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Research review paper

Toward steadfast growth of antibiotic research in China: From natural products to engineered biosynthesis

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ABSTRACT

Antibiotics are widely used for clinical treatment and preventing or curing diseases in agriculture. Cloning and studies of their biosynthetic gene clusters are vital for yield enhancement and engineering new derivatives with new and prominent activities. In recent years, research in this aspect is impressively active in China. This article reviews biosynthetic progress on 28 antibiotics, including polyketides, nonribosomal peptides, hybrid polyketide–nonribosomal peptides, peptidyl nucleoside, nucleoside, and others. Their biosynthetic mechanisms were disclosed, and their derivatives with new structures/activities were obtained by gene inactivation, mutasynthesis and combinatorial biosynthesis.

Contents

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1. Introduction

The antibiotic industry in China is prominent for its enormous production capacity esp. on β-lactam antibiotic penicillins and cephalosporins (Elander, 2003), erythromycin (Zhang et al., 2004), and validamycins. Although most of the antibiotics widely used in clinics and agricultures could be produced in China, worldwide common issues of low productivity, presence of multiple components, long fermentation periods and high costs are still the big problem. On the other hand, calling for new antibiotics with novel structures and/or activities becomes more urgent due to the severely increased antibiotic resistance of pathogens and emerging life-threatening diseases. In order to find solutions for these two abovementioned issues for the development of Chinese antibiotic industry, intensive effort has been made on discovering new antibiotics and engineering the antibiotic producing microbes.

Engineering available antibiotic biosynthetic pathways and their producers are prevalent strategies for structure alternation and yield improvements. Therefore, cloning of the antibiotic gene clusters is prerequisite for better understanding of the biosynthetic and regulatory mechanisms and the ultimate engineering. Since the cloning of the antibiotic FR-008/candicidin biosynthetic gene cluster in 1994 (Hu et al., 1994), totally twenty-eight antibiotic biosynthetic gene clusters have been cloned in China (Table 1), mostly from actinomycetes. According to the biosynthetic origin, these antibiotics can be assigned to different groups including polyketides (PKS), nonribosomal peptides (NRPS), hybrid polyketide–nonribosomal peptides (PKS/NPRS), ribosomal thiopeptides, peptidyl nucleosides, nucleoside, aminoglycosides, and others. This review gives progress on the cloning, functional analysis, and engineering of antibiotic biosynthetic gene clusters after 2006. Detailed biosynthetic studies before 2006 had been previously summarized by Deng and Bai(2006).

2. Biosynthesis of antibiotics

2.1. Polyketides

Backbones of macrolides, polyenes, polyethers, and the polyketide portion of hybrid peptide–polyketides are usually assembled from

Table 1
Antibiotics studies in China for their biosynthesis and engineering.

Antibiotic	Category	Activity	Producer	Reference or source
Antibiotic FR-008/candicidin	PKS	Antifungal	*Streptomyces* sp. FR-008	Zixin Deng Group (Chen et al., 2003)
Calcimycin	PKS	Antibacterial ionophore	*S. chartreusis* NRRL3882	Zixin Deng Group (Wu et al., 2011)
Chlorothricin	PKS	Pyruvate carboxylase inhibitor	*S. antibioticus* DSM40725	Wen Liu Group (Jia et al., 2006)
Meilingmycin	PKS	Insecticidal	*S. nanchangensis* NS3226	Zixin Deng Group (He et al., 2010)
Nanchangmycin	PKS	Insecticidal	*S. nanchangensis* NS3226	Zixin Deng Group (Sun et al., 2003a)
Tetrocarcin A	PKS	Antibacterial and antitumor	*Micromonospora chalcea* NRRL11289	Wen Liu Group (Fang et al., 2008)
Tiacumicin B	PKS	RNA polymerase inhibitor	*Dactylosporangium aurantiacum* subsp. *hamdenensis* NRRL18085	Changsheng Zhang Group (Xiao et al., 2011)
Azinomycin B	NRPS	Antitumor	*S. sahachiroi* NRRL2485	Wen Liu Group (Zhao et al., 2008)
Himastatin	NRPS	Antibacterial, antitumor	*S. himastatinicus*	Jiahua Ju Group (Ma et al., 2011)
Saframycin A	NRPS	Antitumor	*S. lavendulae* NRRL11002	Wen Liu Group (Li et al., 2008a)
FR901464	PKS/NRPS	Antitumor	*Pseudomonas* sp. No. 2663	Gongli Tang Group (Zhang et al., 2011a)
Oxazolomycin	PKS/NRPS	Antibacterial, antitumor, anti-HIV	*S. albus* JA3453	Zixin Deng Group (Zhao et al., 2010a)
Pyridomycin	PKS/NRPS	Antimycobacterial	*S. pyridomyceticus* NRRL B-2517	Zixin Deng Group (Huang et al., 2011)
Sanglifehrin A	PKS/NRPS	Cyclophilin inhibitor	*S. flaveolus* DSM 9954	Wen Liu Group (Qu et al., 2011)
Tirandamycin	PKS/NRPS	RNA polymerase inhibitor	*Streptomyces* sp. SCSIO 1666	Changsheng Zhang Group (Mo et al., 2011b)
Cyclothiazomycin	Thiopeptide	Human plasma rennin inhibitor	*S. hygroscopicus* 10–22	Zixin Deng Group (Wang et al., 2010)
Nocathiacin I	Thiopeptide	Antibacterial	*Nocardia* sp. ATCC 202099	Wen Liu Group (Ding et al., 2010b)
Nosiheptide	Thiopeptide	Antibacterial, feed additive	*Streptomyces actuosus* ATCC 25421	Wen Liu Group (Yu et al., 2009)
Siomycin A	Thiopeptide	Antibacterial	*S. sioyaensis* ATCC 13989	Wen Liu Group (Liao et al., 2009b)
Thiocillin I	Thiopeptide	Antibacterial	*Bacillus cereus* ATCC 14579	Wen Liu Group (Liao et al., 2009b)
Thiostrepton	Thiopeptide	Antibacterial	*S. laurentii* ATCC 31255	Wen Liu Group (Liao et al., 2009b)
Mildiomycin	Peptidyl nucleoside	Antifungal	*Streptoverticillium rimofaciens* ZJU5119	Zixin Deng Group (Li et al., 2008b)
Muraymycin	Peptidyl nucleoside	Translocase I inhibitor	*Streptomyces* sp. NRRL 30471	Zixin Deng Group (Cheng et al., 2011)
Nikkomycin	Peptidyl nucleoside	Chitin synthase inhibitor	*S. ansochromogenes*	Huarong Tan Group (Liao et al., 2010)
Polyoxin	Peptidyl nucleoside	Chitin synthase inhibitor	*S. cacaoi*	Zixin Deng Group (Chen et al., 2009b)
Tunicamycin	Nucleoside	Translocase I inhibitor	*S. clavuligerus* ATCC 27064	Zixin Deng Group (Chen et al., 2010)
Validamycin	Amino-glycoside	Antifungal	*S. hygroscopicus* 5008, *S. hygroscopicus* 10–22	Zixin Deng Group (Bai et al., 2006; Jian et al., 2006)
Thuringiensin	Adenine nucleoside oligosaccharide	Insecticidal	*Bacillus thuringiensis*	Ming Sun Group (Liu et al., 2010)