

## Secondary Metabolites as Mediators of Trophic Interactions Among Antarctic Marine Organisms<sup>1</sup>

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**SYNOPSIS.** Secondary metabolites are widespread among lower phyla and understanding their functional role(s) in the producing organism has been under study in recent decades. Considerable progress has been made in understanding chemical ecological interactions among terrestrial organisms, and similar research in the marine realm has been initiated in recent years. Polar regions are more difficult to access and thus progress has been slower. Nevertheless, the extreme and often unique marine environments surrounding Antarctica as well as the many unusual trophic interactions in antarctic marine communities might well be expected to select for novel secondary metabolites and/or novel functional roles for secondary metabolites. Indeed, recent studies have documented novel, chemically-mediated interactions between molluscs and amphipods, between algae, urchins and anemones, and between sponges and their predators. The Porifera are the dominant phylum on the McMurdo Sound benthos, and representatives of this phylum have been shown to elaborate sea star feeding deterrents, inhibitors of fouling or infectious organisms, and metabolites which mediate predation via molt inhibition. As a result of studies on Antarctic sponges, new insights into functional roles of pigments and the ability of sponges to sequester metabolites have been gained, and a new mechanism of chemical defense has been described. Herein we describe recent results of our studies of trophic interactions between sponges and their predators that are mediated by specific sponge secondary metabolites. Moreover, we highlight unusual chemically-mediated interactions in antarctic marine invertebrates other than sponges.

### INTRODUCTION

Sessile or sluggish organisms must defend themselves from predation or encroachment of competitors since their lack of mobility precludes evasion (Harborne, 1994). Many organisms have been found to defend themselves by producing toxins or other bioactive small molecules (*i.e.*, M.W. <1,000). Many more organisms are known to produce small molecule “secondary metabolites,” possessing unknown functional roles. In Antarctica, where trophic relationships have evolved under differing ecological and physical constraints than are found in temperate and tropical ecosystems (Day-

ton *et al.*, 1994), we have been interested in the nature of chemical defense agents and their functional role(s) (McClintock and Baker, 1997; Amsler *et al.*, 2001a).

Secondary metabolites, also known as natural products, are biochemicals which might be described as lacking a role in the “internal economy” of the producing organism (Williams *et al.*, 1989; Williams and Maplestone, 1992). A characteristic of secondary metabolites is their limited phylogenetic distribution; while primary metabolites such as the common amino acids, carbohydrates, and nucleosides, are chemically identical in virtually all organisms, both simple and advanced, secondary metabolites are generally limited to a specific species or even a chemotypical subset of a species.

There are a number of classes of natural products, recognized on the basis of their biosynthetic origin, such as polyketides, terpenes and alkaloids. For example, in the

