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Research review paper

Systems biology and biotechnology of *Streptomyces* species for the production of secondary metabolites

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ABSTRACT

Streptomyces species continue to attract attention as a source of novel medicinal compounds. Despite a long history of studies on these microorganisms, they still have many biochemical mysteries to be elucidated. Investigations of novel secondary metabolites and their biosynthetic gene clusters have been more systematized with high-throughput techniques through inspections of correlations among components of the primary and secondary metabolisms at the genome scale. Moreover, up-to-date information on the genome of *Streptomyces* species with emphasis on their secondary metabolism has been collected in the form of databases and knowledgebases, providing predictive information and enabling one to explore experimentally unrecognized biological spaces of secondary metabolism. Herein, we review recent trends in the systems biology and biotechnology of *Streptomyces* species.

Contents

Abbreviations: ACP, acyl carrier protein; AT, acyltransferase; COBRA, constraint-based reconstruction and analysis; DoBISCUIT, Database Of BIoSynthesis clusters CUrated and InTegrated; MRSA, methicillin-resistant *Staphylococcus aureus*; NRPS, nonribosomal peptide synthetase; PCP, peptidyl carrier protein; PKS, polyketide synthase; PrISM, Proteomic Investigation of Secondary Metabolism; SBSPKS, Structure Based Sequence Analysis of Polyketide Synthases.

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1. Introduction

Streptomyces species, belonging to the *Actinobacteria* family, are aerobic and Gram-positive soil bacteria that show filamentous growth from a single spore. As their filaments grow through tip extension and branching, they ultimately form a network of branched filaments called a substrate mycelium (Dyson, 2011). Upon environmental stresses, for example nutrient limitation, and on the solid cultivation condition, streptomycetes move from the vegetative phase (i.e., substrate mycelium) to a reproductive sporulation phase in the form of aerial multinucleated mycelium. On the other hand, they have a linear chromosome, approximately 8 Mb to 10 Mb depending on the specific species, with high GC content and several plasmids in a linear or circular form. One of the unique features of the genome in the *Streptomyces* species is the presence of biosynthetic gene clusters that encode enzymes contributing to the production of secondary metabolites with a variety of chemotypes, including polyketides, lactams, nonribosomal peptides, and terpenes (Fig. 1) (Nett et al., 2009). Many of the secondary metabolites are produced during the shifting phase from the substrate mycelium to sporulation, accompanied by morphological differentiation (e.g., formation of the aerial multinucleated mycelium) (Dyson, 2011; Flardh and Buttner, 2009).

Streptomyces species have been an important source of medicines, especially antibiotics (Fig. 1). From the late 1940s to the 1960s, also known as the golden age of antibiotics discovery, many antibiotics were isolated from various *Streptomyces* species and entered clinical use (Berdy, 2005). Although the portion of recently discovered antibiotics isolated from *Streptomyces* species has declined to about 20–30%, recent genome sequencing data indicate that this genus possesses the ability to produce many more bioactive secondary metabolites than had been previously appreciated, many of which have not yet been elucidated. The medical uses of these secondary metabolites are not just confined to antibiotics (e.g., daptomycin), but also include immunosuppressants (e.g., rapamycin), antifungals (e.g., amphotericin B), anticancers (e.g., doxorubicin), and antiparasitics (e.g., ivermectin) (Newman and Cragg, 2007). A major attention for the *Streptomyces* species comes from a current urgent need to discover novel antibacterial compounds because of the rapid rise in antibiotic-resistant microbial pathogens, for example methicillin-resistant *Staphylococcus aureus* (MRSA) and Gram-negative pathogens, such as *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* (Bush et al., 2011; Fischbach and Walsh, 2009).

