MARINE BIOTECHNOLOGY

Marine Sponges as Pharmacy

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Abstract

Marine sponges have been considered as a gold mine during the past 50 years, with respect to the diversity of their secondary metabolites. The biological effects of new metabolites from sponges have been reported in hundreds of scientific papers, and they are reviewed here. Sponges have the potential to provide future drugs against important diseases, such as cancer, a range of viral diseases, malaria, and inflammations. Although the molecular mode of action of most metabolites is still unclear, for a substantial number of compounds the mechanisms by which they interfere with the pathogenesis of a wide range of diseases have been reported. This knowledge is one of the key factors necessary to transform bioactive compounds into medicines. Sponges produce a plethora of chemical compounds with widely varying carbon skeletons, which have been found to interfere with pathogenesis at many different points. The fact that a particular disease can be fought at different points increases the chance of developing selective drugs for specific targets.

Key words: sponge medicine — natural product — cancer — inflammation — virus

Introduction

The relationship between sponges and medicines goes back to Alexandrian physicians and was thoroughly describes by the Roman historian Plinius. Physicians used sponges that were saturated with iodine to stimulate coagulation of the blood, or with bioactive plant extracts to anesthetize patients. Sponges were soaked with pure wine and put on the left part of the chest in case of heartaches and soaked in urine to treat bites of poisonous animals. Plinius recommended the use of sponges against sunstrokes, and they were used against all kinds of wounds, bone fractures, dropsy, stomach aches, infectious diseases, and testicular tumors (Hofrichter and Sidri, 2001), or even as implants after breast operations (Arndt, 1938). At least since the 18th century, Russian, Ukrainian, and Polish physicians have used a freshwater sponge they call Badiaga (Figure 1) for the treatment of patients (Nozeman, 1788). The dry powder of this sponge is rubbed on the chest or back of patients with lung diseases or on the sore places in cases of foot and leg aches (such as rheumatism (Schroder, 1942). Oficjalski (1937) discovered that Badiaga is not really one sponge, but mixtures of several freshwater sponges that differ depending on the region. In Poland it consisted of powder of *Euspongilla lacustris*, *Ephydatia fluviatilis*, and *Meyenia muelleri*, while the Russian Badiaga was a mixture of *Euspongilla lacustris*, *Ephydatia fluviatilis*, *Spongilla fragilis*, and *Carterius stepanowi*. He suggested that the high iodine concentration in all sponge species gives rise to the wholesome effect of Badiaga. At present Stodal, syrup containing roasted *Spongia officinalis*, is used for homeopathic treatment of dry and asthmatic cough in the Western world (Stodal, 2003).

Pharmaceutical interest in sponges was aroused in the early 1950s by the discovery of a nucleosides spongothymidine and spongouridine in the marine sponge *Cryptotethia crypta* (Bergmann and Feeney, 1950, 1951). These nucleosides were the basis for the synthesis of Ara-C, the first marine-derived anticancer agent, and the antiviral drug Ara-A (Proksch et al., 2002). Ara-C is currently used in the routine treatment of patients with leukemia and lymphoma. One of its fluorinated derivatives has also been approved for use in patients with pan-

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Fig. 1. Examples of homeopathic drugs based on sponge extracts currently in use (Badiaga and Stodal syrup).

creatic, breast, bladder, and lung cancer (Schwartsmann, 2000). At the same time it was revealed that certain lipid components such as fatty acids, sterols and other unsaponifiable compounds occur in lower invertebrates in a diversity far greater than that encountered among animals of higher organization (Bergmann and Swift, 1951). These early promises have now been substantiated by an overwhelming number of bioactive compounds that have been discovered in marine organisms. More than 15,000 marine products have been described thus for (MarinLit, 1999; Faulkner, 2000, 2001, 2002). Sponges, in particular, are responsible for more than 5300 different products, and every year hundreds of new compounds are being discovered (Faulkner 2000, 2001, 2002).

Most bioactive compounds from sponges can be classified as antiinflammatory, antitumor, immunosuppressive or neurosuppressive, antiviral, antimalarial, antibiotic, or antifouling. The chemical diversity of sponge products is remarkable. In addition to the unusual nucleosides, bioactive terpenes, sterols, cyclic peptides, alkaloids, fatty acids, peroxides, and amino acid derivatives (which are frequently halogenated) have been described from sponges (Figure 2).

For this review we have surveyed the discoveries of products derived from marine sponges up to now, and attempted to show the variety of potential medical applications of metabolites from sponges and the mechanisms by which they interfere with the pathogenesis of human diseases. This knowledge is a prerequisite for the development of a drug from a bioactive compound. For example, many secondary metabolites inhibit growth of cancer cell lines, but this does not imply

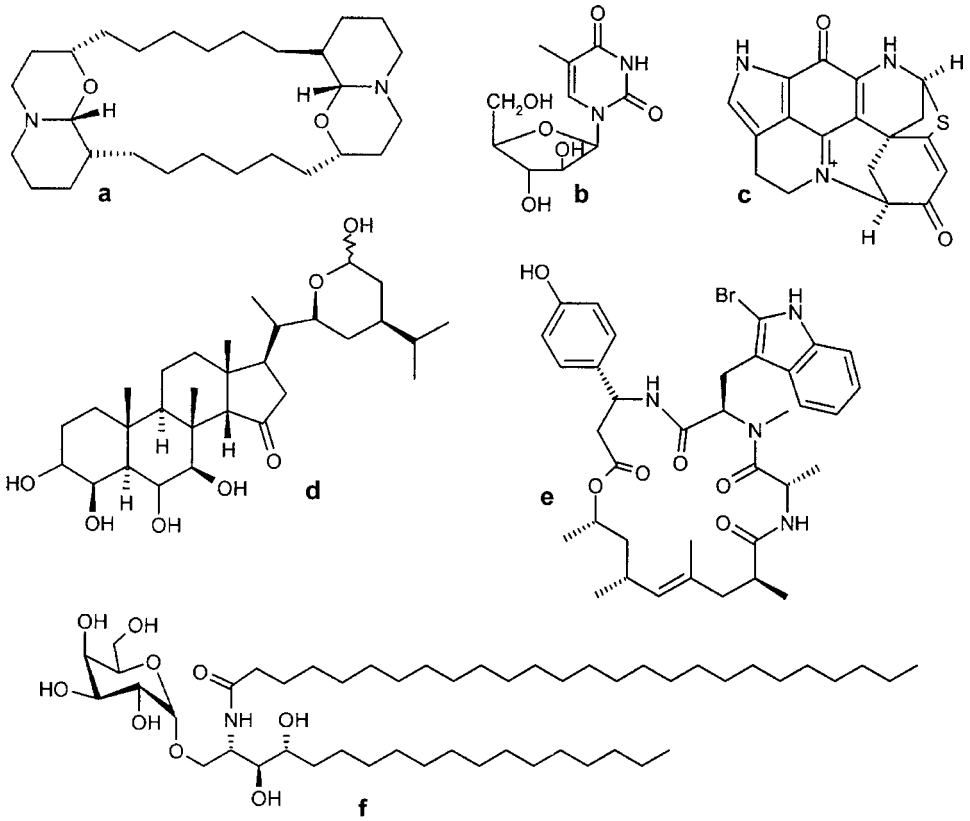

Fig. 2. An illustration of the chemical diversity of sponge-derived molecules. **a:** Xestospongin C (*Xestospongia* sp. / macrocyclic bis-oxaquinolizidine. **b:** Spongothymidine (*Cryptotethia crypta* / unusual nucleoside). **c:** discorhabdin D (*Latrunculia brevis; Prianos* sp. / fused pyrrolophenanthroline alkaloid. **d:** Contignasterol (*Petrosia contignata* / oxygenated sterol). **e:** Jaspamide (*Hemiastrella minor* / macrocyclic lactam/lactone). **f:** agelasphin (*Agelas mauritianus* / α-galactosylceramide).

that they will be suitable as a medicine against cancer, because they may exhibit important side effects. The following sections summarize compounds by disease type and describe their mode of action, and discuss the reasons why sponges would produce these metabolites.

