NATURAL PRODUCTS FROM MARINE MICROORGANISMS

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Keywords: Marine microorganisms, natural products, secondary metabolites, bacteria, fungi, cyanobacteria.

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Summary

An enormous diversity of microorganisms is found in the ocean. It is approximated that 10^2 fungi, 10^3 bacteria, and 10^7 viruses exist in a single milliliter of seawater. They exist throughout the marine environment including in estuaries, suspensions of seawater and sediment, within or on the surfaces of macroorganisms and benthic structures. Microorganisms are fully adapted to survive in extreme marine environments from the frigidity of sub-zero Antarctic waters to deep sea hydrothermal vents, where temperatures are greater than 100 °C and highly acidic conditions exist. We now know that these marine microorganisms are able to produce secondary metabolites, which are defined as molecules that are unnecessary to the normal growth and development of their life cycle, but are now thought to facilitate long-term survival. Secondary metabolites, or natural products, can serve as both initiators and regulators of a diverse set of ecological relationships and processes. This review serves to provide the reader with a brief history of secondary metabolites that have been isolated from marine microorganisms, and to demonstrate a growing distinction between the microbial
products of terrestrial and marine environments. It will also emphasize that distinct microhabitats drive the biodiversity found within, and this results in niches of microbial diversity that are currently being exploited for their ability to produce an assortment of structurally unique secondary metabolites.

1. Introduction

History of Microbial Drug Discovery:

In the late 1930’s, stimulated by the discovery of penicillin by Alexander Fleming, terrestrial microorganisms became the focal point for one of the most prolific drug discovery efforts ever recognized. The discoveries of penicillin and later actinomycin (1940), led to the “Great Antibiotic Era”, which yielded more than 120 drugs for the treatment of infectious diseases, cancer, elevated cholesterol, immunomodulation and others. Some of the most important of these discoveries came from studies of the filamentous actinomycete bacteria, which because of their growth forms were at one time considered to be fungi (hence the suffix “mycetes”). The actinomycetes are responsible for the majority of the antibiotics in clinical use today. From the period 1950 to 1990 most of the pharmaceutical companies invested heavily in microorganism-based drug discovery with financial commitments that reached in the vicinity of $10B per year. The intensity of these explorations led to discoveries of new microorganisms from virtually all accessible terrestrial environments from arctic, and cold temperate regions to tropical environments.

Interestingly, although the world’s oceans occupy more than 70% of the surface of the Earth, this massive resource was never explored. Convinced by some that the ocean was a simple repository for terrestrial strains, and that cultivation of true marine microbes was difficult if not impossible, this component of planet Earth never received serious consideration. However, in 2009 microorganisms are no longer the focus of most drug industries, even though marine researchers are now demonstrating the enormous drug discovery potential of microorganisms isolated from this source.

Given the growth in this field, it is important to emphasize the unambiguous criteria that separate marine microorganisms from their terrestrial counterparts. Three such traits that help define some of the more distinctly marine microorganisms are their ability to display barophily (adaptation to high pressures), halophily (adaptation to high salt environments), and chemoautotrophic growth (ability to use CO2 as a carbon source and derive energy from chemicals rather than light) properties. One tool that has been essential to define distinctions between marine and terrestrial microbes is the use of 16S ribosomal RNA analysis (16S rRNA). Many true marine microorganisms from oceanic environments contain previously unobserved 16S signatures; this is especially true in the case of invertebrate microbial symbionts, as the phenomenon of symbiosis is prevalent in the ocean. Given the aforementioned properties, it remains difficult to prove whether a microorganism collected from an oceanic environment is truly ‘marine’ or whether it is simply a terrestrial strain that has been rinsed into the ocean. Over decades of study, one must simply illustrate that microbes are regularly found in the ocean and not in terrestrial environments. For example, fungi are cosmopolitan organisms that are incredibly adaptive to new environments. Several investigators
mistakenly label fungi collected from the ocean as “marine fungi”. This label is unwarranted until it is demonstrated that a fungal species has an obligate requirement for life in the sea. Until more can be learned, a more appropriate label is “marine-derived fungi”.

Oceanic Microhabitats Drive Biodiversity:

The ocean was formed sometime after the birth of our 4.5 billion year old planet. Evaporation of water from Earth’s crust and return as precipitation from the atmosphere, and the accumulation of ice from colliding comets, afforded us with massive collections of water that dispersed to become today’s ocean. Water, along with moderate temperatures, the development of a unique atmosphere, and other factors provided the foundation for increasingly complex carbon-based life forms to develop.

