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# Molecular Insights into Actinobacterial Genome for Natural Product Discovery

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## Abstract

Actinobacteria are gram positive and filamentous, is one of the dominant bacterial group and are of great economic importance. Actinobacteria are important sources of major bioactive compounds such as antibiotics, antifungals, immunosuppressants, antiviral, antitumor compounds, and enzymes. *Streptomyces*, one of the best characterized genus of the Actinomycetes and diverse with more than 600 species, is responsible for the synthesis of the two-third of the known active biomolecules. The genomes of the actinobacteria contains large gene clusters termed as biosynthetic gene clusters (BGCs) accountable for the synthesis of the secondary metabolites and most of the BGCs which are silent under the laboratory conditions are treasure sources of novel biomolecules. Here we review the important biosynthetic pathways underlying the synthesis of secondary metabolites.

**Keywords**: Actinobacteria, genome, biosynthetic gene cluster, secondary metabolites

## Introduction

Actinobacteria, one of the largest bacterial phylum, consist of different genera of gram positive bacteria with DNA of high GC content ranging from 50 to more than 70%. The members belonging to the class Actinobacteria exhibit significant morphological diversity and can range from coccus (*Micrococcus*) and rods (*Corynebacterium*) to extensively branching mycelium (*Streptomyces*). The typical morphological characteristics of actinobacteria are; dry, chalky texture or leathery, folded appearance and branching filamentous substrate and aerial mycelia. They develop substrate mycelium in both submerged and solid surface cultures. The substrate mycelium of Actinobacteria varies in size, shape, thickness and its color varies from white or nearly colorless to yellow, brown, red, pink, orange, green, or black. The aerial mycelium which extends above the solid substratum, is usually thicker than substrate mycelium and its main role is to produce reproductive spores. Actinobacteria play a vital ecological role by decomposing organic polymers such a chitin and cellulose thereby replenish the nutrient value of the soil. Some species, such as *Rhodococcus* spp., are capable of degrading more complicated, resistant chemicals, including nitro-, di-nitrophenol, pyridine, and nitroaromatic compounds. *Frankia* strains are nitrogen fixing actinomycetes, responsible for nodulation in diverse non-leguminous plants. Many species developed symbiotic relationships between plants and insects, for example the association of bee-wolf wasp and *Streptomyces* sp. Some of them are pathogens for humans e.g. *Mycobacterium leprae* (Kononen & Wade, 2015), animals e.g. *Mycobacterium bovis* (Ertas et al., 2005) and plants e.g. *Streptomyces scabies* (Lerat et al., 2009). Actinobacteria are the prominent sources of antibiotics, enzymes, antiviral, antifungal, antitumor, antiparasitic, insecticide, herbicide agents etc. Actinobacteria are the prominent sources of antibiotics, enzymes, antiviral, antifungal, antitumor, antiparasitic, insecticide, herbicide agents etc. The presence of secondary metabolite biosynthetic gene clusters (smBGCs) in the genome plays the key role in diversity of broad chemical products displayed by actinobacteria. *Streptomyces* the most well-known and largest genus of the phylum Actinobacteria contribute 70-80% of natural bioactive compounds which are relevant in pharmaceutical as well as agrochemical field.

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## Taxonomy of Actinobacteria

