Published in final edited form as:

Curr Opin Biotechnol. 2010 December ; 21(6): 787–793. doi:10.1016/j.copbio.2010.09.019.

Biologically active secondary metabolites from marine cyanobacteria

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Abstract

Marine cyanobacteria are a rich source of complex bioactive secondary metabolites which derive from mixed biosynthetic pathways. Recently, several marine cyanobacterial natural products have garnered much attention due to their intriguing structures and exciting anti-proliferative or cancer cell toxic activities. Several other recently discovered secondary metabolites exhibit insightful neurotoxic activities whereas others are showing pronounced anti-inflammatory activity. A number of anti-infective compounds displaying activity against neglected diseases have also been identified, which include viridamides A and B, gallinamide A, dragonamide E, and the almiramides.

B. Introduction

The pioneering studies of Richard E. Moore at the University of Hawaii in the 1970s through the early 2000s revealed marine cyanobacteria to be an extremely rich source of secondary metabolites [1]. Many of these compounds uniquely combine structural features of peptides with lipid sections, and then become further functionalized with unusual oxidations, methylations, and halogenations [2]. Moreover, these early studies showed that many were highly bioactive exhibiting activity in cancer models [3], toxicity to macroscopic life forms [4], or anti-infective activity [5]. The recent past has shown a continuation of these trends, both in terms of structure types and biological activities, especially in the areas of cancer cell toxicity and neurotoxicity [6,7]. We now recognize that these mixed biosynthesis metabolites derive from an inter-digitation of genes encoding biosynthetic enzymes involved in linking amino acids (Non-Ribosomal Peptide Synthetases, NRPSs) and acetate subunits (Polyketide Synthases, PKSs)(see Figure 1 for an example [8]). In most cases, the metabolites of cyanobacteria can be rationalized as combinations of these diverse biosynthetic subunits configured in different juxtapositions, in effect, a natural combinatorial biosynthesis.

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One reason why marine cyanobacteria may have evolved this extensive capacity to produce such bioactive molecules is that they are prokaryotes that have developed beyond a microscopic life style, and hence, require an arsenal of defensive substances to ward off predation by diverse types of macrograzers [9]. Indeed, an emerging trend in the pharmacology of marine cyanobacterial cytotoxins is that they target hypoxia-inducible factor-1 (HIF-1) and downstream mitochondrial respiration processes [10]. Alternatively, this perspective that cyanobacteria produce an abundance of toxic metabolites may simply result from the ways in which the extracts and compounds therein have been evaluated in biological terms. For example, a number of cyanobacterial natural products have recently been described to possess anti-inflammatory properties [11]. This perspective will update the evolving chemical and biological themes in the secondary metabolites of marine cyanobacteria with an emphasis on the past two years.

C. Cancer cell toxins

Several important classes of cancer cell toxins have been characterized from marine cyanobacteria in the last few years, all of which derive from various strains of the genera *Lyngbya* or *Leptolyngbya*. Nearly all further illustrate the enormous capacity of marine cyanobacteria to integrate NRPS and PKS biosynthetic pathways, and several are perceived to have significant potential for development as chemotherapeutic agents.

Investigation of a Fijian collection of *Lyngbya majuscula* was shown in 2002 to produce a highly unusual neurotoxic dimeric lipopeptide, named somocystinamide A, containing two distinctive *N*-methyl enamide groups [12]. A subsequent screening program revealed that cancer cells with an active caspase 8 system were exquisitely sensitive to the apoptosis-inducing effect of somocystinamide A [13]. The agent was also shown to inhibit neural tube formation in endothelial cells and to associate with lipid rafts. It was proposed that somocystinamide A functions through activation of the death-inducing signaling complex in cell membranes, thus sequentially activating caspase 8 and 3 to induce the extrinsic pathway of apoptotic cell death. An efficient chemical synthesis of somocystinamide A, featuring a novel method for formation of the *N*-methyl enamide functionalities, has provided additional supplies of this unique dimeric compound for further study as an anticancer lead [14].