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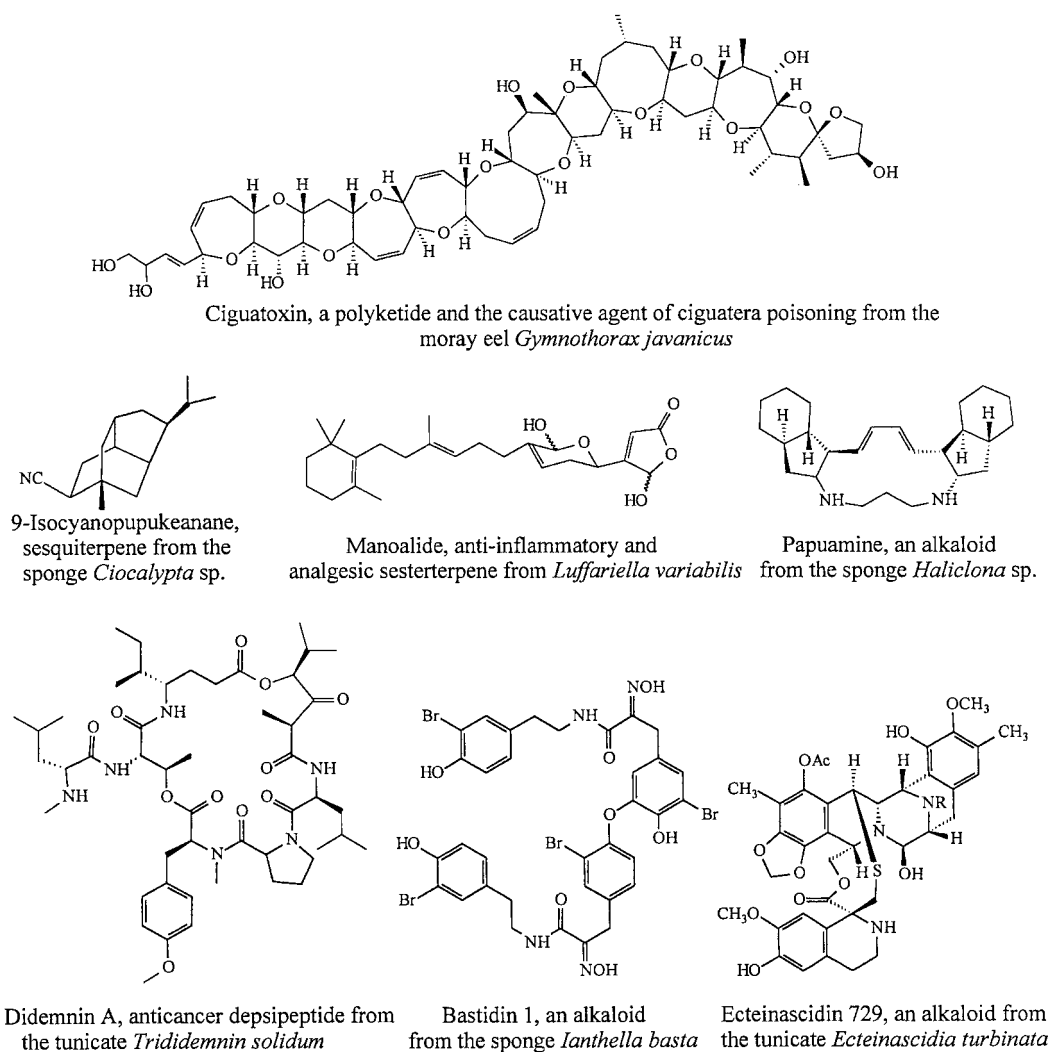


FIG. 1. Examples of several classes of secondary metabolites taken from the marine natural product literature.

marine realm, representative polyketides include the red tide and similar toxins, such as the brevetoxins (Lin *et al.*, 1981) and ciguatoxin (Murata *et al.*, 1989; Scheuer, 1994) (Fig. 1). Polyketides are built primarily of acetate (two carbon,  $C_2$ ) units, with occasional propionate ( $C_3$ ) or, rarely, larger building blocks (Herbert, 1981). Terpenes are characterized by the number of  $C_5$  isoprene units in their structure. Monoterpenes such as halomon (Fuller *et al.*, 1994), an antitumor compound from a red macroalga, contain two isoprene units and are therefore  $C_{10}$  compounds, while sesquiterpenes such as the sponge-derived 9-isocyanopupekaneane (Burreson *et al.*, 1975)

(Fig. 1) contain three isoprene units, diterpenes have four, sesterterpenes, such as the analgesic manoalide (De Silva and Scheuer, 1980) (Fig. 1) have five, and diterpenes, have six isoprene units. Larger terpenes are uncommon, with the exception of polymeric isoprene, well known as rubber. Shikimates generally derive from phenylalanine and include many of the aromatic natural products, such as hydroquinones found in *Sargassum* (see Faulkner, 1999). Other amino acid derived natural products include the small linear or cyclic peptides, which are often composed of unmodified amino acids

connected by peptide bonds, but can incorporate modified amino acids, ester bonds (the depsipeptides), and even polyketide portions. The cytotoxic didemnin depsipeptides (Rinehart *et al.*, 1981) are examples of this class of natural products (Fig. 1). Derivatives of other primary metabolites, including nucleosides, carbohydrates, and fatty acids can also be found as secondary metabolites, though they are less common. The final major class of natural products is the alkaloids, which are nitrogen-containing, often aromatic, compounds which primarily derive their nitrogen from the amino acid pool but have lost much of the appearance of the amino acids. Examples of marine alkaloids include the bastidins (Kazlauskas *et al.*, 1981), ecteinascidins (Wright *et al.*, 1990; Rinehart *et al.*, 1990), and papuamine (Baker *et al.*, 1988), with decreasing degrees of similarity to their amino acid progenitors (Fig. 1).

