTLD within Florida and among Caribbean jurisdictions (Aeby et al., 2019; Alvarez-Filip et al., 2019; Estrada-Saldivar et al., 2020; Heres et al., 2021; Meiling et al., 2021). In the case of the ongoing SCTLD outbreak, the adoption of the same designs, approaches, and species for experiments conducted in southeast Florida, the Florida Keys, and the United States Virgin Islands would be extremely beneficial to understand both how SCTLD varies across region.

It would also clarify whether corals are responding to disease exposure using similar molecular mechanisms and cellular responses across their ranges.

4 Moving from ‘omics to biomarkers

Here we will discuss different approaches to biomarker development, and how ‘omics resources can be better exploited to develop biomarker systems. We focus on biomarker development in other fields and identify common strategies that are likely to increase success of biomarker development and validation in corals. Case studies are examined for multiple ‘omics approaches, particularly those that are gaining popularity for use in the coral field.

4.1 Expanding our approaches beyond biomarker development

The ultimate goals of biomarker development for diagnosing coral health are twofold: (1) to rapidly identify indications of disease, and (2) to characterize disease resistance and susceptibility for tailored management approaches that protect vulnerable populations and/or restore resilient coral genotypes. Biomarkers, particularly when implemented in relatively inexpensive, rapid diagnostic tests modeled after those used in human medicine (e.g., rapid COVID-19 at home test, ketone test strips) could offer the ability to quickly identify the potential for infection, and to respond to coral disease outbreaks by conserving and propagating diseaseresistant genotypes. Biomarker development also facilitates the efficient translation of ‘omics datasets into management initiatives by conservation and restoration practitioners. In theory, this would be expected to greatly reduce the amount of time between initial observations of disease signs in the field and subsequent responses to mitigate the impacts of further disease spread. These same diagnostic and response approaches are likely to be successful in responding to multiple stressors beyond infectious diseases (e.g., bleaching, ocean acidification, sedimentation, eutrophication) by allowing the identification of resilient genotypes. Therefore, it is a priority in coral conservation to develop generic biomarkers to broadly assess coral health holistically across a variety of stressors. This will enable high throughput screening of wild and nursery farmed corals to select resilient genotypes that can withstand future climate change scenarios, remain adaptable in response to pollution, and respond to novel disease outbreaks.

Based on the challenges of biomarker development in corals for disease exposure, there is a clear need to develop a consensus of not only what to target (gene, protein, etc.), but also considerations for experimental design and assaying methods as discussed above. And perhaps it would better serve our community to expand outside of what we consider to be a typical

medical biomarker. Below, we explore some areas where biomarkers could be expanded from ‘omics data, and when combined with other techniques, may support the monitoring of and predict the requirements for. It is critical to establish markers that can be used as widely as possible and can encompass the inherent genetic variability that defines many corals’ molecular responses. Additionally, expanding our approaches beyond targeting the coral host towards understanding the other holobiont components in tandem with the coral host may provide additional insight towards biomarker development. Below we discuss some of the other techniques from ‘omics that have promise for biomarker application.

4.2 Early detection and diagnosis of pathogens

A primary focus area of ‘omics applications has been to understand coral disease mechanisms and develop early detection or monitoring systems for disease outbreaks. However, oftentimes late-stage diagnosis is what can be concluded from the collected data. The motivation for using a large-scale ‘omics approach on the coral host is that we can narrow down possible markers for resiliency or tolerance that can then be used in the future for assaying a wider range of corals. This approach appears to be straightforward in theory, but many challenges have been encountered, namely that a universal biomarker for coral stress and/or disease has not been identified because of the inherent variability within coral genetics, the coral holobiont, and the influence of the environment (Traylor-Knowles and Palumbi, 2014; Louis et al., 2017; Parkinson et al., 2020). Results to date have been more successful in identifying biomarkers for pathogenic bacteria, rather than biomarkers in the coral themselves (Ushijima et al., 2020; Rosales et al., 2020). For example, researchers can identify bacteria with strain-level specificity using an Analytical Profile Index (API) strip. The API strip is a common medical diagnostic tool used to quickly identify bacteria of interest. It is stable at room temperature and can easily be modified to identify different bacteria candidates. The API strip has the potential to be used in water monitoring as an early monitoring system for identifying potentially pathogenic bacteria. For example, the VcpA RapidTest was successfully used in coral to identify *Vibrio coralliilyticus* strains associated with SCTLD (Ushijima et al., 2020). While this approach is applicable for identification of coral-associated bacteria, it does not address the coral host, or other symbiotic partners. Additionally, this approach is not without challenges, most coral diseases are not able to fulfill Koch’s postulates, and the few that have reported doing so are still highly debated (Nagelkerken et al., 1997; Geiser et al., 1998; Richardson et al., 1998; Richie and Smith, 1998; Patterson et al., 2002; Ben-Haim et al., 2003; Pantos et al., 2003; Sussman et al., 2008; Sutherland et al., 2011; Kellogg et al., 2013; Lesser and Jarett, 2014; Pollock