Sponge Products

Antiinflammatory Compounds. Acute inflammations in the human body can result from microbial infection, physical damage, or chemical agents. The body reacts by changing the blood flow, increasing the permeability of blood vessels, and allowing the escape of cells from the blood into the tissues (Tan et al., 1999). Chronic inflammation of the skin or joints may severely damage the body if it leads to psoriasis or rheumatic arthritis (Pope et at., 1999). Sponges have proved to be an interesting source of antiinflammatory compounds (Table 1).

Manoalide, one of the first sesterterpenoids to be isolated from a marine sponge (*Luffariella variabilis*), *was* found to be an antibiotic (De Silva and Scheuer, 1980) and an analgesic (Mayer and Jacobs, 1988). In addition, its antiinflammatory properties have been studied extensively (Bennet et al., 1987). The antiinflammatory action is based on the irreversible inhibition of the release of arachidonic acid from membrane phospholipids by preventing the enzyme phospholipase A_2 from binding to the membranes (Glaser et al., 1989). A rise in the intracellular arachidonic acid concentration would lead to upregulation of the synthesis of inflammation mediators as prostaglandins and leukotrienes (Figure 3). Phospholipase A_2 inhibition has been recorded for many sesterterpenes from sponges of the order Dictyoceratida, but also for bis-indole alkaloids such as topsentin (Jacobs et al., 1994). The mechanism by which they affect the inflammation process is different from commonly used nonsteroidal antiinflammatory drugs. Only a few sponge-derived terpenoids have been found to inhibit lipoxygenase, another enzyme that is involved in the inflammatory response (Carroll et al., 2001).

The antiinflammatory sponge products are selective inhibitors of specific enzymes of a range of diseases, like psoriasis or rheumatic arthritis. The currently used nonsteroidal antiinflammatory drugs often fail to control the disease and present important side effects such as risk of gastrointestinal bleeding and renal complications (De Rosa, 2002). These are caused by unselective inhibition of cyclooxygenases, some of which are also involved in the promotion of the production of the natural mucus that protects the gastrointestinal tract (Bjarnason et al., 1993).

Table 1. Examples of Antiinflammatory Products from Sponges

Compound	*Compound class*	*Species/order*	*Mode of action*	*Reference*
Manoalide	Cyclohexane sesterterpenoid	*Luffariella variabilis*/ Dictyoceratida	Phospholipase A_2 inhibitor	Bennet et al., 1987
Dysidotronic acid	Drimane sesquiterpenoid	*Dysidea* sp./ Dendroceratida	Phospholipase A_2 inhibitor	Giannini et al., 2000
Ircinin-1 and -2	Acyclic sesterterpenoid	*Ircinia oros*/ Dictyoceratida	Phospholipase A_2 inhibitor	Ciminoe et al., 1972
Petrosaspongiolides M-R	Cheilantane sesterterpenoid	*Petrosaspongia nigra*/ Dictyoceratida	Phospholipase A_2 inhibitor	Randazzo et al., 1998a
Spongidines A-D	Pyridinium alkaloid	*Spongia* sp./ Dictyoceratida	Phospholipase A_2 inhibitor	De Marino et al., 2000
Topsentin	Bis-indole alkaloid	*Topsentia genitrix*/ Halichondrida	Phospholipase A_2 inhibitor	Jacobs et al., 1994
Scalaradial	Scalarane sesterterpene	*Cacospongia scalaris*/ Dictyoceratida	Phospholipase A_2 inhibitor	De Carvalho and Jacobs, 1991
Cacospongionolide B	Sesterterpene lactone	*Fasciospongia cavernosa*/ Dictyoceratida	Phospholipase A_2 inhibitor	Garcia Pastor et al., 1999
Jaspaquinol	Diterpene benzenoid	*Jaspis splendens*/ Astrophorida	Lipoxygenase inhibitor	Carroll et al., 2001
Subersic acid	Diterpene benzenoid	*Suberea* sp./Verongida	Lipoxygenase inhibitor	Carroll et al., 2001

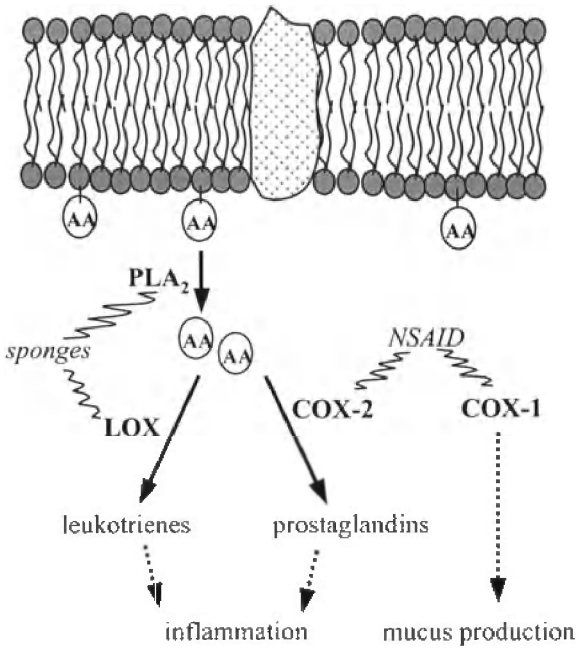

Fig. 3. Inflammatory cascade inside the cell. Phospholipase A_2 (PLA_2) catalyzes the release of membrane-bound arachidonic acid (AA) to free arachidonic acid. Arachidonic acid is converted to leukotrienes and prostaglandins by lipoxygenase (LOX) and cyclooxygenase-2 (COX-2), respectively. Sponge-derived antiinflammatory molecules are mainly inhibitors of PLA_2 or LOX, while nonsteroidal antiinflammatory drugs inhibit COX-2, but also the constitutive COX-1.

Antitumor Compounds. A number of isolated sponge compounds are inhibitors of protein kinase C (PKC). PKC inhibitors have attracted interest worldwide, as there is evidence that too high levels of PKC enzyme are involved both in the pathogenesis of arthritis and psoriasis (owing to regulation of phospholipase A_2 activity), and in tumor development (Bradshaw et al., 1993; Yoshiji et al., 1999). PKC is believed to be the receptor protein of tumor-promoting phorbol esters, and PKC inhibitors prevent binding of carcinosarcoma cells to the endothelium (B. Liu et al., 1991). Glycosylation of the receptors, and especially the presence of fucose residues, plays an important role in the binding of carcinosarcoma cells and leukocytes to the receptors in the endothelium (Springer and Lasky, 1991).