Despite the outward appearance of the ocean as a uniform aquatic tapestry, the regions that lie at the poles and beneath the sea are anything but homogenous, and in each of these oceanic niches a specific set of physical conditions selects for the existence of an incredible diversity of life. Although the terrestrial environment is limited to a relatively thin crust on its surface, life in the sea is distributed in three dimensions to a depth in excess of 13,000 meters. This region is divided into several unique microhabitats that contain a largely unknown microbial diversity. One microhabitat that is known for supporting microbial life is marine sediment. Marine sediment and mud are nutrient-laden surfaces that invite microbial colonization and growth. The organic content of these benthic surfaces differs greatly by region and displays geological diversity that consequently selects for a wealth of microbial taxa. However, surface microbes are not limited to sediment; microorganisms colonize virtually every inanimate and living surface in the ocean, including man-made structures, plants, invertebrates, and larger organisms. These microbial colonizers are known as epibionts. In addition to epibionts, microbes are also found living within marine organisms (endobionts). Some are crucial to their host’s survival (symbionts), whereas others are pathogenic. Unlike its occurrence in terrestrial organisms, the phenomenon of endobiosis is the rule rather than the exception in the largely nutrient-limited ocean. Lastly, a remotely explored diversity of microorganisms is found within the water column, a microhabitat that is the most abundant of all in the marine environment and is the epitome of the nutrient-limiting conditions that broadly exist in the ocean. Recently, the Sorcerer II global ocean sampling expedition set out to attain a preliminary assessment of the genetic diversity in the world’s oceans. While shotgun sequencing samples from the North Atlantic to the South Pacific (via the Panama Canal), 16S rDNA species analysis indicated the presence of distinct microbial communities. It was reported that only a handful of species (ribotypes) were ubiquitously abundant. Further analysis of these metagenomic data confirmed that taxonomic diversities were distinct between coastal, estuarine, and open-ocean environments. Although this was not the first study to show that microbial diversity varied with geographic location, it was certainly the most elaborate and extensive.

Geographic location is not the only determining factor for microbial diversity. Physical parameters such as depth are an integral part of microbial selection. One study utilized genomic analyses of planktonic microbial communities in the North Pacific Subtropical
Gyre as a function of seawater stratification. Samples in the photic zone of the water column (10, 70, 130 meters) harbored sequences associated with photosynthesis, porphyrin and chlorophyll metabolism, and other functions. Conversely, samples greater than 200 meters in depth, and consequently at pressures exceeding greater than 20 atmospheres, exhibited significantly different sequences. As illustrated in the following examples, other physical parameters that select for microbial taxa are temperature, mineral composition of the surrounding water, and salinity.

The structure of the ocean floor varies as distance from the continents into the deep ocean increases. Stretches of sediment 5 km thick are covered by hills, volcanoes, trenches, actively spreading seafloor, and mountain chains known as oceanic ridges. One of the most intriguing of these marine environments was seen for the first time in 1977. Using a submersible remotely operated vehicle (ROV) in the Galapagos mountain range of the eastern Pacific, scientists discovered tall chimney-like structures known as hydrothermal vents. These vents spew mineral-rich water at temperatures as high as 400 °C, and are known to exist along actively spreading plates of every major ocean ridge system on the planet; it is the dispersion of these plates that allows lava to rise, cool, and form elevated seafloor. Seawater penetrates cracks in the ocean crust and is eventually superheated and thrust out of chimneys nearby these ridge systems. Astonishingly, the area surrounding these extreme environments is teeming with life from tube worms to crabs, all of which readily survive in a toxic, sunlight deprived habitat. Studies have shown that it is the chemical makeup of this environment that ultimately drives the distribution of taxa. Unlike photosynthetic organisms, the various vent invertebrates are dependant on large populations of symbiotic bacteria that utilize chemosynthetic processes, in some cases the oxidation of hydrogen sulfide, to generate a supply of carbon-based nutrients that are the basis for the existence of this vent population. Contrary to the notion of life beginning in primordial ‘organic soup’, some believe that life’s origins evolved from ancient chemosynthetic microorganisms that benefited from mid-temperature zones above hydrothermal vents.

In addition to harboring hot environments, Earth is home to extreme cold environments as found near the continent of Antarctica. Located in the southernmost point on the globe, Antarctica is widely believed to have broken off from a massive supercontinent named Gondwanaland approximately 180 million years ago. It is an ice-laden landmass nearly twice the size of Western Europe and harbors approximately 90% of the world’s ice. Its surrounding ocean can be as cold as 1.9 °C, yet still the Antarctic is rich in biodiversity. Most of the ecosystem is reliant upon copious summer blooms of phytoplankton, which serve as food for larger species such as fish, seals, whales, and penguins. In addition, studies have determined contiguous benthic communities to be rich in sessile feeders such as sponges and soft corals. Some have postulated that predation constraints and competition for limited resources in this frigid underwater environment have selected for organisms that produce chemical defenses. However, many aspects of this marine ecosystem remain relatively unexplored, including those involving psychrophilic microorganism occurrence and function.

