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Review Article

Marine actinomycetes: An ongoing source of novel bioactive metabolites

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ABSTRACT

Actinomycetes are virtually unlimited sources of novel compounds with many therapeutic applications and hold a prominent position due to their diversity and proven ability to produce novel bioactive compounds. There are more than 22,000 known microbial secondary metabolites, 70% of which are produced by actinomycetes, 20% from fungi, 7% from *Bacillus* spp. and 1–2% by other bacteria. Among the actinomycetes, streptomycetes group are considered economically important because out of the approximately more than 10,000 known antibiotics, 50–55% are produced by this genus. The ecological role of actinomycetes in the marine ecosystem is largely neglected and various assumptions meant there was little incentive to isolate marine strains for search and discovery of new drugs. The search for and discovery of rare and new actinomycetes is of significant interest to drug discovery due to a growing need for the development of new and potent therapeutic agents. Modern molecular technologies are adding strength to the target-directed search for detection and isolation of bioactive actinomycetes, and continued development of improved cultivation methods and molecular technologies for accessing the marine environment promises to provide access to this significant new source of chemical diversity with novel/rare actinomycetes including new species of previously reported actinomycetes.

Contents

1. Introduction

The sea, covering more than 70% of the surface of planet Earth, contains an exceptional biological diversity, accounting for more than 95% of the whole biosphere (Qasim 1999). Microbial diversity constitutes an infinite pool of novel chemistry, making up a valuable source for innovative biotechnology (Berdy 2005; Fenical and Jensen 2006). So far only the surface has been scratched. The recent estimates suggest that the culturability of microorganisms in marine sediments (0.25%) (Jones 1977; Amann et al. 1995), and especially seawater (0.001–0.10%) (Kogure et al. 1979; Kogure et al. 1980; Ferguson et al. 1984; Amann et al. 1995) is considerably lower compared to soil (0.30%) (Torsvik et al. 1990; Amann et al. 1995). A number of valuable antibiotics and metabolites have been derived from terrestrial microorganisms (99% of the known microbial compounds) although efforts in this area have diminished since the late 1980s because of the feeling that this resource has been exhaustively studied (Zahner and Fiedler 1995). In this respect, researchers switched over to new environments for novel pharmaceutical

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compounds and for combating human pathogens. The ocean floor has been recently demonstrated as an ecosystem with many unique forms of actinomycetes (Jensen et al. 2005b; Fenical and Jensen 2006). It appears that they are widely distributed throughout the ocean and found in intertidal zones (Goodfellow and Williams 1983), seawater (Ramesh et al. 2006; Ramesh and Mathivanan 2009), animals (Ramesh and Mathivanan 2009), plants (Castillo et al. 2005), sponges (Zhang et al. 2008; Sun et al. 2010), and in ocean sediments (Jensen et al. 2005b; Das et al. 2008; Thornburg et al. 2010; Xiao et al. 2011). Some of the rare marine actinomycetes require seawater for their growth (Maldonado et al. 2005a; Jensen et al. 2005b; Jensen and Mafnas 2006). This kind of unique adaptation characteristic of actinomycetes (Maldonado et al. 2005a; Jensen et al. 2005b, 2007) in the marine environment is a source of interesting research for new species and a promising source of pharmaceutically important compounds (Fenical and Jensen 2006). Despite this promise, relatively little work has been done on marine actinomycetes and only a small fraction of that has been directed at examining metabolite profiles (Lam 2006; Bull and Stach 2007). Since environmental conditions of the sea are extremely different from terrestrial conditions (Carte 1996; Kijjoa and Sawangwong 2004), it is felt that marine actinomycetes may have different characteristics from terrestrial actinomycetes and therefore might produce novel bioactive compounds and new antibiotics (Ellaiah and Reddy 1987; Ramesh and Mathivanan 2009). The research to date supports this hypothesis and it has been shown that marine actinomycetes produce novel types of new secondary metabolites (Lam 2006; Fenical and Jensen 2006). Many of these metabolites possess novel biological activities and have the potential to be developed as therapeutic agents (Feling et al. 2003; Maldonado et al. 2005a). Additionally, sequencing marine actinomycete genomes may provide insights useful in the discovery of novel agents (Jensen et al. 2007; Jensen 2010; Rath et al. 2011). This review article highlights the study of marine actinomycetes for the discovery of novel/new secondary metabolites.