et al., 2017). Expanding this approach to also include testing coral lipids, mucous sugars, or coral tissue antioxidant levels could be a valuable tool for assessing coral health to supplement bacterial monitoring (Harriott, 1993; Mydlarz and Palmer, 2011; Seemann et al., 2013; Lee et al., 2016). Additionally, creating approaches to address different partners of the holobiont including Symbiodiniaceae and other microbial partners may generate a more holistic diagnostic tool that can be useful for coral biomarker development, validation, and screening.

4.3 Cellular approaches in combination with 'omics

The most classical approach to examining cellular aspects of disease has been to use histology. It is a downstream tool that can be compared to changes observed in the transcriptome, metabolome, and proteome. Histopathological studies can encompass both morphological and functional changes of cells and tissue in response to disease. Previous research on coral disease histology have revealed changes in the structural arrangements of cells and tissues, indicating functional impairments of both the coral host and associated endosymbionts (Work and Meteyer, 2014; Aeby et al., 2019). It is a valuable tool because it can reveal the physical location of suspected infectious pathogenic microorganisms responsible for coral diseases, be it the coral host or members of the complex microbiome (Peters, 2015). Knowing the physical location of an infection can help with the disease etiology and future intervention efforts (Work and Meteyer, 2014). Histopathology can also be useful as a screening tool to explain different coral disease pathologies. For example, visual signs of disease on corals can look very similar to the naked eye, especially in the field, but at a tissue level the pathologies can be very different. Using histology, one can differentiate between diseases by examining the cellular aspects to interrogate changes in the tissue integrity, cell death, and presence of bacteria, among many other traits (Work and Meteyer, 2014). In addition to histology, other tissue focused techniques can be used. For example, a tool called microdissection has been used to confirm histological observations; using this technique microorganisms can be dissected and sequenced directly from the preserved coral sample (Ainsworth et al., 2015). Reliance on molecular markers or deep sequencing alone can result in attribution of diseases to microorganisms or viruses identified in diseased tissue that are either secondary invaders or bystanders in the environment (Hewson et al., 2014). These types of challenges are more likely to be avoided if a variety of techniques are used, including cellular observations that can be correlated with 'omics outcomes (Work and Meteyer, 2014).

Additionally, incorporation of other classical cell biology techniques, such as cell culture and in situ hybridization, as well as contemporary cellular techniques, such as fluorescent

activated cell sorting (FACS) and single cell sequencing (SCS) technologies, promise to be informative for our understanding of coral disease. Cell culture techniques can be used to isolate specific coral host cells or specific microbial partners to examine their function and behavior *ex vivo*. This is a valuable tool because functional assays can be quickly developed and deployed on live cells that are not accessible using the whole coral organism. In situ hybridization is used to examine the spatial gene expression within tissues. This can be done for any stressor but has traditionally been used in coral biology to examine developmental stages (Traylor-Knowles et al., 2017; Traylor-Knowles, 2018). This method is useful because it can show you what cells are expressing a particular gene, and where those cells are located (Traylor-Knowles, 2018). FACS, while not a new technology in human medicine, is relatively new to use in corals (Rosental et al., 2017; Snyder et al., 2020; Snyder et al., 2021). Using this technology, functional cell markers that are nonspecies specific can be used to identify and quantify the function of different cell populations. It can also be used to collect specific cell populations which can then be sequenced, preserved for microscopy, or grown in cell culture (Rosental et al., 2017; Snyder et al., 2020). SCS encompasses many different types of 'omics targets and can be useful for isolating the function of different cells. Cell atlases can be developed and using functional markers, specific cell populations can be isolated and sequenced (Seb  -Pedr  s et al., 2018; Levy et al., 2021). Using these methods, more targeted biomarkers can be developed that can eventually be species-specific, where in combination with proteomics, peptides for specific markers can be discovered and used as a diagnostic tool that would be useful for understanding disease progression.