The apratoxins are a family of cyclic lipopeptide cyanobacterial metabolites with exceptional cancer cell cytotoxicity [15]. Structurally, they conform quite well to the trends in cyanobacterial secondary metabolism with two polyketide sections interspersed among several amino acid residues. One of the more distinctive features is a tertiary butyl group at one terminus of the molecule; from a biosynthetic perspective, this is likely the initiating step in apratoxin synthesis. A total of seven apratoxins have now been characterized (A-G), and they show a number of interesting modifications, including absence of an *N*- or *C*-methyl group at various locations (B, C, E, G) [16,17,18], an additional PKS module early in the biosynthetic sequence (D) [19], or replacement of a terminating proline residue with an *N*-methyl alanine (F, G) [18]. The most potent of the apratoxins in cancer cell toxicity assays, apratoxins A and F, show low to sub-nanomolar LD₅₀ values in various cell lines [15,18]. Mechanism of action studies from two laboratories have indicated that the apratoxins may have a multitude of effects on cancer cells, including the targeting of Heat Shock Protein (HSP) 90 [20] as well as the secretory pathway [21]. The total synthesis of apratoxin A has been achieved in several laboratories [e.g. 22], and this has provided invaluable access to these compounds for SAR investigations and more detailed pharmacological investigation.

Several collections of marine cyanobacteria from the island of Coiba, a national park and World Heritage site some 40 miles off the Pacific coast of Panama, have yielded bioactive

natural products; however, the flagship discovery to date has been ‘coibamide A’ [23]. Coibamide A possesses a distinctive peptide structure with no apparent PKS elements, and is composed of a large macrocyclic ring as well as a linear section ending with an *N,N*-dimethyl valine at the amino terminus. A high level of *N*- and *O*-methylation is a distinctive feature of coibamide A. Coibamide A shows low nanomolar anti-proliferative activity to cancer cells grown *in vitro*; however, its mechanism of action and biochemical target are not yet known.

Bisebromoamide, a new cancer cell toxin that exhibits an average IC₅₀ of 40 nM to 39 cancer cell lines, was obtained from an Okinawan collection of *Lyngbya* sp. [24]. Its profile of toxicity was not correlated with antitubulin agents, as confirmed by biochemical assay. Rather, a sub-micromolar level of activity was observed in the inhibition of phosphorylation of ERK, an extracellular signal-related protein kinase. Total synthesis of bisebromoamide confirmed the planar structure as well as 7 of the 8 chiral centers; however, a quaternary stereocenter in the thiazoline portion of the molecule was corrected by this synthetic study [25]. Overall, the structure of bisebromoamide is remarkable because six of the eight logical subunits forming the molecule have interesting structural features, including a pivalic acid, a brominated tyrosine, a methylated proline, an α -methyl thiazoline ring, a *n*-leucine, and a 2-(1-oxo-propyl)pyrrolidine residue.

Two cyclodepsides were reported from *L. majuscula* collected in Madagascar (tanikolide dimer) [26] and Panama (malyngolide dimer) [27], both of which were symmetrical dimers of metabolites previously reported in monomeric form (tanikolide and malyngolide, respectively). While planar structures were easily formulated from NMR and MS data, absolute configurations required the chiral monomers as reference materials, and these were obtained from either synthesis or the authentic natural products. Both dimers were active as inhibitors of SIRT2 (176 nM to 2.4 μ M IC₅₀ for tanikolide dimer and 30% at 50 μ M for malyngolide dimer), a potential target for anticancer therapy.

Recently, a collection of *Symploca* sp. from the Florida Keys yielded a highly anti-proliferative mixed PKS and NRPS metabolite, largazole, featuring a thioester [28]. Largazole exhibits nanomolar activity against several cell lines, including MDA-MB-231, NMuMG, and U2OS. The molecular target for largazole is believed to be histone deacetylases (HDACs), and it is categorized as a class I HDAC inhibitor. A number of total chemical syntheses have appeared for largazole, thereby providing additional supplies of this interesting metabolite for further biological testing.

