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Chapter 16

ADVANCES IN MARINE SYMBIOTIC CYANOBACTERIA

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ABSTRACT

Marine microbial symbionts represent a hotspot in the field of marine microbiology. Marine plants and animals, such as sponge, sea squirt, worm, and algae host symbiotic cyanobacteria with great diversity. Most of the symbiotic cyanobacteria are host-specific and can be transmitted directly from parent to offspring. Symbiotic cyanobacteria play an important role in nitrogen fixation, nutrition and energy transfer and are possible true producers of bioactive marine natural products. Though diverse cyanobacteria have been revealed by culture-independent methods, the isolation and culture of symbiotic cyanobacteria is a challenge. In this chapter, the advances in diversity, transmission, symbiotic relationship with the host, isolation and natural products of marine symbiotic cyanobacteria are reviewed.

1. INTRODUCTION

The term *symbiosis* was first used in 1879 by the German mycologist, Heinrich Anton de Bary, who defined it as “the living together of unlike organisms”. Symbiosis commonly describes close and often long-term interactions between different biological species. The symbiotic relationship may be categorized as being mutualistic, parasitic, or commensal in nature, including those associations in which one organism lives on another (ectosymbiosis), or where one partner lives inside another (endosymbiosis). Endosymbiosis plays an important role in the evolution of eukaryotes and is now firmly recognized as a key feature of the origin

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of all eukaryotic life (Lallier, 2006). Symbiotic relationships may be either obligate, i.e., necessary to the survival of at least one of the organisms involved, or facultative, where the relationship is beneficial but not essential to the survival of the organisms (http://en.wikipedia.org/wiki/Symbiosis). For example, tubeworms thrive some 3–5 km deep in the sea. The animals lack a digestive system and their nutritional needs are met by their bacterial chemoautotrophic symbionts contained in a morphologically complex symbiont-housing organ called the trophosome (Maheshwari, 2007). These bacteria can turn hydrogen sulfide, methane, and carbon dioxide into organic molecules that feed the worm. The worm reciprocates by supplying chemical nutrients for the bacteria (Phillips, 2006).

Cyanobacteria, also known as blue-green algae, blue-green bacteria or Cyanophyta, are a phylum of bacteria that obtain their energy through photosynthesis. They are a significant component of the marine nitrogen cycle and an important primary producer in many areas of the ocean. Cyanobacteria are able to form symbioses with a broad range of hosts, serving as “chloroplasts” in symbioses with a variety of non-photosynthetic partners, including marine invertebrates (sponges, ascidians, and echiuroid worms) and fungi. They are also found in symbiosis with photosynthetic hosts, including diatoms, mosses, liverworts, ferns and cycads, where they fix atmospheric nitrogen (N_2) (Usher, 2008). Symbioses between cyanobacteria and marine organisms are abundant and widespread among marine plants and animals (Foster et al., 2006). This chapter mainly focuses on the advances in diversity, transmission, symbiotic relationship with the host, isolation and natural products of the marine symbiotic cyanobacteria.

2. THE DIVERSITY OF MARINE CYANOBACTERIAL SYMBIONTS

In the marine environment, symbioses are known to occur between cyanobacteria and sponges, ascidians (sea squirts) and echiuroid worms in the benthos and diatoms, dinoflagellates and a protozoan among the plankton (Carpenter, 2002). Because there is little success in attempts to cultivate the marine organism-associated microorganisms, to date, most insights into microbial diversity come from non-culture-based methods, including cell separations, 16S rRNA gene library, denaturing gradient gel electrophoresis (DGGE)/ temperature gradient gel electrophoresis (TGGE) (Li et al., 2006a; 2006b), restriction fragment length polymorphism (RFLP), random amplification of polymorphic DNA (RAPD), fluorescence in situ hybridization (FISH), and mass spectrometric imaging (MSI) (Gerwick et al., 2008).

In green algae *Oedogonium oogonia* and *Codium bursa*, different species of filamentous cyanobacteria have been reported (Thajuddin et al., 2005). The heterocystous cyanobacterium *Richelia intracellularis* has been found in three diatom genera, *Rhizosolenia*, *Guinardia* and *Hemiaulus* (Villareal, 1992).