Fucosyltransferase inhibitors, such as the octa- and nonaprenylhydroquinone sulfates that were isolated from a *Sarcotragus* sp. (Wakimoto et al., 1999), may therefore be promising candidates for controlling inflammatory processes such as arthritis or for combating tumor growth.

In addition to PKC inhibitors and fucosyl transferase inhibitors, numerous anticancer molecules with a different mode of action have been discovered in marine sponges (Table 2). These compounds can be divided in 3 classes:

(1) nonspecific inhibitors of cell growth; (2) specific inhibitors of cancer cells; and (3) inhibitors of cancer cells of a certain type of cancer (as the aforementioned PKC inhibitors).

Many nonspecific cell growth inhibitors have been discovered in sponges. They are valuable for treating cancer under certain conditions, but they also affect the division of healthy cells. Therefore, their applications are limited, depending on their specific characteristics. The cytoskeleton is an interesting target for cancer therapy, as the microtubules and microfilaments are involved in cellular organization during cell division. A number of adociasulfates (triterpenoid hydroquinones) from a *Haticlona* sp. were the first inhibitors of the kinesin motor protein to be discovered. These toxins are believed to inhibit the protein by binding to the microtubule binding site, "locking up" the protein's motor function, and thereby blocking cell division (Blackburn et al., 1999). In addition to these triterpenoid hydroquinones, a number of potent microtubule-interfering compounds have been discovered in marine sponges, such as halichondrin B (Bai et al., 1991), spongistatin (Bai et al., 1993), discodermolide (Ter Haar et al., 1996), laulimalide (Moobeny et al., 1999), peloruside A (Hood et al., 2002), and dictyostatin (Isbrucker et al., 2003). Other metabolites, such as latrunculin A from *Latrunculia magnifica* (Coue et al., 1987) and swinholide A from *Theonella swinhoei* (Bubb et al., 1998), disrupt the polymerization of actin. Actin which is the key element of the microfilaments, and it can block many cellular processes including cell division. Spongiacidin B (Inaba et al., 1998) and fascaplysin (Soni et al., 2000) are examples of sponge-derived metabolites that inhibit cell division by inhibition of cyclin-dependent kinase 4, which leads to arrest of cells in the G1 phase. Other metabolites, such as mycalamide (Burres and Clement, 1989) and aragusterol (Fukuoka et al., 2000), disturb cell division by inhibition of protein synthesis. Neoamphimedine (De Guzman et al., 1999) and elenic acid (Juagdan et al., 1995) inhibit the development of tumors by blocking topoisomerase II, the nuclear enzyme which makes transient DNA breaks that are required for replication (L.F. Liu and Chen, 1994).

Nitric oxide synthetase inhibitors, such as the imidazole alkaloid Na amine D that was isolated from the calcareous sponge *Leucetta* cf. *chagosensis* (Dunbar et al., 2000), are not involved in growth inhibition of cancer cells, but may prevent events in the early phases of tumorigenesis. Nitric oxide could participate in the tumorigenesis by mediating DNA

Table 2. Examples of Antitumor Products from Sponges

Compound	*Compound class*	*Species/order*	*Mode of action*	*Reference*
BRS1	Diamino-dihydroxy polyunsaturated lipid	Calcareous sponge/?	Protein kinase C inhibitor[a]	Willis and De Vries, 1997
Isoaaptamine	Benzonaphthyridine alkaloid	*Aaptos aaptos*/ Hadromerida	Protein kinase C inhibitor[a]	Fedoreev et al., 1989
Debromohymenialdisine	Pyrrole-guanidine alkaloid, prenylhydroquinone derivative	*Hymeniacidonaldis*/ Halichondrida	Protein kinase C inhibitor[a]	Kitagawa et al., 1983
		Sarcotragus sp./ Dictyoceratida	A1, 3-fucosyltransferase inhibitor	Wakimoto et al., 1999
Adociasulfates	Triterpenoid hydroquinones	*Haliclona (aka Adocia)* sp./ Haplosclerida	Kinesin motor protein inhibitors	Blackburn et al., 1999
Discodermolide	Linear tetraene lactone	*Discodermia dissolute*/ Lithistida	Stabilization of microtubules	Ter Haar et al., 1996
Laulimalide	Macrocyclic lactone	*Cacospongia mycofljiensis*/ Dictyoceratida	Stabilization of microtubules	Mooberry et al., 1999
Peloruside A	Macrocyclic lactone	*Mycdle hentschett*/ Poecilosclerida	Stabilization of microtubules	Hood et al., 2002
Hemiasterlin	Unusual tripeptide	*Auletta* sp./Halichondrida	Stabilization of microtubules	Anderson et al., 1997
Dictyostatin	Macrocyclic lactone	*Corallistidae* sp./Lithistida	Stabilization of microtubules	Isbrucker et al., 2003
Spongistatin 1	Bis(spiroacetal) macrolide	*Spongia* sp./Dictyoceratida	Tubulin polymerisation inhibitor	Bai et al., 1993
Halichondrin B	Polyether macrolide	e.g., *Halichondria okadai*/ Halichondrida	Tubulin polymerisation inhibitor	Hirata and Uemura, 1986; Bai et al., 1991
Arenastatin A	Macrocyclic lactan/ lactone	*Dysidea arenaria*/ Dendroceratida	Tubulin polymerisation inhibitor	Koiso et al., 1996
Latrunculin A	Thiazole macrolide	*Latrunculia magnified*/ Poecilosclerida	Actin-depolymerisation	Kashman et al., 1980 Coue et al., 1987
Swinholide A	Macrocyclic lactone	*Theonella swinhoei*/ Lithistida	Actin-depolymerization	Bubb et al., 1995
Mycalolide B	Oxazole macrolide	*Mycale* sp./Poecilosclerida	Actin-depolymerization	Fusetani et al., 1989 Saito et al., 1994
Jaspamide	Macrocyclic lactam/ lactone	*Hemiastrella minor*/		
Neoamphimedine	Pyridoacridine alkaloid	*Xestospongia* cf *carbonaria*/ Haplosclerida	Topoisomerase II inhibitor	De Guzman et al., 1999
Elenic acid	Alkylphenol	*Plakinastrella* sp./ Homosclerophorida	Topoisomerase II inhibitor	Juagdan et al., 1995
Naamine D	Imidazole alkaloid	*Leucetta* cf. *chagosensis*/Calcinea	Nitric oxide synthetase inhibitor[b]	Dunbar et al., 2000
Agelasphin (KRN7000)	α-Galactosylceramide	*Agelas mauritianus* / Agelasida	NKT cell activator	Shimosaka, 2002
Agosterol A	Sterol	*Spongia* sp./Dictyoceratida	Reverses drug resistancy of dancer cells	Aoki et al., 1998
Salicylihalamide A	Salicylate macrolide	*Haliclona* sp./Haplosclerida	v-ATPase inhibitor	Erickson et al., 1997
Chondropsin A and B	Macrolide lactam	*Chondropsis* sp./Poecilosclerida	v-ATPase inhibitor	Cantrell et al., 2000; Bowman et al., 2003
6-Hydroximino-4-en-3-one steroids	Oximated steroid	*Cinachyrella* sp./Spirophorida	Aromatase inhibitor	Holland et al., 1992
Crambescidins 1-4	Pentacyclic guanidine derivative	*Crambe crambe*/Poecilosclerida	Ca^{2+}/channel blocker	Jares-Erijman et al., 1991; Berlinck et al., 1993
Haligramides A and B	Cyclic peptide	*Haliclona nigra*/Haplosclerida	Unknown	Rashid et al., 2000
Discorhabdin D	Fused pyrrolophenanthroline alkaloid	*Latrunculia brevis*/Poecilosclerida; *Prianos* sp./Haplosclerida	Unknown	Perry et al., 1988

