Chapter 2
Genomics-Based Insights into the Evolution of Secondary Metabolite Biosynthesis in Actinomycete Bacteria

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Abstract Actinomycete bacteria are known for their ability to produce chemically diverse secondary metabolites with various biological activities, some of which are being used in human therapy as anti-microbial and anti-cancer agents. Recent genome sequencing and analyses revealed that these bacteria have a much larger potential to biosynthesize secondary metabolites that was previously assumed from a conventional bioactivity screening. Indeed, each actinomycete genome was shown to carry 20–30 gene clusters for biosynthesis of secondary metabolites, most of which are not expressed in the laboratory conditions. Detailed analysis of such gene clusters along with comparative genomics studies identified some interesting features reflecting evolution of the clusters upon transfer to a new host. Moreover, insights into the process of forming new, hybrid gene clusters via recombination events at the ends of the linear chromosomes have been gained. This chapter presents and discusses recent advances in genomics of actinomycetes and its impact on our understanding of secondary metabolism evolution in these bacteria.

2.1 Introduction

Bacteria are the most versatile living organisms on Earth, capable of occupying very diverse environmental niches, such as soil, plants and animals, glaciers, hot springs, marine, desert habitats, etc. The ability of bacteria to adapt to a particular environment is unprecedented, owing mainly to their fast mutation rate (e.g., due to SOS-response (Galhardo et al. 2007), flexible regulatory networks linked to the environmental sensors, and efficient acquisition of new genes via horizontal gene

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transfer (Syvanen 2012)). It is well documented that exposure of a particular bacterial species to a new environment drastically changes the gene expression pattern, leading to induction of genes that may be necessary for survival and proliferation under new conditions (Dufour and Donohue 2012). However, a mere survival is not enough for proliferation of the species, and acquisition of new "beneficial" genes from bacteria that dwell and thrive in this environment becomes the next step in the adaptation process. It has also been reported that some genes, no longer required in the new environment, are lost during the adaptation, the process known as "genetic drift" responsible for drastic reduction of genome size in symbiotic bacteria (Lawrence and Hendrickson 2005).

A wide variety of bacteria and fungi are capable of synthesizing secondary metabolites, compounds that are not required for growth, but may give their producers a certain advantage. The latter can be manifested, for example, by antibiotic activity of secondary metabolites against potential competitors for nutritional sources, which occupy the same ecological niche (Challis and Hopwood 2003). Certain secondary metabolites were shown to function as signal molecules, providing means for communication between microbial cells (Yim et al. 2007). Yet other secondary metabolites serve as molecular scavengers binding metal ions (Miethke 2013). A role for secondary metabolites as signalling molecules has also been proposed after discovering their effect on gene expression of other bacteria exposed to subinhibitory concentrations of the compounds (Subrt et al. 2011). Whatever the true biological role of secondary metabolites in nature, they have attracted our attention mostly because of their biological activities. The first microbial antibiotic penicillin described by A. Flemming in 1929, was produced by a fungus *Penicillium* (Abraham 1980). This important milestone in medical science prompted intensive search for new antibiotics produced by soil-dwelling bacteria and fungi. In 1940–1970, this search had overwhelming success, leading to the discovery of many important anti-microbial and anti-cancer drugs. For example, anti-fungal antibiotic amphotericin B, anti-bacterials erythromycin and vancomycin, and anti-cancer drug daunorubicin were all discovered during this period (Fig. 2.1).

The success of microbial secondary metabolites as drugs is based on their unique properties evolved over millions of years to provide efficient interaction with biological targets in living organisms (e.g., inhibiting specific enzymes, binding DNA or RNA, or preventing protein-protein interactions). Unfortunately, irresponsible use of antibiotics has led in recent years to the emergence of pathogens resistant to nearly all existing drugs. Development of resistance to anti-cancer drugs by malignant tumor cells has also been observed. These alarming tendencies prompt immediate action towards discovery and development of novel drugs based on bioactive secondary metabolites. One of possible routs could be the use of modern recombinant DNA technologies, including synthetic biology, to create hybrid molecules that can overcome resistance mechanisms, or possess dual mode of action (Flatman et al. 2005).