4.4 Multiomics approaches

Here we discuss different 'omics approaches that could be incorporated into research on the immune response during disease. Much of the previous work highlighted uses gene expression for biomarker development. While this has been useful, expanding beyond this may give us a more holistic understanding and therefore better equipped to develop informative biomarkers for coral disease.

4.4.1 Proteomics

On its own, proteomics can provide information on the extent of overall peptide expression within a sample, but when combined with other genomic and transcriptomic approaches, proteomics then offers a glimpse into how corals directly respond to disease through changes in protein expression and post-translational modifications. Consequently, while currently limited by the amount of proteomic data available for nonmodel

organisms like corals, its applications within coral disease will continue to grow as the method is used in conjunction with the other technologies. For example, in the most recent reports including that for *O. faveolata* (Mayfield et al., 2021), *Pocillopora. acuta* (McRae et al., 2021), *P. lobata* (Tisthammer et al., 2021), and *P. carnososa* (Wong et al., 2021), peptide identification and annotation benefited from available or developed transcriptomic data for those associated species. In the future, as whole genomes become more available for those and other species, the process could be further improved as transcriptomic data becomes better annotated (Liew et al., 2016). This would subsequently support the associated proteomic analyses by more confidently identifying each peptide, thereby effectively overcoming a current annotation limitation in some analyses.

While the above example highlights the connectivity within the 'omics sciences, results can sometimes be obscured by the complex holobiont community within corals (Vega Thurber et al., 2020). Consequently, it is not just coral genomics or proteomics, but rather an entire suite of tools that will be needed to fully understand coral disease etiology. For example, the protein-expression information from proteomics could help identify peptides associated with a specific coral disease (Garcia et al., 2016; Ricci et al., 2019). Additionally, many tools have been previously developed for deconvoluting microbiome data and have the potential to be modified to use on coral holobiont datasets (Carr et al., 2013; Meyer et al., 2018). By developing antibodies for those peptides, further immunohistochemical and microscopic analysis can be performed and potentially offering new insight into the peptide's cellular expression patterns, timing, and locations (e.g. Mass et al., 2014).

4.4.2 Metabolomics

Metabolomics is representative of changes in metabolite function in response to a specific stressor. Measurement of exogenous or endogenous metabolites in a particular physiological or developmental state, termed metabolomics, is an emerging field in coral biology and not yet as established as genomics even in the field of human cancer biomarker discovery (Bailey et al., 2018). Despite the emerging nature of this technique in human medicine, metabolic disorders can easily be measured using metabolite screening and treatment strategies for bacterial infections can be quickly diagnosed using mass spectrometry approaches (Dénes et al., 2012; Sun et al., 2012). Metabolomics has promise for coral disease research because of its direct application for biomarker development.

Relatively little is understood about coral metabolomes (Garg, 2021); however, we do know that the genetic background of the host, the endosymbionts, the microbiome, and the current and historical environment all contribute to variability in metabolomic patterns (Sogin et al., 2016; Lohr et al., 2019; Garg,

2021). If we want to use metabolomics for coral disease biomarker development and to tailor treatment approaches, we first need to be in "data collection" mode. Unique and shared pathways need to be defined among different coral genera while taking into account differences in seasons, bleaching history, coral spawning, genetic background of both the coral host, the endosymbionts, and the differences in the associated microbiome (Garg, 2021). We then will be able to query whether the unique metabolic pathways shift during a pathogenic infection and better define disease status. Lastly, we need to determine the source of these pathways: the host, the endosymbiont, the microbiome, effects from the environment, or a combination of the above (Garg, 2021). Most coral metabolic studies are done on a slurry of tissue that is composed of the coral host and all of its endosymbiotic partners (Garg, 2021). Together, the coral host and endosymbiotic partners represent many sources of confounding factors that can lead to variation in interpretation of the metabolomic profiling. Due to this, data from healthy corals maintained in nurseries, data from controlled laboratory experiments, and data from different species of corals and timepoints provide a valuable resource for the removal of these confounding factors.

