A review of asteroid biology in the context of sea star wasting: possible causes and consequences

RH: The biology of sea star wasting

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Abstract

Sea star wasting – marked in a variety of sea star species as varying degrees of skin lesions followed by disintegration – recently caused one of the largest marine die-offs ever recorded on the west coast of North America, killing billions of sea stars. Despite the important ramifications this mortality had for coastal benthic ecosystems, such as increased abundance of prey, little is known about the causes of the disease or mechanisms of its progression. Though there have been studies indicating a range of causal mechanisms, including viruses and environmental effects, the broad spatial and depth range of affected populations leaves many questions remaining about either infectious or non-infectious mechanisms. Wasting appears to start with degradation of mutable connective tissue in the body wall, leading to disintegration of the epidermis. Here, we briefly review basic sea star biology in the context of the sea star wasting syndrome and present our current knowledge and hypotheses related to the symptoms, the microbiome, the viruses, and associated environmental stressors. We also highlight throughout the article knowledge gaps and the data needed to better understand sea star wasting mechanistically, its causes, and potential management.

Introduction

In the past decade, sea stars (Echinodermata: Class Asteroidea, "asteroids") have been confronted with a pandemic that has gained increasing attention because of the severity, taxonomic breadth, and geographic extent of the disease. Previously referred to as sea star wasting disease (SSWD), sea star wasting syndrome (SSWS), asteroid idiopathic wasting syndrome (AIWS), or just sea star wasting (SSW), the nomenclature points to a suite of signs observed across a broad range of species that, in the most severe cases, result in death following disintegration of the star (Hewson *et al.*, 2018). Although species-specific variations exist, wasting sea stars generally exhibit modified behavior, such as lethargy and disinterest in nearby prey, pronounced body wall lesions, and arm autotomy (Figure 1; Eisenlord *et al.*, 2016, Kohl *et al.*, 2016, Menge *et al.*, 2016, Jaffe *et al.*, 2019).

While the primary SSW event that is often referred to in current discussion – emerging on the Pacific coast of North America in 2013 – is the most extreme documented example, prior asteroid wasting events matching this general description have been periodically observed, with the first known reported over a century ago (Mead, 1898). Over the years, wasting has been noted independently across many sea star species globally, often with regional mortality, including the North American Pacific (Dungan *et al.*, 1982, Eckert *et al.*, 2000, Konar *et al.*, 2019), and Atlantic coasts (Sieling, 1960, Tiffany, 1978, Menge, 1979, Bucci *et al.*, 2017), Mediterranean Sea (Staehli *et al.*, 2009), Atlantic coast of Europe (Thorpe and Spencer, 2000), East China Sea (Suzuki *et al.*, 2012), Yellow Sea (China), and Port Philip Bay, Australia (Hewson *et al.*, 2019). Importantly, most earlier events targeted only a few species in an area. For example, in the summer of 1978, populations of *Heliaster kubiniji* (sun star) suffered massive mortality in the Gulf of California rocky intertidal zone. The outbreak reduced abundance of *H. kubiniji* from dense aggregations to near-zero values at sites throughout the Gulf of California in just a few weeks (Dungan *et al.*, 1982); there was similarly high intertidal mortality in the smaller high intertidal sea star *Othilia tenuispina*, but this species rebounded in numbers quickly. At least four co-occurring species of subtidal sea stars were reportedly unaffected. The event was coincident with exposure to warmer waters in the intertidal (Dungan *et al.,* 1982). In contrast, the occurrence of SSW in the past decade has profoundly affected more than 20 species of sea stars in the northeastern Pacific and other sites– from intertidal to deeper waters, from Baja California to northern Gulf of Alaska, and beyond (Dawson *et al.*, this issue). In this sense, the current prevalence of wasting is among the most geographically and taxonomically widespread diseases of invertebrates ever recorded.

Many asteroids are top level consumers with direct effects on the structure and function of benthic ecosystems (Menge *et al.*, 1994, Vicknair and Estes, 2012, Schultz *et al.*, 2016, Burt *et al.*, 2018). Indeed, the concept of keystone species was first developed from work on populations of the predatory *Pisaster ochraceus* in the Pacific Northwest (Paine, 1966). When present, *P. ochraceus* consumes the dominant encrusting invertebrate species, thus freeing up space for other sessile macroinvertebrates and algae (Feder, 1959, McClintock and Robnett, 1986, Robles *et al.*, 2009, Lafferty and Suchanek, 2016). Other asteroid species function similarly, sometimes at different size scales (Gravem and Morgan, 2017). In addition to direct predation, some asteroids have important indirect effects by altering prey behavior (Duggins, 1983, Rogers *et al.*, 2018, Kay *et al.*, 2019, Murie and Bourdeau, 2019). Sea stars also directly compete for marine resources with other high-level consumers (Traiger *et al.*, 2016), and can have substantial effects on aquaculture and restoration endeavors (Silina, 2008, Miyoshi *et al.*, 2018, Wilcox and Jeffs, 2019).

Along with the key ecosystem functions of many echinoderms, mass mortality events can generate cascading effects, ranging from temporary local disruptions to long-term ecological phase shifts (Lessios *et al.*, 1984, Burge *et al.*, 2014, Miner *et al.*, 2018). Mass mortality events affecting critical foundation species, ecosystem engineers, or keystone species have been coined ‘marine disease emergencies’ due to the detrimental, and sometimes irreversible, series of events that often succeeds them (Miner *et al.*, 2018). A textbook example of coincident marine disease events with profound ecological effects started with mass die-offs of the sea urchin *Diadema antillarum* that resulted in overgrowth of algae on coral reefs (Lessios *et al.*, 1984) and the subsequent mass mortality through a variety of causes of *Acropora* corals led to complete physical restructuring of Caribbean coral reefs (Hughes, 1994, Hughes *et al.*, 2003, Cramer *et al.*, 2020). Notably, all of these changes promote increasing prevalence of microbial and algal nutrient cycles, a feature of many recent climate-driven shifts leading to eutrophication of marine ecosystems (Petraitis and Dudgeon, 2020).

In this context, recent mass mortality events affecting asteroids threaten the health of coastal ecosystems and additional understanding is needed to manage or mitigate them. As stated above, the most recent SSW event has differed markedly from prior events in their geographic and taxonomic extent. This epizootic killed many billions of asteroids across over 20 taxa (indeed, billions are estimated to have been lost in a single species alone; e.g., *Pycnopodia helianthoides* (Gravem *et al.*, 2021)), primarily along the Pacific coast of North America where the coastal community is regularly monitored, and is considered to be among the most geographically widespread disease events to sweep through marine wildlife in documented history (Gudenkauf and Hewson, 2015, Eisenlord *et al.*, 2016, Hewson *et al.*, 2018). SSW has been forecast to reshape community structure throughout the region (Menge *et al.*, 2016, Gravem and Morgan, 2017) and due to its broad taxonomic effect, is considered a risk for other coastal communities globally (Hewson *et al.*, 2019).

Unfortunately, there is a deficit of fundamental knowledge surrounding the etiology, pathogenesis, and epidemiology of SSW, reflected in the sparse and discontinuous literature on the subject. Thus, in an attempt to generate the framework for a cohesive narrative on SSW for future reference, the aims of our review are to: (1) provide a relevant review of normal sea star biology, anatomy, and physiology in the context of the common outward signs of SSW in affected sea stars and what we have learned, (2) highlight our understanding of the biotic factors associated with wasting including microbial and viral interactions, (3) identify crucial gaps in our understanding of the symptoms and progression of SSW, and (4) point to forthcoming research and point to forthcoming research designed to further our understanding of SSW.

We begin by considering the basic biology of sea stars. Our goal in this first section is to establish which anatomical systems may be initially or overtly affected by SSW, in a way that informs not only the recent and unprecedented mass mortality event, but also prior historical examples. Our paper then reviews each of these organismal systems for indicators of cause or response to SSW.

Asteroid biology as context for SSW

In this section, we review some basic elements of sea star biology to introduce unique aspects, traits, and physiology that come into play – across large phylogenetic breadth (Schiebelhut *et al*, this issue) – when these animals succumb to SSW. The ecological consequences noted above are intertwined with both the density and distribution of sea stars as well as the broadly defined traits that are affected by SSW. Sea stars are widely distributed throughout the world's oceans. They are stenohaline and occur from the deep sea to intertidal zone, and from tropical to polar waters (Binyon, 1961, Gage and Tyler, 1991, Byrne *et al.*, 2017). Across this extensive range, local species richness is highly variable (Cintra-Buenrostro *et al.*, 2005, Iken *et al.*, 2010), with diversity driven by many environmental and ecological factors. Local diversity can encompass deep phylogenetic divergences, as often dozens of genera and several families can be found within any ecoregion (*sensu* Spalding *et al.*, 2007) – this is key because observed effects of SSW affect such great diversity of sea star species (see accompanying papers in this issue) with vastly different life histories and diets (VanVeldhuizen and Oakes, 1981, McClintock *et al.*, 2008, Lawrence, 2015, Martinez *et al.*, 2017, Pratchett *et al.*, 2017).

The size, density, and distribution of sea star populations are highly variable through time (Uthicke *et al.*, 2009), but they are not always closely monitored in the absence of clearly identified economic consequences (Hewson *et al.*, 2019). Nevertheless, demographic variation in sea star populations is associated with recognizable ecological responses such as overgrowth by mussels in the absence of sea star predation (Paine, 1966, Gravem and Morgan, 2017, Kay *et al.*, 2019). Some distributional patterns are difficult to track because they comprise multiple cryptic species. For instance, species of the *Acanthaster* complex are found throughout tropical waters and can form high-density feeding fronts that devastate coral reefs (Pratchett *et al.*, 2017), but the individual *Acanthaster* species and their distributions remain uncertain (Haszprunar *et al.*, 2017). Similar problems have been noted in the taxonomy – and thus the precision in evaluating disease effects – of other asteroid genera (Melroy and Cohen, 2021). What is important about these components of phylogenetic diversity and potential density-dependent effects is not yet clear, but if we are to understand the apparent transmissibility of SSW (Hewson et al. 2014) then we must know how and whether the health of any sea star in an ecosystem is predictive of the health of other individuals, both conspecific and across the phylogeny of asteroids (Schiebelhut *et al.,* this issue). Whether SSW is primarily driven by infectious or non-infectious etiologies is still unclear – and disease etiology likely involves complex interactions – but the broad taxonomic effect indicates the shared traits of sea stars could be a first target for clues into mechanisms of pathogenesis.