Having an insight into the evolution of secondary metabolite biosynthesis could provide clues on how to rationally engineer hybrid secondary metabolites. Recent

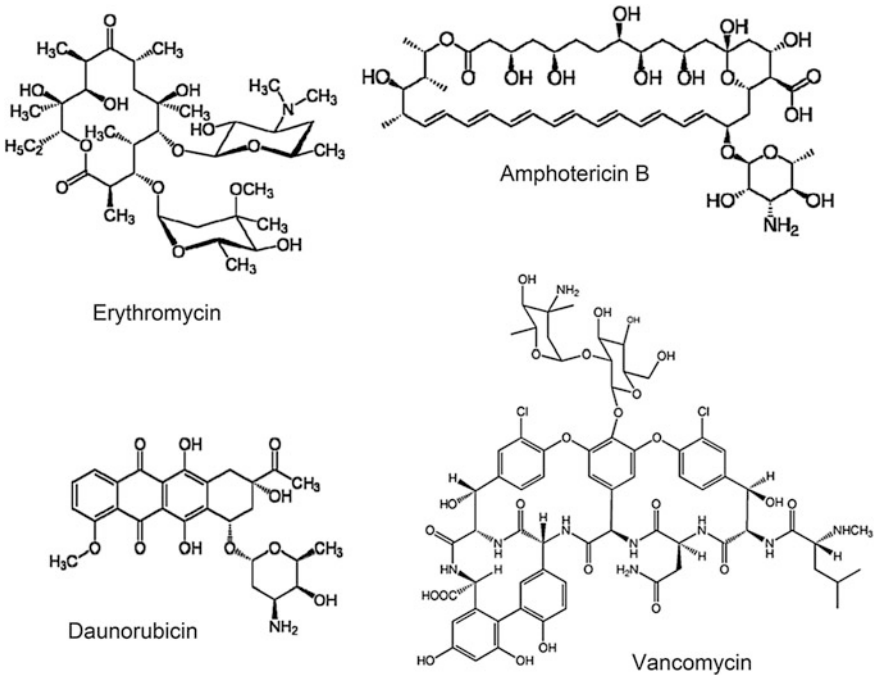

Fig. 2.1 Antibiotics and anti-cancer drugs from actinomycete bacteria

advances in genomics of microbial producers of bioactive secondary metabolites provide unique opportunity for such an investigation, which is the focus of this chapter.

2.2 Actinomycete Bacteria

Actinomycetes are filamentous Gram-positive bacteria of the order *Actinomycetales* found in a variety of diverse environmental niches, where they are usually associated with solid substrates. On solid growth medium these bacteria have a complex life cycle (Chater 1993), starting from a spore that germinates to give rise to a colony-forming mycelium, which invades the substrate and releases hydrolytic enzymes. Aerial mycelium is formed next, protruding from the surface of the colony and forming spores at the tips via septation.

These bacteria are well known for their capacity to biosynthesize biologically active secondary metabolites, which may have several functions in nature. Whatever their role is, it must be very important for actinomycetes, since genome sequencing reveals the presence of 20–30 gene clusters (most of them "silent") dedicated to the biosynthesis of secondary metabolites in each species (Doroghazi

and Metcalf 2013). It seems plausible that secondary metabolites are also important for the adaptation to new environment, as suggested by recent genome analyses of marine actinomycete of the genus *Salinispora* (Penn and Jensen 2012).

2.3 Secondary Metabolite Biosynthesis Gene Clusters and Their Dispersal

Biosynthesis of secondary metabolites (SM), and in particular antibiotics, by the actinomycete bacteria is a complex process typically governed by 10–30 genes. These genes are organized as clusters in the genomes of actinomycetes, allowing coordinated expression of the genes involved in biosynthesis, resistance and efflux of SMs. Typical SM biosynthesis gene cluster is shown in Fig. 2.2.

Biosynthetic machinery for SMs utilizes precursors from primary metabolism (e.g., amino acids, acyl-CoAs) to first build a molecular skeleton with the help of scaffold-synthesizing enzymes. Expression of genes for such enzymes is usually regulated by a positive regulator that responds to particular environmental signals.

Scaffold modification enzymes encoded by distinct genes in the cluster add chemical groups such as sugars, hydroxy, methyl, amino groups, etc., to the scaffold, thereby affording its full biological functionality. The complete molecule is biologically active, and can potentially be harmful to the producing bacterium. To avoid self-toxicity, several resistance mechanisms are usually implemented. One typically depends on the active efflux of the metabolite by a specific transporter encoded by a gene repressed by a negative regulator. The latter is only active in the absence of the molecule to be transported out of the cell, but becomes inactivated upon binding to it. Inactivation of the repressor switches on expression of the transporter, thereby ensuring efflux of SM. The second mechanism often employs a gene encoding resistance protein, which can be enzyme modifying molecular target of SM, or modifying the SM molecule itself, thereby rendering it inactive.