Patellamide and a large number of analog structures, known as cyanobactins, have been isolated from marine ascidians which harbor a resident population of the symbiotic cyanobacterium *Prochloron*, and it is now clear that these are produced by the cyanobacteria through truncation and modification of ribosomally-encoded precursor peptides [29].

D. Neurotoxins

An emerging pharmacological theme among the secondary metabolites of marine cyanobacteria is the production of a variety of neurotoxic substances, many of which appear to target the Voltage Gated Sodium Channel (VGSC). For example, a new class of cyanobacterial metabolites named the ‘hoiamides’ was discovered from several mixed collections of *Symploca* and *Oscillatoria* from Papua New Guinea [30,31]. These new natural products were discovered by a bioassay-guided process using sodium channel activating activity in neuro-2a cells and inhibition of intracellular calcium oscillations in mouse cerebrocortical neurons. The hoiamides are characterized by a remarkable integration of PKS and NRPS subunits, characterized by an unusual 15-carbon long linear polyketide chain, a tri-heterocyclic ring system composed of two α -methyl thiazolines and one thiazole,

a PKS extended isoleucine residue, and a variable number of additional amino- or hydroxy-acids, usually forming an overall cyclic structure. Detailed molecular pharmacological investigations have revealed that hoiamides A and B stimulate sodium influx with EC₅₀ values of 1.7 and 3.9 μ M, respectively, in mouse neocortical neurons, and that hoiamide A is a sodium channel neurotoxin site 2 partial agonist. Both hoiamides A and B were also found to potently suppress spontaneous calcium oscillations in neocortical neurons with EC₅₀ values of 45.6 and 79.8 nM, respectively.

Antillatoxin is another fascinating marine cyanobacterial metabolite with exceptional levels of methylation featuring seven methyl group equivalents on the PKS section [32]. Previously, it was shown that this metabolite is a powerful VGSC activator at a site distinct from, yet interactive with, the brevetoxin and batrachotoxin sites [33]. Recently, it was shown that antillatoxin displays a unique activity in cells heterologously expressing rNav1.2, rNav1.4 and rNav1.5 alpha subunits [34]. In similarity with the marine toxin brevetoxin B, antillatoxin was also shown to enhance neurite outgrowth in immature cerebrocortical neurons through activation of VGSCs [35], suggesting a potential therapeutic application of these marine toxins in the treatment of spinal cord injury.

A Palmyra collection of cyanobacteria composed of *Leptolyngbya* cf. and *Oscillatoria* spp. was found to possess a moderately potent modulator of sodium channel function [36]. The active compound, palmyrolide A, was defined as a cyclic lipopeptide with enamide and lactone connections, similar in overall structure to madangolide and laingolide [37,38]. The C-14 secondary methyl group configuration was determined by chemical degradation studies; however, despite exploration of a number of strenuous conditions, it was not possible to hydrolyze the lactone ring, and thus the configurations at C-5 and C-7 were not determined. In this regard, the tertiary butyl groups found adjacent to lactone junctures in a number of cyanobacterial metabolites are an intriguing structural adaptation for their chemically-stabilizing properties. In pharmacological assays, palmyrolide A inhibited Ca²⁺ oscillations in murine cerebrocortical neurons with an IC₅₀ of 3.7 μ M, blocked VGSCs in neuro-2a cells with an IC₅₀ of 5.2 μ M, and was not cytotoxic up to 20 μ M.

E. Anti-inflammatory Metabolites

A number of secondary metabolites from marine life forms have shown potent and mechanistically-intriguing anti-inflammatory activity, and marine cyanobacteria have contributed to this recognition (e.g. anti-inflammatory *bis*-bromoindoles from *Rivularia* sp.) [39]. Recently, a nitric oxide (NO) inhibition assay in a mouse RAW macrophage cell line was used to screen marine cyanobacterial metabolites, and it was discovered that several malyngamides were quite potent inhibitors, especially those in the F series [40]. Mechanistic investigations revealed that while Interleukin 1 and 6 (IL1 and 6) were depressed, Tumor Necrosis Factor α (TNF α) was enhanced, and subsequently, that the agent was acting by inhibition of the MyD88 pathway versus the TRIF pathway (= MyD88-independent pathway) of inflammation. Additional malyngamides such as malyngamide 2 also show anti-inflammatory activity [41].