2. Actinomycetes in the marine environment

Of the total sea surface, only 7–8% is coastal area and the rest is deep sea, of which 60% is covered by water more than 2000 m deep (Das et al. 2006). The deep sea is a unique and extreme environment characterized by high pressure, low temperature, lack of light and variable salinity and oxygen concentration (Bull et al. 2000). Though the deep sea area is geographically vast, scientific knowledge and research on deep sea microbial diversity is meager (Das et al. 2006). However, it has been shown to be a good source of novel microorganisms for the discovery of new antibiotics (Bull et al. 2000). Actinobacteria isolated from deep sea sediments in earlier studies however poorly characterized (Goodfellow and Williams 1983). More recently, culture independent studies have shown that indigenous marine actinomycetes certainly exist in the oceans (Ward and Bora 2006). These include members of the genera *Dietzia, Rhodococcus* (Nesterenko et al. 1982; Helmke and Weyland 1984; Rainey et al. 1995; Heald et al. 2001), *Streptomyces* (Moran et al. 1995), the newly described genera *Salinispora* (Mincer et al. 2005; Jensen et al. 2005a; Maldonado et al. 2005a) and *Marinispora* (Jensen et al. 2005a; Kwon et al. 2006) both of which require seawater for growth and have marine chemotype signatures; and *Aeromicrobium marinum* (Bruns et al. 2003) which also has an obligate requirement for salt. Another recently characterized genus, *Salinibacterium*, can tolerate up to 10% NaCl but does not have a salt requirement for growth (Han et al. 2003). The recently reported *Verrucosispora* strain AB-18-032 (Riedlinger et al. 2004) also might qualify as an indigenous marine actinobacterium. Some of these species were found to produce unique compounds, such as salinosporamides, that are now in clinical trials as potent anticancer agents (Feling et al. 2003).

The actinomycetes are active components of marine microbial communities (Jensen et al. 2005a,b) and form stable, persistent populations in various marine ecosystems (Das et al. 2006). The discovery of several new marine actinomycete taxa with unique metabolic activity in their natural environments (Fenical and Jensen 2006), and their ability to form stable populations in different habitats and produce novel compounds with various biological activities (Magarvey et al. 2004; Jensen et al. 2005a, 2007; Lam 2006; Prudhomme et al. 2008; Olano et al. 2009; Asolkar et al. 2010; Rahman et al. 2010) clearly illustrate that indigenous marine actinomycetes indeed exist in the oceans and are an important source of novel secondary metabolites.

3. Role of actinomycetes in marine environment

Actinomycetes have a profound role in the marine environment apart from antibiotic production (Das et al. 2006). The degradation and turnover of various materials are a continuous process mediated by the action of a variety of microorganisms (Jensen et al. 2005a; Lam 2006). There is a speculation that the increase or decrease of a particular enzyme-producing microorganism may indicate the concentration of natural substrate and conditions of the environment (Ramesh and Mathivanan 2009). The cellulolytic activity of marine actinomycetes was described by Chandramohan et al. (1972), chitinolytic actinomycetes were reported by Pisano et al. (1992) and various industrially important enzyme producing actinomycetes have been reported (Ramesh and Mathivanan 2009). Actinomycetes are also reported to contribute to the breakdown and recycling of organic compounds (Goodfellow and Haynes 1984). In addition, they play a significant role in mineralization of organic matter, immobilization of mineral nutrients, fixation of nitrogen, improvement of physical parameters and environmental protection (Goodfellow and Williams 1983).

4. Rare actinomycetes and selective isolation

The present relatively low occurrence of rare actinomycetes, in contrast to the diverse *Streptomyces* species, is derived from the facts that they are hard to isolate from the environment and difficult to cultivate and maintain under conventional conditions (Berdy 2005). The assumption is rare actinomycetes are more difficult to cultivate than *Streptomyces* species due to the requirement to use appropriate isolation procedures (Terekhova 2003), and to apply a variety of different selection methods (Qiu et al. 2008; Khanna et al. 2011), each for the isolation of certain taxonomical groups of actinomycetes (Bredholdt et al. 2007; Sun et al. 2010; Khanna et al. 2011). For example, the spores of some rare actinomycete genera including *Streptosporangium* and *Microbispora* can withstand treatment with various chemicals (Khanna et al. 2011). Therefore the isolation of rare actinomycetes warrants suitable isolation procedures including (i) the use of appropriate selective media containing macromolecules like casein, chitin and humic acid for promoting growth of rare actinomycetes present in the samples and simultaneously suppressing and hindering contaminant bacterial/fungal colonies (Qiu et al. 2008; Bredholdt et al. 2008; Hong et al. 2009; Zhang and Zhang 2011; Cuesta et al. 2012), (ii) addition of different antibacterial and antifungal antibiotics to the isolation media enhances the selection of members of the family actinomycetales (Qiu et al. 2008; Hong et al. 2009; Zhang and Zhang 2011), (iii) selective isolation of sporulating actinomycetes known to produce motile spores is done by the use of xylose, chloride, γ-collidine, bromide and vanillin (Hayakawa 2008) which act as chemo-attractants for accumulating spores of *Actinoplanes*, *Dactylosporangium* and