The complexity, diversity, and common occurrence of secondary metabolites raises the question of their functional roles. That natural products have a reputation as toxins and noxins (*vide supra*) addresses one functional role as deterrents of predation, and certainly this role for natural products has been the most thoroughly studied to date (Paul, 1992; Pawlik, 1993; Hay, 1996; McClintock and Baker, 1997, 2001; Amsler *et al.*, 2001a). Other functional roles which have been studied include inhibition of fouling and/or infection and mediation of spatial competition (Sammarco and Coll, 1992; Rittschof, 2001). What is clear is that secondary metabolites are produced under selective evolutionary pressure; energy expenditure for the biosynthesis of natural products detracts from that available to growth and reproduction and therefore must serve a purpose (Barnes and Hughes, 1988; Herms and Matteson, 1992; Berenbaum, 1995). Studies of chemical ecology seek to identify a chemical basis of organismal interrelationships.

#### THE ANTARCTIC MARINE BENTHOS

Early biogeographic comparison of the incidence of chemical defense predicted an inverse relationship with latitude (Bakus and Green, 1974). This theory suggested

that polar marine invertebrates lack sufficient fish predation to drive natural selection for chemical means of protection. However, when this theory was proposed, little was known of the predatory-prey interactions of benthic marine invertebrates in Antarctica, much of which has come to light through subsequent studies (Dayton *et al.*, 1974; Dayton 1979; McClintock and Baker, 1997; Amsler *et al.*, 2000). In McMurdo Sound (77°S, 164°E), for example, benthic invertebrates are exposed to significant predation, primarily by sea stars (Dayton *et al.*, 1974; McClintock, 1997), they are under pressure from fouling diatoms (Amsler *et al.*, 2001b), invertebrate larvae, algal spores, and potentially infectious water-column microorganisms, and they must compete for scarce hard substrate upon which to settle. These are characteristics which would suggest Antarctic marine benthic organisms are likely to evolve chemically-mediated defensive strategies.

The benthos of McMurdo Sound is characterized by extensive cover by sponges, which can occupy as much as 55% of the benthos (Dayton *et al.*, 1974). The fast growing, potentially space dominating sponge *Mycale acerata* is kept in check by the spongivorous sea star *Perknaster fuscus*. *P. fuscus* includes a number of other sponges in its diet and is therefore a major predator of the sponges. Because sponges are well known to elaborate natural products (Faulkner, 1999), the relationship between *P. fuscus* and sponges has been a primary focus of our investigation of chemical ecological relationships in McMurdo Sound, Antarctica. Herein we describe the trophic relationships of five McMurdo Sound sponges and their predators.

#### TROPHIC RELATIONSHIPS INVOLVING ANTARCTIC SPONGES

Among the common members of the sponge community are several conspicuously colored species. *Isodictya erinacea* and *Dendrilla membranosa* are bright yellow sponges and lack structural defenses, being devoid of spicule armamentation (Dayton *et al.*, 1974). Neither of these two sponges are among those consumed by *P. fuscus* (Dayton *et al.*, 1974). *Latrunculia*

*apicalis* is a deep green sponge which also has not been observed to be preyed upon by *P. fuscus*. Perhaps the most striking sponge is the fire-red *Kirkpatrickia variolosa*. This sponge comprises only a minor component of the diet of *P. fuscus* and is composed of soft, fleshy tissue. The seeming lack of predation by *P. fuscus* on these sponges which lack physical deterrence make them likely candidates for chemical investigation (Dayton *et al.*, 1974).

