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Regulation Mechanisms Underlying the Biosynthesis of Daptomycin and Related Lipopeptides

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ABSTRACT

Daptomycin is a lipopeptide antibiotics used to treat Gram-positive pathogens infections, including drug-resistant strains. In-depth exploration of its biosynthesis and regulation is crucial for metabolic engineering improvement of this ever-increasing important antibiotic. The past years have witnessed the significant progresses in the understanding of the molecular mechanisms underlying the biosynthesis and regulation of daptomycin. This information was updated in our review, with special focus on the regulatory network integrating a wide variety of physiological and environmental inputs. This should provide novel insight into the regulatory mechanism of biosynthesis of daptomycin and nodes for strain improvement to increase the yields of daptomycin. J. Cell. Biochem. 113: 735–741, 2012.

KEY WORDS: DAPTOMYCIN; METABOLIC REGULATION; BIOSYNTHESIS; NETWORK

Daptomycin is a lipopeptide approved for treatment of skin and skin structure infections, endocarditis, and bacteremia caused by Gram-positive pathogens [Baltz, 2009]. Daptomycin, produced by *Stretomyces roseosporus*, is a member of the 10-membered cyclic lipopeptide family of antibiotics with potent activity against Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) or Vancomycin-resistant Enterococci (VRE). These compounds are under intensive investigation for better novel derivative antibiotics. The biosynthetic gene clusters responsible for this family antibiotics, including Calcium-dependent antibiotics (CDA) from *Streptomyces coelicolor* A(3)2 [Hojati et al., 2002], daptomycin from *Stretomyces roseosporus* [McHenney et al., 1998], A54145 from *Streptomyces fradiae* A54145 [Miao et al., 2006], and friulimicin from *Actinoplanes friuliensis* [Muller et al., 2007] have been isolated and characterized (Fig. 1), offering unprecedented opportunity for daptomycin derivatives with enhanced activity through combinatorial biosynthesis. This topic has been covered extensively in previous reviews [Baltz, 2008].

In addition to the substantial progress on the understanding of the biosynthetic mechanism of daptomycin and related lipopeptides, a wealth of information on the regulatory mechanisms governing the biosynthesis of daptomycin and related lipopeptides has been unveiled. Multiple regulatory proteins coordinate these lipopeptides biosynthesis, directly or indirectly, forming complex network to fine-tune the expression. These data were reviewed in this paper.

THE CHEMICAL STRUCTURE OF DAPTOMYCIN

Daptomycin, produced by *Streptomyces roseosporus*, is a member of the A21978C factors, which share the same 13 amino acids cyclized to form a 10-membered macrolactone ring with three exocyclic residues. The factors can be distinguished by the fatty acids coupled to the N-terminal Trp, which contains n-decanoyl, *anteiso*-undecanoyl, *iso*-dodecanoyl, and *anteiso*-tridecanoyl. Daptomycin is the n-decanoyl analog of A2178C with chemical formula $C_{12}H_{107}N_{17}O_{26}$ and molecular mass 1620.67. The peptide portion of daptomycin contains seven proteinogenic amino acids and six nonproteinogenic amino acids including D-Asn_2, Orn_6, D-Ala_8, D-Ser_{11}, $MeGlu_{12}$, and Kyn_{13} which forms the ester bond with the hydroxyl group of Thr_4. Daptomycin requires Ca^{2+} for antibacterial activity, and has a specific EF-hand motif (DXDG) at positions 7–10 involving in Ca^{2+}-binding. This is also a common feature of the