Interestingly, it has been shown that certain secondary metabolite biosynthesis gene clusters can be found in diverse bacterial species dwelling in geographically distinct locations (Green et al. 2008). It seems plausible that this phenomenon is due to a horizontal gene transfer (HGT) after accidental delivery of bacterial species from one location to another (e.g., by birds or fish). However, whether the same gene cluster is functional (i.e., genes expressed and compound produced) in various hosts remains unclear. In several cases it has been observed that the same, seemingly intact gene cluster for antibiotic biosynthesis is functional in one actinomycete species, while being silent in another (Zotchev unpublished data).

The method of HGT used by actinomycete bacteria to disperse SM gene clusters seems to be conjugation involving giant linear plasmids, GLPs (Kinashi et al. 1987) frequently found in actinomycetes, especially those belonging to the order *Streptomyces*. Some of these mobile genetic elements were shown to harbor single complete SM gene clusters, while others can carry several of them (Kinashi 2011).

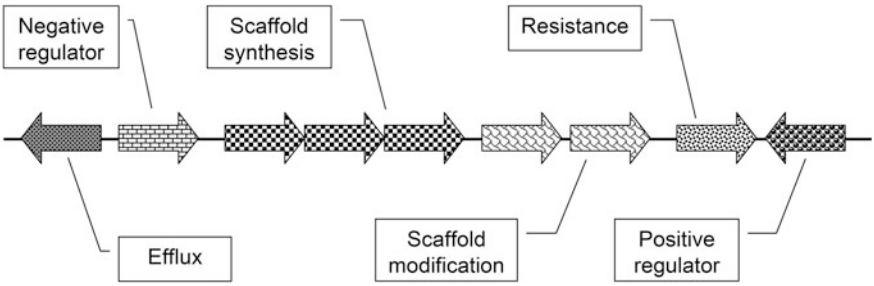

Fig. 2.2 Organization of a typical secondary metabolite biosynthesis gene cluster

The actinomycete GLPs also usually carry several IS elements and transposons, copies of which can also be found on chromosomes. It is conceivable that such elements play an important role in gene exchange between a GLP and a chromosome, thus delivering SM gene clusters to a more genetically stable location.

One of the best studied examples of a GLP carrying SM biosynthetic gene cluster is SCP1 plasmid of *Streptomyces coelicolor* A3(2). This mobile genetic element is 356 kb in size and has 75-kb terminal inverted repeats (TIRs) (Bentley et al. 2004). SCP1 is self-transmissible, and was shown to carry a complete set of genes for the biosynthesis of antibiotic methylenomycin, which can be transferred together with the plasmid to another host during conjugation (Kirby and Hopwood 1977). Recently, it has been demonstrated that SCP1 can interact with the linear chromosome of the host, forming superficial circles through interaction between terminal proteins capping ends of both linear replicons (Tsai et al. 2011). It has also been suggested that such interaction triggers recombination between GLP and chromosome to resolve post-replicational complication resulting from the formation of a superficial circle. Taking all the above into consideration, it seems plausible that GLPs play a major role in spreading the SM biosynthesis gene clusters among actinomycete bacteria, and their integration into the chromosomes.

2.4 Evolution of Secondary Metabolite Biosynthesis Pathways

In order to better understand the evolution of SM biosynthesis, one must remember that proteins participating in their biosynthetic pathways are most likely evolved from the enzymes of primary metabolism. Indeed, scaffold-building enzymes utilize precursors from primary metabolism, linking them in a particular fashion to afford a complex molecule that is distinct from a primary metabolite. Polyketide synthases type I (PKSI), enzymes governing biosynthesis of various biologically active SMs, represent a clear example of evolution of SM biosynthesis from a primary anabolic pathway. These enzymes are composed of several modules, each