To understand patterns of spongivory in *Perknaster fuscus* to McMurdo Sound sponges, we developed a tube-foot retraction assay (McClintock *et al.*, 1994). When placed on their aboral side in a finger bowl of fresh, ambient temperature ( $-1^{\circ}\text{C}$ ) sea water, the tube-feet of the sea star are readily accessible. The tube-feet are chemosensory, used by the sea star for, among other things, assessment of prey suitability (Sloan, 1980). Contact of the tube-feet with sponge extracts elicits a characteristic chemosensory response; an unsuitable extract, applied to a glass rod for accurate positioning, may elicit a retraction for up to 60 sec, whereas extracts from acceptable sponges or controls typically causes attachment of the tube-foot to the glass rod (McClintock *et al.*, 1994; 2000). We have used this assay to assess McMurdo Sound sponge extracts for the presence of chemical agents which might deter predation (McClintock *et al.*, 1994; 2000).

Validation of the tube-foot retraction assay was achieved by its ability to accurately predict sea star feeding preferences in the field (Dayton *et al.*, 1974; Amsler *et al.*, 2000). Primary dietary sponges of *P. fuscus*, for example, elicit a response commensurate with controls, while several sponges known to elaborate toxic chemistry display characteristically long tube-foot retraction times. Compare, for example, *P. fuscus* commonly preyed upon sponges *M. acerata*, *Homaxinella balfourensis*, *Haliclona scoti* (Dayton *et al.*, 1974; personal observations by the authors) with the composite control response (Fig. 2). Similarly, sponges eliciting the longest tube-foot retraction times, such as *Isodictya spingerosa* and *Latrunculia apicalis*, are not found among the sponges preyed upon by *P. fuscus* (Dayton

*et al.*, 1974; personal observations of the authors).

#### CHEMICAL ANALYSES OF BIOACTIVE MCMURDO SOUND SPONGES

Extracts from *Latrunculia apicalis* elicit a significant tube-foot retraction response in *Perknaster fuscus* (McClintock *et al.*, 1994). Fractionation of the extract yielded discorhabdin alkaloids (Yang, 1994; Yang *et al.*, 1995). This group of pigments was first reported from sponge species found in temperate and tropical waters, and they are routinely toxic (Perry *et al.*, 1988). Discorhabdin C and G (Fig. 3) were found in *L. apicalis* from McMurdo Sound and were bioactive in both the tube-foot retraction assay and in antimicrobial assays using sympatric or other bacteria; discorhabdin C is a potent mammalian cytotoxin, emphasizing its bioactive nature (Yang 1994; Yang *et al.*, 1995). The discorhabdins are clearly serving a role in *L. apicalis* as defensive agents, both toward predators and potential infectious agents.

It is noteworthy that the sea star feeding deterrent bioactivity mediated by the discorhabdins is an interaction that takes place near the sponge surface. Sea stars feed by extruding their cardiac stomach over their prey, thus predation begins at the pinacocytic layer. This contrasts with tropical marine systems where spongivory occurs primarily by fish or turtles and their biting activities encroach deeply in the mesohyle. To test the ability of *L. apicalis* to sequester chemical defenses at this most vulnerable site, an analysis of discrete sponge layers was undertaken (Furrow *et al.*, in preparation). While interspecific variation of discorhabdin G content was found among these layers, mean levels of discorhabdin G were highest in the outer surface (top 2 mm) of the sponge and fell off rapidly toward the center (Furrow *et al.*, in preparation). Other instances of sponges sequestering natural products in more susceptible tissues have been demonstrated (Thompson *et al.*, 1983; Schupp *et al.*, 1999), though this is the first example of sequestration near the surface of a sponge.