Body plan and life history

Echinoderms possess four main features that distinguish them from other metazoans: their calcareous endoskeleton composed of ossicles of varying sizes, a water vascular system, mutable collagenous tissues, and pentaradial body organization in adults (Hyman, 1955, Sloan, 1980, Jangoux, 1982, Blake, 1989, Chia and Koss, 1994, Byrne, 1999, Mooi and David, 2000, McEdward and Miner, 2001, McEdward *et al.*, 2002, Byrne, 2013, Lawrence 2013, Mercier and Hamel, 2013, Martinez *et al.*, 2016). The present-day global asteroid fauna includes approximately 1,900 species in 37 families (Mah and Blake, 2012, Feuda and Smith, 2015, Byrne *et al.*, 2017, Linchangco Jr *et al.*, 2017).

Asteroid life histories have been studied across diverse taxa (Strathmann, 1985, Chia *et al.*, 1993, McEdward and Miner, 2001, McEdward *et al.*, 2002, Byrne, 2013), though most such studies are biased towards those taxa that are most available near prominent marine research facilities. Most species are dioecious free-spawners that release their gametes into the water column for fertilization, followed by development of a planktonic larva (Emlet *et al.*, 1987), and then metamorphosis and settlement back to the sea floor. Some species deposit eggs that adhere to rocks on the shore and have benthic development (Chia, 1968, Byrne, 1995). Other asteroids retain their eggs in brood chambers on or within the body cavity (Chia *et al.*, 1993, McEdward and Janies, 1993). Variation in reproductive strategies such as these may influence the capacity of a species to recover from mass mortality events. There does not appear to be a close link between larval dispersal and SSW (Schiebelhut *et al*, this issue), and it is still unclear if early life stages are susceptible to – or could transmit - the disease.

Surface and skeleton

The breakdown of the body surface and its integrity is a feature of SSW, and so an understanding of these tissues is important for understanding the disease. The surface of a sea star is one of the more complicated types of external barriers in the Metazoa. The surface can be covered by abundant spines, or have no spines in species with a thick, soft epidermis (e.g., *Dermasterias imbricata*). The surface consists of an external columnar epithelium (containing secretory cells, supporting cells, sensory cells, and glandular cells). The epithelial cells are covered by a thin cuticle that is only visible microscopically (McKenzie and Grigolava, 1996). The body wall connective tissue has mutable properties (MCT - mutable connective tissue), is capable of reversible rapid changes of tensile strength from stiff to viscous, is under neural control, and is mediated by proteinaceous neurotransmitters (for review see Wilkie, 2002, Barbaglio *et al.*, 2013). Ossicles composed of magnesium calcite are embedded in the MCT and form the endoskeleton. This internal calcareous skeleton is considered a synapomorphy of the echinoderms (but see Cameron and Bishop, 2012).

In sea stars, MCT is found in the body wall dermis, spine joint ligaments, and in the epithelial cells of the tube feet (Motokawa, 1986, O'Neill, 1989, Santos *et al.*, 2005, Motokawa, 2011), and is composed of spindle-shaped collagen fibers in a proteoglycan/glycosaminoglycan matrix to which they are covalently bound (Motokawa, 1982, O'Neill, 1989, Trotter and Koob, 1989, Wilkie *et al.*, 1992, Erlinger *et al.*, 1993, Barbaglio *et al.*, 2012). Cells in the MCT include immune cells, nerve cells, and juxtaligamental cells that are unique to the MCT. The juxtaligamental cells are recognized by their possession of dark granules which are thought to have effector molecules involved in the nervous system innervation of MCT (Wilkie, 1979, 2002).

The coelomic cavity is a hemocoel lined by a layer of myoepithelial, secretory, and supporting cells. This epithelium tissue also forms the papulae that project through the thick body wall and into the overlying sea water. Papulae are covered both externally and internally by the two epithelial layers noted above; however, the intervening connective tissues between the epithelial layers are greatly thinned (Hyman, 1955, Cobb, 1978). Papulae also can be retracted in recessed “pockets” with the use of muscles and cavities at the base of the papula, or they can be extended quickly above the surface by relaxation of the muscles and diversion of the fluid contents of the perivisceral coelom into the papular lumen. Papulae function in oxygen exchange and waste disposal (Binyon, 1972, Cobb, 1978).

Pedicellariae are small pincer-like compound ossicles covered by epithelium and controlled by muscles. Pedicellariae are found primarily on the aboral body surface, and function in removal of small particulates or fouling organisms that settle on the body wall (Campbell and Rainbow, 1977, Ruppert, 2004), defense (Jensen, 1966, Chia, 1969, VanVeldhuizen and Oakes, 1981), aggression (Menge and Menge, 1974, Wobber, 1975), and prey capture (Robilliard, 1971, Chia and Amerongen, 1975, Hendler and Franz, 1982, Dearborn, 1991, Emson and Young, 1994, Lauerman, 1998).

On the ventral side of the sea star, the centrally-located mouth faces the benthos. Ambulacral grooves bearing the tube feet radiate from the oral surface to the ends of each arm; the highly distensible tube feet enable locomotion and prey capture. These may have terminal adhesive suckers for attachment or be pointed in species that burrow in soft sediments (Paine, 1926, Smith, 1937). Paired ambulacral ossicles (skeletal elements) form an arch-like arcade spanning the entire arm and overlaying the water vascular canal and tube feet that project into the ambulacral groove.

Nervous system

The nervous system organization reflects the pentaradial symmetry and is composed of a circumoral nerve ring from which the radial nerve cords originate that run along the arms just internal to the ambulacral grooves. At the end of each arm, the radial nerve cord connects with the ocelli of the eye spot, which is a phototactic sensory organ. The nervous system is divided into ectoneural and hyponeural systems which are separated from one another by a thin connective tissue layer (Hyman, 1955, Cobb, 1987). The ectoneural system is mainly associated with sensory and motor components. The hyponeural tissue is considered to be exclusively motor and comprises the thinner inner layer of the radial nerve cords (Cobb, 1987). Perception of physical and chemical change in the environment influences hormonal and immune responses in echinoderms (Hamel *et al.*, 2021). Autotomy itself is a component sign of SSW; it is a complex behavioral response and can be induced by a number of diverse stressors (Alupay, 2013, Mladenov *et al.*, 1989; Byrne et al., 2019). For this reason, much research has focused on how autotomy and nerve regeneration interplay, but the details remain elusive (Byrne, 2020).

Digestive system

Sea stars have a complete digestive system. The mouth located toward the substrate is surrounded and controlled by a peristomial membrane. The mouth is connected to a short esophagus that leads to the cardiac stomach (Anderson, 1954, 1959). Sea stars can often evert their cardiac stomach to catch and digest their prey and retract the stomach afterward (Semmens *et al.*, 2013, Tinoco *et al.*, 2018). The cardiac stomach is separated from the pyloric stomach by a slight constriction and the pyloric stomach reaches the anus via a short intestine. The pyloric stomach also connects via a pyloric duct to a pair of pyloric caeca in each arm. These pyloric caeca, which consist of complex, ramified evaginations, have been described as the most important parts of the gut (both in volume and function) in asteroids (Binyon, 1972). Pyloric caeca provide the majority of digestive enzymes and also absorb and store nutrients (Ferguson, 1969). Their structures have been well described in *Asterias forbesi* and *Marthasterias glacialis* (Anderson, 1953, Martinez *et al.*, 1989). The connection between the digestive system and SSW is unclear. Sunflower stars (*Pycnopodia helianthoides*) in captivity that are fed a regular diet will only seem to refuse food when they are in poor condition – such as suffering from a wound – or otherwise stressed, such as shortly after collection. However, stars of this species have been observed to feed even when exhibiting early signs of ultimately fatal cases of SSW (J.H., unpublished)

Coelomic system

As is typical of echinoderms, asteroids have a hydraulic system known as the water vascular system, used for locomotion as well as particle transportation. This system consists of a central ring canal that connects with the radial canals which in turn connect with the tube feet. In asteroids, the stone canal connects the water vascular system with environmental water at the sieve plate called the madreporite (Hyman, 1955, Ferguson and Walker, 1991). Tube feet are connected to the radial canals through ampullae that can contract or relax to move water in each tube foot.

Within the body and surrounding all organs, including the water vascular system components, is the perivisceral coelom. The concentrations of electrolytes (Binyon, 1962, Stickle and Denoux, 1976, Held and Harley, 2009, Wahltinez *et al.*, 2019), amino acids, and ammonium (Diehl and Lawrence, 1984) in coelomic fluid are not substantially different from those in seawater (Binyon, 1962). Tube foot activity depends on the water vascular system and seems to be maintained by an active transport of potassium leading to an osmotic influx of water directly through their walls (Prusch and Whoriskey, 1976, Ferguson, 1990). While sea stars are osmoconformers, they are partially able to regulate coelomic fluid volume (Pearse, 1967, Ellington and Lawrence, 1974) though the mechanism remains unknown.

The hyponeural coelom runs parallel to the water vascular system from the madreporic ampulla to the lateral canals. The hyponeural coelom surrounds the vertical axial hemal canal, the hyponeural hemal ring, and the radial and lateral hemal vessels. The hyponeural coelom also forms the genital coelom that surrounds and connects the genital hemal ring and the gonads. The hyponeural canal and the stone canal both connect to the madreporic ampulla, and sea water is thought to supply both systems (Hyman, 1955, Ferguson and Walker, 1991). The “flattening” that is associated with SSW (see below) likely involves coelomic processes.

The echinoderm immune system

An important milestone in the identification of an immune system in biological organisms was reached in sea stars over a century ago. Eli Metchnikoff inserted a rose thorn into a sea star larva and to his surprise, saw cells migrate to this thorn and eventually encompass the intruder (see e.g., (Gordon, 2016b)). This was a novel characterization of the process of phagocytosis in an immune defense and helped earn Metchnikoff the Nobel Prize in 1908. Since then, our understanding of the immune system of this and other echinoderms has increased enormously; later sections will detail what we have learned because of SSW itself.

As with many invertebrates, host defenses comprise behavioral and cellular changes in response to non-self recognition, an intact epidermis with functional pedicellariae, and immune cells. Asteroids only have an innate system of immune defense. That is, cells and molecules are present in the organism that can recognize an invader as non-self and minimize infectivity by encapsulating, consuming through phagocytosis, or killing it (Smith *et al.*, 2010). Evidence for an adaptive system of immune memory is lacking. Limited analyses of available echinoderm genomes show a lack of elements known to adapt to pathogen exposure, e.g., (Sea Urchin Genome Sequencing *et al.*, 2006, Smith *et al.*, 2010, Hall *et al.*, 2017).

Much of the early work on immune function in sea stars was accomplished through grafting experiments. Grafts of a piece of tissue from one sea star to a different conspecific or heterospecific individual results in the host animal killing cells of the donor tissue at the border, and eventually releasing the graft (Hildemann and Dix, 1972, Karp and Hildemann, 1976). These similar responses demonstrate that individuals within a species can recognize one another as non-self, and can do this in as robust a manner as seen in animals with adaptive immune mechanisms (Silva, 2000, Furukawa *et al.*, 2009).