Actinobacteria is now recognized as the one of the largest taxonomic units among the 18 major lineages of the Bacteria domain. Actinobacteria were included separately in the fifth volume of Bergey's Manual of Systematic Bacteriology's second edition. *Actinobacteria, Acidimicrobiia, Coriobacteriia, Nitriliruptoria, Rubrobacteria,* and *Thermoleophilia* are the six classes that make up the phylum. Class *Actinobacteria* is subdivided into 16 orders: *Actinomycetales, Actinopolysporales, Bifidobacteriales, Catenulisporales, Corynebacteriales, Frankiales, Glycomycetales, Jiangellales, Kineosporiales, Micrococcales, Micromonosporales, Propionibacteriales, Pseudonocardiales, Streptomycetales, Streptosporangiales*, and *Incertae sedis*. However, several novel taxa are still being identified, thus this list is undoubtedly incomplete. Actinobacteria were traditionally identified using morphological observations, chemotaxonomy and physiological criteria. Morphological observations for identification include the determination of the presence of aerial mycelium, the color of the substrate mycelium and aerial mycelium, the ornamentation of the spores, and the formation of soluble pigments (Shirling & Gottlieb, 1966; Amin et al., 2018). Chemotaxonomic criteria such as the detection of diaminopimelic acid (DAP) isomers, levo form or the meso form is sufficient for characterizing the Actinobacteria groups (Hasegawa et al., 1983; Messaoudi et al., 2015). A wide range of physiological characteristics such as carbohydrate utilization profile, nitrogen source utilization profile, degradation or hydrolysis of numerous substrates, and sensitivity to various inhibitors have been identified as key parameters for classification (Shirling & Gottlieb, 1966; Messaoudi et al., 2015). Nowadays 16S rDNA sequence based molecular identification is the most employed method for the identification of inadequately characterized, rarely isolated, or phenotypically aberrant strains that may also result in a novel phylogenetic study of freshly isolated strains (Yokota, 1997). However, there may be ambiguity because rRNA sequences cannot effectively distinguish closely related species or even taxa. Therefore, additional genetic markers such as *rpoB* and 3*ssgB* have been utilized to distinguish between closely related genera, which is very helpful in case of closely related genera (Girard et al., 2013). Additionally, the vast recent expansion in the accessibility of genome sequence data has allowed for the identification of genes specific to particular organisms at the level of genera and families (Kirby, 2011).

## Insights into the Actinobacterial genome

### *Biosynthetic gene clusters (BGCs)*

The majority of actinobacterial genomes are circular like other bacterial genomes, with genome sizes ranging from 0.5 to 15 Mbp. *Actinomyces, Amycolatopsis, Actinoplanes, Streptomyces, Streptoverticillium*, and *Micromonospora* are among the other mycelial Actinobacteria species whose genomes are also linear with genome sizes range from 7.7 Mb to 9.7 Mb (Redenbach et al., 2000). Secondary metabolites are synthesized by bacteria in order to communicate and compete in their environment. These can be novel natural compounds with potential for pharmaceutical use. The synthesis of the bioactive compounds depends upon the presence of genes that encode the enzymes required for producing these bioactives and in the genomes of microbes, these genes are organized in clusters called biosynthetic gene clusters (BGCs) (Cimermancic et al., 2014). Biosynthetic gene clusters (BGCs) such as polyketides, non-ribosomal peptides, saccharides, alkaloids, and terpenoids produce natural products. Ultimately, the diverse chemical compounds can be employed as cholesterol controllers, immunosuppressants, antibiotics, anticancer medications, food additives, plant protection chemical etc. (Passari et al., 2017). Polyketide synthases (PKS) and nonribosomal peptide synthase systems (NRPS) are the pathways involved in the synthesis of majority of the bioactive compounds. The genes in the NRPS and PKS pathway encode enzymes which have similar function that enable the synthesis of hybrid compounds through the combination of two pathways (Wang et al., 2014). Terpene Synthase systems (TS) and Ribosomally synthesized and Post-translationally Modified Peptide Systems (RiPP) also contribute to the synthesis of secondary metabolites.

### *Polyketide Synthases (PKSs)*

The multifunctional enzyme, polyketide synthases (PKSs) are responsible for the biosynthesis of a wide range of natural compounds. PKSs are divided into three categories based on the architecture and mode of action of enzymatic assembly lines: type I PKSs are large multifunctional proteins made up of numerous functional domains, found in both

bacteria and fungus; type II PKSs are made up of distinct catalytic domains, typically found in bacteria; type III PKSs are simple chalcone synthase type, that catalyze the formation of the compound within a single active site and are found in bacteria and plants. The PKSs are classified as iterative or non-iterative in addition to the structures of the enzyme complexes, i.e. whether or not each KS is repeated in more than one round of elongation catalyzed by the domain. Non-iterative type I PKS systems are mainly found in prokaryotes. The colinearity concept describes how PKS architecture and metabolite structure match up exactly and serve to rationally reprogramme complicated polyketides using genetic engineering but also allow predicting metabolite structures based on the architecture of enzymes (Cane et al., 1998). Iterative type II PKS systems are far more prevalent in prokaryotes and are restricted in these organisms. These systems utilize a small number of iteratively utilized enzymes, each of which is necessary for polyketide assembling and expressed via different genes. This "minimal PKS" is made up of two ketosynthase units (KS α and KS β, or chain length factor (CLF)), and an ACP domain serves to tether the developing polyketide chain. Actinomycetes are the primary hosts of Type II PKS system, and there are just two examples of Gram-negative bacteria known to have Type II PKS system (Brachmann et al., 2007).

