Marine Actinomycetes

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Contributor: William Soto

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1. Introduction

Actinomycetales is an order of Gram-positive bacteria consisting of both benign and pathogenic bacteria belonging to the phylum Actinobacteria [1]. Actinobacteria have historically been characterized by high GC content in their DNA [2], though some members, particularly freshwater-dwelling ones, have been found in recent years to have relatively low GC content [3]. Members of this order are often distinguished by their mycelial morphology with branched hyphae and the ability to form spores, although not all actinomycetes are sporulating [4]. They exhibit great diversity in a variety of characteristics including moisture tolerance [5], habitat, optimal pH, and thermophilicity [4]. Actinomycetes are often found at moderate pH levels [6][7], though some acidophilic and alkaliphilic species are known [5][8][9][10]. While some thermophilic actinomycetes have been recorded [11], most species appear to prefer moderate temperatures [12][13]. This diversity is also reflected in the near ubiquity of actinomycetes in the environment [14][15][16][17], with samples having been discovered in remote locations such as the Mariana Trench [18] and Antarctica [19]. Actinomycetales diversity may even be greater than previously estimated, as flaws in traditional methods of bacterial classification such as 16S rRNA comparison may have led to errors in Actinomycetal identification [20][21][22]. Actinomycete species are primarily found in soils [2] and were originally thought to be solely terrestrial. This belief was supported by the observation that some terrestrial actinomycete spores wash into the sea, which was thought to explain their presence in water samples [23]. In fact, the first discovery of a marine actinomycete was not until 1984 [24]. Since then, many marine species have been discovered in aquatic systems worldwide [25][26][27][28][29] and even single species have been shown to have widespread distribution in the world's oceans [27][30].

Marine actinomycetes associate with a variety of aquatic organisms, including invertebrates such as sponges [27][31], corals [32][33], and echinoderms [7], as well as vertebrates such as pufferfish [34]. These interactions may encourage unique chemical ecologies that might influence the evolution of secondary metabolic pathways. In addition to associating with other organisms, marine actinomycetes can exist in both planktonic and biofilm niches, although the majority of strains have been isolated from sediments [35]. The characteristics that promote and result from these different life strategies are not yet well understood. General studies of planktonic and biofilm-forming bacteria indicate that these communities differ in species composition [36][37]. Population sizes of actinomycetes in ocean sediment have been shown to vary with physico-chemical parameters including temperature, pH, pressure, total organic carbon, and salinity, the preferred levels of these parameters varying with location. Strains including *Streptomyces*, *Micromonospora*, and *Actinomyces* have been found at depths as great as 500m [26]. *Micromonospora* in particular may have greater relative abundance at 450 m than at shallower depths [38]. In addition, studies have shown greater heat resistance of actinomycete samples collected from marine sediment than from seawater, leading to the hypothesis that the more heat-resistant spore form of actinomycetes predominates in sediment compared to the vegetative form [39]. Comparatively little research has been conducted on planktonic actinomycetes in comparison to those in sediments. Early evidence suggests that some planktonic strains are non-sporulating [29] and vary in their temperature optima [40], indicating that they fill a diversity of ecological niches. The relative dearth of discovered planktonic varieties may in part reflect problems with sampling, as bacterial abundance is affected by temporal variations in nutrient availability that are caused by geological activity [41]. Free-floating bacteria may also be more vulnerable to predation by grazers [42] and infection by marine viruses, which are widespread in ocean waters. Populations of rare bacteria may be especially depressed by the presence of viruses, hindering detection efforts [43]. In contrast, bacterial communities in sediment may gain some protection against infection as viral adsorption to sediment may reduce phage replication rates [44].

Although the ocean presents a vast and varied environment for bacterial populations, most microbiological research has focused on samples from terrestrial environments [45]. This trend may in part be due to greater difficulties in sampling and culturing microbes from seawater and ocean sediment [46]. However, marine and terrestrial environments differ substantially. Marine microbes develop adaptations not present in their land-based counterparts [38][47]. The need for novel adaptations suggests that marine actinomycetes possess unique metabolic and genetic characteristics that are a promising subject for future research. This biological potential is especially important given that actinomycetes have been exploited for decades as a source of bioactive compounds, especially antibiotics. *Streptomyces* species alone produce over 7600 bioactive microbial metabolites [48], with an increasing proportion of new metabolites being discovered from rare actinomycetes. As much initial research focused on soil-derived species, these have mostly been exhausted as a source of easily detectable compounds. In contrast, marine actinomycetes are only beginning to be characterized and exploited for bioactive compounds [49], and much of their species diversity remains unexplored. Even closely related strains possess unique biosynthetic gene clusters (BGCs) [50][51], groups of genes in proximity to each other on the chromosome that encode secondary metabolites [52]. The existence of these BGCs in close marine relatives suggests the continued investigation of metabolic potential will lead to the discovery of additional natural products that are important, useful, and valuable.