*Dendrilla membranosa* is among the few antarctic sponges known to produce ter-

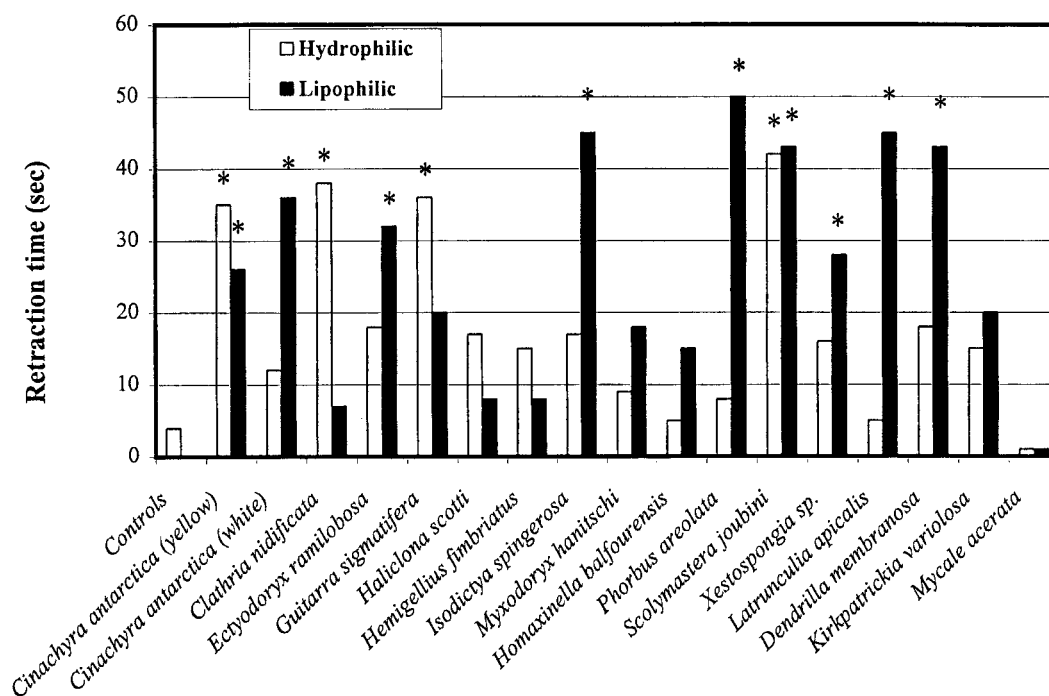


FIG. 2. Chemotactic tube-foot responses of the Antarctic sea star *Perknaster fuscus* to hydrophilic and lipophilic extracts of Antarctic sponges. Each bar shows the mean tube-foot retraction time (sec) for 10 trials, except the control where  $n = 60$  trials. Asterisks indicate statistical significance ( $P < 0.05$ ; Kruskal-Wallis One-Way Analysis of variance ranks followed by pairwise comparison with a Mann-Whitney  $U$ -test) when compared with the control. "0" indicates that assays were performed but with mean retraction time = 0 seconds. Adapted from McClintock *et al.*, 1994 and McClintock *et al.*, 2000; data for *Latrunculia apicalis*, *Dendrilla membranosa*, *Kirkpatrickia variolosa*, *Mycale acerata* and *Homaxinella balfourensis* include composite "lipophilic extract" bars derived from original data (McClintock *et al.*, 1994) on hexane and chloroform extracts.

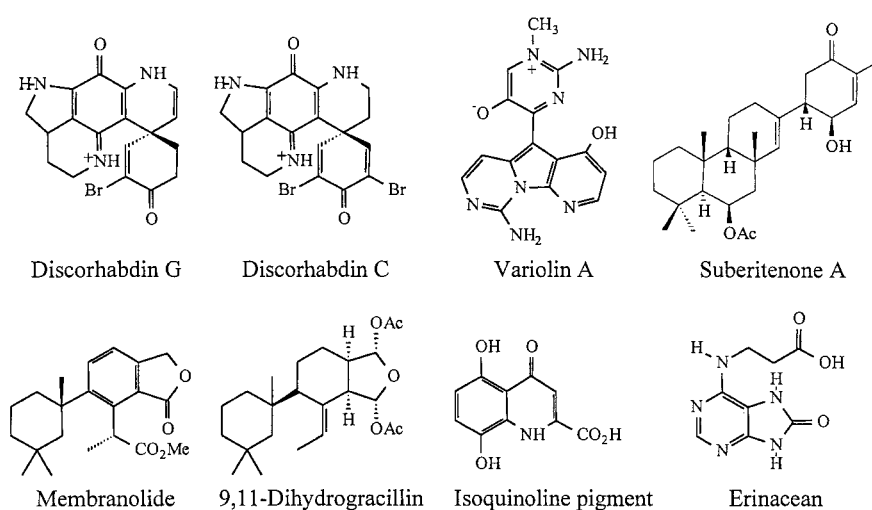


FIG. 3. Chemical structures of bioactive compounds isolated from antarctic sponges.