Cyanobacteria have been found in cells of the subepidermal connective tissue of two marine echiuroid worms, *Ikedosoma gogoshimense* and *Bonellia fuliginosa* (Thajuddin et al., 2005). In the *Didemnidae* family of sea squirts, five genera form associations with either of two cyanobacterial genera, *Synechocystis* and *Prochloron*. *Trididemnum miniatum,* a colonial ascidian, is found to harbor the photosymbiotic prokaryote *Prochloron* sp. (Hirose et al., 2006). Metagenomic analysis reveals 7% cyanobacteria of the microbial community associated with the coral *Porites astreoides* (Wegley et al., 2007).

Cyanobacteria are common members of sponge-associated bacterial communities. Symbiotic cyanobacteria, situated both intercellularly and intracellularly, have been reported in a large variety of marine sponges (Thajuddin et al., 2005; Usher, 2008). In the so-called “cyanobacteriosponge” *Terpios hoshinota*, half or more of the sponge tissue is taken up by cyanobacteria of the *Aphanocapsa raspaigellae* type (König et al., 2006). According to the study of Usher et al. (2001) on the cyanobacterial symbionts of the marine sponge *Chondrilla australiensis* (*Demospongiae*) using fluorescent microscopy and transmission electron microscopy, unicellular cyanobacteria with ultrastructure resembling *Aphanocapsa feldmannii* occur in the cortex and bacterial symbionts are located throughout the mesohyl. Cyanobacteria within the genera *Aphanocapsa*, *Synechocystis*, *Oscillatoria* and *Phormidium* are present in sponges, and most species occur extracellularly. For example, the cortical layer of sponge *Tethya orphei* was found to be permeated by filamentous cyanobacteria, *Oscillatoria spongeliae*. Phylogenetic analyses of 16S rRNA sequences of sponge-associated cyanobacteria show them to be polyphyletic. For example, most of the symbiont sequences are affiliated to a group of *Synechococcus* and *Prochlorococcus* species (Steindler et al., 2005). The unicellular cyanobacterium *Synechococcus spongiarum* is the most prevalent photosynthetic symbiont in marine sponges and inhabits taxonomically diverse hosts from tropical and temperate reefs worldwide (Erwin et al., 2008). Cyanobacteria fill the cortical region of the sponge and penetrate inward into the upper choanosomal region, where they sometimes overlap the siliceous spicule bundles (Gaino et al., 2006).

It is known that marine sponges can host a variety of cyanobacterial and bacterial symbionts, but it is often unclear whether these symbionts are generalists that occur in many host species or specialists that occur only in certain species or populations of sponges. For *Dysidea n.* sp. *aff. herbacea* 1A and 1B and *Dysidea n.* sp. *aff. granulose*, Thacker et al. (2003) found each of these three sponge species hosts a distinct cyanobacterial clade, suggesting a high degree of host specificity and potential coevolution between symbiotic cyanobacteria and their host sponges. Hill et al. (2006) also found sponge-specific bacterial symbionts in the Caribbean sponge, *Chondrilla nucula* (*Demospongiae*, *Chondrosida*). According to the investigation by Thacker (2005), the marine sponge *Lamellodysidea chlorea* contains large populations of the host-specific, filamentous cyanobacterium *Oscillatoria spongeliae*, and other marine sponges, including *Xestospongia exigua*, contain the generalist, unicellular cyanobacterium *Synechococcus spongiarum*. Recent research has revealed new cyanobacterial symbionts that may be host specific and two major clades, *Candidatus Synechococcus spongiarum* and *Oscillatoria spongeliae*, that occur in widely separated geographic locations in unrelated sponge hosts (Usher, 2008).

3. THE TRANSMISSION OF CYANOBACTERIAL SYMBIONTS

Symbionts may be acquired vertically (symbiont transmitted directly from parent to offspring) or horizontally (offspring acquire symbiont from the environment) (Usher, 2008). The former is an important strategy for the formation of host specific symbiosis. In *C. australiensis*, the presence of cyanobacterial symbionts inside developing eggs and nurse cells in 25% of female *Chondrilla australiensis* has been established using transmission electron microscopy, suggesting that these symbionts are sometimes passed on to the next generation of sponges via the eggs (Usher et al., 2001). Cyanobacterial symbionts in the sponge *Diacarnus erythraenus* from the Red Sea have been identified in both adult sponges and their larvae by 16S rRNA sequencing together with the morphological analysis by electron and fluorescence microscopy, as a result, evidence is provided for vertical transmission of the symbionts in the sponge *Diacarnus erythraenus* (Oren et al., 2005). A budding specimen of *T. orphei* shows that cyanobacteria are present in the single bud protruding from the sponge surface, demonstrating that asexual reproduction can vertically transmit these symbionts from sponge to sponge. The occurrence of filaments in all the specimens studied is consistent with the assumption that filamentous cyanobacteria are not mere intruders but mutualistic symbionts with *T. orphei* (Gaino et al., 2006).