Salt marshes represent another category of extreme marine environments. They may exist across all temperature gradients, though many are found on the Atlantic coast of North America and near the Gulf of Mexico. These environments are protected from
strong ocean currents and are an intermediate point between land and sea. Their salinity level typically ranges from 5 to 40 parts per thousand and is at times greater than that of the open ocean. Many salt marshes form in estuaries, shallow areas where fresh water from a flowing river meets a body of salt water. Small plants such as sea grasses are abundant in this habitat and often root themselves deep into muddy sediment. The decomposition of salt-tolerant plants in addition to nutrient deposits from incoming rivers are critical components of estuarine food chains. The microorganisms (such as photosynthetic sulfur bacteria) and other small animals that contribute to these chains are part of a unique environment whose biomass per unit of surface area is among the greatest of all marine environments.

One of the most densely populated oceanic environments is the coral reef, a structure made as a result of the symbiosis between coral polyps and zooxanthellae (phototrophic dinoflagellates). Formed with tough calcium carbonate skeletons, corals grow best in waters with temperatures above 21 °C and depths from 5 to 10 meters deep, so as to harness the power of sunlight for optimal growth. Considering the very low nutrients present in tropical seawater, microorganisms have often adapted to live within the tissues of invertebrates. Sponges, for example, can be as high as 50% microorganisms by weight.

The aforementioned marine habitats were briefly described in order to illustrate a point: Earth’s ocean is capable of sustaining a wide variety of living conditions, and these environments ultimately select for their associated biodiversity. Furthermore, the circumstances that support this delicate balance of life involve ecologically significant populations of microorganisms. The occurrence of microbes in the ocean is massive. As previously discussed, they occur in the open water column and in sediment, in the tissues of marine organisms and on benthic surfaces, in mid-ocean ridge hydrothermal vents and freezing temperatures of Antarctic waters, and in hyper-saline pools at the junction of rivers and the sea. Given this array of marine habitats, little is known about the overall quantitative diversity of marine microorganisms. New species are discovered daily. And, research expeditions such as the Sorcerer II further emphasize that exploration of this elusive complexity has only just begun.

Secondary Metabolite Production by Marine Microorganisms:

Finally, one very important aspect of these microorganisms is their capacity to produce secondary metabolites. The ecological significance of these naturally-occurring compounds has been mostly overlooked, predominantly because we have lacked the sensitive analytical tools to actually measure the presence of these compounds under natural conditions. Consequently, little is known about the origin, diversity, and role that secondary metabolites fulfill in their surrounding microenvironments. This review provides a brief history of the structurally interesting secondary metabolites that have been isolated from cultured marine microorganisms, and hopefully will demonstrate a growing distinction between the microbial products of terrestrial and marine microorganisms. Due to the expanse of the topic, it is beyond the scope of this chapter to provide a comprehensive review of the metabolites produced by all marine microorganisms (e.g. phototrophic eukaryotes such as dinoflagellates and diatoms, yeasts, etc.). Instead, an overview of those metabolites produced by various taxa of
marine bacteria and marine-derived fungi is offered. For each category of marine microorganisms, a few highlights will be shared of the more interesting environments, methods, or structures found within. For further information on specific topics the reader is referred to more comprehensive review articles located in the bibliography. With a few exceptions, the articles published after January 2009 have not been included.

This overview is organized by taxon, beginning with unicellular Gram-negative bacteria and increasing in complexity to end with eukaryotic fungi. This chapter is written with a focus on chemistry and the environments, and not from the perspective of microbial taxonomy. We chose to organize this chapter following the taxonomic classifications of Bergey’s Manual of Determinative Bacteriology and of “The Prokaryotes – A Handbook on the Biology of Bacteria”.

2. Secondary Metabolites from Gram-negative Marine Bacteria

In this section, bacteria have been broken down into two classifications: Gram-negative and Gram-positive bacteria. This is based on their ability to retain a purple dye (the Gram stain). In brief, Gram-negative bacteria do not retain this dye due to the structure of their cellular envelope. They possess a tough outer membrane that consists of lipopolysaccharides in addition to a thinner peptidoglycan cell wall. In the following sections, the chemistry of marine Proteobacteria and Bacteroidetes are demonstrated to be the most prolific of the Gram-negative strains.