penes (Amsler *et al.*, 2001a). Membranoli-  
de and 9,11-dihydrogracillin (Fig. 3) are re-  
ported to have antibiotic activity (Molinski  
and Faulkner, 1987), though the most po-  
tent biological activity is associated with  
the alkaloids from *D. membranosa*, such as  
the yellow isoquinoline pigment (Fig. 3),  
which has antibiotic activity (Molinski and  
Faulkner, 1988), and picolinic acid, which  
has tube-foot retraction activity (Baker *et al.*,  
1993, 1995).

The bright red sponge *Kirkpatrickia var-  
iolosa* produces the unusual variolin alka-  
loids (Trimurtulu *et al.*, 1994; Perry *et al.*,  
1994), such as variolin A (Fig. 3). Despite  
considerable cytotoxicity (Perry *et al.*,  
1994), variolin A does not cause significant  
tube-foot retraction in *Perknaster fuscus*.  
Other pigments in the polar extract of this  
sponge have been implicated as sea star  
feeding deterrents, though none has been  
isolated to date (Baker *et al.*, 1994).

*Suberites* sp. is a common McMurdo  
Sound sponge that has a muted yellow col-  
oration. Suberitenones A and B, originally  
described from King George Island (Shin *et al.*,  
1995) were also isolated from McMurdo  
Sound collections of the sponge (Baker  
*et al.*, 1997). Suberitenones were active in  
both the tube-foot retraction assay and in  
an antibiotic assay using sympatric bacteria.  
Similar to the situation with *Latrunculia  
apicalis*, *Suberites* sp. is a spherical sponge  
amenable to layer removal, and the bioac-  
tivity of the natural products suggested that  
sequestration on the surface would be ad-  
vantageous to the sponge. Quantitative  
analysis a single specimen located 90% of  
suberitenone A in the outer layer of the  
sponge (Tipton, Baker and McClintock, un-  
published results).

The discorhabdins from *Latrunculia ap-  
icalis*, the isoquinoline pigment from *Den-  
drilla membranosa*, the variolins from *Kirk-  
patrickia variolosa*, and, to a lesser extent,  
the suberitenones from *Suberites* sp., are all  
pigments. It is compelling to note that these  
pigments are bioactive toward a predator,  
*Perknaster fuscus*, which lacks visual ori-  
entation. The role of pigments in aposo-  
matic coloration (Guilford and Cuthill,  
1991) has recently been questioned (Chanas  
and Pawlik, 1995); the evolution of pig-

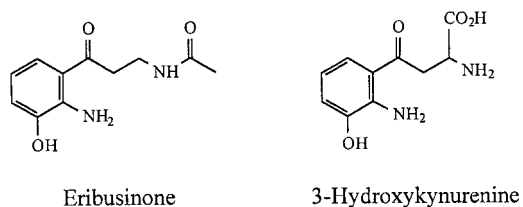


FIG. 4. Structural comparison of eribusinone, isolated from the Antarctic sponge *Isodictya erinacea* to that of 3-hydroxykynurenine.

mented chemical defenses in an ecosystem devoid of visually oriented predators argues against aposomatic roles. Pigments are almost exclusively employed in energy capture or serve as antioxidants in other sessile organisms such as marine and terrestrial plants (Lobban and Harrison, 1994). These are unlikely roles for pigments of benthic marine invertebrates. There is little information on whether pigments from temperate or tropical benthic marine invertebrates may serve as antifeedants.

Not all bioactivity of McMurdo Sound sponges investigated to date is limited to tube-foot retraction and/or antibiotic activity. *Isodictya erinacea*, for example, has yielded a number of secondary metabolites (Moon, 1997; Moon *et al.*, 1998), at least one of which appears to be involved in an unusual trophic relationship. A host of purines and nucleosides, including the cytotoxic erinacean, was found in *I. erinacea*, and *p*-hydroxybenzaldehyde was identified as the metabolite responsible for tube-foot retraction activity of the lipophilic extract (Moon *et al.*, 1998).