(continued)

Table 2. Continued

Compound	*Compound class*	*Species/order*	*Mode of action*	*Reference*
Callystatin A	Polyketide	*Callyspongia truncata*/Haplosclerida	Unknown	Kobayashi et al., 1997
Tedanolide	Macrocyclic lactone	*Tedania ignis*/Poecilosclerida	Unknown	Schmitz et al., 1984
Glaciasterols A and B	9, 11-Secosterol	*Aplysilla glacialis*/Dendroceratida	Unknown	Pika et al., 1992
Axinellins A and B	Cyclic peptide	*Axinella carteri*/Halichondrida	Unknown	Randazzo et al., 1998b
Incrustasterols A and B	Sterol	*Dysidea incrustans*/Dendroceratida	Unknown	Casapullo et al., 1995

[a]Also has antiinflammatory activity.
[b]Also has immunosuppressive activity.

damage and support tumor progression through the induction of angiogenesis (Lala and Orucevic, 1998). However, inhibition of nitric oxide synthetase may also affect other physiologic processes in which nitric oxide is involved, such as intracellular or transcellular messaging, and it is involved in regulation of the immunogenic respons by T lymphocytes. Agelasphin (KRN7000) from *Agelas mauritianus* (E. Kobayashi et al., 1995) has been found to stimulate the immune system by activation of dendritic and natural killer T (NKT) cells. The NKT cell level is lower in the blood of patients with cancer or autoimmune disease, such as type 1 diabetes (Shimosaka, 2002), and in mice it was shown that tumors could be rejected by stimulation of the immune system by agelasphin (Yamaguchi et al., 1996).

The activity of other compounds is more specific toward tumor cells. Multidrug resistance in human carcinoma cells caused by overexpression of two kinds of membrane glycoproteins is reversed by agosterol A from the marine sponge *Spongia* sp. It has been suggested that an altered cytosolic pH plays a role in drug resistance. Vascular (H^+) ATPase (v-ATPase) is an enzyme involved in many cellular processes that are often upregulated in cancer cells, such as acidic vesicular organelle formation, which is a response to radiation injury or manipulation of the pH to decrease entry of chemotherapeutics into the cells (Martinez-Zaguilan et al., 1999). Salicylihamide A was isolated from a *Haliclona* sp. as a selective inhibitor of v-ATPase and has been shown to be 60-fold more cytotoxic to certain cancer cells than to their normal noncancerous counterparts (Erickson et al., 1997). The first natural 6-hydroximino-4-en-3-one steroids were isolated from *Cinachyrella* spp. (Rodriguez et al., 1997) and are examples of molecules that can be deployed against a specific type of cancer. They displayed high affinity to aromatase (Holland et al., 1992), which is the rate-limiting enzyme that catalyzes the conversion of androgens to estrogens (Figure 4). Blockade of this step allows treatment of hormone-sensitive breast cancer that is dependent on estrogen (Lonning et al., 2003). A peculiar fact about the 6-hydroximi no-4-en-3-one steroids is that they were chemically synthesized before they were even discovered in nature.

In addition, many more compounds that displayed growth inhibition activity of tumor cell lines have been isolated (Table 2), although their exact effects are still unclear. Discorhabdin D (Perry et al., 1988), chondropsin A and B (Cantrell et al., 2000), haligramides A and B (Rashid et al., 2000), and glaciasterols A and B (Pika et al., 1992) are only a few examples of these molecules.

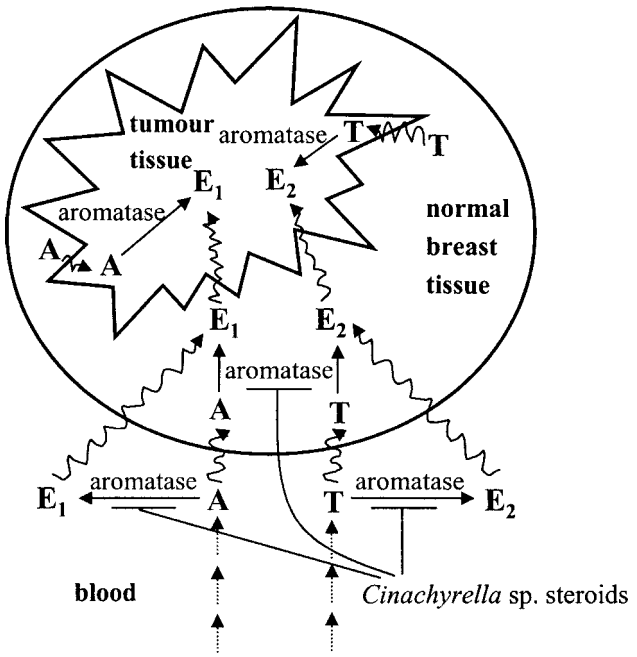

Fig. 4. Inhibition of breast cancer by *Cinachyrella* sp. steroids. Aromatase is the key enzyme in the formation of the estrogens estrone (E_1) and estradiol (E_2). It catalyzes the final steps, from androstenedione (A) to estron and from testosterone (T) to estradiol, in the estrogen pathway. Estrogen conversion can occur in the blood, in normal breast tissue, as well as in breast tumor tissue (adapted from Geisler, 2003). The 6-hydroximino-4-en-3-one steroids from *Cinachyrella* sp. are inhibitors of aromatase. The inhibition of aromatase in the tumor tissue is not shown to maintain the clarity of the illustration.

Immunosuppressive Compounds. In addition to their potential for treatment of cancer, nitric oxide synthetase inhibitors downregulate T-cells are, suppressing the immune system, and they diminish the fierceness of migraine attacks (Griffith and Gross, 1996). Immune system suppression is desired in cases of hypersensitivity to certain antigens (e.g., allergies) or organ transplantations. Patients who receive a donor organ need life-long medication to prevent rejection by the immune system, and for that reason it is extremely important that these medicines are very specific suppressors. Therefore there is a continuous demand for new immunosuppressives. A number of new molecules with immunosuppressive activity, which interfere at different points of the immune response have been discovered in marine sponges (Table 3; Figure 5).

Three polyoxygenated sterols from a *Dysidea* sp. from Northern Australia are selective immunosuppressive compounds that inhibit the binding of interleukin 8 (IL-8), a cytokine that attracts neutrophils into an area of tissue injury, to the IL-8 receptor (Leone et al., 2000). The simplexides from the Caribbean sponge *Plakortis simplex* are a group of immunosuppressive glycolipids that inhibit proliferation of activated T cells by a noncytotoxic mechanism (Costantino et al., 1999). Pateamine A, from a *Mycale* sp., inhibits the production of IL-2 (Romo et al., 1998) and thereby the activation of resting T cells and B cells to a lesser extent. Contignasterol from *Petrosia contignata* (Burgoyne and Andersen, 1992) inhibits allergen-induced histamine release from rat mast cells (Takei et al., 1994) and from guinea-pig lung tissue in vitro (Bramley et al., 1995), and the activation of eosinophils into airways in guinea-pigs and could be used to treat asthma (Langlands et al., 1995).