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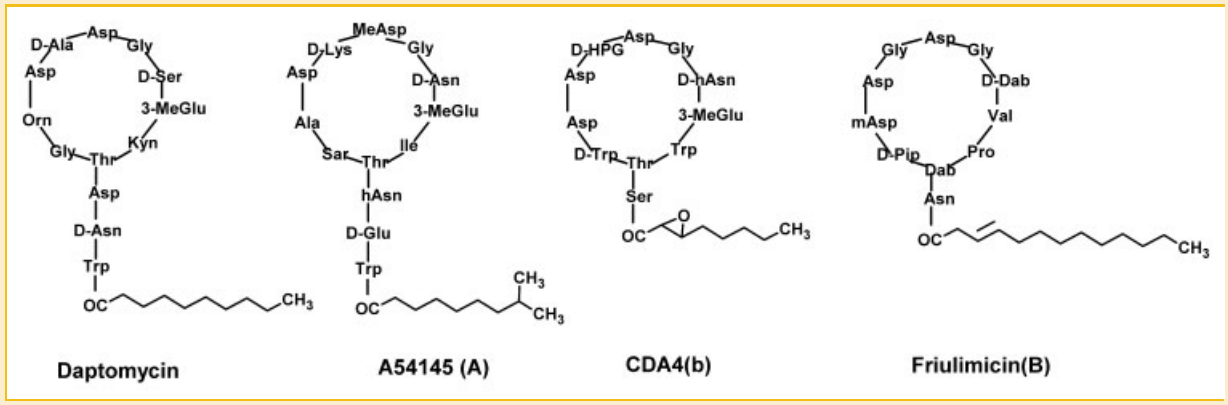

Fig. 1. The structures of daptomycin and related lipopeptides. Abbreviations for unusual amino acids are as follows: hASn, hydroxyasparagine; Dab, 2,3-diaminobutyric acid; HPG, hydroxyphenylglycine; Kyn, kynurenine; MeASp, methylaspartic acid; 3-MeGlu, 3-methylgulutamic acid; Orn, ornithine; Pip, pipecolinic acid; Sar, sarcosine.

10-membered cyclic lipopeptide family antibiotics, including CDA and A54145 [Baltz, 2008].

DAPTOMYCIN PRODUCER- STREPTOMYCES ROSEOSPORUS

Streptomyces roseosporus NRRL11379 that can produce daptomycin was first isolated from Mount Ararat soil in Turkey by scientists from Eli Lilly and Company. Culture of NRRL11379 is characterized by the generation of a predominant red aerial spore mass color, with a reddish-brown reverse color on several agar plates (Fig. 2a). Culture of NRRL11379 has Rectus-Flexibilis (RF) type spore morphology, smooth spore surface, and melanin negative. Carbon utilization experiments demonstrated that Culture of NRRL11379 can employ L-arabinose, D-galactose, D-glucose, D-fructose, D-mannitol, L-rhamnose, salicin, and D-xylose as sole carbon source, rather than i-inositol, D-raffinose, and sucrose. This strain is sensitive to the