In PKS system each module of the assembly line comprises a ketosynthase (KS), acyltransferase (AT), and acyl carrier protein (ACP) domain that work together to catalyze the elongation of polyketide acyl chains. The AT domain trans-esterifies α - carboxyacyl extender unit from an appropriate acyl-CoA metabolite on to the ACP; the KS domain obtain the expanding polyketide chain from the ACP of the previous module and then catalyzes decarboxylative Claisen condensation reaction between the extender unit and the polyketide intermediate. The ACP-bound intermediate of β – ketothioester can be altered by additional domains such as ketoreductase (KR), enoylreductase (ER), dehydratase (DH), and methyltransferase (MT). Finally, a thioesterase (TE) domain catalyzed hydrolysis or macrocyclization releases the full-length polyketide from the PKS (Nivina et al., 2019). Antibiotics such as rifamycin from *Amycolatopsis mediterranei* (Stratmann et al., 1999), tetracycline from *Streptomyces rimosus* (Petkovic et al., 2006), and actinorhodin from *Streptomyces coelicolor* are synthesized through type 1 PKS system. Only a few basic building blocks are used in combinatorial elongation and template-directed elongation to produce the remarkable structural and functional diversity found in polyketides. The majority of the monomer units incorporated during chain elongation are composed of malonyl-CoA and methylmalonyl-CoA. The chain starter units can be structural variants like malonamyl-CoA or methoxymalonyl-CoA or thioesters of monoacyl groups like acetyl-, propionyl-, and benzoyl-CoA (Moore & Hertweck, 2002).

### *Non-Ribosomal Peptide Synthetase Systems (NRPSs)*

The NRPS mechanism was initially discovered in 1971 while conducting research on the production of gramicidin S and tyrocidin. A NRPS is modularly structured, with each module responsible for the addition of a certain amino acid. Each module contains at least three core domains that catalyze a specific reaction involving a monomer inclusion. The adenylation (A) domain comes first, which chooses the corresponding amino acid and activates it by converting into an aminoacyl adenylate. The thiolation or peptidyl carrier protein (PCP) domain connects the activated monomer to the synthetase through phosphopantetheinyl arm. Condensation domain (C) catalyzes the formation of peptide bond between the amino acids linked with two nearby modules (Lipmann et al., 1971). The modules of many NRPSs have supplementary, specialized domains that permit residue modifications. D-isomer forms of amino acids are generated by epimerization (E) domains; oxidation (Ox); reduction (R); methylation (M); formylation (F) and heterocyclization (Cy) domains make NRPSs capable of biosynthesizing remarkable diverse peptides with broad biological functions that cannot be produced through ribosome translation process (Felnagle et al., 2008). For nonribosomal peptides, the monomer building blocks for oligomerization and diversification during chain elongation and after chain termination include the 20 proteinogenic amino acids and a far greater variety of nonproteinogenic amino and aryl acids (Schwarzer et al., 2003). Important antibiotics such as amphomycin, produced by *Streptomyces canus* (Yang et al., 2014), cephamycin, produced by *Streptomyces clavuligerus* (Alexander & Jensen, 1998), daptomycin, produced by *Streptomyces roseosporus* (Miao et al., 2006) and teicoplanin, produced by *Actinoplanes teichomyceticus* (Somma et al., 1984) are produced through NRPS pathways.