The yellow pigment eribusinone (Moon, 1997), an apparent tryptophan catabolite (Fig. 4), has also been isolated from *Isodictya erinacea*. Tryptophan catabolites are involved in crustacean molt regulation (Naya *et al.*, 1993). Kynurenine (Fig. 4) and xanthurenic acid, for example, lie on the molt regulatory pathway. Xanthurenic acid inhibits the cytochrome P450 enzyme which is responsible for hydroxylation of ecdysone to 20-hydroxyecdysone, the molt hormone in crustaceans. Structural similarity of kynurenine and eribusinone (Fig. 4) led to studies of the functional role of eribusinone in crustacean molt regulation.

The amphipod *Orchomene plebs*, a voracious omnivorous predator (personal observations), was fed a diet enriched in eribusinone. Despite the fact that *O. plebs* consumed more eribusinone-enriched diet than control (krill enriched), diet, molt events were significantly reduced and mortality significantly increased (Moon *et al.*, 2000). This is the first example of molt regulation as a potential mechanism of chemical defense in the marine realm and differs from terrestrial molt regulation mechanisms in being molt inhibitory, rather than stimulatory, as is found among land plant chemical defenses against insects (Harborne, 1994).

#### OTHER CHEMICALLY-MEDIATED TROPHIC INTERACTIONS OF NOTE

This report focuses largely on the interactions of sponges and their predators. However, in the context of Antarctic chemical ecology investigations, a number of other significant trophic interactions are noteworthy (McClintock and Baker, 1997). The unusual relationship between the pelagic mollusc *Clione antarctica*, a pteropod, and its amphipod (*Hyperietta dilatata*) abductor (McClintock and Janssen, 1990) has been described as "antagonistic symbiosis" (McClintock and Baker, 1998). *Clione antarctica* elaborates a fish feeding deterrent, pteroenone (Bryan *et al.*, 1995; Yoshida *et al.*, 1995), which protects it from several sympatric fish predators. *Hyperietta dilatata* is a major prey item of these same fish predators and has evolved the ability to capture *C. antarctica* from the water column, position it on its dorsum, and thus avoid fish predation (McClintock and Janssen, 1990).

Another unique trophic interaction is a "feeding triangle" involving defensive interactions of macroalgae, sea urchins, and sea anemones. The sea anemone *Isotealia antarctica* is a voracious, opportunistic predator of macroinvertebrates (Dayton *et al.*, 1970) and is involved in a mutualistic relationship between one of its prey, the sea urchin *Sterechinus neumayeri*, and two of the urchin's potential prey items, the macroalgae *Phyllophora antarctica* and *Iridaea cordata* (Amsler *et al.*, 1999). *S. neu-*

*mayeri* preferentially covers itself with these macroalgae and this cover significantly increases the likelihood of escape from *I. antarctica* because the anemones' tentacles attach to the algae which the anemone or both the urchins and anemone then release. Macroalgae benefit from this relationship because fertile drift plants are retained in the photic zone where they continue to contribute to the gene pool. Both macroalgal species are chemically defended against herbivory by *S. neumayeri* (Amsler *et al.*, 1998). Hence this relationship differs from the antagonistic symbiosis of *Clione antarctica* and *Hyperietta dilatata* by being a true defensive mutualism benefiting both the macroalgae and urchins.

#### SUMMARY

Chemical ecological investigations of antarctic sponges have demonstrated that chemical defenses have evolved in numerous species. This contradicts corollaries of early theories concerning biogeographic variation in predation and in chemical defense but agrees with predictions that could have been made based on the intense predation demonstrated by more recent investigators. The Antarctic offers unique opportunities to study selected ecological relationships, such as the role of pigments in chemical defense in the absence of visually oriented predators, and the role of secondary metabolite sequestration in predators which attack surface tissues. We have also documented several unique chemically-mediated trophic relationships, including a new mechanism of chemical defense in the marine realm (molt inhibition), antagonistic symbiosis, and an unusual chemically-mediated "feeding triangle."

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