Alternatively, multiomics approaches, wherein the genetic background of the host, the microbiome profiles, the variability in endosymbionts paired with metabolome, proteome and transcriptome analysis can enable grouping of variation by its source. We know from previous studies that coral genotypes have unique metabolomes, and that fragments of the same genotype have conserved metabolomes, highlighting the importance of knowing the genotype prior to investigation (Lohr et al., 2019). Visualization of spatial variation in 'omics data can further enable delineation of source of variation (Little et al., 2021). Together, multi-genotype experiments that use multiomics approaches will enable the development of a knowledge base to stratify corals in terms of disease resilience and holobiont composition to enable biomarker evaluation, and linkage of specific pathways in disease (Muller et al., 2018; Miller et al., 2019).

4.4.3 Holobiome

In abiotic stressors such as thermal stress, Symbiodiniaceae has been used as a marker for stress tolerance. Corals harboring Symbiodiniaceae that are less susceptible to thermal stress will not bleach as easily as corals possessing highly susceptible Symbiodiniaceae. Different Symbiodiniaceae taxa have different thermal tolerances and Symbiodiniaceae switching is known to be a critical strategy for coral survival (Silverstein et al., 2014; Baker, 2004; Cuning et al., 2018). Additionally, the bacterial microbiome of corals has been used as a proxy for health, where the more severe the stress is, the higher beta diversity is observed (Zaneveld et al., 2017). In biotic diseases

such as WBD, this same pattern was observed indicating that the bacteria have the potential to be a useful marker for stress (Rosales et al., 2019; Rosales et al., 2020). Within SCTLD, evidence is mounting that the Symbiodiniaceae may harbor or interact with the pathogen(s) that are causing this deadly disease (Work et al., 2021; Veglia et al., 2022), and that the type of Symbiodiniaceae may affect susceptibility to SCTLD (Dennison et al., 2021). While we know that not all diseases are alike, it is important to consider the relationship of the Symbiodiniaceae communities along with the coral host, as the interactions are so tightly linked. By not examining this, we may be missing critical pieces of information including more context to the overall host reaction.

4.4.4 Epigenetic approaches

Environmental epigenetics is a burgeoning field that seeks to unveil the mechanisms that drive gene expression changes without changing the DNA sequence (Bollati and Baccarelli, 2010). Given the major pressure of anthropogenic activities such as increasing sea surface temperatures or eutrophication, these tools are starting to be applied to scleractinian corals to understand both phenotypic plasticity as well as role of transgenerational non-mendelian inheritance (Bollati and Baccarelli, 2010; Rodriguez-Casariago et al., 2018; Rodriguez-Casariago et al., 2020). Although the studies on corals are emerging, new genomic approaches that combine high throughput bioinformatics and single cell technology have opened new opportunities to examine a broad range of epigenetic modifications (e.g., DNA methylation or histone modification) (Eirin-Lopez and Putnam, 2019; Zhao et al., 2020; Cowen and Putnam, 2022). With the continual improvement of current coral genome models and the ever-growing availability of new coral 'omics data, using epigenetic tools such as Assay for Transposase-Accessible Chromatin with high-throughput sequencing (ATAC-seq) is becoming more accessible. ATACseq has already been used on *Exaptasia pallida*, a sea anemone model used to study cnidarian/algal symbiosis but has not yet been applied to the study of coral disease (Weizman and Levy, 2019). In corals, emerging epigenetic tools will be critical for better understanding the diverse phenotypic outcomes in response to disease within and between genotypes.