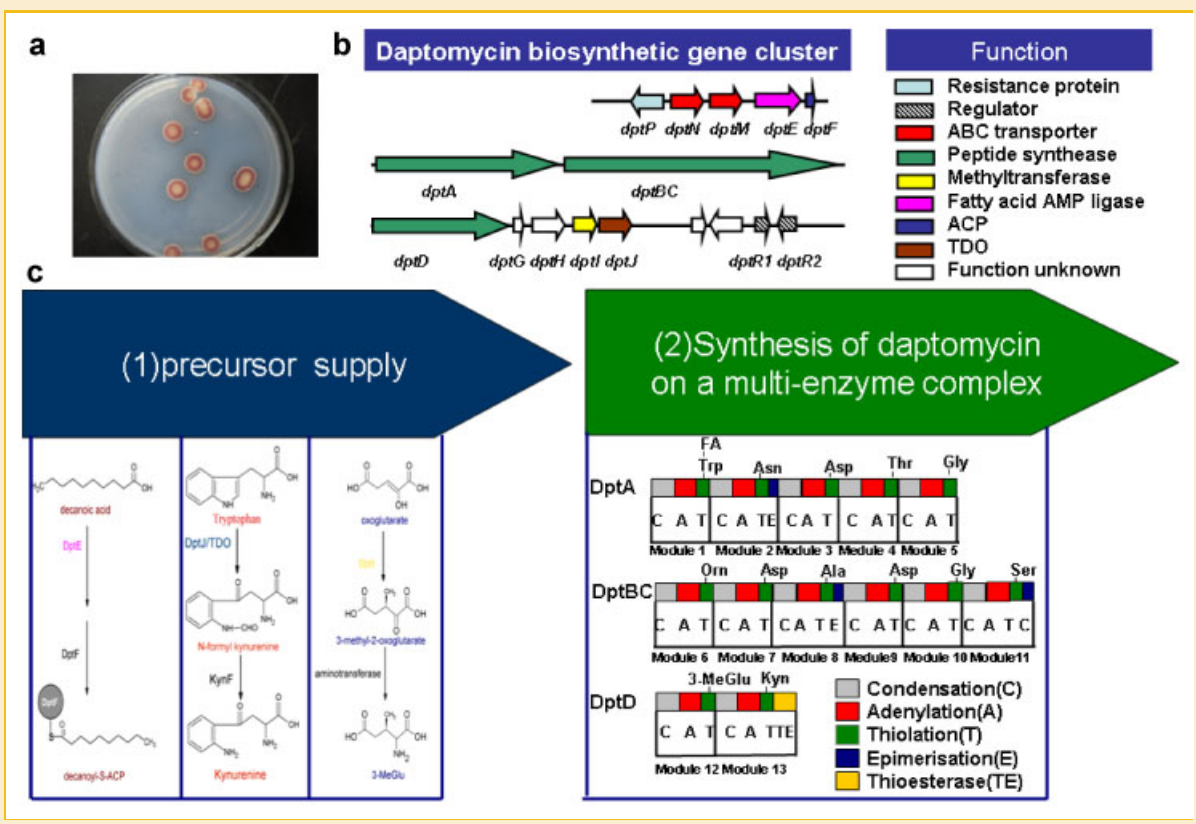

Fig. 2. Overview of daptomycin biosynthesis. a: Pictures of the daptomycin producer Streptomyces roseosporus. b: Daptomycin biosynthetic gene cluster and the description of the functions encoding by the genes. c: Summary of the two steps of the daptomycin biosynthesis. [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/jcb]

class of glycoside (lincomycin) and polyene (nystatin), but resistant to other class of antibiotics, including macrolide (erythromycin), beta-lactam (cephalothin), aminoglycoside (streptomycin), tetracycline (tetracyclin), and glycopeptide (vancomycin).

THE BIOSYNTHETIC PATHWAY OF DAPTOMYCIN

The daptomycin biosynthetic genes found in *S. roseosporus* consist of at least 12 known genes clustered in a region spanning approximately 100 kb. Daptomycin is assembled by a nonribosomal peptide synthetase (NRPS) mechanism and daptomycin gene cluster (Fig. 2b) contains three genes encoding NRPS (*dptA*, *dptBC*, and *dptD*), two genes involving in activating the fatty acids (*dptE* and *dptF*), seven genes participating in precursor supply, resistance or transport (*dptG*, *dptH*, *dptI*, *dptJ*, *dptM*, *dptN*, and *dptP*). All biosynthetic genes are oriented in the same direction and can be transcribed as a single transcript [Coeffet-Le Gal et al., 2006], implying a co-regulation modality.

N-TERMINAL ACYLATION

Acylation of the N-terminal amino acid in daptomycin is important for its bioactivity and bioselectivity. DptE and DptF are responsible for activation of fatty acids which are then catalyzed by N-terminal C domain of DptA to form N-acylation of Trp_1 (Fig. 2c). DptE, a novel acyl-AMP ligase, activates fatty acid with ATP consumption, then transfers fatty acids from acyl AMP to the 4′-phosphopantethein group of DptF which is an acyl carrier protein (ACP) [Wittmann et al., 2008]. In vitro kinetic analysis demonstrated that DptE favors linear fatty acids with chain lengths ranging from 8 to 14 carbon units, particularly decanoic acid and *iso*/*anteiso*-branched chain fatty acids, implying that the diversity of fatty acids in A2178C depends on the substrate selectivity of DptE and manipulation of DptE may generate analogs of daptomycin with a variety of fatty acids moiety.