Subsequent work on sea star immunity has focused on immune cells in the coelomic fluid and tissues, referred to as coelomocytes (Smith *et al.*, 2010). Asteroids have several types of coelomocytes including phagocytic amoebocytes, phagocytes, amoebocytes, spherule cells, vibratile cells, haemocytes, crystal cells, and progenitor cells (Smith, 1981). Each of these circulating cells appear to have unique characteristics and functions, in combination similar to the innate immune system functions of vertebrates, including clot formation, phagocytosis, encapsulation, clearance of bacteria or other foreign materials, and even oxygen transport (Pinsino and Matranga, 2015, Smith *et al.*, 2018).

Innate immune systems rely on recognition of evolutionarily-conserved structures on pathogens, also known as pathogen-associated molecular patterns (PAMPs), which act through a limited number of pattern recognition receptors (PRRs), notably the family of Toll-like receptors (TLRs). As in other invertebrates, analyses of the sea urchin genome revealed a profound complexity of innate immune recognition receptors, regulators, and effectors (Hibino *et al.*, 2006, Rast *et al.*, 2006, Smith *et al.*, 2018), generated perhaps by combinations of gene recombination, gene duplication, and selection for sequence diversification in response to high rates of change in their pathogens. Generally, these gene regions have been identified in asteroid genomes as well (Rast *et al.*, 2006, Ruiz-Ramos *et al.*, 2020). While our insights are still limited to a few species that have been well-characterized, echinoderms have more than 10 times the number of gene copies in these families than found in vertebrates, providing a diverse innate immune complexity.

Like other ectotherms, environmental factors such as temperature, salinity, heavy metals, and UV light (Pinsino and Matranga, 2015) can affect the immune response of sea stars. Recent work has shown that the interaction of an echinoderm with stressors such as perceived predation rapidly influence the hormonal regulation of coelomocytes and other components of the innate immune system (Hamel *et al.*, 2021), and nutrient deprivation can drive wasting-like responses in some sea stars (VanVolkom *et al.,*2021). Thus, interpreting experimental data on immune and disease responses in echinoderms in the context of SSW would need to account and control for these environmental variables.

A challenge in our understanding of disease in echinoderms is the lack of basic knowledge of cell physiology and mechanisms of host cell responses to insults. Moreover, there is a lack of functional evidence to understand host cell gene expression and its role in cell death and genesis of lesions, all rich avenues for future investigative efforts.

Virology and Microbiology of grossly normal asteroids

Early microscopic study of apparently healthy asteroids found an abundance of subcuticular bacteria of varying morphologies (Holland and Nealson, 1978, Kelly *et al.*, 1995, Foret and Lawrence 2001). However, these studies highlighted the large abundance of spiral-shaped bacteria (which were distinctive for Spirochaetes) beneath the outer epidermis and embedded within body wall tissues (Holland and Nealson, 1978, Kelly *et al.*, 1995, Foret and Lawrence 2001). Cultivation-based surveys, which are highly biased towards taxa that grow on surfaces and in nutrient-rich conditions, reflected mostly copiotrophic taxa (i.e. microorganisms capable of rapid assimilation of compounds and subsequent rapid cell division) (e.g., Narita *et al.*, 1987, Choi *et al.*, 2003, Beleneva and Zhukova, 2009, Rivera-Posada *et al.*, 2011b, Luo *et al.*, 2013, Hewson *et al.*, 2018), Table A1). However, most bacterial taxa in marine habitats cannot yet be cultivated; as a consequence, less-biased molecular barcoding approaches are typically used to examine the structure of microbial communities inhabiting marine habitats.

Despite the known cultivation biases, many commonly reported orders, families, and genera of bacteria in culture collections (Table A1) are also common constituents of cultivation-independent surveys (Nakagawa *et al.*, 2017, Hewson *et al.*, 2018, Hoj *et al.*, 2018, Jackson *et al.*, 2018, Lloyd and Pespeni, 2018, Nunez-Pons *et al.*, 2018; Table A2). These taxonomic groupings represent microorganisms that are typically found in organic nutrient-rich environments in marine habitats.

By contrast, other aspects of asteroid-associated microdiversity (e.g., fungi and protists) have not been extensively documented. Nunez-Pons *et al.* (2018) examined fungal communities associated with grossly normal *Odontaster validus* and found that communities were dominated by asco- and basidiomycetes (notably, Saccharomycetes, Eurotiomycetes, Dothideomycetes, and Agaricomycetes). The parasitic ciliate *Orchitophrya stellarum* is known to infect testes of males and castrate them (Cepede, 1907, Peters, 1992, Lawrence, 2015) in a range of species (Vevers, 1951, Leighton *et al.*, 1991, Byrne *et al.*, 1997, Byrne *et al.*, 1998, Stickle *et al.*, 2001, Stickle and Kozloff, 2008, Sunday *et al.*, 2008). While *Orchitophrya* does not cause gross disease signs (Cepede, 1907, Bang, 1982), it may lead to mortality, especially for males (Leighton *et al.*, 1991, Claereboudt and Bouland, 1994) and reduced gamete abundance or fertility. Otherwise asymptomatic individuals may also be infected by an unidentified apicomplexan parasite reported in *Asterias amurensis* (Goggin and Bouland, 1997). Asteroids may host labyrinthulids (FioRito *et al.*, 2016) and mesomycetozoa (Kerk *et al.*, 1995, Ragan *et al.*, 1996, Glockling *et al.*, 2013, Paps *et al.*, 2013, Hewson and Sewell, 2021). The functions of these less well-studied organisms in sea star health and disease are unclear, and they raise questions of whether such diversity is involved in SSW transmission or symptomatic progression.

Viruses inhabiting tissues of grossly normal sea stars are diverse and include both DNA and RNA viruses (Hewson *et al.*, 2014, Jackson *et al.*, 2016, Hewson *et al.*, 2018, Jackson *et al.*, 2020a). While much early attention in the SSW outbreak focused on the sea star associated densovirus (SSaDV, renamed Asteroid ambidensovirus-1 by the International Committee on Taxonomy of Viruses; Hewson *et al.*, 2014), this viral genotype was one of many inhabiting clinically normal asteroids, and appears to be a common constituent across grossly normal echinoderms worldwide (Gudenkauf *et al.*, 2014, Hewson *et al.*, 2018, Jackson *et al.*, 2020a, Jackson *et al.*, 2020b, Hewson and Sewell, 2021). Recent work has demonstrated that these taxa may develop persistent infections (Jackson *et al.*, 2020a). Asymptomatic individuals also bear picornaviruses, dicistroviruses (Hewson *et al.*, 2018, Hewson *et al.*, 2020a), circular rep-encoding single-stranded DNA viruses (Jackson *et al.*, 2016), and nucleocytoplasmic large DNA viruses (NCLDVs), as well as abundant bacteriophage (Hewson *et al.*, 2014). As such, due to the diversity of potential pathogens identified in affected organisms, and the inherent challenges of fulfilling Koch's postulates – even using molecular data (Fredericks and Relman, 1996) – in an invertebrate for which no cell cultures for viral isolation are available, it has become very difficult to point to any virus as a cause of SSW; hence additional mechanisms are being considered.

Sea star wasting

SSW has affected dozens of sea star species, spanning a broad phylogenetic breadth (Schiebelhut *et al.*, this issue). There are also numerous instances preceding the 2013-2014 outbreak and comparing the signs and etiology across such instances can be difficult (Hewson *et al.*, 2019). For this reason, it is not clear if the 2013-2014 outbreak is mechanistically related to prior or ongoing observations of wasting; we do not know if the causes are the same across species or across events. A focus in this paper is on common structural traits of sea stars that may provide clues as to the signs and mortality that follow multiple potential causes, ranging from apparent pathogens to environmental stressors (Hewson *et al.*, 2018).

Sea stars, like other invertebrates, have a limited host response repertoire, so it would not be surprising that they respond to insults by manifesting lesions in the tissues that are most abundant (epidermis, MCT). As many of the affected species during the 2013-2014 SSW event are sympatric, they likely have similar exposure rates to the causal agent(s) of the disease (Eisenlord *et al.*, 2016), or environmental stressors (Dawson *et al*, this issue). This indicates that differences in the appearance or outcome among species may, instead, be driven by variations in the host immune response or other physical and physiological vulnerabilities. Understanding such variation may guide researchers in interpreting prior and ongoing asteroid wasting events that have similar signs or outcomes.

Regardless of why particular species were disproportionately affected by SSW over others, the die-off noted in 2013-2014 led to ecological shifts in echinoderm populations (Dawson *et al.*, this issue). For example, *Dermasterias imbricata* (the leather star) has increased in abundance at many sites (Montecino-Latorre *et al.*, 2016), and Kay *et al.* (2019) document “reciprocal abundance shifts” in the Salish Sea between the heavily affected *P. ochraceus* and the less affected *Evasterias troschelii*. Other species, such as the sunflower star (*Pycnopodia helianthoides*), experienced sharp declines across its entire range, resulting in a nearly complete loss south of Oregon and functional depletion in much of its northern range

(Harvell *et al.*, 2019). *P. helianthoides* was recently listed by the International Union for Conservation of Nature as critically endangered, with greater than 90% of individuals lost (Gravem *et al.*, 2021). By contrast, it is unclear why species like *D. imbricata* persisted so successfully, but one hypothesis is that this species may have morphological or life history characteristics that affect disease severity (see Schiebelhut *et al*, this issue). As an example of structural or ontogenetic variation that may be important, *Pisaster ochraceus* ochre morphs appear to be affected more than purple morphs (Raimondi *et al.*, 2007, Work *et al.*, 2021). This trait itself may be plastic (Harley *et al.*, 2006), serving as an indicator of other factors in the life of an asteroid that may be associated with severity of response.

Disease signs

While minor visible and pathological differences exist among host species, the onset of SSW is generally characterized by a progression of key visual signs. Sea stars first appear lethargic and uninterested in nearby prey (Kohl *et al.*, 2016), followed by an overall loss of body turgor and the ability to attach (Schultz *et al.*, 2016). Signs become more pronounced as arm rays twist and contort; and the sea stars quickly develop characteristic white lesions that mottle the epidermis (Figures 1 and 2; Hewson *et al.*, 2014, Eisenlord *et al.*, 2016, Bucci *et al.*, 2017).

Autotomy, or the detachment of arms (Figure 1) is a regular occurrence as lesions extend more deeply and wider into the tissues. Body wall tissues degrade and slough off, and the sea stars are often described as dissolving or “melting” from the outside inward as the animal dies (Eisenlord *et al.*, 2016). Progression of the disease may occur at a rapid pace; Menge *et al.* (2016) observed one star struggling to maintain its grip during a changing tide; 4 hours later they returned to find the animal in the final stages of disintegration and death.