4. THE RELATIONSHIP BETWEEN CYANOBACTERIAL SYMBIONTS AND THE HOST

The symbiotic association is very important for chemical defense, carbon or nitrogen fixing, compound and energy transfer in the marine environment. There is close metabolic relationship between symbionts and the host. For example, on the coral reefs of *Papua New Guinea*, transmission electron microscopy and pigment analyses show that episymbiont biomass is dominated by large (20–30 mm) cyanobacterial cells. The isopods consume these photosymbionts and ‘cultivate’ them by inhabiting exposed sunlit substrates, a behavior made possible by symbionts production of a chemical defense that is repulsive to fishes (Lindquist et al., 2005). The impact of cyanobacterial photosynthesis on host sponges has been investigated by shading these sponge-cyanobacteria associations. It is suggested that *Oscillatoria* symbionts benefit their host sponge *L. chlorea* in a mutualistic association. *Synechococcus* symbionts may be commensals that exploit the resources provided by their sponge hosts without significantly affecting sponge mass. This supports the hypothesis that more specialized symbionts provide a greater benefit to their hosts (Thacker, 2005).

The interaction of *Prochloron* spp. bacteria with host ascidian animals in tropical oceans provides an excellent example of exchange of nutrients between animals and bacteria—a symbiosis based on small molecules. The sharing of photosynthate fixed by *Prochloron* with the host animal is suggested, and in some cases nearly all required carbon by the host comes from the bacteria. In return, the host provides waste nitrogen and other metabolic byproducts that allow *Prochloron* to be highly productive in a relatively nitrogen-poor environment. *Prochloron* also recycles this nitrogen, providing back to host usable nitrogen from waste sources. *Prochloron*-containing ascidians often contain extremely diverse natural products, such as the patellamides and relatives, produced by *Prochloron* (Schmidt, 2008). Cyanosymbionts are of advantage for their host since some of the potently active natural products that they produce, which may protect the sponge from environmental threats such as overgrowth, UV irradiation or attack by feeders. Cyanobacteria may, however, also damage their host sponge, if their growth is supported by favorable conditions (König et al., 2006).

By forming symbioses, host dinoflagellates and diatoms may obtain fixed carbon or fixed nitrogen (or both), whereas cyanobacteria may receive buoyancy. The fixation of N_2 or the release of dissolved organic carbon (DOC) will benefit the host organism. For example, ascidians, it is presumed that the hosts benefit from the release of DOC. Cyanobacteria may also benefit sponges through fixation of atmospheric nitrogen. Gordon et al. (1994) proposed that heterotrophic dinoflagellate hosts may provide the cyanobacterial symbionts with the anaerobic microenvironment necessary for efficient N fixation. In the study of Lesser et al. (2004), colonies of the Caribbean coral *Montastraea cavernosa* exhibit a solarstimulated orange-red fluorescence. The source of this fluorescence is phycoerythrin in unicellular, nonheterocystis, symbiotic cyanobacteria within the host cells of the coral. The cyanobacteria coexist with the symbiotic dinoflagellates (zooxanthellae) of the coral and express the nitrogen-fixing enzyme nitrogenase. The presence of this prokaryotic symbiont in a nitrogen-limited zooxanthellate coral suggests that nitrogen fixation may be an important source of this limiting element for the symbiotic association.

Metabolic relationships between symbiotic cyanobacteria and sponge have been investigated in the marine species *ChondrilIa nucula* and *Petrosia ficiformis*. Results show that in the absence of light (i.e., in the absence of cyanobacteria) *C. nucula* undergo metabolic collapse and thiol depletion. In contrast, *P. ficiformis* activates heterotrophic metabolism and mechanisms which balance the loss of cell reducing power. This suggests that cyanobacteria effectively participate in controlling the redox potential of the host cells by the transfer of reducing equivalents. Cyanobacterial symbionts release fixed carbon in the form of glycerol and other small organic phosphate (Arillo et al., 1993).