BIOSYNTHESIS OF NONPROTEINOGENIC AMINO ACIDS

There are 13 amino acids involving in biosynthesis of daptomycin, 7 L-amino acids are recognized and activated by cognate A domain and incorporated into core peptide and 3D-amino acids (D-Asn_2, D-Ala_8, D-ser_{11}) are incorporated into the L-form and cognate E-domains in DptA, DptBC catalyse stereochemical conversion. Genes responsible for producing Kyn_{13} and $MeGlu_{12}$ were identified in daptomycin cluster, while none genes were implicated in yielding Orn, indicating that primary metabolism provides enough Orn to support daptomycin biosynthesis.

Kynurenine is an immediate of kynurenine pathway for degradation of L-trytophan and could only be found in daptomycin among tens of thousands of natural products. Tryptophan is cleaved by tryptophan-2, 3-dioxygenase (TDO) to yield N-formylkynurenine (Fig. 2c). Removal of the formyl group by N-formylkynurenine formamidase (KFA) results in kynurenine [Kurnasov et al., 2003]. Subsequently, kynurenine is degraded to yield NAD in eukaryotes or generate different kinds of compounds depended on species in bacteria, including signal molecules regulating a number of biological processes and precursor associated with biosynthesis of secondary metabolites [Lima et al., 2009; Sheoran et al., 2008; Matthijs et al., 2004]. *dptJ* encoded putative TDO, the rate-limiting enzyme of kynurenine pathway, and disruption of *dptJ* resulted in reducing the yield of daptomycin by 50% [Nguyen et al., 2006]. These results demonstrated that *dptJ* was indeed involved in daptomycin biosynthesis and another TDO encoding gene probably existed in the chromosome. A gene locus, *SSGG3688* encoding TDO, *SSGG3689* encoding kynureninease which catalyses kynurneine to generate anthranilate and *SSGG3690* encoding KFA was identified by bioinformatic analysis of genomic sequences (www.broadinstitute.org/annotation/genome/streptomyces_group). It is common that isozymes (e.g., SSGG3688 and DptJ) locate in the gene cluster and other locus in the chromosome in order to provide sufficient precursors for antibiotics production.

MeGlu is essential for maximum activity of daptomycin and characteristic amino acid of lipopeptides, residing in the same position in CDA and A54115 core peptide. In daptomycin gene cluster, *dptI* encodes a SAM-dependent methyltransferase. Deletion of *dptGHIJ* led to obtain A21978C analogs substituted Glu_{12} with $MeGlu_{12}$ [Nguyen et al., 2006]. Complementation of the resulting mutant with *dptJ* restores the A21978C production containing $MeGlu_{12}$, indicating that *dptI* indeed involved in methylation of Glu. Recently, biochemical analysis revealed that *dptI* encods a novel methyltransferase adding a methyl group from SAM to ketoglutarate to form 3-methyl-2-oxoglutarate, which can be transaminated by a conserved IlvE transaminase to give MeGlu (Fig. 2c) [Mahlert et al., 2007].

PEPTIDE FORMATION AND RELEASE

DptA, DptBC, and DptD are responsible for the peptide extension and finally releasing from the peptide assembly line (Fig. 2c). DptA containing five modules, recognizes, activates, and couples the first five amino acids. At the N-terminal of DptA, a special C-domain (type C^{III}) is responsible for coupling the long chain fatty acids to the N-terminal of Trp_1. An E-domain in module 2 epimerizes the L-Asn_2 to give D-Asn_2. DptBC harbors six modules to form the next six amino acids. E-domain in module 8 and module 11 are responsible for generating D-Ala_8 and D-ser_{11}, respectively. DptD containing two modules accounts for forming MeGlu and Kyn, and a thioesterase domain catalyzes the formation of ester bond between Kyn_{13} and Thr_4 and releases the completed daptomycin from the NRPS multienzyme.