Of course, SSW does not always progress linearly; there are cases documented where lesions form and then go away; limbs autotomize prior to lesions; or the lesions can form in the absence of deflation or arm twisting (Kohl et al., 2016, Menge et al., 2016). The progression can vary between species or even between individuals within a species (Wares and Schiebelhut, 2016). The signs of SSW can also differ among species. For example, as opposed to the deflated *Pycnopodia* presented in Figure 1, *Dermasterias* can appear bloated and may have blue lesions rather than white. In some cases, the gonads are larger than in healthy animals and protrude out of the body through the lesions (SJW and Lesanna L. Lahner, Seattle Aquarium,WA, United States, oral communication, June 2020). This gonadal bloating is suggestive of a problem with osmotic homeostasis, and this hypothesis is also supported by the increase in chloride concentration detected in the coelomic fluid of affected sea stars (see Wahltinez et al., (2020) and section below on Immune responses in SSW).

The aforementioned outward signs of sea star wasting are not by themselves definitive proof that the animal has SSW. For example, loss of body turgor can occur normally in intertidal sea stars when exposed at low tide. Arm curling appears to be a normal response to a physical wound (Figure 3A,B), and may be observed in healthy, unwounded sea stars as well (Figure 3C). Arm autotomy also occurs following predation attempts (Ramsay *et al.*, 2000) and temperature stress (Pincebourde *et al.*, 2013). A related natural process of asexual reproduction, by splitting the body in half (fission) followed by regeneration, is seen in a few taxa such as *Coscinasterias muricata* (Byrne, 2020). Interestingly, SSW seems to be an extreme expression of these behaviors that occur typically in sea stars.

Histology

During the summer of 1991, an epizootic of SSW occurred in *Asterias forbesi*, with numerous animals washing up on the beaches along the coast of Long Island Sound and the Gulf of Maine (R.S., unpublished data). The animals had not autotomized arms, but did show flaccidity and extensive erosive, ulcerative, and penetrating lesions of the dorsal and dorsolateral surfaces of the arms. The ambulacral groove and tube feet were not affected, and no internal abnormalities were apparent. Gonads were shrunken in evaluated specimens; however, gonad maturity is seasonal and it is not clear if this is a sign associated with the SSW event. In terms of histology, internal organs showed no lesions while examination of the dorsal epithelium showed areas of progressively, necrotizing dermatitis characterized by an accumulation of coelomocytes in the superficial dermis and the base of the overlying epithelium with vacuolation of epithelial cells and sloughing of the epithelial layer. Edema and necrosis of the deeper dermal connective tissues and underlying ossicles occurred in the ulcerated regions.

During the SSW epizootic that occurred on the Pacific Coast in 2013, histology was evaluated for symptomatic and asymptomatic individuals of 13 asteroid species affected by the event (A.L.N., unpublished data). Histologic lesions in *Pisaster ochraceus* and *Pycnopodia helianthoides* were similar to those described above for *Asterias forbesi* (Figures 4 and 5; as in Bucci *et al.*, 2017). Some areas exhibited epidermal degeneration and necrosis with ulceration. Areas of epidermal loss were associated with edema in the subjacent dermal connective tissue and coelomocyte infiltrates. In addition to the epidermal and dermal changes, coelomocyte aggregates were apparent within the coelomic cavity, vascular system, and papulae with frequent adhesion of coelomocytes to the coelomic epithelial lining. There were no primary lesions noted within the coelomic viscera or dermal ossicles and no infectious agents were apparent (A.L.N., unpublished data). More recent studies looking at experimental induction of SSW in *P. ochraceus* revealed that pathology involved a basal to surface process starting with infiltration, breakdown of MCT, and lysis leading to epidermal ulceration that had a greater effect on the purple than the ochre morphs. Indeed, ochre stars survived longer, with more apparent and extensive signs of SSW, than those that are purple (Work *et al.*, 2021).

The function and pathophysiological changes seen in the body wall in afflicted stars is similar to that observed with the breakdown/autolysis of MCT during arm autotomy and at the separation plane during and asexual reproduction by fission in sea stars, processes that are modulated by the nervous system (Mladenov and Burke, 1994, Wilkie, 2002; Byrne *et al.*, 2019). Hence, the changes in the body wall during SSW might, fundamentally, be a neurological disease leading to inability to control softening of the MCT to the point that total dissolution occurs. Additional research is needed to test this hypothesis and indeed to better understand neural control of MCT tensility. Fuess *et al.* (2015) noted changes in transcript abundance for genes associated with nervous system processes when comparing wasting versus non-wasting stars. These differentially expressed transcripts included many associated with MCT, supporting concern that the arm twisting and autotomy could be related to dysregulation of this system.

Pedicellariae

As noted previously, a difficulty in defining disease in organisms like sea stars is to separate abnormal condition from injury – this is not easy when body structures such as pedicellariae are involved. In 2014, a mixed species group of sea stars including *Pisaster brevispinus*, *Pisaster ochraceus*, *Evasterias troschelii*, *Dermasterias imbricata*, and *Orthasterias koehleri* were placed in tanks for a study on SSW. Detached pedicellariae from *Pisaster ochraceus* were noted independently moving and penetrating the coelomic cavity of *D. imbricata*. This observation was associated with clinical signs of SSW in *D. imbricata* (epidermal lesions, drooping limbs). Removal of the pedicellariae reversed these clinical signs (SJW and Lesanna L. Lahner, Seattle Aquarium,WA, United States, oral communication, June 2020). Though a sudden and dramatic uptick in agonistic interactions would itself be of interest, these interactions became a focus of study into mechanisms driving SSW.

To investigate the potential connection between pedicellaria attack and SSW, flow-through holding tanks were set up, each with two adult *D. imbricata* and two adult *P. ochraceus*. Both species initiated contact, and physical contact was required for pedicellariae transfer (i.e. defense response) from *P. ochraceus* to *D. imbricata,* with the majority of the pedicellariae (88.9%) transferred to the oral surface. In the area surrounding the transferred pedicellariae, the ambulacral groove closed and tube foot dysfunction was noted. These signs immediately resolved following manual removal of the pedicellariae (SJW and Lesanna L. Lahner, Seattle Aquarium,WA, United States, oral communication, June 2020). These signs are consistent with what has been noted after pedicellariae transfer from *Pisaster giganteus* and *Pisaster brevispinus* to *Pycnopodia helianthoides* (Wobber, 1975) and from *Pisaster ochraceus* to *Solaster dawsoni* (VanVeldhuizen and Oakes, 1981). The disuse of a limb following pedicellariae transfer could be due to a toxin as seen in echinoid globiferous pedicellariae (Jensen, 1966, Chia, 1969), irritation, or another mechanism. Transfer of pedicellariae could represent a novel pathway for pathogen transmission or may predispose the recipient to infection through disruption of the epidermis or could contain an agent that causes the MCT to break down.

Immune responses in SSW

Very limited information is available on the immune responses of wasting stars. This is in part because of unclear associations of a putative pathogen across taxa – the densovirus initially proposed as a causal agent (Hewson *et al.* 2014) is now known to be as frequently found in asymptomatic individuals as in those showing signs of SSW. The overall class of viruses that have been primarily focused on (Sea Star associated Densovirus, SSaDV) is still potentially associated, in terms of viral load, with wasting disease in *Pycnopodia helianthoides* (Hewson *et al.* 2018) but does not correspond with the outcome of other challenged species – and the lack of mechanistic knowledge on the immune systems of the highly diverse group of species that are affected by wasting (Schiebelhut *et al.,* this issue). Coelomic fluid in *Pisaster ochraceus* with SSW had significantly increased chloride concentration, increased osmolality and coelomocyte count, suggestive of an osmotic breakdown (Wahltinez *et al.*, 2020), when compared to clinically normal conspecifics (Wahltinez *et al.*, 2019). The increased chloride concentrations and hypertonic coelomic fluid may be due, at least in part, to wound healing or inability to regulate osmolality of the coelomic fluid secondary to skin ulceration. An increase in chloride permeability was noted in sea star oocytes after wounding (Fein and Terasaki, 2005). In a more recent study, *P. ochraceus* manifesting experimental SSW showed a significant increase in a heretofore undescribed type of coelomocyte illustrating our very limited knowledge of sea star host responses to insults (Work *et al.*, 2021).

Another approach of great relevance to SSW is to measure the transcriptional profile in the coelomocytes of a wasting animal compared to healthy individuals. Fuess *et al.* (2015) used *Pycnopodia helianthoides* to explore the transcriptomic response of coelomocytes from sea stars injected with a <0.2 µm-tissue filtrate from an afflicted sea star. Within several days, disease signs were seen in the test animals, but not in the control injected animals. Remarkably, over 1000 immune-related genes were identified that were significantly changed in expression profile compared to the coelomocytes of the control animals. These included pattern recognition receptors (PRRs) and other immune receptors, intracellular signaling, transcription factors, cytokines and growth factors, and immune effector genes, as well as genes involved in coagulation and the complement system, and homologues of genes that function in the vertebrate adaptive immune system.

The study of Fuess *et al*. (2015) raises a series of questions. Specifically, which of these genes are most important to SSW pathogenesis, and just how does this gene expression profile relate to host pathology at the cellular level? Also lacking in this experiment was a control for allorecognition reactions, such as a heat-killed tissue homogenate. Recall that the immune system of the sea star was defined early on by allorecognition and tissue rejection (Smith *et al.*, 2010, Gordon, 2016a). Indeed, Aquino *et al.* (2021) argued that the < 0.2 µm size fraction of sea star-derived filtered homogenate used in similar challenge studies may contain a broad array of dissolved organic matter, which ultimately may lead to allorecognition, but also may stimulate heterotrophic bacteria in subcuticular space or on/near surfaces, which ultimately may cause oxygen depletion and tissue degradation.

Regardless, the study of Fuess *et al*. (2015), as one of the very few contemporary studies on sea star molecular immunity, yielded valuable information on the transcriptomic response of sea stars to 'non-self' that could be used to develop more precise tests. An important follow up experiment could involve exposure of healthy stars to recombinantly expressed proteins of candidate virus particles associated with SSW, as well as with specific antigens (PAMPs), environmental toxins, pedicellaria attack or isolated pathogens (e.g., bacteria) to test immune responses. The signature of SSW in these transcriptomic data has already been partially picked up in independent post-selection and heat stress experiments that are mapped to the genome of *Pisaster ochraceus* (Ruiz-Ramos *et al.*, 2020). The search for consilience across several studies exploring wasting or stressors is a hopeful guide towards key mechanisms involved in the response.