Cardiovascular Agents. In addition to regulators of the white blood cells, a number of sponge-derived molecules have been found to interfere with other blood-related diseases such as thrombosis, atherosclerosis, or diabetes (Table 4). The process of blood coagulation is triggered by a complex proteolytic cascade that leads to the formation of fibrin. Thrombin is a serine protease that cleaves a peptide fragment from fibrinogen, which then leads to the generation of fibrin, a major component of blood clots (Shuman et al., 1993). Cyclotheonarnide A,

Table 3. Examples of Immunosuppressive Products from Sponges

Compound	*Compound class*	*Species/order*	*Mode of action*	*Reference*
Simplexides	Glycolipid	*Plakortis simplex*/ Homosclerophorida	Inhibitor of T-cell proliferation	Costantino et al., 1999
Polyoxygenated sterols	Sterol	*Dysidea* sp./ Dendroceratida	IL-8 inhibitor	Leone et al., 2000
Contignasterol	Oxygenated sterol	*Petrosia contignata*/ Haplosclerida	Histamine release inhibitor	Takei et al., 1994; Bramley et al., 1995
Xestobergsterols A and B	Pentacyclic sterol	*Xestosponga berquistia*/ Haplosclerida	Histamine release inhibitor	Shoji et al., 1992
Taurodispacamide A	Pyrrole-imidazole alkaloid	*Agelas oroides*/Agelasida	IL-2 inhibitor	Fattorusso and Taglialatela-Scafati, 2000
Pateamine A	Thiazole macrolide	*Mycale* sp./Poecilosclerida	IL-2 inhibitor	Northcote et al., 1991

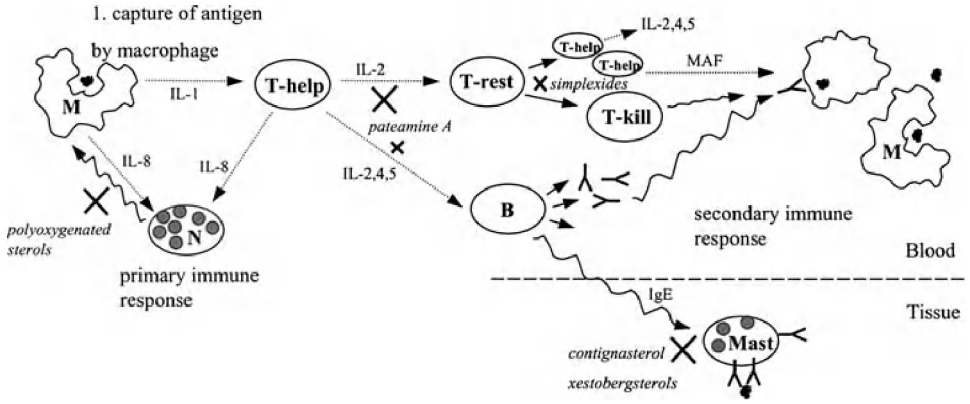

Fig. 5. Simplified representation of the immune respons after capture of an antigen by macrophages (M). Both macrophages, but especially T-helper cells (T-help), secrete many interleukins (IL-x) or macrophage activation factor (MAP), to trigger the primary immune response via neutrophils (N), or the secondary immune respons by activating resting T cells (T-rest) and B cells (B). Activated B cells secrete antibodies that bind to macrophages that have phagocytized an antigen, and they are subsequently destroyed by T-killer cells (T-kill). Mast cells (Mast) release histamine as a response to binding of an antigen to IgE molecules present in their cell membranes. The black crosses indicate position where sponge-derived immunosuppressive compounds interfere with the immune response.

isolated from a *Theonella* sp. (Fusetani et al., 1990), represents an unusual class of serine protease inhibitors and is a potential drug for the treatment of thrombosis (Maryanoff et al., 1993). Eryloside F from *Erylus formosus* was found to be a potent thrombin receptor antagonist (Stead et al., 2000). Thrombin receptor activation is likely to play a key role not only in arterial thrombosis but also in atherosclerosis (Chackalamannil, 2001). Atherosclerosis starts with damage to the endothelium and subsequent deposition of fats, cholesterol platelets, cellular waste products, calcium, and other substances in the artery wall. These may stimulate endothelial cells to produce a vascular cell adhesion molecule that results in further buildup of cells and shrinkage of the arterial diameter (Zapolska-Downar et al., 2001). Halichlorine from *Halichondria okadai* is an inhibitor of the expression of vascular cell adhesion molecule 1 (Kuramoto et al., 1996) and may thus impede atherogenesis (Arimoto et al., 1998).

Callyspongynic acid, isolated from *Callyspongia truncata*, is an α-glucosidase inhibitor (Nakao et al., 2002). α-Glucosidase inhibitors interfere with the hydrolysis of glycogen, keeping the glucose concentration in the blood at a lower level, and can be used to treat patients with diabetes (Lebovitz, 1992).

Neurosuppressive Compounds. Keramidine, isolated from an *Agelas* sp. (Nakamura et al., 1984), is an example of a number of neurosuppressive compounds that have been isolated from marine sponges (Table 5). It is a serotonergic receptor antagonist and blocks serotonin-mediated neural communication. Several different serotonin receptors have been identified. They are related to (1) platelet aggregation, and may therefore be useful against thrombosis (Ruomei et al., 1996); (2) smooth muscle contraction (Garcia-Colunga and Miledi, 1996); (3) vomiting, owing to their presence in the gastrointestinal tract (Lang and Marvig,

Table 4. Examples of Sponge Products that Affect Blood-Related Diseases

Compound	*Compound class*	*Species/order*	*Mode of Action*	*Reference*
Cyclotheonamide A	Cyclic pentapeptide	*Theonella* sp./ Lithistida	Serine protease inhibitor	Maryanoff et al., 1993
Eryloside F	Penasterol disaccharide	*Eryltus formosus*/ Astrophorida	Thrombin receptor antagonist	Stead et al., 2000
Halichlorine	Cyclic aza-polyketide	*Halichondria okadai*/ Halichondrida	VCAM-1 inhibitor	Arimoto et al., 1998
Callyspongynic acid	Polyacetylene	*Callyspongia truncata*/ Haplosclerida	α-glucosidase inhibitor[a]	Nakao et al., 2002

[a]Also has potential antiviral activity.

Table 5. Examples of Neurosuppressives and Muscle Relaxants from Sponges

Compound	*Compound class*	*Species/order*	*Mode of action*	*Reference*
Dysiherbaine	Unusual amino acid	*Dysidea herbacea*/ Dendroceratida	Glutamate receptor antagonist	Sakai et al., 1997
Keramadine	Pyrrole-guanidine alkaloid	*Agelas* sp. / Agelasida	Serotonergic receptor antagonist	Nakamura et al., 1984
1-Methylisoguanosine	Nucleoside analogue	*Tedania digitata* / Poecilosclerida	Unknown (muscle relaxant, antiallergic)	Quinn et al., 1980
Xestospongin C	Macrocyclic bis-oxaquinolizidine	*Xestospongia* sp./ Haplosclerida	IP_3-inhibitor	De Smet et al.,1999
Okinonellin B	Furanosesterterpenoid	*Spongionella* sp./ Dendroceratida	Unknown (muscle relaxant)	Kato et al., 1986
Bromotopsentin	Bis-indole alkaloid	*Spongosorites* sp./ Halichondrida	α_1-Adrenergic receptor antagonist	Phife et al., 1996
Penaresidin A	Azetidine alkaloid	*Penares* sp./ Astrophorida	Actomyosin ATPase inhibitor	Kobayashi et al., 1991
S1319	Benzothiazole derivative	*Dysidea* sp./ Dendroceratida	Unknown (antiasthmatic, uterine relaxation)	Suzuki et al., 1999

1989); (4) and most interestingly, may function as antidepressant drugs in the brain (Nagayama et al., 1980).