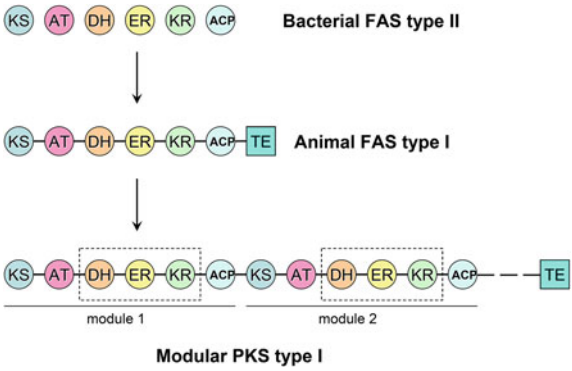

Fig. 2.3 Possible evolution of polyketide synthases type I from a fatty acid synthase. *KS* ketoacyl synthase domain, *AT* acyltransferase domain, *DH* dehydratase domain, *ER* enoyl reductase domain, *KR* ketoreductase domain; *ACP* acyl carrier protein; *TE* thioesterase domain

performing condensation of two acyl building blocks to assemble a polyketide chain. Following condensation, several reductions on the β-carbon of the polyketide chain can be catalyzed by reductive domains embedded within the module. Both the structural organization of PKS I, condensation and reduction reactions that these proteins catalyze are highly similar to an animal fatty acid synthase. The latter has most likely evolved from a bacterial type fatty acid synthase, which is not organized in modules, but is represented by discrete catalytic domains that form a multi-protein complex (Hertweck et al. 2007). A possible scheme for evolution of type I PKS is shown in Fig. 2.3. PKSI are, however, distinct from the animal type fatty acid synthase in that their modules may or may not contain all the reductive domains. Consequently, unlike fatty acids, polyketides synthesized by PKSI may have various chemical groups on their acyl chains, e.g., keto and hydroxyl groups. This chemical variability of the product is programmed into the PKSI via its structural features—number of modules, specificity for incorporated acyl units, and presence or absence of reductive domains in the modules (Cane 2010).

The diversity of SM biosynthetic pathways that must be encoded by actinomycetes genomes is astounding. So far, ca. 10,100 chemically distinct bioactive SMs from actinomycete bacteria have been reported (Mahajan and Balachandran 2012). Considering the fact that actinomycete genomes on average harbour 20–30 SM biosynthesis gene clusters, while only up to 4 of them are expressed, the number of different gene clusters (even considering redundancy) must exceed 100,000. How such diversity has been achieved during the evolution is a mystery, but some insights into the process can be gained via studying structural organization of clusters and phylogenetic analysis of their genes. Jørgensen et al. (2010) cloned a biosynthetic gene cluster for the biosynthesis of a cytotoxic macrolactam ML-449 structurally similar to the earlier reported compound BE-14106 (Jørgensen et al. 2009). Comparison of biosynthetic gene clusters for ML-449 and BE-14106 clearly indicated that the latter cluster undergone an in-frame deletion affecting PKS responsible for the biosynthesis of an aminoacyl precursor. This has resulted in reduction of length of the precursor acyl chain by two carbon atoms,

substantially increasing the cytotoxic activity of BE-14106 compared to ML-449. Moreover, detailed phylogenetic analysis of the KS domains of the PKS proteins involved in the biosynthesis of macrolactams suggested distinct evolutionary origins of the enzymes responsible for assembly of different parts of the molecules. Apparently, convergence of several biosynthetic pathways during evolution resulted in a hybrid pathway leading to production of these macrolactams.

Another example of pathway convergence leading to a hybrid SM is represented by simocyclinone D8, an inhibitor of bacterial DNA gyrase with dual mode of binding to the target (Sissi et al. 2010). The simocyclinone D8 molecule consists of several distinct chemical moieties: aminocoumarine, polyene acyl chain, deoxysugar, and angucycline. Cloning and analysis of the simocyclinone D8 gene cluster revealed the presence of four subclusters, each responsible for the biosynthesis of a separate moiety, which are joined together by specialized enzymes (Trefzer et al. 2002). Unfortunately, no phylogenetic analysis on this cluster which could reveal evolutionary origins of the sub-clusters has been reported.