As an alternative to whole animal studies, *in vitro* approaches have been performed by exposing purified immune cells (coelomocytes in absence of serum from the water vascular system) to various insults and then measuring in real time their responses using medium to high-throughput assays (Matranga *et al.*, 2002, Pinsino and Matranga, 2015). It may be more efficient to study responses in sea star larvae; immunocytes of sea star larvae share several similarities with adult coelomocytes, showing the capability for phagocytosis of cellular debris and foreign agents that invade blastocoel. Furukawa *et al.* (2009) showed that sea star larval immune cells phagocytose small foreign particles injected into the blastocoel within two hours. When small amounts are inserted, few cells respond. However, when larger particles are inserted into the blastocoel, multiple cells converge onto the site from within the blastocoel and undergo cell–cell fusion to form a syncytial multinucleated giant cell that encapsulates the aggregated particles. Similar syncytial formations have also been noted for adult phagocytes in vitro (Majeske *et al.*, 2013). The number of recruited immune cells is dependent on the amount and size of the foreign substance, indicating that the process of clearing the blastocoel is strictly regulated.

Candidate genes involved in this regulation appear to be two macrophage migration inhibitory factors (MIFs): ApMIF2 and ApMIF1 (Furukawa *et al.*, 2016). These immune effectors are evolutionarily ancient and highly conserved (Furukawa *et al.*, 2016). Therefore, the immune cell behaviors of chemotaxis, cytoskeletal modifications, and syncytia formation provide excellent nodes to investigate how the innate immune system functions generally, in a larva, and likely elements that are shared in an adult. Intriguingly, in sea cucumbers, the virus associated with the Acute Peristome Edema disease has been detected in both adults and 30 days old diseased larvae (Wang *et al.*, 2007). Currently, it is unknown whether embryos and larvae of sea stars are affected by SSW as well.

Potential agents associated with SSW

It is difficult to isolate the cause of SSW, which remains unknown in all spatial, temporal, and taxonomic context, from the proliferation of microbial or viral agents that may be found in compromised sea star tissues. There are often changes in microbial communities of affected individuals that indicate proliferation of several bacterial taxonomic groups and viruses (Hewson *et al.*, 2014, Hewson *et al.*, 2018, Lloyd and Pespeni, 2018, Hewson *et al.*, 2020a, Aquino *et al.*, 2021). Comparative viral metagenomic study of asymptomatic and wasting-affected tissues revealed a proliferation of a virus (SSaDV or AaV-1; Hewson *et al.*, 2014). However, further study with redesigned qPCR primers targeting only SSaDV and excluding homologous non-SSaDV densoviruses, revealed no association with wasting (Hewson *et al.*, 2018). More recent approaches also found no association between viruses and disease, and that densoviruses form persistent infections in their hosts (Jackson *et al.*, 2020a, Jackson *et al.*, 2020b). More recent work tracking viral populations during progression of SSW in controlled laboratory experiments has revealed that wasting is associated with elevated richness of all viral genotypes, which may indicate a general proliferation of viruses in affected tissues or a down-regulation of the immune responses (Hewson *et al.*, 2020a).

Screening of SSW-affected tissues by histopathology in 2013 yielded no protist cells associated with lesions (Hewson *et al.*, 2014). Comparisons of fungal communities in *Odontaster validus* revealed no difference in associates between asymptomatic and SSW-affected states (Nunez-Pons *et al.*, 2018). While there have been no pan-eukarya surveys of protistan diversity in wasting asteroids, viral metagenomes also yield sequences of co-extracted and amplified ribosome bound rRNAs (Hewson and Sewell, 2021). A survey of unicellular fungal and other eukaryotic 18S and 28S rRNAs in *Pisaster ochraceus* during wasting progression (Hewson *et al.*, 2020a) did not reveal any single OTU (operational taxonomic unit) consistently associated with wasting (Figure A1). In summary, there is little consistent evidence that infectious agents were responsible for the 2013-2014 mortality event on the west coast of North America. Though the information available sometimes suggests association of viral load with signs of disease in certain populations (Hewson et al. 2018), the diverse and complex observations of SSW across the breadth of environmental and viral/prokaryotic communities that can be detected have made it challenging to narrow the likely sources.

Bacteria and Archaea also change in abundance and composition during SSW. It is believed that this is mainly due to stimulation of taxa that degrade organic matter released from decaying tissues. It is therefore unsurprising that the bacterial orders that associate with wasting tissues (Table A2) – notably Flavobacterales (Lloyd and Pespeni, 2018), Rhodobacteriales (Nunez-Pons *et al.*, 2018), and Campylobacterales (Hoj *et al.*, 2018) are copiotrophs (Haggerty and Dinsdale, 2016). In terms of overall community structure, assemblages are different between healthy and diseased states (Nunez-Pons *et al.*, 2018). In *Acanthaster* sp., disease was associated with increasing dominance by fewer OTUs in the pyloric caeca but decreasing dominance (i.e. greater evenness) in the body wall tissues (Hoj *et al.*, 2018). Indeed, injection of bacterial culture media into *Acanthaster* sp. causes wasting-like lesions and animal death; isolated bacterial cultures from lesions included taxa in the genera *Vibrio* and *Photobacterium* (Rivera-Posada *et al.*, 2011a, Rivera-Posada *et al.*, 2011c). Moreover, healthy animals in contact with these infected animals also displayed signs of disease and died within 24 h, indicating that these first observations were not due to a toxic shock after injection of the media. Because SSW is mainly defined by gross lesions that could have multiple etiologies, sorting out causes of sea star mortalities will require more systematic effort combining careful observations of tissues at the cellular level coupled with studies to relate molecular processes to tissue changes for each species.

Environment

Environmental effects on agents

Environmental conditions potentially affect the abundance and composition of microorganisms associated with SSW as both commensals and opportunists. Although much attention has been given to environmental correlates with SSW since 2013 (Eisenlord *et al.*, 2016, Kohl *et al.*, 2016, Menge *et al.*, 2016, Hewson *et al.*, 2018, Miner *et al.*, 2018, Aalto *et al.*, 2020), no link has been found between the microbiome composition in affected asteroids and an environmental perturbation. Environmental stressors may be linked to dysbiosis, a change in microbiome composition relative to the "normal" state (Egan and Gardiner, 2016); they could induce a proliferation of opportunistic pathogens when host tissues are compromised (Burge *et al.*, 2014). These stressors could lead to hypoxia through bacterial heterotrophic respiration (Haas *et al.*, 2011, Gregg *et al.*, 2013, Aquino *et al.*, 2021). Environmental conditions could directly affect the ability of the host to respond to insults. Although viruses do not bear innate metabolism, their replication in tissues may be influenced by the intracellular conditions of their hosts. Thus, their proliferation may reflect breakdown in homeostatic properties as a consequence of environmental stressors in their poikilothermic hosts (Frakolaki *et al.*, 2018, Hewson *et al.*, 2020a). It is worth noting that common taxa inhabiting asymptomatic asteroid specimens – including *Rhodobacter* (*Erythrobacter*), Flavobacteria, and Alteromonads – include some of the largest genome-bearing and fastest growth rate taxa in the picoplankton, which emphasizes their ability to rapidly adapt to changing conditions. The proliferation of these taxa during SSW may reflect their ability to rapidly assimilate organic matter from the environment surrounding asteroids (Aquino *et al.*, 2021).

Environmental stressors

A common hypothesis is that anomalies in temperature may elicit or exacerbate SSW. Although most studies have revealed that SSW is positively correlated to elevated sea surface temperatures (Bates *et al.*, 2009, Eisenlord *et al.*, 2016, Kohl *et al.*, 2016, Harvell *et al.*, 2019, Aalto *et al.*, 2020), other studies have found either no empirical relationship between the two variables (Hewson *et al.*, 2018), or concluded instead that a reduction in sea surface temperature (Menge *et al.*, 2016) is inducing or exacerbating the wasting disease. The context-dependent relationship between temperature and SSW may result from an integration of both short- and long-term stressors, but may also instead indicate that the magnitude of the temperature anomaly induces wasting, regardless of the direction. In addition, some basic environmental variables can serve as proxies to environmental stressors, such as low-tide exposure and wave action (Dawson *et al.*, this issue). Early symptoms of SSW are similar to those resulting from other sources of stress in sea stars, such as starvation, desiccation, or injury (Miner *et al.*, 2018, VanVolkom *et al.*, 2021). What is most intriguing about SSW is that in many locations, predictive environments for sea star assemblages are changing rapidly (Kay *et al*, 2019, Konar *et al.*, 2019).

Recently, Aquino *et al.* (2021) provided evidence that SSW could be related to microbial processes – driven by temperature and organic matter availability – at the animal-water interface. Microorganisms inhabiting the diffusive boundary layer around individual specimens may respond to inputs from surrounding waters. In marine environments, a large proportion of this organic matter is in the form of phytoplankton exudates (Ogawa and Tanoue, 2003). Aquino *et al.* (2021) observed correspondence between chlorophyll *a* peak (and decline) and SSW mass mortality at a field site, and Hewson (2021) noted correspondence between SSW and upwelling at several sites, so it is plausible that SSW is influenced by water column processes such as stratification, nutrient availability, and temperature. Linking SSW to biological oceanographic phenomena may also help explain the multi-host nature of SSW and the apparent discontinuous geographic appearance of SSW in 2013-2014, and seasonal nature of the condition in years since (Bates *et al.,* 2009). We note here that mass mortalities of echinoderms from other possible environmental mechanisms, such as the toxins from harmful algal blooms, can be contrasted in parts of California (Jurgens *et al.*, 2015) with those of SSW. Related toxins were evaluated in sea stars, with no relationship to wasting status (Hewson *et al.*, 2018).

Finally, asteroids produce chemical compounds under stress that may induce wasting-like conditions in grossly normal specimens when challenged via direct injection. In response to short exposure (45-90 sec) to heat stress, asteroids release proteinaceous compounds within their coelomic fluid that cause almost immediate body wall softening, limb autotomy, and death when injected into healthy specimens (Chaet, 1962, Mladenov *et al.*, 1989). Although these factors were obtained by immersing specimens at 76ºC, an extreme that these species would never experience, these results illustrate that stressed asteroids have the potential to affect the health of surrounding individuals. Because these compounds also occur within the material tested during challenge experiments (Hewson *et al.*, 2014, Bucci *et al.*, 2017, Hewson *et al.*, 2018, Aquino *et al.*, 2021), it is possible that such factors may have been responsible for the observation of apparent transmission, and bring us full circle with questions about changing density and abundance.

Contrasts with other marine diseases and mass mortality events

Unfortunately, SSW is not a unique phenomenon in terms of huge, sudden impacts on marine communities. Our growing recognition of mass mortality events in the ocean (e.g., coral bleaching and death (Hughes *et al.*, 2018a, Hughes *et al.*, 2018b)) dovetails with the associated recognition of how climate change will ultimately affect many taxa, e.g, dolphins (Duignan *et al.*, 2020), manatees (Hardy *et al.*, 2019), and other invertebrates (Petraitis and Dudgeon, 2020). The difficulties in pinpointing a cause for disease are increased when the environmental background is rapidly changing (Burge *et al.*, 2014, Groner *et al.*, 2016, Tracy *et al.*, 2019).