Dysiherbaine from *Dysidea herbacea* (Sakai et al., 1997) is a potent excitatory amino acid that causes seizures by interfering with the L-glutamate-based neurotransmitter communication and may provide a lead compound in therapeutical agents for neurologic disorders (Sakai et al., 2001).

Muscle Relaxants. Disturbances in neuromuscular communication resulting from stress cause permanent muscle activation (Lundberg, 1995; Edgar et al., 2002). In addition to the above-mentioned centrally acting muscle relaxants, which mediate neuromuscular communication, peripherally acting muscle relaxant may be used for local muscle relaxation. They are applied for relief of strokes, or during intubations and surgery (Frakes, 2001). 1-Methylguanosine from *Tedania digitata* (Quinn et al., 1980) and xestospongin C, which was isolated from a *Xestospongia* sp. (Gafni et al., 1997), are examples of muscle relaxants that discovered in sponges (Table 5). Xestospongin C is a potent inhibitor of the inositol 1,4,5-triphosphate (IP_3) receptors and the endoplasmic-reticulum Ca^{2+} pumps (De Smet et al., 1999) and inhibits IP_3-induced increase in the oscillatory contraction of muscles (Miyamoto et al., 2000). ß-Adrenoreceptor agonists, such as S1319 isolated from a *Dysidea* sp. (Suzuki et al., 1999), have utero-relaxant properties, which can be therapeutically used for the preterm delivery of infants (Dennedy et al., 2002), and are widely used as antiasthmatic drugs (Suzuki et al., 1999). However, owing to their low selectivity ß-adrenoreceptor agonists may have severe side effects such as arterial hypertension, corony heart disease, and tachycardia (Borchard, 1998). Therefore, there is continued interest in finding more selective ß-adrenoreceptor agonists such as S1319.

Antiviral Compounds. Sponges are also a rich source of compounds with antiviral properties (Table 6). The high number of HIV-inhibiting compounds discovered does not reflect greater potential of sponges to fight AIDS compared with other viral diseases, but rather the interest of many researchers. The strong focus on screening for anti-HIV activity has led to discovery of numerous compounds, but the mechanism of inhibition is still poorly characterized. Papuamides C and D (Ford et al., 1999), haplosamates A and B (Qureshi and Faulkner, 1999), and avarol (Muller et al., 1987), which has also been patented as antipsoriasis (Muller et al., 1991), are examples of HIV-inhibiting compounds from different sponges. Avarol is one of the few compounds for which the mechanism by which it inhibits progression of HIV infection is more or less known. In vitro and animal data indicate that avarol combines useful properties of an increased humoral immune response, as IgG and IgM production is significantly increased, and interference with the posttranscriptional processes of viral infection (Muller et al., 1987). Avarol inhibits HIV by almost completely blocking the synthesis of the natural UAG suppressor glutamine transfer tRNA. Synthesis of this tRNA is upregulated after viral infection, and it is important for the synthesis of a viral protease, which is necessary for viral proliferation (Muller and Schroder, 1991). Low concentrations of only 0.9 and 0.3 μM avarol resulted in 80% and 50% inhibition of virus release from infected cells, respectively (Schroder et al., 1991), while

Table 6. Examples of Antiviral Products from Sponges

Compound	*Compound class*	*Species/order*	*Activity*	*Reference*
Dragmacidin F	Indole alkaloid	*Halicortex* sp./?	Antiviral	Cutignano et al., 2000
Papuamides C and D	Cyclic peptide	*Theonella mirabilis, T. swinhoei*/Lithistida	Antiviral (HIV-1)	Ford et al., 1999
Mololipids	Tyramine lipid	?/Verongida	Antiviral (HIV-1)	Ross et al., 2000
Haplosamates A and B	Sulfamated steroid	*Xestospongia* sp./ Haplosclerida	Antiviral (HIV-1 integrase inhibitor)	Qureshi and Faulkner, 1999
Hamigeran B	Phenolic macrolide	*Hamigera tarangaensis*/ Poecilosclerida	Antiviral (herpes and polio)	Wellington et al., 2000
Weinbersterols A and B	Sulfated sterol	*Petrosia weinbergi*/ Haplosclerida	Antiviral (feline leukemia, mouse influenza, mouse corona)	Sun et al., 1991
Variolin B	Pyridopyrrolopyrimidine alkaloid	*Kirkpatrickia varialosa*/ Poecilosclerida	Antiviral	Perry et al., 1994
Avarol	Hydroquinone, sesquiterpenoid	*Dysidea avara*/ Dendroceratida	UAG suppressor glutamine tRNA inhibitor[a]	Muller et al., 1987 Muller et al., 1991
2-5A	2′, 5′ Linked oligonucleotide	Many sponges	Interferon mediator	Kelve et al., 2003
Hennoxazole A	Bisoxazole	*Polyfibrospongia* sp./ Dictyoceratida	Antiviral	Ichiba et al., 1991

[a]Also has antiinflammatory potential antitumor activity.

uninfected cells were highly resistant against avarol (Muller et al., 1985; Kuchino et al., 1988). Furthermore, it was shown that the avarol derivatives, 6′-hydroxy avarol and 3′-hydroxy avarone (Figure 6), were very potent inhibitors of HIV reverse transcriptase. This enzyme has a key role in the early stages of HIV infection and is a specific target for antiviral drugs, as it is responsible for converting the viral genomic RNA into proviral double-stranded DNA, which is subsequently integrated into the host chromosomal DNA (Loya and Hizi, 1990).

In addition to their applications to treat diabetes, α-glucosidase inhibitors, such as callyspongymc acid, are potentially broad-based antiviral agents.

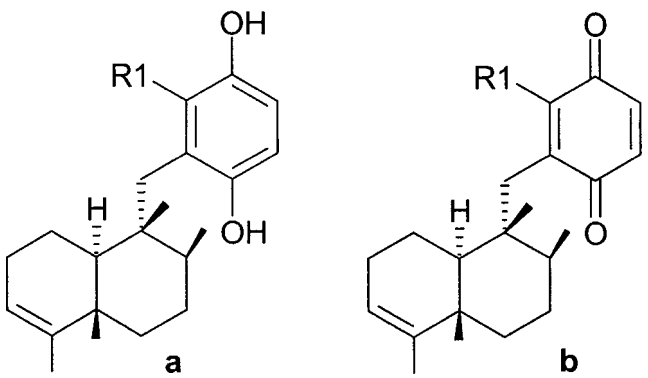

Fig. 6. Molecular structures of avarol (**a:** R1 = H) and 6′-hydroxy avarol (**a:** R1 = OH) and avarone (**b:** R1 = H) and 3′-hydroxy avarone (**b:** R1 = OH).