2.5 Clues on the Evolution of Secondary Metabolism from Comparative Genomics

Recent advances in genome sequencing and bioinformatic analysis revolutionized our view on bacterial evolution. Comparative genomics allows to trace recent loss and acquisition of specific genes, and to distinguish between vertical and horizontal gene transfer (VGT and HGT). Actinomycete bacteria possess next largest (after myxobacteria) genomes in the bacterial domain of prokaryotes, ranging in size from ca. 5 to 11 Mb and represented by both linear (e.g., *Streptomyces*) and circular (e.g., *Salinispora*) replicons (Zhou et al. 2011; Udwary et al. 2007). Recent study by Doroghazi and Metcalf (2013) compared 102 complete genomes of actinomycetes belonging to six different genera: *Mycobacterium*, *Corynebacterium*, *Rhodococcus*, *Arthrobacter*, *Frankia*, and *Streptomyces*, focussing of SM biosynthetic gene clusters. It has been found that certain SM gene clusters are genus—specifically conserved within *Mycobacterium*, *Streptomyces,* and *Frankia*, suggesting that these clusters and corresponding SMs may play an important ecological role for these organisms.

From this point of view, it is interesting to take a closer look at the SM biosynthesis gene clusters in the genomes of actinomycetes occupying the same environmental niche. We have recently isolated several *Streptomyces* spp. from a marine sponge *Antho dichotoma* collected at the bottom of the Trondheim fjord (Norway). Draft genome sequencing of 4 phylogenetically distinct (16S RNA sequence identity <95 %) isolates and analysis of the genomes using online software antiSMASH (Blin et al. 2013) revealed gene clusters that are common to certain isolates (Zotchev, unpublished data). For example, genomes of *Streptomyces* sp. MP99-11 and *Streptomyces* sp. 115-17 share 2 clusters for the biosynthesis of

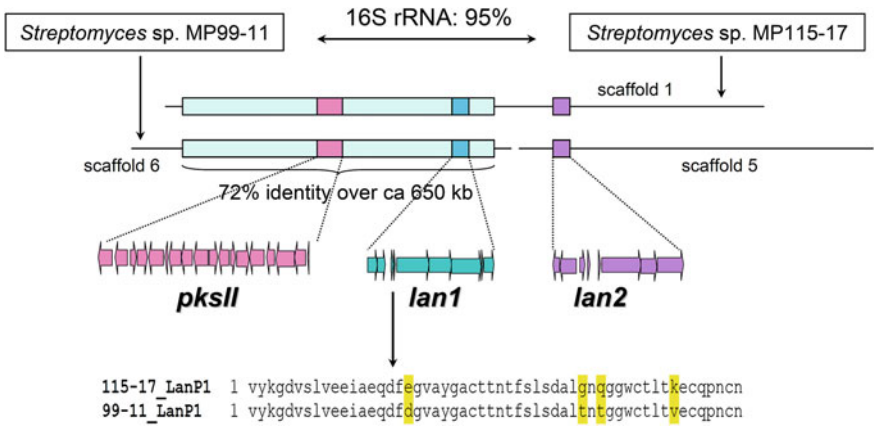

Fig. 2.4 Alignment of genomic regions of *Streptomyces* sp. MP99-11 and *Streptomyces* sp. MP115-17 harbouring gene clusters for aromatic polyketide (*pksII*) and lantibiotics (*lan1* and *lan2*). Alignment of the prepropeptides encoded by the cluster *lan1* in two genomes is shown

lantibiotics (ribosomally synthesized and post-translationally modified peptides) and an aromatic polyketide (synthesized by type II PKS). Alignment of the genomic regions harboring these cluster is presented in Fig. 2.4. Interestingly, both *pksII* and *lan1* gene clusters were co-localized within a ca 650-kb genomic region that shares overall 72 % identity on the nucleotide level. Such high degree of conservation over a large DNA fragment clearly suggests that it has been inherited by both isolates from a common ancestor, i.e., via VGT. We also observed a functional evolution of the *lan1* cluster, where the genes for prepropeptides of lantibiotics differ significantly between the species, the major differences being in the region encoding part of the peptide that represent a final product prior to modifications.

The latter suggests that both structures and perhaps biological properties of these lantibiotics will be different, possibly reflecting their roles in two distinct bacterial hosts. In contrast to *pksII* and *lan1*, the *lan2* gene cluster was surrounded by nonhomologous DNA in two isolates (Fig. 2.4), and is more conserved, suggesting a relatively recent acquisition of this gene cluster by both isolates via HGT.