Extraordinary waves of disease are now more frequently the focus of marine research (Harvell *et al.*, 1999). Multiple outbreaks of seagrass wasting are being explored in the western Atlantic, northeastern Pacific, and elsewhere (Short *et al.*, 1987, Muehlstein *et al.*, 1991, Sullivan *et al.*, 2018). A series of devastating diseases have reduced coral abundance in the Caribbean – the most recent wave being 'stony coral tissue loss' disease (Aeby *et al.*, 2019, Landsberg *et al.*, 2020) – concomitant with increasing frequency of climate-driven bleaching. Sponges (Olson *et al.*, 2006), shrimp (Frischer *et al.*, 2017), and salmon (Asche *et al.*, 2009) were also affected by major disease outbreaks, that together with climate change, are shifting entire ecosystems (Tracy *et al.*, 2019).

Focusing on echinoderms, we are left to look back on previous mass mortality events for lessons of what comes next. Echinoids are known to be affected by "bald sea urchin disease" (Johnson, 1971). They present symptoms such as body wall lesions where spines, tube feet, pedicellaria and epidermis are lost. Sometimes necrosis leads to the perforation of the test and the death of the animals. The bacteria later detected in this disease were found to be opportunistic instead of specific (Becker *et al.*, 2008). In the case of *Diadema antillarum*, no mechanism is known for the mass mortality in the Caribbean; current study is focused on how and where it is recovering its numbers (Myhre and Acevedo-Gutiérrez, 2007, Lessios, 2016). In the Sea of Cortez, the recovery of *Heliaster kubiniji* has been spatially variable (Eckert *et al.*, 2000).

Currently, some species have not recovered from SSW (Gravem *et al.*, 2021) while others are returning to their former abundance (Dawson *et al.*, this issue) but with localized die-offs from this unknown cause (Moritsch and Raimondi, 2018). We know there have been similar outbreaks and apparent recovery (Hewson *et al.*, 2018), and we know that asteroids cycle demographically over long-time scales (Uthicke *et al.*, 2009). Finally, there are current studies documenting new losses in holothuroids (Hewson *et al.*, 2020b), and the ecological effects of loss are likely to have substantial effects on coastal benthic communities (Harrold and Pearse, 1987, McPherson *et al.*, 2021).

Conclusions and future directions

Sea star wasting, characterized by behavioral changes, body lesions, and arm autotomy, has triggered periodic mass mortality events across a broad range of sea star species – and possibly with similar mechanisms across disparate events. To better characterize the etiology, the epidemiology, and the effect of SSW, it is essential to build a community of investigators that can share knowledge, samples, and protocols (Table A3, and Supplement S1, available online) and monitor the corresponding environmental parameters around the world.

Understanding SSW – especially the most recent iterations – is challenging because it is now affecting so much diversity, the ecological consequences of which have yet to be fully appreciated. Our primary challenge is that the basic biology of the sea stars is surprisingly poorly known, making it difficult to directly compare healthy and symptomatic animals. This challenge is further compounded by studying these dynamics in a rapidly changing environment and with increased scrutiny of species and populations that have previously not been closely monitored. A deeper knowledge of the basic biology, health, disease, and life stage dynamics and of the growth of sea stars with insights from a range of disciplines will be essential to understand how and why these animals are so profoundly affected by or react to SSW conditions.

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Figure legends:

Figure 1: Examples of sea star species affected by SSW. The left column represents animals with no or with early symptoms. The right column represents animals with late symptoms. (A) *Pycnopodia helianthoides*, the left image shows terminal stages of SSW, Photo credit: Mark Nayer (B) *Asterias forbesi*, the arrow on the left image shows a small lesion. (C) *Pisaster ochraceus*, the arrow on the left image shows a small lesion, Photo credit: Melissa Miner (D) *Orthasterias*, the arrow on the left image shows a small lesion, Photo credit: Feiro Marine Life Center (left).

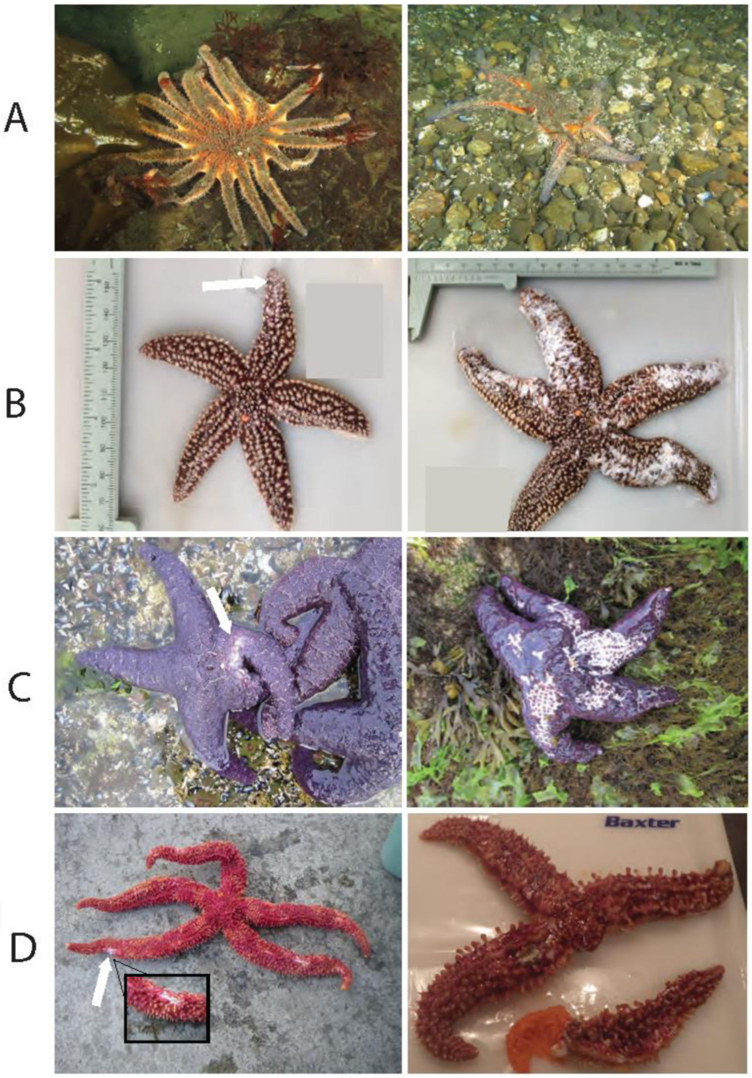


Figure 2: Progression of gross lesions in the aboral side of sea star wasting in *Asterias forbesi.* (A) Arm tip of an affected sea star showing a progression from healthy-looking tissue (chevron, top right) to broad areas of discoloration and loss of cuticle and epithelial tissue (narrow arrow) and severe ulcers leading to loss of tissue at the tip of the arm and exposure of underlying ossicle and the tip of the radial canal (broad arrow). (B) Close up of early stage lesion with small pinpoint white lesions (broad arrow) and early degradation of the spines. (C) Close up of a more advanced lesion showing further development of pinpoint white lesions (broad arrow) and spine degradation. (D) Close up of the tip of the arm in (A) showing advanced lesions with total loss of epithelium (narrow arrow) and exposure of the underlying tissues and ossicles and the tip of the radial canal (broad arrow).

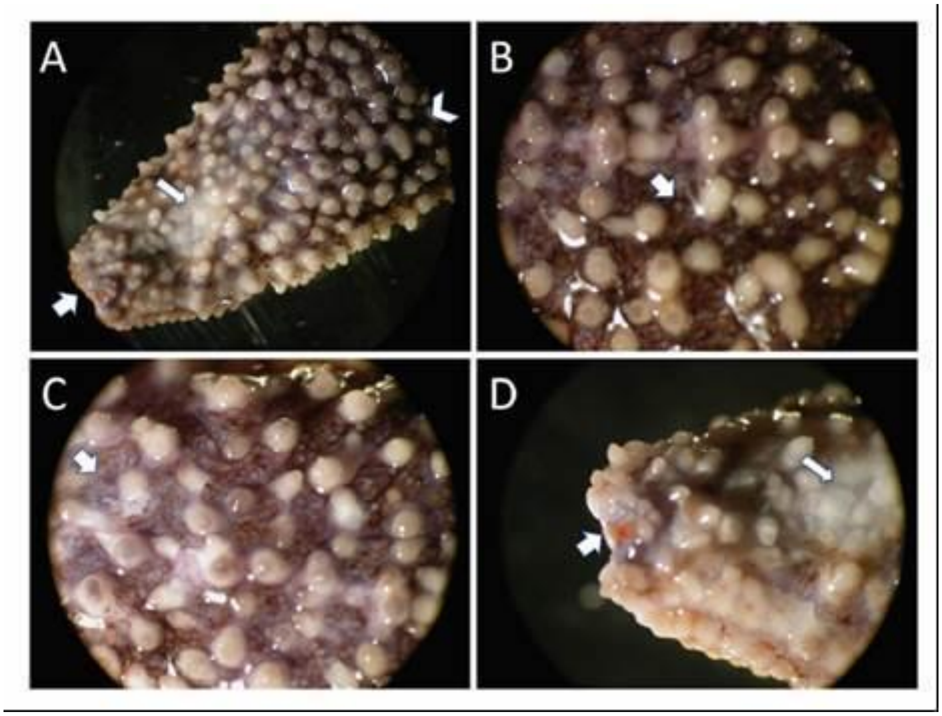


Figure 3: Arm twisting is a behavior that can be present in both healthy and wasting sea stars, and thus cannot always be attributed to SSW. (A,B) *Pycnopodia helianthoides*. (A) shows the wound, and (B) shows how the non-wasting sea star covers this wound by twisting its arms. (C) *Pisaster ochraceus*, The twisting behavior is here observed in a sea star that showed no other signs of SSW. Photo credits: A,B–Julia Kobelt; C–Mike Dawson.

Figure 4: Early lesions of the dorsal epithelium of an *Asterias forbesi* with SSW. (A) vacuolation and necrosis of epithelial cells with influx of hemocytes (arrow heads) and disruption of the cuticle; (B) edema of underlying connective tissues; (C) necrosis of muscle and associated underlying connective tissues. (Bar = 32 μm).