REGULATION OF THE BIOSYNTHESIS OF DAPTOMYCIN AND RELATED LIPOPEPTIDES

The complex and exquisite regulation of antibiotics biosynthesis integrates both physiological cues and environmental factors such as carbon, nitrogen, pH, and temperature. In general, two classes of transcription factors are critical for expression of cluster genes [van Wezel and McDowall, 2011]. One class is specific to a particular metabolic pathway, perhaps the best studies being *Streptomyces* antibiotic regulatory proteins (SARPs). Another group is responsible for mediating environmental signals and acts on many clusters. Due to the importance of daptomycin and related lipopeptides, a great

deal of research has been carried out in the field of regulation of the biosynthesis of these antibiotics. Great strides have been achieved in the understanding of regulatory mechanism of CDA biosynthesis in *S. coelicolor*. Given the structural and biosynthetic pathway similarity among acid lipopeptides, the knowledge gained from one strain could provide important information for understanding the regulatory mechanism of daptomycin and related lipopeptides.

PATHWAY SPECIFIC REGULATORY GENES

Generally, lipopeptide gene clusters contain two putative pathways specific regulatory genes, with the CDA cluster as an exception which just harbors *cdaR* belonging to the well-characterized SARP family (Fig. 3). As expected, regulatory genes from different clusters are the members of same regulatory family, such as *regB* and *lptJ* encoding syrP-like proteins in friulimicin and A54145 gene cluster respectively, *regA* and *dptR1* encoding LuxR family proteins in cognate friulimicin and daptomcyin gene cluster.

LuxR family proteins regulate a variety of important bacterial physiology, including large ATP-binding regulators of the LuxR (LAL) governing the biosynthesis of macrolide through polyketide synthase (PKS) mechanism in *Streptomycetes*, such as PikD for pikromycin biosynthesis in *Streptomyces venezuelae* [Wilson et al., 2001]. LALs are relatively large proteins (872–1159 aa) and comprised of N-terminal ATP binding domain and C-terminal LuxR-like DNA binding domain. In contrast to LAL, RegA is a small protein (254 aa) with a helix-turn-helix motif of LuxR type at the C-terminal end. Deletion of *regA* results in friulimicin nonproducing mutants, indicating that RegA positively regulates friulimicin biosynthesis [Nolden et al., 2009]. Gene expression analysis shows that the expression of most of friumicin biosynthetic genes is impaired in the mutant, while the expression of *regA* is enhanced, indicating that RegA negatively controls its own expression. RegA, shows 37% identity to DptR1, 29% identity to PrpA from *S.viridochromogenes* [Schwartz et al., 2004], and BrpA from *S. hygroscopicus* [Raibaud et al., 1991]. The latter two strains also could produce a peptide through NRPS mechanism, indicating that those small LuxR regulators may represent a novel pathway specific regulator for NRPS-governing peptide.

SIGNAL TRANSDUCTION AND TWO-COMPONENT SYSTEM (TCS)

TCS serves as the main bacterial signal transduction system and regulates most aspects of bacterial life, including global responses to stresses, nutrients, and biosynthesis of secondary metabolites. It is shown that two TCSs (AfsQ1/AfsQ2, AbsA1/AbsA2) and one orphan histine kinase (OhkA) are associated with CDA production [Ryding et al., 2002, Shu et al., 2009, Lu et al., 2011]. While the identity of the extracellular signals receipted by AfsQ1, AbsA1, and OhkA unknown, the response regulators (AfsQ2 and AbsA2) exert their regulatory role through binding to the promoter region of pathway specific regulatory gene *cdaR*, resulting in modulating its expression.