4.4.5 Ecological approaches: Monitoring and 'omics

Ecological approaches including (1) ecological monitoring of the reef biodiversity, (2) environmental monitoring in conjunction with 'omics sampling, and (3) uses of environmental DNA (eDNA) to monitor DNA in the context of a changing environment can be and have been used as "biomarker" systems. Ecological monitoring to determine the overall biodiversity of a reef system is a proxy for overall reef condition (Kramer, 2003;

Rogers, 2013; Diaz-Pérez et al., 2016). This process is usually focused on monitoring the physical state of the reef, environmental monitoring, and coral reef biodiversity but it can incorporate 'omics approaches including gene expression, protein expression, and recently eDNA monitoring (West et al., 2020). Previous work on environmental monitoring in conjunction with 'omics sampling has primarily focused on thermal stress (Barshis et al., 2013; Kenkel et al., 2013; Kenkel et al., 2014;

Palumbi et al., 2014; Anderson et al., 2016; Davies et al., 2016; Wright et al., 2019; Dixon et al., 2020; Studivan et al., 2021), freshwater discharge (Edge et al., 2013; Mayfield et al., 2013; Aguilar et al., 2017; Aguilar et al., 2019), and synergistic stressors (Wright et al., 2019; Studivan et al., 2021). These environmental stressors can promote the development of disease in reef organisms and reduce reef biodiversity. Several of the previous studies also incorporated genotypic factors into experimental designs using colony fate-tracking or reciprocal transplants, allowing comparisons of genotype x environment impacts on molecular processes. These efforts to monitor wild corals' responses to environmental variability are extremely useful, especially to characterize 'normal' behavior and common responses to multiple stressors but are also time consuming in terms of experimentation and field monitoring, validating the findings, and downstream analysis. Recently, the method of eDNA monitoring has developed into a potentially useful way of monitoring biodiversity (Leray and Knowlton, 2015; Formel et al., 2021). eDNA is a metabarcoding method to detect and quantify multiple types of DNA from environmental samples including water samples (Beng and Corlett, 2020). While this technology still has many challenges including issues with assigning taxa, and incomplete detection, it is currently being developed for use on coral reefs, in conjunction to in-person monitoring practices (Leray and Knowlton, 2015; West et al., 2022). eDNA promises to aid in the discovery of novel species on coral reefs and lead to a more comprehensive picture of reef condition (Leray and Knowlton, 2015; West et al., 2022).

4.4.6 Use of artificial intelligence and machine learning approaches

The utilization of specific biomarkers will be directly connected to the development of economically scalable tools that can accurately diagnose or predict coral health. The level of vast complexity in corals calls for an evolution within research institutions that perform these post-genomic investigations to consider the integration of modeling or machine learning tools for enhanced predictive capacity. Research groups performing 'omics investigations have the computational familiarity that is suitable to evolve into adopting machine learning and modeling tools to better understand 'omics data. These tools are being developed and innovated in human research and have seen

successful application within coral research as well (Hartmann et al., 2017; Mallick et al., 2019; Lima et al., 2020). Human cancer research has integrated gene expression research to identify biomarkers specific to types of cancer, tumor growth patterns, and even the stage and location of cancer (Henry and Hayes, 2012). This research has allowed for predictive modeling in disease and healthy individuals that are at risk among populations (Duan et al., 2005; Kourou et al., 2015; Meyer et al., 2021). Advances in human medical research provide theoretical and technical tools that can be leveraged to achieve overlapping goals in coral research.

The opportunity to forecast bleaching susceptibility from machine learning that utilized proteomic data has already been successfully demonstrated (Mayfield, 2022). Another approach is trait-space modeling, which uses hierarchical clustering and random forest analysis to identify traits that are the most predictive of survival or susceptibility (Darling et al., 2012). This approach is scalable as metrics of microbial ecology, gene expression, immune assays, life history strategies, and other parameters can collectively be compared and ranked for their predictive potential of coral survival. By identifying the metrics that predict survival, these biomarker candidates can be expanded to the broader population. Machine learning and novel computational biology programs can help interpret complex 'omics datasets to identify a set of genes or microbial targets ideal for biomarker development. The potential of this has been recognized by leading conservation organizations, such as National Oceanic and Atmospheric Administration (NOAA), whose strategic plans are explicitly allocating funds to develop machine learning pipelines (LeBoeuf et al., 2021). The untapped use in machine learning and modeling has the potential to help provide clarity to complex 'omics datasets and have the potential to aid in the discovery of less variable biomarkers (MarcosZambrano et al., 2021).