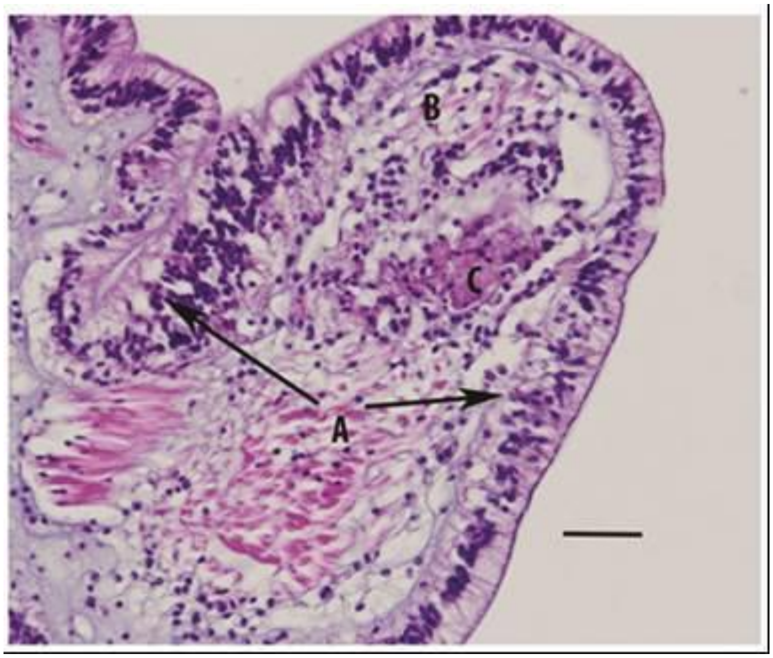
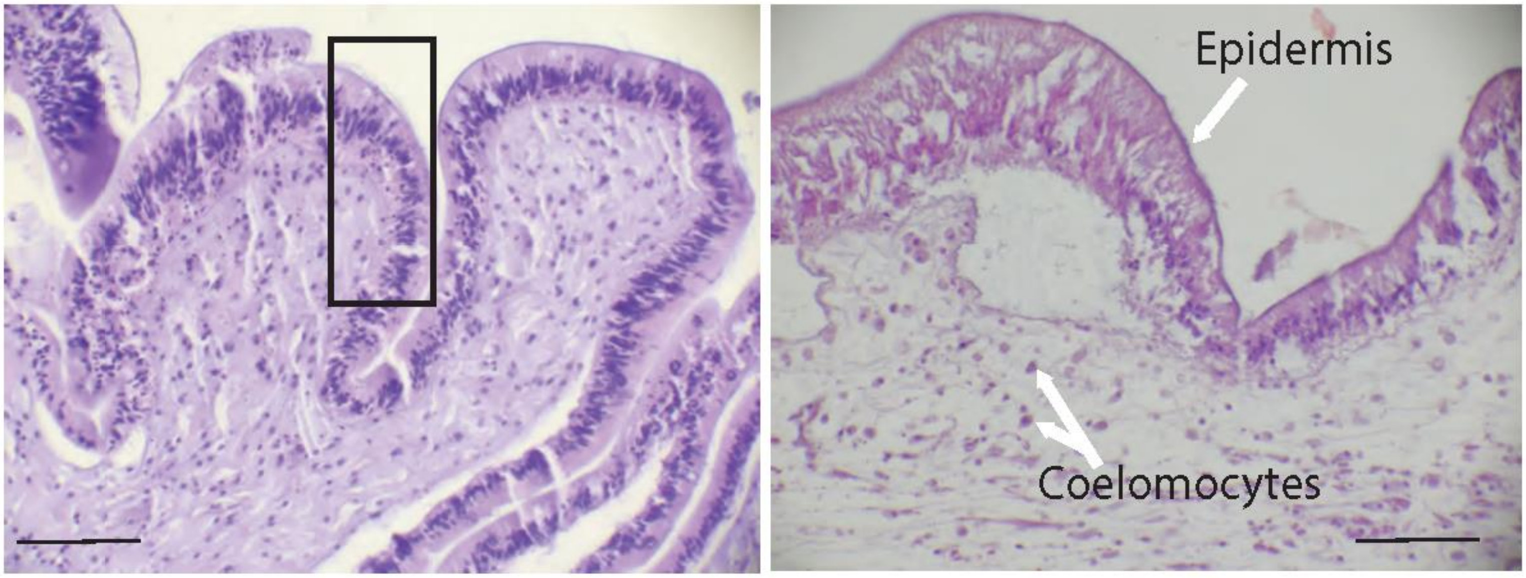
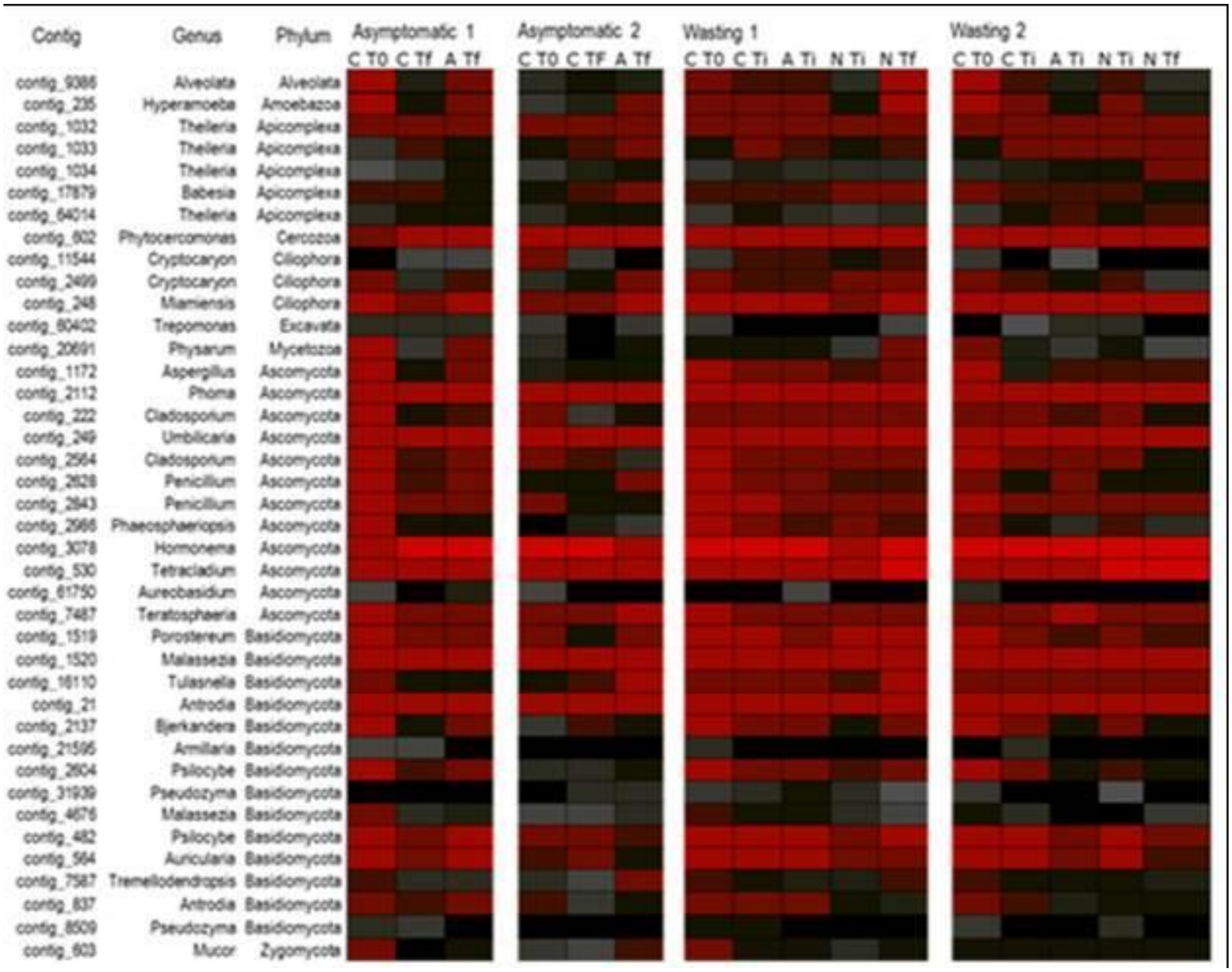


Figure 5: Common lesions noted in the epidermis and dermis. On the left (*Pisaster ochraceus*), within the box, there is multifocal epidermal degeneration and lytic necrosis characterized by a loss of cell distinction, nuclear condensation and fragmentation (karyorrhexis). On the right (*Pycnopodia helianthoides),* there is coagulation type epidermal necrosis characterized by loss of cellular detail, particularly nuclear and cell margin distinction with increased uptake of eosin stain (pink staining) by the cytoplasm. Both types of lesions were associated with microscopic epidermal loss or ulceration in some specimens. The right image also shows the two most common lesions within the dermis: separation of the connective tissue fibers by edema and infiltrates of coelomocytes consistent with inflammation. A low instance of dermal degeneration and necrosis also occurred. Scale bars are 50µm.



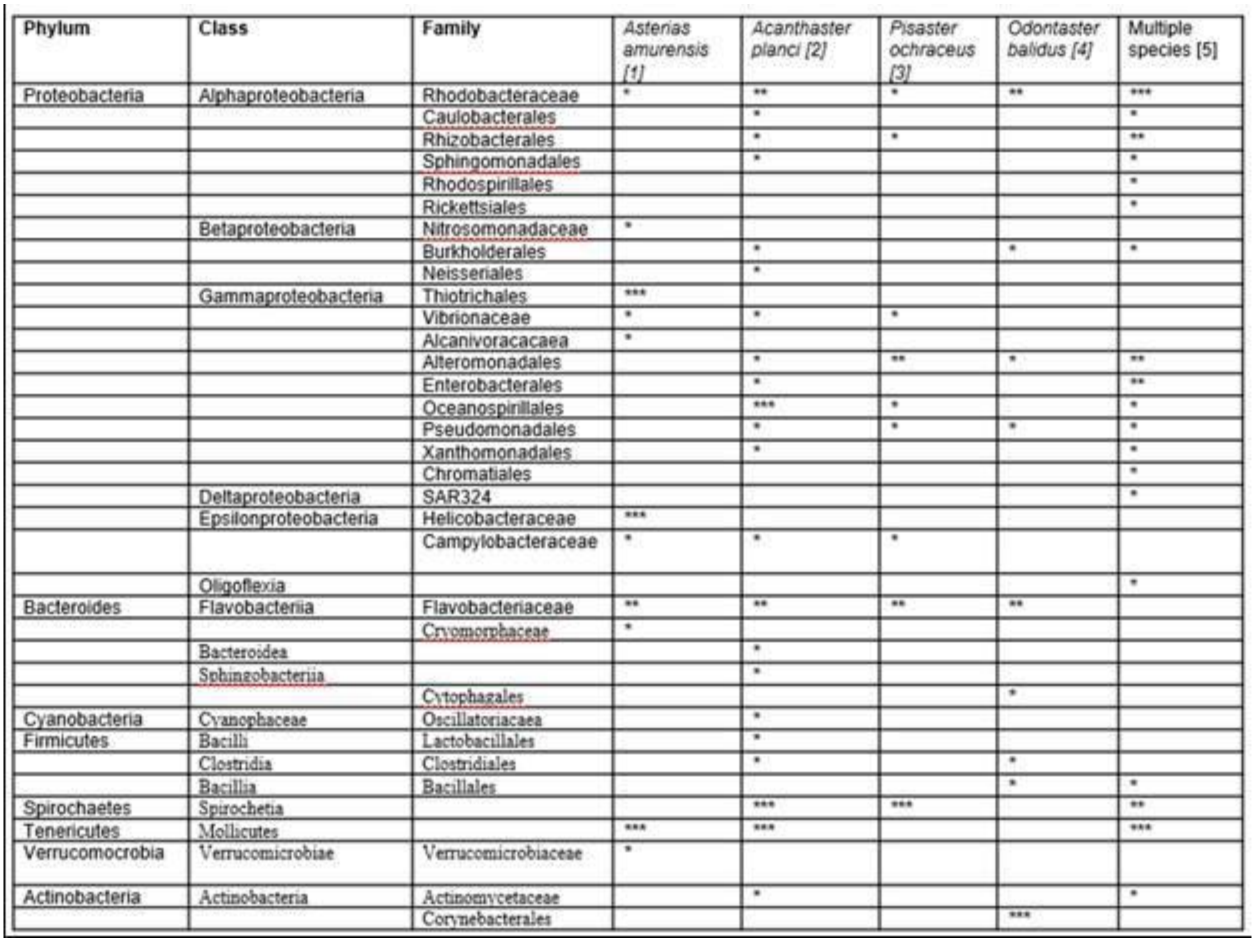
Appendix Figure 1: Heat map representation of 18S and 28S rRNAs recovered from metagenomes targeting material < 0.2 µm during longitudinal study of asteroid wasting progression in control tissues, artificial scars, and wasting lesion margins. Red hues indicate greater numbers of library reads associated with taxonomy; black indicates no reads associated with taxonomy. There were no operational taxonomic units (OTUs) which were consistently present in wasting tissues across individuals but which were also absent from asymptomatic tissues on the same animal at the same time or in artificial scar tissues. C = asymptomatic tissue; A = artificial scar tissue; N = wasting lesion margin; T0 = experiment initiation; Ti = Time of appearance of lesion; Tf = Time at death or for controls the end of observation period. Data derived from Hewson et al. (2020).