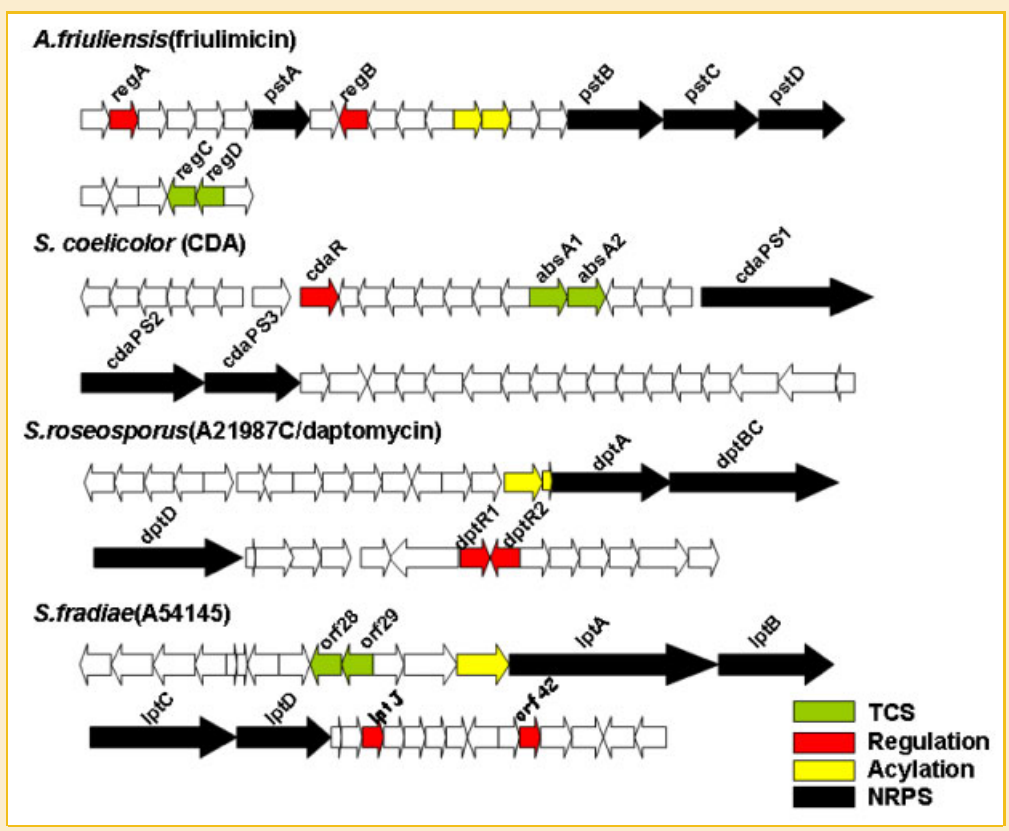

Fig. 3. Biosynthetic gene clusters for friulimicin, CDA, daptomycin, and A54145. TCS is an abbreviation for two-component system. regA and dptR1 encode regulator belonging to LuxR family; regB and lptJ encode a syrP-like protein; cdaR encodes a SARP protein; orf46 in A54145 encodes a MerR family regulator; dptR2 encodes a DeoR family regulator. [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/jcb]

AbsA1/AbsA2 the well-characterized TSC and its encoding genes locate within CDA gene cluster. AbsA1 believed to phosphorylate the response regulator AbsA2. Phosphorylated AbsA2 transcription of *cdaR*, which a SARP family regulator presumed to control the expression of structural genes involved in CDA biosynthesis.

Besides the kinase activity, AbsA1 also phosphotase activity, which could dephosphorylate phosphorylated AbsA2. Mutants with impaired the kinase activity could increase the CDA production, while mutants with abrogation of the phosphotase activity significantly decrease the yield of CDA, indicating that the AbsA1/AbsA2 may contribute negatively to the CDA production [Sheeler et al., 2005, McKenzie and Nodwell, 2007].

It is noteworthy to mention that TCS displaying high sequence similarity to *absA1/absA2* are also identified in A54145 (*orf27/orf28*) and friulimicin (*regC/regD*) gene clusters (Fig. 3), indicating that TSC may be a universal and unique regulatory system that controls daptomycin-related lipopeptide biosynthesis.