F. Anti-infective Metabolites

Recently, marine cyanobacterial metabolites have been more actively investigated for their anti-infective and anti-parasitic type activities, largely in the context of a NIH Fogarty Center sponsored effort in Panama through the International Cooperative Biodiversity Group (ICBG) program [42]. For example, cultures of *Oscillatoria nigro-viridis* were found to have anti-protozoal activity, and this led to the isolation of two new lipopeptides, viridamides A and B, with a methyl ester at the C-terminus and a methoxylated fatty acid with a terminal acetylene functionality at the N-terminus [43]. Pure viridamide A showed an

IC₅₀ of 5.8 μ M to chloroquine-resistant *Plasmodium falciparum* (malaria), an IC₅₀ of 1.37 μ M to *Leishmania donovani* (leishmania), and an IC₅₀ of 1.0 μ M to *Trypanosoma cruzi* (Chagas), and thus may be a good lead for medicinal chemistry efforts.

Similarly, bioassay-guided isolation efforts led to the discovery of several unique linear peptides with anti-parasitic activity, including the highly modified lipopeptide gallinamide A with anti-malaria activity (IC₅₀ = 8.4 μ M) [44], dragonamide E with anti-leishmanial activity (IC₅₀ = 5.1 μ M) [45], and the almiramides also with promising anti-leishmanial activity [46]. This latter study was especially remarkable in its utilization of the natural product's structure to first explore semi-synthetic derivatives for biological activity, and then employing this information to simplify synthetic strategies to produce a focused combinatorial library of related substances. Gallinamide A is an interesting structure because it contains two amino residues that are modified with ketide extensions, further illustrating the general theme of inter-digitation of NRPS and PKS motifs. A closely related, possibly identical compound named 'symplostatin 4' (configuration defined as 25*S*, 26*S* in symplostatin 4 but left undefined in gallinamide A), was subsequently isolated from a Florida *Symploca* sp. with modest cancer cell cytotoxicity (IC₅₀ 12 μ M to HeLa cervical cells and 53 μ M to H-29 colon adenocarcinoma cells) [47]. Interestingly, it was found to possess synergistic cancer cell cytotoxicity with the co-occurring metabolite, largazole, which inhibits HDAC6.

H. Conclusions

There are only a few groups of organisms, such as myxobacteria and streptomycetes that are as chemically prolific as cyanobacteria. These prokaryotic life forms, which can become abundant under favorable environmental conditions in shallow tropical waters, are readily collectable and culturable, and thus, have become prime targets of many natural products chemists. Amazingly, almost every new strain has its own unique complement of secondary metabolites. As cyanobacteria continue to be explored and their metabolites evaluated in an expanding number of biological areas, such as the neurosciences and inflammation, they are becoming exceptional sources of lead compounds for drug discovery efforts. Combined with an increasing knowledge of how these molecules are made at the biochemical and genetic levels [48,49], they have a rich potential for biotechnological development and application.

Acknowledgments

On behalf of the various author's work described above, we thank the countries of Curaçao, Jamaica, Papua New Guinea and Fiji, as well as the State of Hawaii, for permission to collect research specimens. Research in the author's laboratories has largely been supported by NIH grant U19CA52955, CA100851 and NS053398.

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Fig. 1. Biosynthetic gene cluster for curacin A, a mixed NRPS/PKS metabolite with potent cancer cell cytotoxicity [8,49].

Fig. 2.
Cyanobacterial metabolites exhibiting cytotoxic or anti-proliferative activities.

Fig. 3.
Cyanobacterial metabolites exhibiting neurotoxic or anti-inflammatory activities.

Fig. 4.
Cyanobacterial metabolites exhibiting anti-infective activities.