Appendix Table 1: Cultivated bacterial isolates from grossly normal asteroids. [1] (Narita *et al.*, 1987), [2] (Rivera-Posada *et al.*, 2011b), [3] (Hewson *et al.*, 2018), [4] (Luo *et al.*, 2013), [5] (Beleneva and Zhukova, 2009), [6] (Choi *et al.*, 2010a), [7] (Choi *et al.*, 2003), [8] (Choi *et al.*, 2010b), [9] (Ivanova *et al.*, 2004), [10] (Zhang *et al.*, 2016).

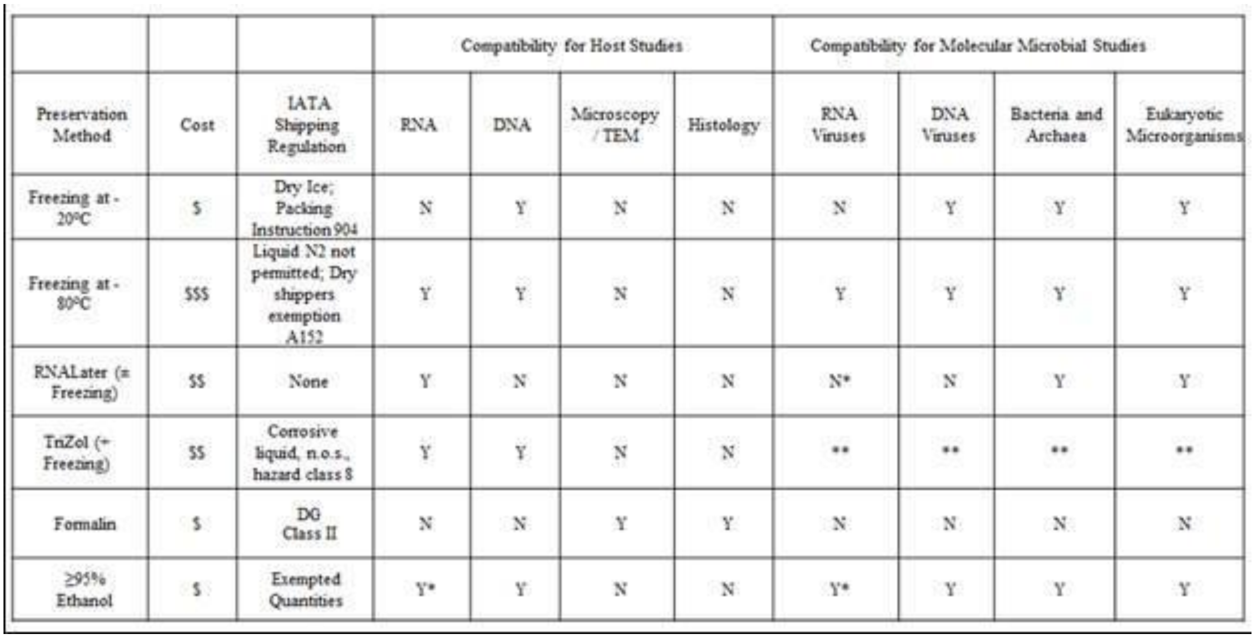
Phylum	Class	Order	Family	Genus	Reference
Proteobacteria	Gammaproteobacteria	Vibrionales	Vibrionaceae	*Vibrio, Photobacterium, Aliivibrio*	[1,2,3]
		Alteromonadales	Pseudoalteromonadaceae	*Pseudoalteromonas*	[3,4]
			Shewanellaceae	*Shewanella*	[3,5]
			Colwelliaceae	*Colwellia*	[6]
			Alteromonadaceae	*Marinobacter*	[7]
		Pseudomonadales	Pseudomonadaceae	*Pseudomonas*	
			Moraxellaceae	*Psychobacter*	[7]
		Oceanospirillales	Halomonadaceae	*Halomonas*	[5]
			Hahellaceae	*Kistomonas*	[8]
	Alphaproteobacteria	Rhodobacteriales	Rhodobacteriaceae	*Sulfitobacter* *Lutimaribacter* *Paracoccus*	[7,9.10]
		Sphingomonadales	Sphingomonadaceaea	*Erythrobacter*	[7,9]
	Betaprotobacteria	Rhodocylales	Rhodocyclaceae	*Zooglea*	[7]
Actinobacteria	Actinobacteria	Corynebacterales			[5]
		Actinomycetales	Micorcoccaceae	*Arthrobacter* *Microbacterium* *Kocuria*	[5,7]
Firmicutes	Bacilli	Bacillales	Bacillaceae	*Bacillus*	[5,7]
			Staphylococcaceae	*Staphylococcus*	[5,7]
Bacteroidetes	Flavobacteria	Flavobacterales	Flavobacteraceae	*Psychoserpens*	[3,5]
Planctomycetes					[5]

Appendix Table 2: Dominant bacterial taxa represented in cultivation-independent surveys. Data derived from [1] (Nakagawa *et al.*, 2017), [2] (Hoj *et al.*, 2018), [3] (Jackson *et al.*, 2018), [4] (Lloyd and Pespeni, 2018), [5] (Nunez-Pons *et al.*, 2018) and [6] (Hewson *et al.*, 2018). *** indicates taxon comprised >50% of sequences surveyed; ** indicates taxon comprised > 20% of sequences surveyed; * indicates taxon comprised < 20 % of sequences surveyed.



Phylum	**Class**	**Family**	*Asterias amurensis [1]*	*Acanthaster planci [2]*	*Pisaster ochraceus [3]*	*Odontaster balidus [4]*	Multiple species [5]
Proteobacteria	Alphaproteobacteria	Rhodobacteraceae	*	**	*	**	***
		Caulobacterales		*			*
		Rhizobacterales		*	*		**
		Sphingomonadales		*			*
		Rhodospirillales					*
		Rickettsiales					*
	Betaproteobacteria	Nitrosomonadaceae	*				
		Burkholderales		*		*	*
		Neisseriales		*			
	Gammaproteobacteria	Thiotrichales	***				
		Vibrionaceae	*	*	*		
		Alcanivoracacaea	*				
		Alteromonadales		*	**	*	**
		Enterobacterales		*			**
		Oceanospirillales		***	*		*
		Pseudomonadales		*	*	*	*
		Xanthomonadales		*			*
		Chromatiales					*
	Deltaproteobacteria	SAR324					*
	Epsilonproteobacteria	Helicobacteraceae	***				
		Campylobacteraceae	*	*	*		
	Oligoflexia						*
Bacteroides	Flavobacteriia	Flavobacteriaceae	**	**	**	**	
		Cryomorphaceae	*				
	Bacteroidea			*			
	Sphingobacteriia			*			
		Cytophagales				*	
Cyanobacteria	Cyanophaceae	Oscillatoriacaea		*			
Firmicutes	Bacilli	Lactobacillales		*			
	Clostridia	Clostridiales		*		*	
	Bacillia	Bacillales				*	*
Spirochaetes	Spirochetia			***	***		**
Tenericutes	Mollicutes		***	***			***
Verrucomocrobia	Verrucomicrobiae	Verrucomicrobiaceae	*				
Actinobacteria	Actinobacteria	Actinomycetaceae		*			*
		Corynebacterales				***	

Appendix Table 3: How to store the samples? Appropriate preservation and storage of the samples are key elements in these studies, and consistent sampling and storage are critical for current and future studies of wasting. In particular, we would like to offer simple sampling and storage protocols so that researchers anywhere can take advantage of wasting (and non-wasting) specimens to be most useful to the research community at large. In the online supplement, we provide best practices for characterizing and analyzing individuals that are encountered with wasting-like symptoms. *Indicated significant loss of target organism or intact particles suitable for metagenomic approaches; ** the effects of TriZol with freezing on the stability of microbial nucleic acids has not been assessed. In the cost column, the expected price of the method is described from the cheapest ($) to the most expensive ($$$). The abbreviation IATA means International Air Transport Association.



			Compatibility for Host Studies				Compatibility for Molecular Microbial Studies			
Preservation Method	Cost	IATA Shipping Regulation	RNA	DNA	Microscopy / TEM	Histology	RNA Viruses	DNA Viruses	Bacteria and Archaea	Eukaryotic Microorganisms
Freezing at -20°C	$	Dry Ice; Packing Instruction 904	N	Y	N	N	N	Y	Y	Y
Freezing at -80°C	$$$	Liquid N2 not permitted; Dry shippers exemption A152	Y	Y	N	N	Y	Y	Y	Y
RNALater (± Freezing)	$$	None	Y	N	N	N	N*	N	Y	Y
TriZol (+ Freezing)	$$	Corrosive liquid, n.o.s., hazard class 8	Y	Y	N	N	**	**	**	**
Formalin	$	DG Class II	N	N	Y	Y	N	N	N	N
≥95% Ethanol	$	Exempted Quantities	Y*	Y	N	N	Y*	Y	Y	Y

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