Consequently, the systematic investigation of *Streptomyces* species is becoming more important given that they are already a proven source of medically-useful compounds with diverse structures and that they have the potential to produce even more secondary metabolites than what has been isolated from them to date (Baltz, 2008, 2011; Craney et al., 2013). Importantly, vast amount of information collected on the *Streptomyces* species makes them better amenable to the application of high-throughput techniques (e.g., combination of genome mining and mass spectrometry) and gene manipulations to maximize their potential of producing potent antibiotics, compared to other antibiotics-producing microorganisms (Nett et al., 2009). The *Streptomyces* species also stand competitive in comparison with plant cells as extracting and

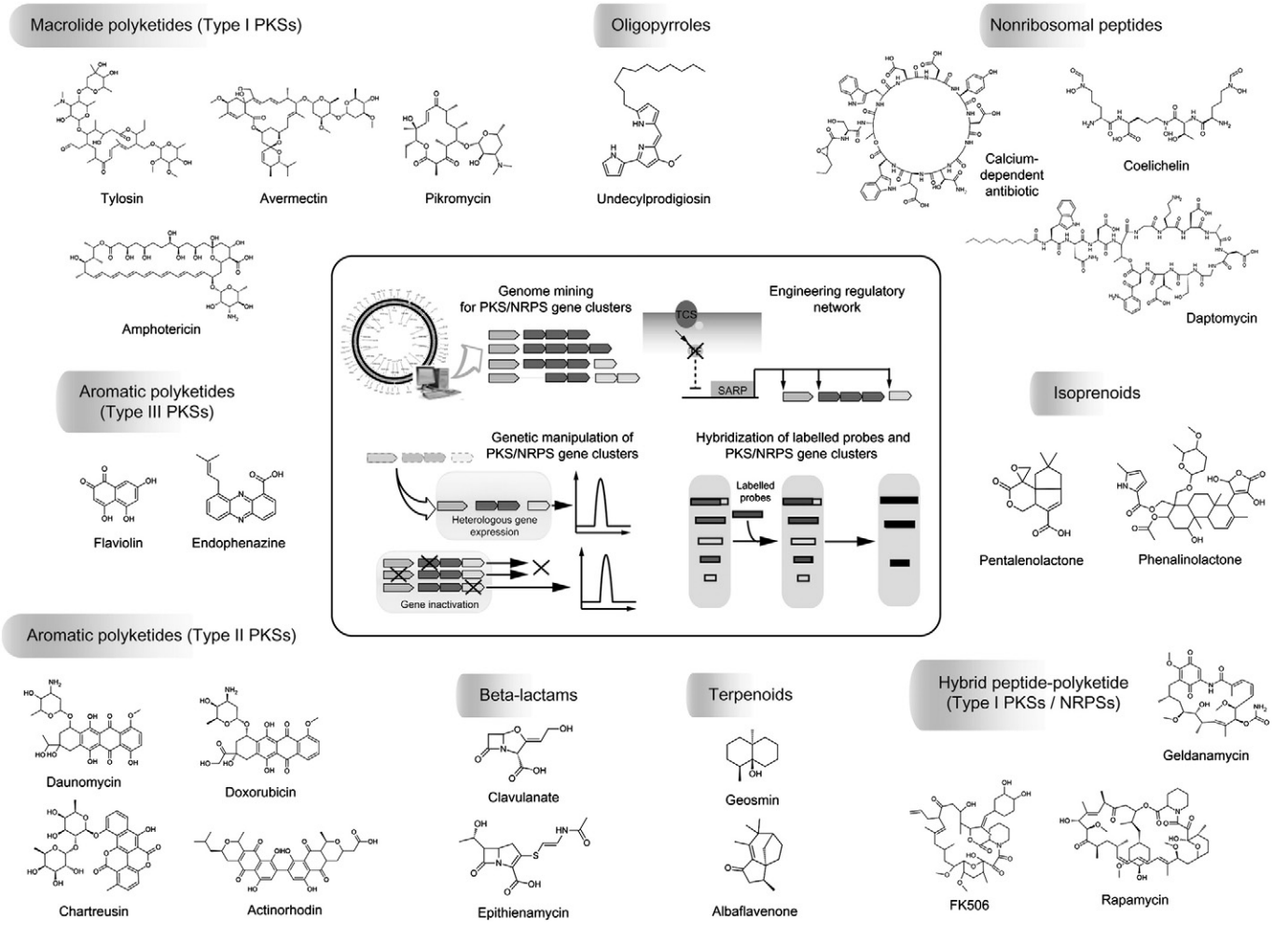

Fig. 1. Representative secondary metabolites produced from *Streptomyces* species with molecular and computational tools available shown in the middle. Parentheses next to each secondary metabolite type indicate the types of associated biosynthetic enzymes. Abbreviations: SARP, *Streptomyces* antibiotic regulatory protein; TCS, two-component system.