PPGPP AND THE STRINGENT RESPONSE

In *Streptomyce coelicolor* A3 (2), stringent response requires RelA to synthesize ppGpp (guanosine tetraphosphate) [Chakraburtty and Bibb, 1997]. Under nitrogen limited condition, synthesis of ppGpp results in significant change of cell physiology, including activation of expression of structural genes and regulatory gene (*cdaR*) for CDA biosynthesis, inhibition of genes related to cell growth [Hesketh et al., 2007]. ppGpp exerts an effect on transcription by binding to RNAP. Supportive evidence includes mutation in *rpoB* (RNA polymerase beta-subunit) results in increased the CDA production [Hu et al., 2002]. It is proposed that the mutations in *rpoB* mimic the ppGpp-bound form of RNAP, leading to elevated level of the regulator, CdaR.

N-ACETYLGULCOSAMINE AND NUTRIENT SENSING

N-acetylgulcosamine is an important carbon source and a building material for cell wall in *Streptomycetes*. In *Streptomyce coelicolor* A3 (2), high concentration N-acetylgulcosamine (>5–10 mM) inhibited CDA production in rich media, while enhanced CDA production in minimal media [van Wezel and McDowall, 2011]. This complex phenomenon is mediated by a GntR family regulator, DasR, which may directly control the expression of *cdaR*, resulting in decreased production of CDA. The effect of DasR on antibiotics production mainly depends on the abundance of glucosamine-6-phosphate (GlcN-6-P), which is the intermediate during N-acetylgulcosamine metabolism and the ligand for DasR [Rigali et al., 2008]. GlcN-6-P