As mentioned in Sect. 2.3, it seems plausible that self-transmissible GLPs carrying (and/or capable of "picking up") SM biosynthetic gene clusters are responsible for their transfer and integration into a new actinomycete host. From this point of view, it is interesting to compare the existing genomic data for actinomycetes with linear and circular chromosomes. The latter is represented by *Salinispora* spp., obligatory marine actinomycete bacteria known as producers of a novel anti-cancer drug candidate, salinosporamide (Gulder and Moore 2010). Genome analyses of several *Salinispora* strains revealed that their circular chromosomes have genomic islands, where most of the SM biosynthetic gene clusters are located (Penn et al. 2009). Moreover, such islands were shown to contain multiple IS elements and transposons, which may assist in recruiting SM gene

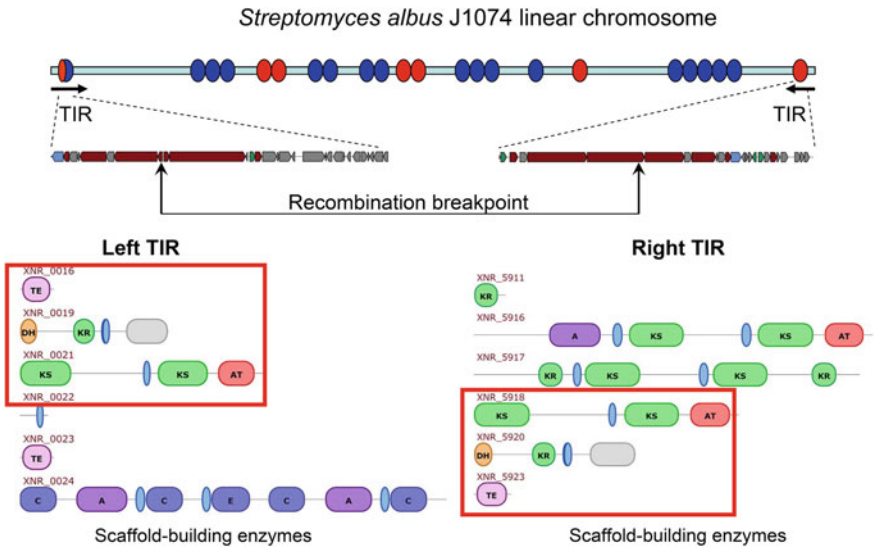

Fig. 2.5 SM gene clusters at the TIRs of *S. albus* J1074 chromosome (see text for details)

clusters to these specific locations via recombination with the incoming DNA carrying homologous sequences. In this case, a double crossover recombination would be required to stably integrate a SM gene cluster into the chromosome. Situation may be different with linear chromosomes of *Streptomyces* spp., which have terminal inverted repeats ranging in size from 35 kb in *Streptomyces davawensis* (Jankowitsch et al. 2012) to 1 Mb in *S. coelicolor* A3(2) (Weaver et al. 2004). In several *Streptomyces* spp., SM biosynthetic gene clusters are located within the TIRs, e.g., in *Streptomyces ambofaciens* (Pang et al. 2004) and *Streptomyces albus* J1074 (Zaburannyi et al. 2014; Zotchev unpublished data). This duplication of clusters at chromosomal ends may provide substrates for recombination that can fuse the existing clusters with the incoming ones carried by GLPs or those present in the vicinity of TIRs on the chromosome. This recombination may be facilitated by the presence of IS elements, which are almost always present at the TIRs of both chromosomes and GLPs (Zotchev unpublished data).

Under selective pressure from the environment, such recombination may lead to the formation of hybrid SM gene clusters that may govern biosynthesis of novel compounds beneficial to the host. Analysis of SM gene clusters at the 29-kb TIRs of a linear chromosome of *S. albus* J1074 presented in Fig. 2.5 supports the notion above. The SM gene cluster located within the right-TIR appears to be responsible for the biosynthesis of a polyketide assembled by a hexamodular PKSI enzyme complex and utilizing an amino acid as a starter. The left-TIR, however, contains genes encoding only two last modules of the same PKSI, which is now fused with what appears to be three modules of a non-ribosomal peptide synthetase (NRPS—enzymes that act in a fashion similar to PKS, but use amino acids as building blocks). An NRPS gene cluster encoding modules identical to these three modules

is also located on the chromosome close to the right-TIR, and detailed analysis allowed identification of the recombination breakpoint, where the PKS and NRPS clusters have merged.

It seems likely that this observation is not unique, and similar phenomena can be found upon analyses of other linear genomes of *Streptomyces*. Deciphering the mechanisms behind such events may not only shed light on the evolution of SM gene clusters, but also assist in rational design of novel gene clusters for biosynthesis of potential new drugs.

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