### *Terpene Synthase Systems (TSs)*

Secondary metabolites produced by terpene synthase (TS) systems include more than 80,000 identified chemicals. The building blocks for the synthesis of all terpenoids include C5 isoprenoid precursors, isoprenoid diphosphate (IPP) and dimethylallyl diphosphate (DMAPP), that are joined by isoprenyl transferases to develop substrates with varying lengths. Terpenoids have a variety of industrial uses because of their diverse structural makeup, such as insecticides, flavorings, scents, antimicrobials, and alternative sources of energy. A fundamentally distinct logic governs terpene production. Isoprenes, which are five-carbon units, are linked to form a linear polyene with branching methyl groups that forms the core hydrocarbon structure in a single enzyme-catalyzed process (Austin et al., 2008). The terpene cyclase enzyme stabilizes the linear methyl-branched polyene and starts a series of carbocation-driven cyclizations and rearrangements that result in the development of the fundamental hydrocarbon structure of a terpene (Driller et al., 2018). The addition of other building blocks, such as sugars, amino acids, or fatty acids, can further modify this basic hydrocarbon skeleton to produce a wide range of terpenoid structures. Type I and Type II TSs are differentiated by the abstraction of diphosphate and protonation of an olefinic double bond resulting in highly reactive allylic cations, respectively (Christianson, 2017). Intramolecular electrophilic attack of the intermediate allylic cations on the central or distal double bonds of the substrate, followed by well-known cationic transformations, such as hydride shifts and carbon-carbon backbone rearrangements (Wagner-Meerwein reactions), and final quenching of the positive charge either by deprotonation or by capture of a nucleophilic water molecule results in the generation of enormous cyclic terpene compounds. One enzyme can make dozens of distinct hydrocarbon skeletons that are remarkably diverse from one another, which is the basic characteristic of TSs. Through the addition of various functional groups, mediated by specialized enzymes, primarily those from the cytochrome (P450s) family, the terpene skeleton is modified.

Terpenoids and meroterpenoids produced by actinomycetes are of interest as a source of new antibiotics efficient against drug-resistant pathogenic bacteria. *Streptomyces* is the genus that produces the majority of the known terpene derivatives, although new research has revealed that members of the genera *Actinomadura, Allokutzneria, Amycolatopsis, Kitasatosporia, Micromonospora, Nocardiopsis, Salinispora, Verrucosispora*, etc. also produce terpenes (Tarasova et al., 2023).The first studies of a bacterial terpene synthase originated from the synthesis of the sesquiterpenoid antibiotic pentalenolactone, identified from *S. exfoliatus* UC5319 (Cane et al., 1990). An odorous irregular monoterpenoid called 2-Methylisoborneol has been found in the cultivation medium of some species of *Streptomycetes* (Komatsu et al., 2008).

### *Ribosomally Synthesized and Posttranslationally Modified Peptides (RiPPs)*

RiPPs are a class of naturally occurring systems that produce compounds with intricate chemical structures. They are created from a brief precursor peptide (PP) that the ribosome synthesizes and is made up of a leader peptide and a core peptide (Ortega et al., 2016). The core peptide normally undergoes changes and finally turns into the active peptide product once the leader peptide is removed. Typically, the leader peptide is involved in early recognition by modifying enzymes called RiPP tailoring enzymes (RTE), which yield different peptide structural characteristics. After changes are made, the core peptide is separated from the leader peptide to produce an active final product (Zhang et al., 2018). Lanthipeptide, cyanobactin, bottromycin, glycocin, lassopeptide, microcin, sactipeptide, thiopeptide are the major classes of RiPPs (Arnison et al., 2013). A typical example is the lanthipeptide, nisin which is employed as a food preservative in the food industries and compounds such as bottromycin, cytotoxin and plantazolicin belong to antibiotics.

## Conclusion

In this review, the biosynthetic potential of Actinobacteria which include antibacterial, antifungal, antiviral, antitumor, cytotoxic properties and the biosynthetic machineries responsible for the generation of the secondary metabolites are discussed. *Streptomyces sp*. strains contribute to more than 70% of the reported metabolites, whereas the other genera of Actinobacteria such as *Amycolatopsis, Micromonospora, Nocardia* are also the contributors. The genes coding for the biosynthetic gene clusters (BGCs) which are responsible for the synthesis of the secondary metabolites are organised into clus-

ters in actinobacterial chromosomes and the genome mining of these BGCs will lead to the discovery of novel biomolecules. Majority of the biosynthetic gene clusters which are silent or cryptic in the laboratory conditions can be effectively awakened by knowing the architecture of the domains and the modules of the metabolic pathways. The enormous potential of actinomycetes as top producers of cutting-edge bioactive compounds, which are regarded as intriguing candidates for clinical testing in drug development are nowadays exploited to its high end using innovative approaches like OMICS technologies combined with bioinformatics.

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