5. THE ISOLATION OF MARINE CYANOBACTERIAL SYMBIONTS

It is known that the vast majority of microbes in natural environment still remain uncultured in laboratory, cyanobacteria is not exceptional. The characteristics of cyanobacteria make it more difficult to culture, for instance, *Lyngbya*, *Phormidium* and *Oscillatoria* are characterized by multicellular filaments, and thus difficult to separate single filaments for isolation purposes. Cyanobacteria are easily contaminated with diatoms and heterotrophic bacteria. In addition, the problem associated with the culture of cyanobacteria is their slow growth rate. In order to study the chemical diversity of cyanobacterial symbionts, it is important to develop effective culture methodologies. Although some methods for cyanobacterial isolation and cultivation have been successfully used (Waterbury, 2006), at present, only a small percentage of cyanobacteria have been successfully cultured. Traditional microbiological methods are often unsuccessful because the factors of cyanobacterial growth environment are still poorly understood. In the case of cyanobacterial symbionts, they are inherently difficult to culture because of the complex unknown microenvironmental conditions in host.

Some novel strategies have been adopted to isolate cyanobacterial symbionts. For example, flow-cytometric separation of the cyanobacterial symbiont from the sponge cells has been attempted by Unson et al. (1993). The tropical marine sponge *Dysidea herbacea* is always found associated with the filamentous cyanobacterium *Oscillatoria spongeliae*, which occurs abundantly throughout the sponge mesohyl. *O. spongeliae* has been successfully isolated from sponge *Dysidea herbacea* by chopping the sponge tissue with a razor blade and squeezing the trichomes into a seawater-based medium containing polyvinylpyrrolidone, bovine serum albumin, dithiothreitol, glycerol, KCl and Na_2CO_3 (Hinde et al., 1994). Though some advances have been made, until now the isolation of cyanobacteria in a mutualistic association with host remains a big challenge.

6. CYANOBACTERIAL SYMBIONT: THE POSSIBLE TRUE PRODUCER OF MARINE NATURAL PRODUCTS

Marine cyanobacteria are one of the richest sources of known and novel bioactive compounds including toxins with unusual structures and wide pharmaceutical applications (Burja et al., 2001; Gerwick et al., 2008; Tan, 2007). The presence of symbiotic cyanobacteria raises questions as to the exact origin of the biologically important metabolites which have been isolated from the hosts. Is the compound produced by the host, the symbiotic cyanobacteria, or through a combined effort of both organisms? It is now realized that cyanobacteria are the true biosynthetic origin of many bioactive molecules isolated from marine invertebrates or at least involved in the biosynthesis of some metabolites.

Some supports come from the structural similarity of natural products from cyanobacteria and invertebrates. Sponge *Dysidea* (*Lamellodysidea*) *herbacea,* which hosts the cyanobacterium *Oscillatoria spongeliae,* varies in their production of polychlorinated peptides, which are often halogenated and include dysidin, dysidinin, and a series of chlorinated diketopiperazines (Flatt et al., 2005). These kinds of peptide natural products previously isolated from marine cyanobacterium *Lyngbya majuscule*. According to Sings et al. (1996), tunicates of the family *Didemnidae* host two genera of symbiotic cyanobacteria *Synechocystis* and *Prochloron.* The occurrence of ascidian metabolites in symbiotic cyanobacteria cells suggests that some of these metabolites may at least in part be synthesized by the cyanobacterial symbiont. A further example of structurally similar peptides in sponges and cyanobacteria is the nonribosomal cyclic peptide leucamide A from the sponge *Leucetta microraphis* (König et al., 2006).

Unson et al. (1993) firstly demonstrated that a unique group of polychlorinated compounds isolated from the whole sponge tissue is limited to the cyanobacterial filaments. Unson et al. (1994) provided another proof on the origin of marine natural product. Polybrominated biphenyl ethers such as 2-(2', 4’-dibromophenyl)-4, 6-dibromophenol are characteristic secondary metabolites of some specimens of sponge *Dysidea herbacea*. The dominant prokaryotic endosymbiont in the mesohyl of the sponge is a filamentous cyanobacterium *Oscillatoria spongeliae*. By cell-sorting experiments based on the fluorescence properties of cyanobacteria, it was revealed that the major brominated compound isolated from the intact symbiotic association is found in the cyanobacteria and not in the sponge cells or heterotrophic bacteria. This suggests that the production of the compound is due to the cyanobacterium, and not to the sponge or symbiotic heterotrophic bacteria. Several bioactive compounds isolated from *S. longicauda* have been ultimately tracked to cyanobacteria such as majusculamide (Burja et al., 2001). By the dietary dissemination of cyanobacteria, dolastatins of cyanobacteria origin are found to be accumulated in the Indian Ocean sea hare, *Dolabella auricularia* (Harrigan et al., 2002).