5 Future applications

In this review, we discussed what we have learned about coral immunity using 'omics during disease outbreaks, how 'omics experiments can be designed to address these immunological questions, and how to move beyond 'omics to biomarker development, with an emphasis on broadening our definition of what a biomarker may be. However, in compiling this review, we reflected on how and why we got here as a community and identified the many potential future directions and research needs. Here we will discuss these opportunities and describe the priority needs for furthering our understanding of coral immunity and disease outbreaks.

5.1 The need for fast decision-making, coordination, and infrastructure

As a community, we know that there will be another disease outbreak. So we need to be prepared. However, to be ready, this will require infrastructure and coordination. A great example of coordination is the Disease Advisory Committee (DAC), which was started to engage different stakeholders and communities to discuss science quickly and to disburse funding to help push research forward more quickly when the south Florida SCTLD outbreak was recognized (Florida Coral Disease Response Research & Epidemiology Team, 2018). There have been many successes with the development of the DAC including more communication in the coral disease community, engagement, and interaction of scientists in different professional sectors, and funding to support small- and large-scale coral disease studies. This large-scale coordination has helped to promote a lot of important coral disease science that had direct conservation applications. These successes have required a lot of effort, coordination, and funding to be achieved, but despite these big successes, there are still some challenges. For example, with the speed at which coral diseases spread, the ability to get funding dispersed and sample collection permits obtained can lag behind the ecological threat. Coordinating different professional sectors can also be challenging which can inadvertently slow down progress.

As a community, we need the ability to pivot quickly and respond to these new threats and most importantly be prepared before the threat occurs. Ways in which we can be better prepared include developing dedicated facilities and staff that will oversee responding to these threats as well as provide training and facilities for investigation when the disease outbreak occurs. Additionally, a coordinated strategy to establish and maintain a tissue bank for reference samples to be shared and preserved would be beneficial. Lastly, 'omics research produces a lot of data, and these data would ideally be shared openly and quickly. There have been many previous efforts to share coral 'omics data through the development of many different databases (Traylor-Knowles et al., 2011; Sun et al., 2013; Liew et al., 2016; Zhang et al., 2019), however these databases require long term support and upkeep. Development of facilities to maintain such resources would benefit the coral research by streamlining resources and creating less redundancy.

5.2 Further integrating coral immunity into disease outbreak response

In this review we described what is known about the coral immune response during disease and identified areas of overlap between different diseases that include many important signaling

pathways and immune receptors. However, translation of these mechanisms into what it means for coral health needs to be would need further development. For example, the range of a normal immune response in many coral species is still not well understood, and so translating these findings into effective biomarkers can be challenging. How the range of a normal immune response interacts with changes in the environment and microbiome disruption are still not well understood but will have big implications for our understanding of coral disease mechanisms. There is also a gap in linking these ‘omics outcomes with cellular pathologies observed during disease outbreaks. We propose that coordinated efforts to correlate immune metrics into existing metrics of coral health will be informative and useful for future conservation applications. Lastly integrating the effects of coral disease treatments on the immune response will also be informative, as many wild corals are currently being treated with antibiotics and probiotics. The long term effects of these treatments is not known and therefore warrants active long-term monitoring.

Conclusions

The use of ‘omics as a tool for studying the coral immune response to disease is powerful and has potential to push forward our understanding of resilience in corals. Quick and coordinated sampling and experimental design efforts, expanding our ideas on how we think of and develop biomarkers, and a better understanding of overall coral immune health will all be essential for us to respond to current and future disease outbreaks. Lastly community efforts to standardize, preserve, and openly share data would be beneficial.

Author contributions

NT-K designed the overall concept for this review and led the discussions. AH designed Figure 1. ECP provided the pictures for Figure 2. All authors contributed to conceptualization, writing, and editing of the manuscript. All authors contributed to the article and approved the submitted version.

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