2.1. Proteobacteria

The Proteobacteria, formerly known as purple bacteria, constitutes the largest and most physiologically diverse phylum of all bacteria. Indicative of this diversity, the phylum was named after the Greek god Proteus, son of Poseidon, who had the ability to assume different shapes. This phylum comprises the majority of medically and agriculturally significant Gram-negative bacteria. The chemically prolific gliding bacteria are found within the Proteobacteria but are restricted to the β-, δ-, γ-divisions. It is home to a large group of gliding bacteria called the myxobacteria, which are aerobic, chemoorganotrophic, typically rod-shaped, and which form fruiting bodies under low-nutrient conditions. In the following two sections proteobacterial secondary metabolites are organized by class.

2.1.1. Alpha- and Delta-Proteobacteria

Categorized within the broad phylum Proteobacteria are the classes α- and δ-Proteobacteria. The mitochondria, found in the eukaryotic cell, are believed to have originated from α-Proteobacteria, a class that is crucial to the regulation of Earth’s carbon, sulfur and nitrogen cycles. The majority of α-proteobacteria are rod-shaped and contain strains that are prokaryotic predators (Bdellovibrio), strains that have the ability to glide (myxobacteria), and those that can reduce sulfur. To date, relatively few secondary metabolites have been identified from marine representatives of these classes.

From the cells of an undescribed species of the unicellular marine α-proteobacterium Agrobacterium, agrochelin A (1), a cytotoxic thiazole alkaloid was isolated. This strain
was cultivated from a tunicate collected in the Mediterranean Sea, off the east coast of Spain. It displayed inhibitory activity against a panel of tumor cell lines and was shown to form a complex with $[\text{Zn}]^{2+}$ ions. In the search for endothelin-converting enzyme (ECE) inhibitors, B-90063 (2), a dimeric oxazole-pyridone analog was isolated from an undescribed species of the marine $\alpha$-proteobacterium Blastobacter. This strain was isolated from the water column on the coast of Ojika Peninsula, Japan, and required seawater for growth. It exhibited antagonistic activities toward endothelins, peptides responsible for the constriction of blood vessels. In addition to the two aforementioned metabolites from $\alpha$-proteobacteria, two polyketide-derived metabolites were discovered from two marine-derived myxobacterial strains. An ethylated polyene-substituted pyrone metabolite (phenylnannolone A, 3) was isolated from the marine $\delta$-proteobacterium Nannocystis exedens. Though polyene pyrones have been reported from various terrestrial sources, the presence of an ethyl group on the polyene chain represented a novel deviation from this class of molecules. Biosynthetic studies suggested unprecedented biochemical reactions are employed to form phenylnannolone A. In a program designed to isolate true marine myxobacteria, the $\delta$-proteobacterium Haliangium luteum, was isolated from a seaweed in Kanagawa, Japan. This myxobacterium required approximately 2–3 % NaCl for growth and production of the metabolite haliangicin (4). Compound 4 was found to display antifungal activity toward a number of fungi, including the pathogenic strain Phytophthora capsici.

Figure 1. Secondary metabolites from $\alpha$- and $\delta$- Proteobacteria.

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**Biographical Sketches**

**Brian T. Murphy** obtained both BS and MS degrees in chemistry from the University of Massachusetts, Dartmouth under the direction of Professor Catherine C. Neto. He obtained his Ph D in chemistry from Virginia Polytechnic Institute and State University while studying under the direction of Professor David G. I. Kingston. There Brian focused on the isolation of anticancer molecules from plants and ascidians of Madagascar. Currently Brian holds a position as assistant professor of medicinal chemistry and pharmacognosy at the University of Illinois, Chicago (www.uic.edu/~btmurphy).

**Katherine N. Maloney** obtained her BS in chemistry at Pacific Lutheran University. Under the supervision of Professor Jon Clardy, Katherine earned her Ph D at Cornell University on the discovery
bioactive natural products from plants and endophytic fungi. Katherine continued her training in natural products isolation as a postdoctoral fellow in the laboratory of Professor William Fenical at Scripps Institution of Oceanography, where she focused on the isolation of cancer chemopreventive agents from marine actinomycetes. Currently Katherine holds a position as assistant professor of chemistry at Harvey Mudd College in Claremont, California.

**William Fenical** obtained his BS and MS degrees within the California State University system (California State Polytechnic University and San Jose State University). He obtained his Ph.D. in synthetic organic chemistry from the University of California, Riverside and did postdoctoral work with James Sims (UC-Riverside) in the field of marine natural products. Fenical has been a faculty member of the Scripps Institution of Oceanography (SIO, UC-San Diego) since 1973 and currently holds the title of distinguished professor of oceanography, pharmacy and pharmaceutical sciences at the University of California-San Diego. Professor Fenical is director of SIO’s Center for Marine Biotechnology and Biomedicine.