In another recent example, Ridley et al. (2005) made an effort to localize natural products to specific cell types using formalin or glutaraldehyde fixed sponge-cyanobacterial tissues from the tropical sponge *Dysidea herbacea*. After the sponge tissues being disrupted, individual cells are separated by using a fluorescence-activated cell sorter (FACS). Chemical analysis of the sorted cell types shows sesquiterpenoid compounds to be physically associated with the sponge cells, whereas chlorinated peptides are found to be localized to the associated cyanobacterium, *Oscillatoria spongeliae*.

Recently, evidence at the molecular genetic level has been found to support the hypothesis of natural products of symbionts origin. For instance, in the study of Flatt et al. (2005), a barB1 homolog (dysB1) from *D. herbacea* was successfully amplified by polymerase chain reaction (PCR). Catalyzed reporter deposition fluorescence in situ hybridization (CARD-FISH) analysis showed that dysB1 oligonucleotide probes hybridized to sequences in the filamentous cyanobacterial symbiont *O. spongeliae*. This finding revealed the cellular site of polychlorinated peptide biosynthesis in the marine sponge *Dysidea* (*Lamellodysidea*) *herbacea* and symbiotic cyanobacterium *Oscillatoria spongeliae*. A genome sequence of the cyanobacterium *Prochloron* sp., a symbiont in the tunicate *Lissoclinum patella*, identified the cyanobacterium as the biosynthetic source of the ribosomally encoded peptides patellamides A and C (Milne et al., 2006; Schmidt et al., 2005). Generally, it is thought that cyclic peptides that are associated with the tunicate *Lissoclinum patella* are produced in tunicate’s own tissues. However, subsequent studies involving gene cloning, expression and genomic sequencing indicate that symbiotic cyanobacteria actually produce these peptides (Gerwick et al., 2008).

Marine invertebrates often contain dominant taxa-specific populations of cyanobacteria, which are considered to be the true biogenic source of a number of pharmacologically active polyketides (PKS) and nonribosomally synthesized peptides (NRPS) produced within the host. Cyanobacteria are proven to be rich in modular biosynthetic pathways that integrate features from both the PKS and NRPS families. The biosynthetic gene cluster of cyanobacteria from algae for curacin A, hectochlorin and lyngbyatoxin biosynthesis have been investigated (Gerwick et al., 2008).

7. CONCLUSION AND PERSPECTIVE

Abundant and diverse marine symbiotic cyanobacteria have been revealed in sponges, sea squirts, worms and algae. Based on culture-independent molecular methods, it has been proven that marine organisms host a distinct cyanobacterial clade, suggesting a high degree of host specificity and potential coevolution between symbiotic cyanobacteria and their hosts. Symbiotic cyanobacteria can be transmitted directly from parent to offspring. Diverse cyanobacteria have been revealed by culture-independent methods, but the isolation and culture of symbiotic cyanobacteria is a challenge. Although metabolic relationships between symbiotic cyanobacteria and hosts have been investigated recently, it is still not clear as well as the related symbiotic mechanisms.

Symbiotic cyanobacteria play an important role in chemical defense, nitrogen and carbon fixation, nutrition and energy transfer and are the possible true producers of some natural products isolated from the host. Metagenomic screening to identify key polyketide synthase

(PKS) and nonribosomal peptide synthetase (NRPS) genes, and new cloning and biosynthetic expression strategies may provide a sustainable method to obtain new pharmaceuticals derived from the uncultured cyanobacterial symbionts.

Today, marine microbial symbionts represent a hotspot in the field of marine microbiology. The following areas are recommended to be strengthened in future: the development of a novel isolation strategy imitating natural environment conditions, a metagenomic approach for the revelation of cyanobacterial diversity and gene cluster involved in the biosynthesis of second metabolites, the site and origin identification of natural products, the symbiotic mechanisms and the relationship between symbionts and hosts.

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