Despite the plethora of BGCs harbored by marine actinomycetes, the genetic diversity discovered by genome sequencing is not fully reflected in laboratory attempts to elicit secondary metabolite production. This relative sparsity of obtained secondary metabolites is due in part to cryptic gene clusters that are only activated under certain conditions [53]. For example, because marine actinomycetes often live in close proximity to other microorganisms, they may possess secondary metabolites for purposes of chemical defense that are only expressed in the presence of competing microbial strains [54]. In addition, the production of some antimicrobial compounds is enhanced by the presence of seawater [39][55][56], implying the existence of unique secondary metabolic pathways not present in terrestrial actinomycetes. To fully exploit the metabolic capacities of marine actinomycetes, new technologies and techniques to increase BGC expression must be utilized [57]. Strategies include the optimization of fermentation conditions [10], as well as advanced techniques such as pathway engineering [58] and gene cloning [59]. Despite the technological demands of natural product discovery, this method continues to promote significant development of novel drugs [60]. In contrast, synthetic approaches have yielded few approved compounds [61]. A final challenge lies in the selective isolation of rare actinomycete strains for further investigation and characterization [62]. Other potential targets for the sustained search of secondary metabolites are plasmids, which are well-documented in marine environments [63]. As in many bacteria, plasmids are common in actinomycete species, with some strains possessing a multitude [64]. Although actinomycetes may possess either linear or circular chromosomes [65][66], their plasmids are usually linear [64]. These extrachromosomal DNA elements can harbor genes encoding secondary metabolites similarly to BGCs [67][68], helping the host better adapt to its environment.

Some of the most extensively researched Actinomycetales are members of the genus *Streptomyces*. *Streptomyces* spp. are saprophytic bacteria found in soil as well as aquatic environments, which possess a variety of morphological forms that often resemble fungi [69]. Under unfavorable conditions, aerial hyphae extend away from the mycelium to release spores for dispersal [70]. Most importantly, *Streptomyces* spp. are the source for the majority of antibiotics discovered from Actinomycetales [48] and possess significant potential for new natural product discovery. It has been predicted that *Streptomyces*' capacity for antibiotic production is on the order of 10^5 and that increasing screening efforts would lead to an improved rate of antimicrobial discovery [71]. Whole-genome sequencing has revealed that individual *Streptomyces* strains can contain as many as 34 BGCs with secondary metabolite potential, many of which are yet to be explored as sources of antibiotics [72][73]. Due to their ubiquity and reliable history of secondary metabolite discovery, much actinomycete research has focused on members of *Streptomyces*. However, the study of rare actinomycetes is gaining popularity in an attempt to address the problem of natural product rediscovery [74]. As researchers exhaust the readily isolable products of common species, rare strains provide an alternative resource for the identification of novel secondary metabolites.

While marine actinomycetes are renowned as sources for the acquisition of antibiotics, they are also responsible for the production of other medically important compounds. The gene clusters responsible for these drugs are thought to partially originate from lateral gene transfer [72][75]. Some of these drugs have anticancer effects [76][77]. Coral-associated actinomycetes have shown the ability to inhibit the formation of biofilms [32][78], including those formed by antibiotic-resistant *Staphylococcus aureus* [79][80], which cause infection via medical devices. Some actinomycetes can also form biofilms that allow them to degrade complex polymers in the environment [81][82][83][84], indicating their value in composting or bioremediation efforts, especially toxic pesticides [85][86]. Actinomycetes are also being investigated for their ability to improve agricultural productivity [87][88]. The myriad functional capacities of actinomycetes may reflect their vast repertoire of secondary metabolic pathways, a survival advantage that granted them significant importance in the search for novel bioactive compounds.

2. Medical Applications

Over 80% of all antibiotics used in the medical field originate from Actinobacteria [89], with 50% of clinically relevant antibiotics originating from the *Streptomyces* [90]. Each actinobacterial strain has the potential to produce 10 to 20 secondary metabolites [91], reaffirming the phylum's profound capacity to produce antibiotics. The primary drug classes for clinical antibiotics are aminoglycosides, β-lactams, glycopeptides, macrolides, and tetracyclines [92]. Specific antibiotics derived from actinomycetes that are used in clinics today include neomycin, streptomycin, kanamycin, cephamycin, vancomycin, erythromycin, and tylosin [2]. Here, we present a limited representation of actinomycete clinical applications.

3. Environmental Applications

In addition to their utility in medical contexts, actinomycetes are being evaluated for a variety of environmental applications, including anti-biofouling and the bioremediation of inorganic and organic wastes, metals, and radioactive wastes. Aquatic actinomycetes may be especially useful for these purposes as they preclude the need to adapt terrestrial bacteria to survive in marine or freshwater conditions.

4. Industrial Applications

Members of the Actinomycetales order are also highly regarded in various industrial applications. They are being evaluated for probiotic use in aquaculture, biofuel production, and the production of compounds used in the development of plastics, detergents, and other products. While these applications are still in the research and development phase, it is likely that the use of Actinomycetales in these industrial contexts will become more prevalent in the coming years.

5. Areas of Further Exploration

To aid in the isolation and development of actinomycete products, several actinomycete characteristics should be explored in further detail. Some of these characteristics, discussed here, include their ability to perform quorum sensing, transfer and receive genes through plasmids, form symbiotic relationships, and interact with phages. In combination with genetic engineering and other development techniques, the investigation of these characteristics should provide stronger foundational knowledge of actinomycete function, as well as more efficient product development methodologies.

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