They disturb protein glycosylation and cause some viral envelope proteins to be misfolded, which leads to arrest of these proteins within the endoplasmic reticulum, where protein folding takes place. It has been demonstrated that alteration of the glycosylation pattern of HIV, hepatitis B virus, and bovine viral diarrhea virus by α-glucosidase inhibitors attenuates viral infectivity (Ratner et al., 1991; Mehta et al., 1998).

A very different class of virus inhibitors that has been found in many different sponges are 2′-5′ oligoadenylates (2–5A), which are involved in the interferon-mediated response against a wide range of viruses in mammals. The antiviral action is based on the activation of a latent endoribonuclease that prevents viral replication by degradation of its mRNA as well as cellular RNA (Kelve et al., 2003). For many other antivirals, the mechanism of inhibition is still unclear, but they are active against range of viruses. Hamigeran B from *Hamigera tarangaensis*, for example, showed 100 % in vitro inhibition against both the herpes and polio viruses (Wellington et al., 2000), and the weinbersterols A and B from *Petrosia weinbergi* exhibited in vitro activity against feline leukemia virus, mouse influenza virus, and mouse corona virus (Sun et al., 1991; Koehn et al., 1991).

In general, antiviral molecules from sponges do not give protection against viruses, but they may result in drugs to treat already infected persons. In addition, broad-based antiviral agents such as 2-5A

Table 7. Examples of Antimalarial Products from Sponges

Compound	*Compound class*	*Species/order*	*Reference*
Axisonitrile-3	Sesquiterpenoid isocyanide	*Acanthella klethra*/ Halichondrida	Angerhofer et al., 1992
Manzamine A	Manzamine alkaloid, diterpene isocyanates, isothiocyanates and isonitriles, norditerpenoid and norsesterterpenoid endoperoxides	e.g., Haliclona sp./ Haplosclerida *Cymbastela* hooperi/ Halichondrida *Diacarnus levii*/ Poecilosclerida	Ang et al., 2001 Konig et al., 1996 D'Ambrosio et al., 1998
Kalihinol A	Isonitril-containing kalihinane diterpenoid	*Acanthella* sp./ Halichondrida	Miyaoka et al., 1998

and α-glucosidase inhibitors may be useful in cases of sudden outbreaks of (unfamiliar) viruses like SARS and Ebola.

Antimalarial Compounds. Several sponge-derived antimalarial compounds have been discovered during the last decade (Table 7). New antimalarial drugs are needed to cope with the increasing number of multidrug-resistant *Plasmodium* strains that cause malaria. *Plasmodium falciparum* has become resistant against chloroquinone, pyrimethamine, and sulfadoxine (Bwijo et al., 2003). Kalihinol A from a *Acanthella* sp. (Miyaoka et al., 1998) and a number of terpenoid isocyanates, isothiocyanates, and isonitriles from *Cymbastela hooperi* (Konig et al., 1996) display selective in vitro antimalarial activity against *P. falciparum*. Also a number of free carboxylic acids from *Diacarnus levii* were used as precursors to yield new cyclic norditerpene peroxides after esterification. These epidioxy-substituted norditerpenes and norsesterterpenes displayed selective activity against both chloroquine-sensitive and chloroquine-resistant *P. falciparum* strains (D' Ambrosio et al., 1998). The manzamines, the most promising antimalarial compound, have been discovered in a number of sponges (Sakai et al., 1986; Ang et al., 2000; Youssaf et al., 2002). It has been suggested that the antimalarial effect of manzamine A is due to an enhanced immune response (Ang et al., 2001).

Antibiotics and Fungicides. With respect to antibiotics and fungicides, similar multiresistance problems have concerned physicians for a long time. Many new molecules with antibiotic properties are discovered every year, but in marine sponges their ubiquity is remarkable (Table 8). An early screening by Burkholder and Ruetzler (1969) revealed that 18 of 31 sponges tested showed antimicrobial effects, of which some were very strong against a range of gram-positive and gram-negative bacteria. The added value of some new sponge-derived antibiotics was shown by the inhibitory effect of arenosclerins A–C from *Arenosclera brasiliensis* on 12 antibiotic-resistant bacteria isolated from a hospital (Torres et al., 2002). Fungicides that are currently used are less diverse than antimicrobials, and the use of many of them is restricted because of toxic effects to humans, animals, and plants (Nakagawa and Moore, 1995; Rahden-Staron, 2002). It remains to be demonstrated whether antifungals like topsentiasterols D and E from *Topsentia* sp. (Fusetani et al., 1994), acanthosterol sulfates I and J from an *Acanthodendrilla* sp. (Tsukamoto et al., 1998) or the macrolide leucascandrolide A from the calcareous sponge *Leucascandra caveolata* (D'Ambrosio et al., 1996) will have different characteristics than the fungicides that are currently used, but the fact that they are produced by eukaryotic organism (if not produced by a symbiont) may imply that they are less toxic to other nonfungal eukaryotes.

Antifouling Compounds. A last class of bioactive compounds from marine sponges are antifouling molecules (Table 9). They are not associated with the development of new drugs, but could be environmentally friendly substitutes for chemical antifoulants. Biofouling organisms such as blue mussels, barnacles, and macroalgae cause serious problems to ship's hulls, cooling systems of power plants, and aquaculture materials (Holmes, 1970; Houghton, 1978). Long-term use of chemical antifoulants has led to increased concentrations of tributyltin and its current replacements in coastal sediments (Konstantinou and Albanis, 2004) and to mortality and change of sex of nontarget organisms (Katranitsas et al., 2003). Natural marine antifouling molecules have recently been reviewed (Fusetani, 2004) and may provide less toxic and more specific antifouling activity. Sponge-derived antifouling molecules have been found to inhibit the settlement of barnacle larvae (Okino et al., 1995; Tsukamoto et

Table 8. Examples of Antibacterial and Antifungal Products from Sponges

Compound	*Compound class*	*Species/order*	*Activity*	*Reference*
Discodermins B, C, and D	Cyclic peptide	*Discodermia kiiensis*/ Lithistida	Antibacterial	Matsunaga et al., 1985
Topsentiasterol sulfates A–E	Sulfated sterol	*Topsentia* sp./Halichondrida	Antibacterial/ antifungal (D and E)	Fusetani et al., 1994
Arenosclerins A, B, and C	Alkylpiperidine alkaloid	*Arenosclera brasiliensis*/ Haplosclerida	Antibacterial	Torres et al., 2002
Axinellamines B–D	Imidazo-azolo-imidazole alkaloid	*Axinella* sp./Halichondrida	Antibacterial	Urban et al., 1999
Acanthosterol I and J	Sulfated sterol	*Acanthodendrilla* sp./ Dendroceratida	Antifungal	Tsukamoto et al., 1998
Oceanapiside	Bisaminohydroxylipid glycoside	*Oceanapia phillipensis*/ Haplosclerida	Antifungal	Nicolas et al., 1999
Spongistatin	Polyether macrolide lactone	*Hyrtios erecta*/ Dictyoceratida	Antifungal	Pettit et al., 1998
Leucascandrolide A	Oxazole-containing polyether macrolide	*Leucascandra caveolata*/ Calcarea	Antifungal	D'Ambrosio et al., 1996

al., 1996a, 1996b), inhibit fouling by macroalgae (Hattori et al., 1998; Kubanek et al., 2002), or repell the blue mussel *Mytilus edulis galloprovincialis* (Sera et al., 1999).