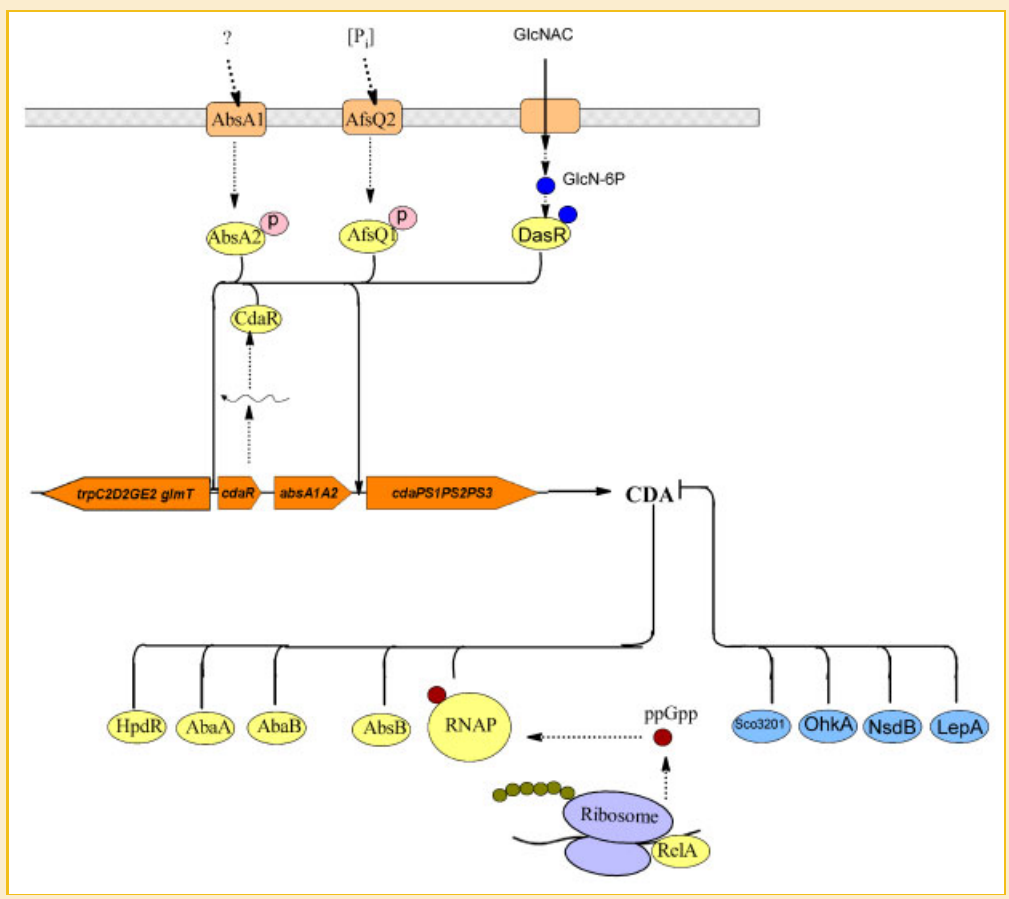

Fig. 4. Summary of the genetic regulation of CDA production in Streptomyces coelicolor A3(2). Activation is represented by triangular arrow; repression is shown by flat-arrow. Details of individual pathways are described in the text except for AbsB, a homologue of Escherichia coli Rnase III, AbaA(antibiotic biosynthetic activator), AbaB, HpdR, NsdB, LepA, and sco3201. [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/jcb]

TABLE I. Selected Genes Involved in Regulation of CDA Biosynthesis and Their Homologues in *S. roseosporus*

Gene number in *S. coelicolor*	Name	Gene number in *S. roseosporus*	Function	Identity/positive
Sco0702	AbaA	SSGG2923	Histone kinase-like ATPase	39%/50%
Sco1513	RelA	SSGG 0606	GTP pyrophosphokinase	89%/93%
Sco1596	OhkA	SSGG 0699	Orphan histine kinase	79%/84%
Sco2562	LepA	SSGG 1718	Elongation factor 4	90%/96%
Sco2935	HpdR	SSGG0227	IclR family regulator	86%/92%
Sco3201		SSGG 6854	TetR family regulator	35%/53%
Sco3225	AbsA1	SSGG 1969	Two component sensor kinase	48%/63%
Sco3226	AbsA2	SSGG 1967	Two-component system response regulator	58%/75%
Sco3919	AbaB	SSGG 6063	LysR family regulator	48%/59%
Sco4906	AfsQ2	SSGG 4474	Two component sensor kinase	71%/81%
Sco4907	AfsQ1	SSGG 1967	Two-component system response regulator	58%/75%
SCO5231	DasR	SSGG 4867	A gntR family regulator links nutrient stress to antibiotic production	89%/92%
Sco5572	AbsB	SSGG 5279	Ribonuclease III	90%/92%
Sco7252	NsdB	SSGG 5291	Proteins contains Tetratricopeptide repeat (TPR) domains	43%/57%

could reduce the affinity of DasR to target DNA, and relieve the inhibition effect of DasR on CDA production. Addition of N-acetylgulcosamine (50 mM) to minimal medium results in induced production of antibacterial substances from *S. hygroscopicus*, *S. collinus*, *S. venezuelae*, and *S. clavuligerus*. Unexpectedly, it results in lower antibiotics production in *S. roseosporus*, implying further studies are merited to clarify the yet unknown mechanism.

REGULATORY NETWORKS

It is obvious that numerous physiological signals are sensed and complex genetic networks are applied to detect and integrate those signals into the biosynthesis of daptomycin related lipopeptide. We have assembled a network that connects the steps involved in biosynthesis of CDA (Fig. 4). The regulatory relationships shown are based on diverse line of evidence, which include mutant phenotypes, gene overexpression phenotypes, microarray analysis, and proteomic analysis. Thus, some relationships are indirect or tentative. Given that genes related to regulation of the biosynthesis of CDA have highly conserved homologues in the chromosome of *S. roseosporus* (Table I), the network is intended as a framework for the identification and characterization of genes involved in the regulation of daptomycin biosynthesis.

CONCLUSIONS AND FUTURE DIRECTIONS

Emergence of multi-drug resistant bacteria requires discovery of new antibiotics with novel mechanism. Lipopeptide is a promising novel antibiotics family, exemplified by the daptomycin capable of treating Gram-positive resistant pathogens. Daptomycin biosynthetic pathway has been unveiled; however, underlying regulatory network remains elusive. Genome-wide approaches, such as diverse "omics", will undoubtedly hasten this understanding and reveal key metabolic nodes for strain improvement to raise the yield of daptomycin and other relevant important lipopeptides.

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