Ecologic Role of Sponge Metabolites. Such an extensive collection of sponge-derived bioactive compounds raises the question of why sponges produce so many metabolites that can be useful to treat our human diseases. The huge number of different secondary metabolites discovered in marine sponges and the complexity of the compounds and their biosynthetic pathways (and corresponding kilobases of DNA for the programming of their synthesis) can be regarded as an indication of their importance for survival. An obvious example of the benefits of their secondary metabolites for the sponge itself, is the presence of antifouling products. To safeguard their water-pumping capacity, sponges cannot tolerate biofilm formation or settlement of barnacles or bryozoans on their surface (Proksch, 1994), The level of cytotoxicity of some sponge products is high enough to even create a bare zone around the sponge (Thompson, 1985) that is maintained by the emission of a mucus containing the toxins (Sullivan et al., 1981). This allows the conquest of densely populated rocks or corals and competition with faster growing organisms, but it is striking that the sponge can selectively use its poisons without self-destruction.

Secondary metabolites can protect the organism against predation, which is especially important for physically unprotected sessile organisms like sponges (Becerro et al., 1997). Relatively few animals, such as the hawksbill turtle and some highly evolved teleost fishes (Meylan, 1990), are largely dependent on sponges for their diet. Also some nudibranches feed on sponges and even manage to use the sponge's metabolites for their own chemical defence (Pawlik et al., 1988). However, these spongivores represent only a tiny fraction of the animals inhabiting the seas. Secondary metabolites can also protect their producers against bacteria, fungi, or parasites (Davies, 1992). In sponges the role of the chemical constituents is clouded by the complexity of the sponge-symbiont relationship (Dumdei et al., 1998). Many different bacterial species permanently inhabit sponges and contribute considerably to the total sponge biomass (Wilkinson, 1978). It has been suggested that the growth of "useful" microorganisms may be under control of the sponge host and serve as source of food or supply other metabolic products (Muller et al., 1981). However, it has also been found that associated bacteria might be the actual producers of a number of compounds that

Table 9. Examples of Antifouling Products from Sponges

Compound	*Compound class*	*Species/order*	*Reference*
Kalihinene X	Isocyanoterpenoid	*Acanthella cavernosa*/ Halichondrida	Okino et al., 1995
Kalihipyran B	Isocyanoterpenoid	*Acanthella cavernosa*/ Halichondrida	Okino et al., 1996
10β-Formarnidokalihinol	Isocyanoterpenoid	*Acanthella cavernosa*/ Halichondrida	Hirota et al., 1996
Pseudoceratidine 2	Dibromopyrrole-containing spermidine derivative	*Pseudoceratina purpurea*/ Verongida	Tsukamoto et al., 1996b
Ceratinamide A and B	Bromotyrosine derivative	*Pseudoceratina purpurea*/ Verongida	Tsukamoto et al., 1996a
C_{22} ceramide	Ceramide	*Haliclona koremella*/ Haplosclerida	Hattori et al., 1998
Formoside	Striterpene glycoside, sterol diperoxide	*Erylus formosus*/ Astrophorida	Kubanek et al., 2002
		Lendenfeldia chondrodes / Dictyoceratida	Sera et al., 1999
Axinyssimides	Sesquiterpene carbonimide cdichlorides	*Axinyssa* sp./Halichondrida	Hirota et al., 1998

have been isolated from sponges. *Oscillatoria spongelia*, a cyanobacterial symbiont that can constitute up to 40% of *Dysidea herbacea*, is the producer of antimicrobial polybrominated biphenyl ethers and might keep the sponge free of other bacteria (Unson, et al., 1994).

For many products it is not yet known whether they are produced by the sponge or by a symbiont. It is clear, however, that sponges are responsible for the production of a rich arsenal of "chemical weapons." Their early appearance in evolution has given them a lot of time for the development of an advanced chemical defense system. It is interesting to note that the synthesis of secondary metabolites is regulated depending on conditions that the sponge experiences. Specimens of *Crambe crambe* in well-illuminated regions grow faster than their counterparts exposed to darker conditions, but the specimens in the dark are better defended as they accumulate higher concentrations of cytotoxic metabolites (Turon et al., 1998). Another example is the production of halichondrin B by *Lissodendoryx* sp., which varies seasonally, with depth, and with the condition of the sponge. Halichondrin B yields could be enhanced by an order of magnitude during serial cloning, suggesting a defensive response to damage (Battershill et al., 2002). The ability to stimulate the production of secondary metabolites by sponges is an important consideration when one wants to harvest compounds from sponges for the production of potential new medicines.

Conclusion

Marine sponges produce an enormous array of antitumor, antiviral, antiinflammatory, immunosuppressive, antibiotic, and other bioactive molecules that can affect the pathogenesis of many human diseases. The relationship between the chemical structures of the secondary metabolites from sponges and the diseases they affect is usually not obvious. Different components affect the targeted disease by different mechanisms (e.g., microtubule stabilization or interaction with DNA to combat tumors). Moreover, inhibitors of transcription may be effective against both cancer and viral diseases. To make things more complex, there are many relations between, for instance, inflammation, cancer, and viral infections via the immune system, which plays a key role in certain responses of the body to these diseases. Chronic inflammation of the lungs by cigarette smoke often leads to lung cancer (Ohwada et al., 1995) and cervical and liver cancer can follow chronic inflammation caused by papilloma viruses (Smith-McCune et al., 1996) and hepatitis B and C viruses, respectively (Zhu et al., 1997). In addition, limited activity testing (e.g., only on cell growth inhibition and not on antiviral properties) yields an incomplete overview of the actual properties of the metabolites. Finally, for many bioactive molecules from sponges, the exact mode of action and their origin (sponge or symbiont) are still unclear. Most bioactive metabolites from sponges are inhibitors of certain enzymes, which often mediate or produce mediators of intracellular or intercellular messengers involved in the pathogenesis of a disease. As this is usually a cascade of reactions inside the cell or tissue, many enzymes in the cascade are targets for potential therapy. The different enzymes in the cascade can be structurally completely different proteins; therefore, it is not surprising that a wide range of metabolites can be used for the treatment of one disease. This applies in particular to a complex disease,

such as cancer, which is affected by so many different factors. Furthermore, antiviral molecules also appear to encamps a wide array of chemical structures, such as peptides, lipids, alkaloids, sterols, oligonucleotides, and a phenolic macrolide. A similar diverse pattern is observed for antibacterial and immunosuppressive metabolites. Most compounds that display antiinflammatory activity are sesterterpenoids. Nevertheless, in these cases the activity of the sponge metabolites is concentrated on certain steps; for instance, most antiinflammatory compounds act against phospholipase A_2.

The potency of sponge-derived medicines lies in the fact that each of these thousands of metabolites and their derivatives has its own specific dose-related inhibitory effect, efficacy, and potential (diminished) side effects that determine its suitability for medicinal use. In addition, the skeleton or active core of these molecules may be used as a vehicle to develop derivatives with their own specific efficacy and side effects. Therefore, the most important challenge in transforming bioactive molecules into medicines is now to screen the treasurehouse of sponge metabolites and select those that display a specific mode of action with the desired characteristics against a disease. An important question for the future remains how to actually prepare the potential novel drugs on a large scale.

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